Understanding the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial Implications for current and future clinical practice

Vasim Farooq

Financial support for the publication of this thesis was generously provided by:
Volcano, USA
Boston Scientific, USA
HeartFlow, USA
Terumo, Japan
Cardialysis BV, Rotterdam, The Netherlands
Department of Public Health, ERASMUS MC, Rotterdam, The Netherlands
Abbott, USA

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Quotation back cover: Taggart DP, 2013 Lancet.
Printed by Optima Grafische Communicatie, Rotterdam, The Netherlands

ISBN: 978-94-6169-488-1

Understanding the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial Implications for current and future clinical practice

Inzicht in de synergie tussen percutane coronaire interventie met taxus en hartchirurgie (SYNTAX) trial Implicaties voor de huidige en toekomstige klinische praktijk

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 11 april 2014 om 11:30 uur

door
Vasim Farooq
born in Farnworth, Bolton, England

PROMOTIECOMMISIE

Promotor:
Prof.dr. P.W.J.C. Serruys
Prof.dr. E.W. Steyerberg

Overige leden:
Prof.dr. A.P. Kappetein
Prof.dr. A. Banning
Prof.dr. F.W. Mohr

To my mother and father

TABLE OF CONTENTS

General Introduction and Outline of Thesis

INTRODUCTION

The landmark Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial[1-4] has aided in reducing the area of uncertainty in decision making between percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery in patients with complex coronary artery disease.[5-8]

As part of the SYNTAX Trial, quantification of the coronary artery disease burden was undertaken with the anatomical SYNTAX Score (www.syntaxscore.com),[9-11] and has since been implemented in international revascularisation guidelines.[5-8] In addition, recognising the importance of quantifying coronary artery disease burden in decision-making between CABG and PCI, the US Food and Drugs Association mandates the SYNTAX Score as entry criteria in ongoing contemporary stent and structural heart disease trials. Namely, the EXCEL (Evaluation of XIENCE PRIME™ or XIENCE V® Everolimus Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) Trial (ClinicalTrials.gov identifier: NCT01205776), and SURTAVI (Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) Trial (ClinicalTrials.gov identifier: NCT01586910).

The SYNTAX Trial was conceived in an era when the potential benefits of drug eluting stents were first being realised between 2002-2006.[12-19] After multiple prior attempts comparing CABG against PCI using older technologies – namely plain 'old' balloon angioplasty (POBA) and bare metal stents (BMS) – in over 20 randomised trials,[20, 21] including the Bypass Angioplasty Revascularization Investigation (BARI)[22] and Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI)[23] trials, the time had once again come to rechallenge the cardiac surgeons in the management of complex coronary artery disease.

Historically one of the major criticisms of randomised trial design comparing CABG against PCI was that the trials enrolled highly selected, "cherry-picked," patients, with approximately 2-12% of screened subjects actually randomised in most trials, and thus being largely unrepresentative of conventional clinical practice.[20, 24] At the time of the SYNTAX Trial design, one of the key requirements put forth by seven cardiac surgeons, dubbed the "magnificent seven," and fully endorsed by the clinical and interventional cardiologists at the time, was the need for an 'all-comers' trial design, free from selection bias.

One of the unique aspects of the SYNTAX Trial was that a Heart Team – consisting of at least a cardiac surgeon and an interventional cardiologist – were required to use the SYNTAX Score as an objective anatomical scoring tool that forced the Heart Team

to systematically analyse the coronary angiogram, and agree that equivalent anatomic revascularisation between CABG and PCI could be achieved, based on a vessel size of 1.5 mm. Subjects were randomised if the Heart Team agreed that equivalent anatomic revascularisation could be achieved; subjects not suitable for randomisation were nested in CABG (PCI-ineligible patients) and PCI (CABG-ineligible patients) registries and followed up.[4] Notably, at the time of the SYNTAX Trial, the potential importance of the SYNTAX Score in stratifying patient outcomes and guiding decision making between CABG and PCI was unknown.

The aim of the thesis was to systematically study all aspects of the SYNTAX Trial, in order to better understand the results of this landmark trial, and its potential implications for current and future clinical practice. In addition, the development and/or validation of various SYNTAX based clinical tools are examined.

In Part I we explore the progress made prior to the thesis, and describe contemporary and evolving anatomical, myocardial jeopardy, and clinical risk scoring systems, to aid in identifying higher risk subjects undergoing coronary revascularisation, and decision making between CABG and PCI.

In Part II we show, through examination of the randomised and nested registries (more representative of an all-comers population) of the SYNTAX Trial, that incomplete revascularisation has a negative impact on long term mortality in both CABG and PCI treated patients. In addition, we show that the clinical impact of incomplete revascularisation is dependent on the complexity of the baseline coronary disease and risk profile of the CABG and PCI populations.

In Part III we develop and validate SYNTAX based clinical tools that objectively define levels of incomplete revascularisation. These tools may aid the clinician in determining a level of reasonable incomplete revascularisation which would not have an adverse effect on long term morbidity and mortality.

In Part IV we explore the use of novel intravascular imaging modalities to help further understand the complexities of the coronary bifurcation and stenting of this unique structure. In addition, we explore left main bifurcation angulation, and its relationship to the systolic and diastolic part of the cardiac cycle, and how this appears to impact on clinical outcomes in patients undergoing left main PCI.

In Part V we move to understanding the mechanisms of drug eluting stent and bypass graft failure, through exploring mechanisms and clinical sequelae of stent thrombosis and graft occlusion in the SYNTAX Trial, and understanding the mechanisms leading to in-stent restenosis.

In Part VI we examine the role of peri-procedural cardiac enzyme elevation on clinical outcome reporting and its prognostic implications in the SYNTAX Trial.

In Part VII we examine predictors of mortality in the PCI and CABG arms of the SYNTAX Trial and discover some unexpected findings, such as female gender being shown to an independent predictor of mortality in the PCI arm of the SYNTAX Trial.

In Part VIII we describe the process of the development and validation of the SYNTAX Score II, through augmenting the anatomical SYNTAX Score with clinical factors, and the move away from categorical based decision making between CABG and PCI (i.e. low, intermediate or high risk) to individualised decision making.

Part IX offers several editorials and letters on the author's viewpoints relating to diabetics, trial design and hypotheses relating to what if the SYNTAX Trial had been conducted using contemporary drug eluting stents.

Lastly, Part X offers a summary and conclusion of the thesis's contents, as well as future perspectives, including prospective validation studies of the anatomical SYNTAX Score and SYNTAX Score II in ongoing and planned contemporary drug eluting stent trials. The Appendix details the finalised protocol of the SYNTAX II Trial investigating the treatment of de novo three vessel disease. The SYNTAX II Trial will use the newly developed SYNTAX Score II as a tool to recruit subjects on the grounds of patient safety.

REFERENCES

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;**360**(10):961-72.
2. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;**32**(17):2125-34.
3. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;**381**(9867):629-38.
4. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. American heart journal 2006;**151**(6):1194-204.
5. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012;**59**(9):857-81.
6. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. Eur Heart J 2010;**31**(20):2501-55.
7. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM, Jr., Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;**58**(24):e123-210.
8. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;**58**(24):e44-122.

9. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the SYNTAX study. EuroIntervention 2009;**5**(1):50-6.
10. Sianos G, Morel MA, A.P. K, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;**1**(2):219-27.
11. SYNTAX score calculator: http://www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.
12. Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Van Langenhove G, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001;**104**(17):2007-11.
13. Rensing BJ, Vos J, Smits PC, Foley DP, van den Brand MJ, van der Giessen WJ, de Feijter PJ, Serruys PW. Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with 6-month angiographic and intravascular ultrasonic follow-up. Eur Heart J 2001;**22**(22):2125-30.
14. Serruys PW, Regar E, Carter AJ. Rapamycin eluting stent: the onset of a new era in interventional cardiology. Heart 2002;**87**(4):305-7.
15. Serruys PW. ARTS I -- the rapamycin eluting stent; ARTS II -- the rosy prophecy. Eur Heart J 2002;**23**(10):757-9.
16. Valgimigli M, van Mieghem CA, Ong AT, Aoki J, Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smits PC, Regar E, Van der Giessen WJ, Sianos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). Circulation 2005;**111**(11):1383-9.
17. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;**46**(4):575-81.
18. Ong AT, Serruys PW, Aoki J, Hoye A, van Mieghem CA, Rodriguez-Granillo GA, Valgimigli M, Sonnenschein K, Regar E, van der Ent M, de Jaegere PP, McFadden EP, Sianos G, van der Giessen WJ, de Feyter PJ, van Domburg RT. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. J Am Coll Cardiol 2005;**45**(7):1135-41.
19. Serruys PW, Daemen J, Morice MC, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins KD, Vranckx P, Bressers M, van Domburg R, Schuijer M, Wittebols K, Pieters M, Stoll HP. Three-year follow-up of the ARTS-II - sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. EuroIntervention 2008;**3**(4):450-9.
20. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal

coronary angioplasty: one- to eight-year outcomes. Journal of the American College of Cardiology 2003;**41**(8):1293-304.

21. Soran O, Manchanda A, Schueler S. Percutaneous coronary intervention versus coronary artery bypass surgery in multivessel disease: a current perspective. Interact Cardiovasc Thorac Surg 2009;**8**(6):666-71.
22. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. N Engl J Med 1996;**335**(4):217-25.
23. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. Lancet 1995;**346**(8984):1179-84.
24. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;**82**(6):1966-75.

PART I

Understanding conventional anatomical and clinical based scores for decision making

Chapter 1

Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention

Farooq V, Brugaletta S, Serruys PW

Heart. 2011;97(23):1902-13 (Impact Factor: 5.014)

Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention

Vasim Farooq, Salvatore Brugaletta, Patrick W Serruys

Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands

Correspondence to
Professor Patrick W Serruys, Professor of Medicine, Head of the Interventional Cardiology Department, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands; p.w.j.c.serruys@erasmusmc.nl

Received 5 July 2011
Revised 29 August 2011
Accepted 6 September 2011

ABSTRACT

Risk stratification is an essential part of appropriately informing patients electing to undergo percutaneous coronary intervention (PCI). This process is also an integral part of the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery)-pioneered heart team approach in determining the most appropriate revascularisation modality for patients with complex coronary artery disease. The SYNTAX score was pioneered as an anatomical-based risk score to aid in this decision-making process; the lack of clinical variables in this score has, however, been its main limitation. This review examines the important established and evolving contemporary risk models used to aid this risk-stratification process. Risk scores based on clinical and anatomical variables alone and in combination—the latter of which is the subject of continuing research—are all explored. Other areas of discussion include risk scores based on the completeness of revascularisation and emerging concepts such as functional anatomical risk scores and the patient-empowered risk-benefit trade-off between PCI and coronary artery bypass grafting, to help personalise the choice of revascularisation modality.

INTRODUCTION

Risk stratification is an essential component of appropriately informing patients electing to have percutaneous coronary intervention (PCI). This process is also an integral part of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) Trial-pioneered heart team approach in selecting the most appropriate revascularisation modality (coronary artery bypass grafting (CABG) or PCI) in patients with complex (three-vessel disease (3VD) or left main stem (LMS) disease) coronary artery disease. Despite the landmark SYNTAX Trial having established that surgery is the standard of care for patients with LMS disease or 3VD, an important finding from this study was that patients with less complex disease had equivalent outcomes to surgical and percutaneous revascularisation at up to 3 years follow-up.[1–4] The heart team approach in managing patients with complex coronary disease has therefore recently been incorporated as a class I recommendation in recent European myocardial revascularisation guidelines.[5]

In cardiothoracic surgical practice, the use of risk models to appropriately risk-stratify patients is well established. These risk scores are predominantly related to clinical variables alone, with scores such as the EuroSCORE[6 7] or Society of Thoracic Surgery Score[8] being in widespread contemporary use. The use of anatomical variables for cardiothoracic risk models, eg, the SYNTAX Score, has been shown not to provide any additional predictive benefit over clinical variables. This is likely to be related to bypass grafts being anastomosed distal to the coronary disease, regardless of the complexity of the proximal segments, provided that there are suitable graftable targets.[4 9]

The SXscore was pioneered as an anatomical-based score to aid the heart team decision-making process—its main application being identification of less complex coronary artery disease, which would be equally amenable to surgery or PCI in terms of efficacy and safety. However, criticism emerged that clinical factors were not being taken into account in the risk stratification of the PCI patient, and potentially important morbidity and prognostic information may be missing.[4 10–13] Several risk scores have consequently attempted to merge the SXscore with clinically based risk scores, such as the Clinical SYNTAX Score (a combination of the SXscore and the modified ACEF (age, creatinine clearance, ejection fraction) Score) and the Global Risk (a combination of the SXscore and the EuroSCORE). These are discussed later in this review.

The purpose of this review article is to give the clinician a concise overview of the important established and evolving contemporary risk models for risk-stratifying patients electing to undergo PCI. Risk scores based on clinical and anatomical variables alone and in combination, and on the completeness of revascularisation are all discussed. Furthermore, attention is drawn to which clinical outcomes—and over what time period (ie, in-hospital, short or long term)—the risk model is stratifying risk for, and also if the risk model is validated in a population other than that from which it was derived (table 1). Emerging concepts such as functional anatomical risk scores, based on invasive and non-invasive assessments, and the novel concept of patient-empowered risk—benefit trade-off between CABG and PCI to help personalise the choice of revascularisation modality are also explored.

ANATOMY-BASED RISK SCORES

In 1981, Leaman *et al*[44] developed a scoring system that assessed the severity and extent of the underlying coronary artery disease. This system was based on the severity of luminal diameter narrowing and weighted according to the usual flow to the left ventricle in each coronary vessel. Consequently, the most weight was given to the LMS, followed by the left anterior descending, circumflex, and right coronary arteries. This early

Table 1 Summary of a selection of established and contemporary risk models categorised by anatomical, clinical or combined types, for the assessment of risk in patients proposing to undergo percutaneous coronary intervention

Clinical risk score	Number of variables used to calculate risk: Clinical	Number of variables used to calculate risk: Angiographic	PCI outcomes (surgical outcomes in italics)
Anatomy-based scores			
ACC/AHA lesion classification*	0	11 (per lesion)	Pre-DES era: predictive of angiographic success of PCI and prognostic effect on early and late clinical outcomes. Conflicting results in the DES era.[14–18]
SYNTAX score (SXscore)	0	11 (per lesion)	Quantifies coronary artery disease complexity by tertiles of SXscore: correlated with clinical outcomes (Death, MACCE) at 1 year.[2 4] Subsequently validated in multiple other populations.[16 19 20]
Functional anatomy-based scores			
Functional Syntax Score	0	11 (per lesion)	FFR-guided SXscore calculation improved prognostic ability of the SXscore in a retrospective study: Death/MI, MACE at 1 year.[21] Validation in larger All-Comers populations, including patients with LMS and 3VD, are awaited.
Myocardial Jeopardy Scores			
Duke Jeopardy Score	0	Coronary tree divided into six segments: LAD, diagonal, septal perforating branches, LCx, OM and PDA, with a segment distal to ≥70% considered at risk. Each segment assigned 2 points with a maximum number of 12 points.† [22 23]	
Myocardial Jeopardy Index (BARI)	0	Distal terminating portions of LAD, LCx, RCA and major branch vessels (diagonals, OM, ramus, PDA and LV branches) assigned units of 1, 2 or 3 on basis of length/size of vessel. Septal perforators arbitrarily assigned a maximum of 3 units. Extent of jeopardy defined by units jeopardised by ≥50% stenosis summated and divided by total LV territory.† [23 24]	
APPROACH Lesion Score	0	Based on principle from autopsy studies that the LAD generally subtends 41% of the LV, with the LCx and RCA supplying the remainder, dependent on vessel dominance. Score calculated by % of myocardium supplied by a vessel or its branches, jeopardised territories supplied by vessels with ≥70% stenosis (≥50% in the LMS)—maximum score 100.† [23]	
Clinically based scores			
New Mayo Clinic Risk Score*	7	0	Procedural Death and MACE for PCI; model has been externally validated for Death.[25 26] (*In-hospital death with CABG*).[27]
Parsonnet Score	14	0	Independent predictor of long-term MACE after LMS PCI in two registry populations.[19 28] (*Operative mortality after open-heart surgery*).[29]
EuroSCORE (additive or logistic)	17	0	Evidence for predicting Death or MACCE in high-risk tertiles for PCI.[10–12 30] *(Operative mortality for all forms of cardiothoracic surgery)*.[6 7]
NCDR CathPCI Risk Score*	8	0	Developed from 181 775 procedures performed in Medicare patients; in-hospital and 30-day mortality after all PCI patient types; internally validated in two separate cohorts.[31]
ACEF Score (age, creatinine, ejection fraction)	3	0	Predictor of Cardiac Death and MI at 1 year after PCI, inferior to the SXscore at predicting overall MACE and repeat revascularisation in two separate populations.[32 33] *(Operative mortality in elective cardiac operations)*.[34 35]
Combined (anatomy and clinically based) risk scores			
Global Risk	17	11 (per lesion)	Predictive of Death and MACCE, at up to 3 years, in 3VD and LMS patients from the randomised and All-Comers populations of the SYNTAX Trial. Application of the model to other populations is required.[36 37]
EuroHeart PCI Score*	10	6	Developed from 46 000 patients from the Euro Heart Survey; in-hospital mortality in all PCI patient types; internally validated. The score has strong applicability for European practice.[38]
New Risk Classification Score (NERS)	17	Angiographic: 33 Procedural: 4‡	6-month Cardiac Death and cumulative MACE after unprotected LMS PCI. Although internally validated—application to larger All-Comers population required (see text).[39]
Parsonnet + SYNTAX Score	14	11	Addition of the Parsonnet Score as a covariate to the SYNTAX Score improved the long-term (~4 years) predictive ability of the score in predicting MACCE after LMS PCI.[19]
Clinical SYNTAX Score	3	11 (per lesion)	MACCE and Death in patients with complex coronary disease treated with PCI at 5 years,[40] and 2 year follow-up after LMS PCI.[33] Not predictive of low-risk population, thereby limiting its clinical use.

Continued

Table 1 Continued

Clinical risk score	Number of variables used to calculate risk: Clinical	Number of variables used to calculate risk: Angiographic	PCI outcomes (surgical outcomes in italics)
New York PCI Risk Score*	8	1	In-hospital Death after PCI. Developed on the basis of data from 46 090 procedures in 2002 and validated from 50 046 procedures in 2003 in New York.[41] Excellent predictive ability in validation cohort (c-statistic 0.905).
The Texas Heart Institute Risk Score*	8	Angiographic: 2 Procedural: 1§	Predictors of in-hospital MACE after PCI or CABG. Developed in 9494 patients (BMS era) and validated in 5545 patients (DES era).[42]
Mayo Clinic Risk Score*	6	2	In-hospital Death, Q-wave myocardial infarction, emergent or urgent CABG or CVA after PCI; validated using the NHLBI Registry.[43]

*These risk models include prediction of in-hospital mortality or MACE.
†All myocardial jeopardy scores validated in one population-based cohort consisting of >20 000 patients and were predictive of 1 year mortality in patients treated with PCI (or medically).[22–24]
‡Need for intra-aortic balloon pump (IABP), 2-stent technique, intravascular ultrasound (IVUS) guidance.
§Number of stents.
CABG, coronary artery bypass grafting; DES, drug-eluting stent; FFR, fractional flow reserve; LAD, left anterior descending artery; LCx, left circumflex artery; LMS, left main stem; LV, left ventricle; MACE, mortality and major adverse cardiac events; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; NHLBI, National Heart, Lung, and Blood Institute; OM, obtuse marginal artery; PCI, percutaneous coronary intervention; PDA, posterior descending artery; RCA, right coronary artery.

pioneering work, with further information derived from adverse characteristics of coronary lesions from the American College of Cardiology/American Heart Association (ACC/AHA) lesion classification system,[45 46] and the modified Duke/Institut Cardiovasculaire Paris Sud (ICPS) System classification for bifurcation lesions,[14 47] ultimately formed the basis of the SXscore.[4 48 49]

ACC/AHA lesion classification system

The ACC/AHA lesion classification system was one of the first angiography scoring systems developed, comprising 11 angiographic variables with all lesions categorised into types (A, B1, B2 and C).[45 46] This system predicts the angiographic success of PCI with a subsequent prognostic effect on the early and late clinical outcomes in the pre-drug-eluting stent era (box 1).[50] Registry data from the drug-eluting stent era have, however, had conflicting results. The German Cypher Registry (n=6755) failed to show any significant association with clinical outcomes at 6 months;[15] conversely, data from a small registry (n=255) was potentially predictive of mortality in unprotected LMS PCI at 1-year follow-up.[16]

SYNTAX Score

The SXscore is an anatomical-based risk score that takes into account features such as bifurcations, total occlusions, thrombus, calcification and small vessels (figure 1). Each coronary lesion with a >50% luminal obstruction in vessels ≥1.5 mm is scored separately and the scores summated to provide the overall SXscore. This is calculated using dedicated software that integrates the number of lesions with their specific weighting factors, based on the amount of myocardium distal to the lesion and the morphological features of each lesion.[4 44 48 49]

In the SYNTAX Trial,[1] the distribution of the SXscore was found to be Gaussian in the randomised CABG and PCI populations, with the curves almost superimposable on each other (figure 2). When the scores of the randomised SYNTAX population were divided into tertiles, the upper boundary of the lowest tertile was 22 (low risk), the second tertile ranged from 23 to 32 (intermediate risk), and the lower boundary for the highest tertile was equal to or greater than 33 (high risk).

The SXscore has since consistently been shown to identify poorer outcomes and to be an independent predictor of major adverse cardiovascular and cerebrovascular events (MACCE) in the high-tertile group of risk for PCI at 1 year,[4 19 51] and in the Arterial Revascularization Therapies Study II (ARTS II) population (a population with two (46%) or three (54%) vessel disease) at up to 5 years of follow-up (figure 3).[52 53] Furthermore, the 3-year SYNTAX Trial showed that a low SXscore (ie, <23) in the 3VD cohort and low–intermediate SXscore (ie, <33) in the LMS disease cohort were able to identify a subset of patients who could safely and efficaciously be treated with CABG or PCI and have comparable clinical outcomes in terms of death and MACCE.[2]

Early-submitted results from the 3-year SYNTAX Trial have, however, indicated that the SXscore appears to be poorly predictive of clinical events in the 3VD cohort, unless combined with clinical variables; the high SXscore was, however, predictive of clinical events in the LMS disease population at 3 years.[36 37] It was hypothesised that a high SXscore in patients with LMS disease and an intermediate–high SXscore in patients with 3VD were markers of a more adverse risk profile. This is supported by the 10-year predicted Framingham risk scores, which were recently shown to have a significant and direct relationship to the prevalence and magnitude of coronary artery calcium scores.[54] Furthermore, the ankle–brachial index and common carotid intima–media thickness have both previously been reported to be associated with the extent and severity of coronary artery disease.[55–57] Consequently, not only is the presence of a higher SXscore associated with anatomical complexities, such as multiple bifurcations and the presence of total occlusions—which would potentially make PCI more technically challenging with consequent increased procedural risk—but the apparent association with clinical comorbidity would also place these patients at greater long-term risk. As was clearly demonstrated in the SYNTAX Trial, patients with a higher SXscore would be better managed by CABG provided that an acceptable threshold of risk for the patient and surgeon was achievable.[36 37] The reason for this is that CABG protects the entire coronary vessel compared with PCI which treats the individual.

With the next generation drug-eluting stent in the All-Comers LEADERS (Limus Eluted from A Durable vs ERodable Stent coating)[58] and All-Comers Resolute[59] randomised populations undergoing PCI for a broad spectrum of indications, it has been shown that the highest tertile of the SXscore was associated with a significantly higher incidence of mortality and major adverse cardiac events (MACE). Moreover, in the MULTISTRATEGY and STRATEGY Registries, composed of patients presenting with a ST-elevation myocardial infarction (MI), it was reported that the SXscore was an

Box 1 Characteristics of American College of Cardiology/American Heart Association (ACC/AHA) type A, B and C lesions[50]

Type A lesions (high success, >85%; low risk)
Discrete (<10 mm length)
Concentric
Readily accessible
Non-angulated segment <45°
Smooth contour
Little or no calcification
Less than totally occlusive
Not ostial in location
No major branch involvement
Absence of thrombus

Type B lesions (moderate success, 60–85%; moderate risk)
Tubular (10–20 mm length)
Eccentric
Moderate tortuosity of proximal segment
Moderately angulated segment, 45–90°
Irregular contour
Moderate to heavy calcification
Ostial in location
Bifurcation lesions requiring double guidewires
Some thrombus present
Total occlusion <3 months old
Subdivided into type B1 (one type B characteristic) and B2 (two type B characteristics) types

Type C lesions (low success, <60%; high risk)
Diffuse (>2 cm length)
Excessive tortuosity of proximal segment
Extremely angulated segments, >90°
Inability to protect major side branches
Degenerated vein grafts with friable lesions
Total occlusion >3 months old

independent predictor of mortality, MACE, and stent thrombosis at 1-year follow-up; when however the SXscore was combined with clinical variables, the risk model proved significantly more predictive of adverse clinical events at 1 year.[60]

FUNCTIONAL ANATOMY-BASED RISK SCORES

Functional SXscore

Fractional flow reserve (FFR) is a technique that uses a pressure wire to assess physiological variables that reflect both the severity of epicardial stenosis and the amount of myocardium supplied.[61] This was investigated in the The FFR versus Angiography for Guiding PCI in Patients with Multivessel Evaluation (FAME) Study, which determined the potential prognostic impact of PCI guided by FFR measurements to determine the functional significance of an individual coronary lesion before intervention.[62 63]

Consequently, by incorporating FFR measurements into the SXscore to form the recently dubbed 'Functional SXscore', it was shown in a retrospective sub-analysis of almost 500 patients with multivessel disease from the FFR-guided arm of the FAME Study that this improved the risk stratification of patients compared with the conventional angiography-based approach to the calculation of the SXscore.[21] The primary benefit appeared to be in reclassifying a significant proportion of the higher-risk groups into lower-risk categories while still maintaining a significantly higher event rate (death/MI and MACE at 1 year) in the high-risk groups. It should, however, be emphasised that no patients with LMS disease were involved in this study, and prospective validation of the Functional SXscore in LMS disease and multivessel disease is required.

One further caveat to the Functional SXscore approach is that two-dimensional (2D) and three-dimensional (3D) quantitative coronary angiography (QCA) have been shown to be far more reliable than visual estimation of vessel size, the latter being associated with poor reproducibility and often overestimation of lesion significance.[17 64–67] Yong *et al*[65] recently showed that 3D QCA assessment of the minimum lumen area was superior to the 2D QCA-derived minimum lumen diameter in determining the functional significance of a coronary lesion as assessed by FFR. The 3D QCA measurements of the minimum lumen area were derived from two orthogonal angiographic views of the target lesion, enabling better assessment of vessel tortuosity and coronary lesion asymmetry compared with 2D QCA.

If 2D QCA and, in particular, 3D QCA had been used to assess vessel size to calculate the SXscore, this may have reduced the benefits of the Functional SXscore compared with the SXscore derived from visual estimation. Visual assessment of vessel/lesion size is, however, representative of real-life practice and was also the basis for calculation of the SXscores in the SYNTAX Trial. It should also be emphasised that, although FFR may be regarded as the 'gold standard' method for detecting reversible ischaemia, the ischaemic potential of the small grey zone of FFR (between 0.75 and 0.80) remains unclear, and an abnormal FFR (ie, >0.80) excludes ischaemia in 90% of cases.[68–70] Further study is required to validate the Functional SXscore compared with a visually or QCA derived SXscore.

Non-invasive Functional SXscore

Novel techniques in development to potentially simplify the generation of the newly developed Functional SXscore include the use of non-invasive coronary CT angiography (CTA), which allows the simultaneous assessment of anatomy and measurement of the haemodynamic significance of lesions—to permit non-invasive computation of FFR—using computational fluid dynamic techniques applied to the coronary CTA (Heartflow, Redwood City, California, USA) (figure 4). Preliminary validation of this technique was recently reported in the DISCOVER FLOW Trial,[71] where it was found that the non-invasive FFR technique could dramatically improve the diagnostic accuracy of CT imaging without any immediate need for invasive FFR imaging. The larger-scale multicentre DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) Trial (NCT01233518) is ongoing.

Limitations of anatomy-based and functional anatomy-based risk scores

The progressive development of anatomical-based risk scores culminating in the Functional SXscore has undoubtedly improved the performance of these risk models in terms of risk stratification for the individual patient. However, a limiting factor is the inevitable intervariability in coronary angiogram assessment if visual assessment is used to assess the vessel/lesion size.[4] With the potential use of the QCA-derived SXscore or Functional SXscore, this problem may be circumvented.

Another limiting factor is that no clinical variables are used, which are less subjective than angiographic variables; this is of

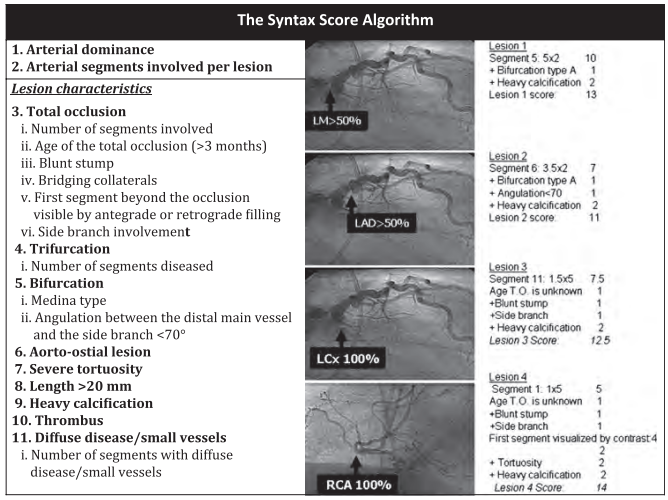


Figure 1 SYNTAX Score (SXscore) algorithm. The algorithm is applied to each individual coronary lesion that has a diameter stenosis >50% and located in a vessel >1.5 mm in diameter. The individual lesion scores are added together to give the final SXscore.[3 4 48 49] LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main stem; RCA, right coronary artery. Reproduced, with permission, from Serruys *et al*.[4]

paramount importance given that the lack of clinical variables is likely to reduce the predictive ability of the risk model if anatomical variables alone are relied on.

MYOCARDIAL JEOPARDY SCORES

Myocardial jeopardy scores are used to estimate the amount of myocardium at risk on the basis of assessment of both the severity of the coronary artery lesion and the volume of myocardium it supplies. Examples of such scores include the Duke Jeopardy Score, the Myocardial Jeopardy Index from the Bypass Angioplasty Revascularization Investigation (BARI) Score, and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Score (figure 5; table 1). The Duke and BARI Scores were developed and validated in relatively small populations. All three models have since been validated in one population-based cohort consisting of >20 000 patients and were found to be predictive of 1-year mortality in patients treated with PCI (or medically); in this population, all three scores also had similar risk model performance measures with only minor differences in c-statistics evident.[22–24]

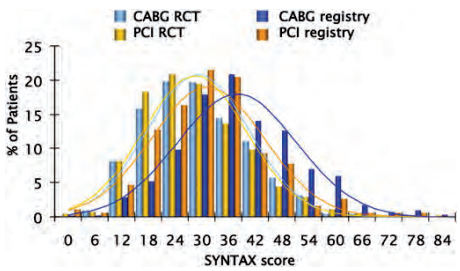


Figure 2 Distribution of the SYNTAX Score (SXscore) in the randomised controlled trial (RCT) and nested registry percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) populations from the SYNTAX Trial. Note how the distributions for both the RCT, CABG and PCI populations are almost superimposable on each other, whereas the nested registries—consisting of patients with more complex coronary disease—are shifted to the right.[1 4] Adapted and reprinted from *EuroIntervention*, Serruys PW *et al*, Assessment of the SYNTAX score in the Syntax study. Copyright 2009, with permission from Europa Edition.[4]

The Jeopardy Score has since been shown to be an independent predictor of adverse clinical outcomes (ie, death/MI) in medically treated patients with acute coronary syndromes at up to 1 year, in the post hoc Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial.[72]

The recently described BCIS-1 Myocardial Jeopardy Score, a variant of the Duke Jeopardy Score which has been reported to be simpler to use, has been shown to have a strong correlation with the myocardial ischaemia burden as assessed by cardiac magnetic resonance perfusion imaging.[73 74] A BCIS-1 Jeopardy Score of 10–12 and a Revascularisation Index (pre- minus post-procedural Jeopardy Scores divided by pre-procedural Jeopardy Score, with 1 indicating complete revascularisation) of 0–0.33 were both shown to be highly predictive of mortality after contemporary PCI in a single UK centre experience involving over 600 patients.[75] Larger-scale, multicentre trials are, however, required. A correlation with the underlying complexity of coronary anatomy (SXscore), which appears to have different prognostic outcomes as previously described, and the correlation between QCA- and FFR-derived jeopardy scores should in our opinion be incorporated into future trials.

CLINICALLY BASED RISK SCORES

The main advantages of these scores are that they are potentially easier to perform and less subjective than purely anatomical-based scores, which require interpretation of the coronary angiogram. They can also be performed relatively quickly and often at the bedside if necessary.

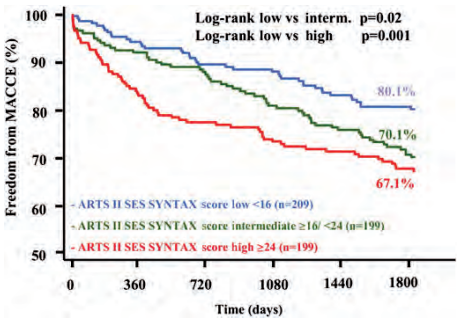


Figure 3 Kaplan–Meier curves of freedom protocol-defined major adverse cardiac and cerebrovascular event (MACCE) rate according to SYNTAX Score tertiles, from the 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) Trial. Reproduced, with permission, from Serruys *et al*.[53] MACCE, major adverse cardiovascular and cerebrovascular events; interm., intermediate; SES, sirolimus eluting stent.

New Mayo Clinic Risk Score

The New Mayo Clinic Risk Score was designed to replace the Mayo Clinic Risk Score by predominantly excluding angiographic variables, namely the presence of LMS or multivessel disease, and a few of the interaction effects of specific clinical variables.[25 26 43]

The New Mayo Clinic Risk Score is based solely on baseline clinical and non-invasive assessments and incorporates seven pre-procedural variables (age, serum creatinine, left ventricular ejection fraction, MI ≤24 h, pre-procedural shock, congestive heart failure and peripheral vascular disease) for the prediction of procedural Death or MACE. The risk model had c-statistics of 0.74 and 0.89 for MACE and procedural death, respectively, in the population from which the risk model was derived.[25 26] The risk model has since been validated for in-hospital mortality in the National Cardiovascular Data Registry (NCDR);[26] it has, however, not been validated for MACE. The New Mayo Clinic Risk Score has also been shown to be predictive of in-hospital mortality after CABG surgery.[27]

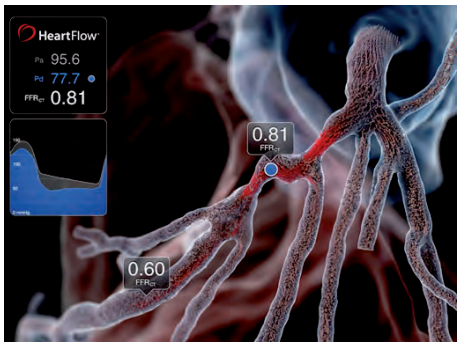


Figure 4 The principle of non-invasive CT angiography that allows the simultaneous assessment of anatomy and measurement of the haemodynamic significance of lesions by fractional flow reserve (FFR) guidance. This principle can allow for the non-invasive assessment of the Functional Syntax Score. In this clinical case example, tandem lesions in the left anterior descending artery (LAD) are evident, the haemodynamic significance of which was unclear from the CT coronary angiogram: non-invasive FFR in the distal LAD was 0.60 and therefore haemodynamically significant, but FFR just proximal to the distal lesion was 0.80, indicating that the proximal LAD lesion was not haemodynamically significant; FFR at the ostial LAD was normal (0.98, not illustrated).

CathPCI Risk Score System

The NCDR CathPCI Risk Score System was developed from 181 775 procedures performed in Medicare patients over a 2-year period (table 2); the model was independently validated in two separate validation cohorts.[31] The risk model was based on eight key pre-procedural factors and was found to have excellent discriminative ability in predicting in-hospital mortality (c-statistic 0.89), with the model still able to have good predictive ability for 30-day mortality after PCI (c-statistic 0.83). A full risk model, from which this model was derived (incorporating 35 pre-procedural and angiographic features), resulted in a marginally better risk model (c-statistic 0.90 and 0.86 for in-hospital and 30-day mortality, respectively).

European system for cardiac operative risk evaluation (EuroSCORE)

The EuroSCORE is an established risk model, using 17 clinical variables, in cardiothoracic surgical practice for predicting operative mortality and has been validated in many populations around the world.[6 7 76] In use since 1999, the model was derived from almost 20 000 consecutive patients from 128 hospitals in eight European countries. The additive EuroSCORE assigns an individual score to 17 clinical variables (table 3), with a low EuroSCORE risk tertile ranging from 1 to 2, intermediate risk tertile from 3 to 5, and a high risk tertile of 6+.

The subsequently developed logistic EuroSCORE has been suggested to allow a more accurate risk prediction in the CABG cohort, in particular for the high-risk population, where the additive model was found to lead to a potential underestimation of risk.[6 7 76 77] Conversely, the logistic EuroSCORE has been shown to potentially overestimate observed mortality, with its accuracy for predicting risk varying in different surgical subgroups.[77 78]

Kim *et al* first demonstrated that the high-risk tertile of the additive EuroSCORE was an independent predictor of Death/MI after unprotected LMS intervention with sirolimus-eluting stents.[11] Subsequently, Romangoli *et al* applied the additive EuroSCORE to predict in-hospital mortality in 1173 consecutive patients undergoing PCI in a single high-volume centre and correlated the higher-risk tertiles of the EuroSCORE with in-hospital mortality; the study population also included patients who had undergone unprotected LMS PCI.[10] In addition, several studies have since all identified the additive EuroSCORE as an independent predictor of MACCE in patients with unprotected LMS PCI at up to 4 years follow-up.[11 12 30] Only one study has examined the logistic EuroSCORE in PCI patients, with few differences being demonstrated in stratifying risk when compared with the additive EuroSCORE.[10] Our group has recently applied the additive and logistic EuroSCOREs to the SYNTAX PCI population; risk model performance measures[79 80] suggested that the additive EuroSCORE was superior to the logistic EuroSCORE in risk-stratifying PCI patients.[36 37]

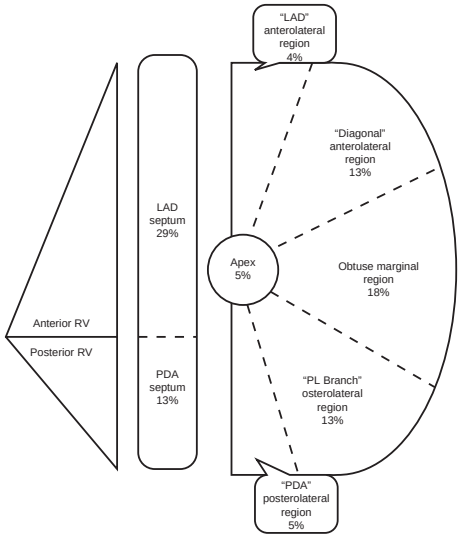


Figure 5 Example of a Myocardial Jeopardy Score. The APPROACH Lesion Score illustrating the weighting factors for myocardial regions is illustrated. LAD, left anterior descending artery; RV, right ventricle; PDA, posterior decending artery; PL, posterolateral. Reproduced, with permission, from Graham *et al*.[23]

ACEF Score

Ranucci *et al* demonstrated a relatively simple risk model (consisting of only three clinical variables, namely age, preoperative serum creatinine value and left ventricular ejection fraction) for assessing operative mortality risk in elective cardiac operations. It is noteworthy that, despite the simplicity of the model, its clinical performance appeared to be comparable to either the additive or the logistic EuroSCORE.[34 35]

The ACEF Score is calculated using the formula:

$$\text{ACEF} = [\text{Age/Ejection fraction (\%)}] + [1 \text{ (if creatinine} > 2 \text{ mg/dl)}]$$

From this score, a mortality risk can be calculated from a graphic relationship of the score with an operative risk or an equation.[34 35]

The ACEF model was recently applied to PCI patients from the All-Comers LEADERS population at 1-year follow-up.[32] Despite the ACEF Score being demonstrated to be superior to the SXscore alone as a predictor of cardiac death and MI after PCI, it was found to be inferior to the SXscore at predicting overall MACE and the risk of repeat revascularisation, reflecting the observation that anatomical and clinical variables appear to be necessary requirements for a comprehensive risk model in predicting clinical outcomes with PCI. It should however be emphasised that the ACEF model has not been validated in the PCI population.

Limitations of clinically based risk scores

The main limitations of the clinically based risk scores, apart from not incorporating anatomical-based variables, are that they rely on predominantly registry data—proposed to be more representative of contemporary 'real-life' practice. The potential for selection bias in patients receiving coronary angiography—for example, in limiting the number of octogenarians—may lead to the risk model potentially underestimating risk in these patient subsets.

COMBINED (ANATOMICAL AND CLINICAL BASED) RISK SCORES

SXscore and Parsonnet Score

Combining the Parsonnet Score, an operative risk score published in 1989 consisting of 14 clinical variables,[29] with the

Table 2 NCDR CathPCI Risk Score System

Variable	Scoring response categories				Total points	Risk of in-patient mortality
Age	<60	≥60, <70	≥70, <80	≥80	0	0.0
	0	4	8	14	5	0.1
Cardiogenic shock	No	Yes			10	0.1
	0	25			15	0.2
Prior CHF	No	Yes			20	0.3
	0	5			25	0.6
Peripheral vascular disease	No	Yes			30	1.1
	0	5			35	2.0
Chronic lung disease	No	Yes			40	3.6
	0	4			45	6.3
GFR	<30	30–60	60–90	>90	50	10.9
	18	10	6	0	55	18.3
NYHA functional class IV	No	Yes			60	29.0
	0	4			65	42.7
PCI status (STEMI)	Elective	Urgent	Emergent	Salvage	70	57.6
	12	15	20	38	75	71.2
PCI status (no STEMI)	Elective	Urgent	Emergent	Salvage	80	81.0
	0	8	20	42	85	89.2
					90	93.8
					95	96.5
					100	98.0

Reproduced, with permission, from Peterson *et al*.[31]
CHF, chronic heart failure; GFR, glomerular filtration rate; NCDR, National Cardiovascular Data Registry; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 3 Additive EuroSCORE, calculated by summating the individual scores from 17 different variables[6]

Factor	Description	Score
Patient factors		
Age	Per 5 years or part thereof over the age of 60 years	1
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for respiratory disease	1
Peripheral arteriopathy	Claudication/carotid stenosis >50%/previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction	Severely affected mobility or day-to-day function	2
Previous cardiac surgery	Previous opening of the pericardium	3
Serum creatinine	>200 μmol/l before surgery	2
Active endocarditis	Antibiotic therapy at time of surgery	3
Critical preoperative state	Preoperative cardiac arrest, ventilation, renal failure, inotropic support, intra-aortic balloon pump use, ventricular arrhythmia	3
Cardiac factors		
Unstable angina	Rest pain requiring IV nitrates	2
Left ventricular function	Moderate (30–50%)	1
	Poor (<30%)	3
Recent MI	Within 90 days	2
Pulmonary hypertension	Systolic pulmonary artery pressure >60 mm Hg	2
Operative factors		
Emergency operation	Performed before the start of next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta		3
Post-infarct septal rupture		4

CABG, coronary artery bypass grafting; IV, intravenous; MI, myocardial infarction.

SXscore has been shown to potentially improve the performance of the SXscore alone.

In 2005, Valgimigli *et al* showed that the Parsonnet Score was an independent long-term (~3 years) predictor of MACE after LMS intervention from the Rotterdam RESEARCH and T-SEARCH Registries.[28] More recently, Chakravarty *et al* showed that adding the Parsonnet Score as a covariate to the SXscore improved the long-term (~4 years) predictive ability of the score in predicting MACCE after LMS PCI.[19]

Clinical SYNTAX Score

The underlying rationale for the Clinical SXscore was to combine the SXscore and a variant of the ACEF Score (modified ACEF Score).[34 35] The modified ACEF Score was used instead of the ACEF Score in this model because it had previously been shown to potentially allow a more accurate assessment of the underlying renal function, and had subsequently improved the accuracy of cardiac prediction models such as the EuroSCORE in patients receiving CABG.[40 81 82] The modified ACEF Score is calculated using the formula: age/ejection fraction +1 point for every 10 ml/min reduction in creatinine clearance below 60 ml/min/1.73 m^2 (up to a maximum of 6 points).

This model was applied to the ARTS II population treated with sirolimus-eluting stents for multivessel (two or three) coronary artery disease.[40 83] By dividing the calculated Clinical SXscores into tertiles of risk, it was demonstrated that the risk model for predicting outcomes for MACCE and death at 5 years was superior to the SXscore or modified ACEF Score alone. One of the limiting factors of the Clinical SXscore that has prevented its clinical use is that, despite being able to potentially predict events more accurately in the high-risk tertile, the risk model was unable to differentiate between the clinical events for the low- and intermediate-risk tertiles[40]; this was also demonstrated when applied to a different similar-sized registry by another group.[33]

New Risk Classification Score (NERS)

NERS[39] is a risk model developed within four centres in China (n=260) to predict long-term outcomes after unprotected LMS PCI. Reflecting the long time period over which this registry was performed (~10 years), the patients included either had bare metal or drug-eluting stent implantation. The model was subsequently tested (internally validated) in a different consecutive group of patients in the same registry all treated with drug-eluting stents (n=337).

This risk model consists of 54 variables (17 clinical, four procedural and 33 angiographic features). A substantially higher c-statistic was evident for NERS compared with the SXscore (0.89 vs 0.69, respectively), indicating that it had excellent discriminatory ability. When NERS was separated into two groups of risk (high and low) and clinical outcomes were assessed, the NERS model was able to identify a high-risk population for MACE, at 30 days and at over 5 years follow-up. Importantly, the high-risk NERS group was shown to be significantly more predictive of MACE compared with the intermediate or high SXscore tertiles.

Conversely, in the low-risk NERS group, outcomes were similar to the low SXscore group, suggesting, at least from this study, that anatomical variables alone may be sufficient to predict clinical outcomes in the low-risk group. One of the main limitations of this risk model is that comorbidity in the NERS patient population was significantly less prevalent compared with the All-Comers SYNTAX population;[1 3] the latter was

Table 4 The Global Risk approach, combining historically defined tertiles of risk for the EuroSCORE and the SYNTAX Trial-defined ranges for SXscore[36 37]

	Low SXscore (≤22)	Intermediate SXscore (23–32)	High SXscore (≥33)
Low additive EuroSCORE (0–2)	Low risk	Low risk	Intermediate risk
Intermediate additive EuroSCORE (3–5)	Low risk	Low risk	Intermediate risk
High additive EuroSCORE (≥6)	Intermediate risk	Intermediate risk	High risk

designed to overcome many of the limitations/selection bias inherent in small registries. Validation of the NERS risk model in a much larger All-Comers type population is therefore required to overcome many of these issues.

Global Risk

The SYNTAX Trial established a complex interaction between the EuroSCORE and SXscore in preliminary unpublished data.[84] Given that the EuroSCORE has been shown to be an independent predictor of MACE for either CABG or PCI as previously described,[30 85] the need to combine the angiography and clinical scores into a single approach has become evident.[86]

One of the main advantages of potentially combining the EuroSCORE and SXscore to give a 'Global Risk' assessment is that the same risk model can be used during the heart team approach in selecting the optimal revascularisation modality for the patient. To facilitate this process, it is our opinion that the historically accepted cut-offs for the level of risk (low, intermediate and high) for the additive EuroSCORE, each of which have previously been demonstrated to have a different prognostic value,[4 6 7 48 49] and the SYNTAX Trial-defined anatomical SXscore ranges[4 48] should be incorporated into the Global Risk model (table 4).

In variants of this model using differing and inconsistent cut-off levels of risk for the SXscore and/or additive EuroSCORE in a non-randomised population, it has recently been shown that this may potentially improve the ability to predict outcomes in patients undergoing surgical or percutaneous LMS revascularisation.[33 87]

The main goal of using the Global Risk model is therefore to combine anatomical and clinical variables to potentially further aid risk stratification of patients with 3VD or LMS disease considering revascularisation, and to identify a low-risk group of surgically or percutaneously treated patients who would have comparable outcomes in terms of safety and efficacy. This concept has recently been applied by our group to the randomised and All-Comers SYNTAX population, and proved to be potentially useful in the identification of the previously described low-risk population in the LMS disease cohort. In the SYNTAX 3VD cohort, the interaction between anatomical and clinical variables proved to be more complex; the Global Risk model, however, still proved to be clinically useful when interpreted through a treatment algorithm. The results of these studies are forthcoming.[36 37]

EuroHeart Score

On the basis of the Euro Heart Survey (a European PCI registry consisting of over 46 000 patients from 176 European centres who underwent PCI for different indications), a logistic regression model comprising 10 clinical variables and six anatomical variables was developed (figure 6).[38] The risk model was shown to be highly predictive of in-hospital mortality (c-statistic 0.91).

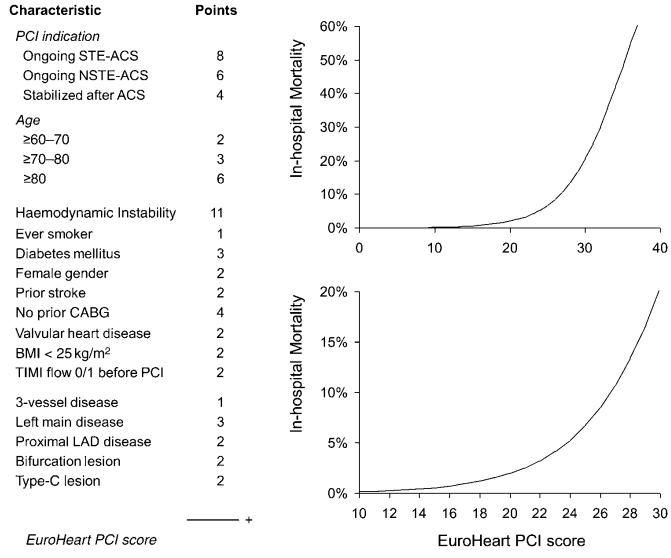


Figure 6 EuroHeart PCI Score. STE-ACS, ST-elevation acute coronary syndrome; NSTE-ACS, non ST-elevation acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; TIMI flow, thrombolysis in myocardial infarction flow. Reproduced, with permission, from de Mulder *et al*.[38]

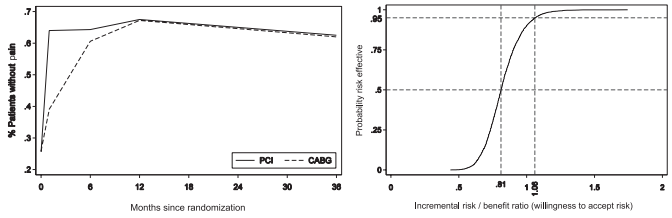


Figure 7 Principle of the risk—benefit trade-off in determining the choice of revascularisation modality from the ARTS II multivessel study population. Left panel, between 0 and 6 months, patients who selected percutaneous coronary intervention (PCI) were more likely to be free from pain compared with those who selected coronary artery bypass grafting (CABG). After 6 months, no statistically significant differences in pain between CABG and PCI were evident. Right panel, risk—benefit acceptability curve for incremental risk of additional revascularisation in 3 years versus freedom from pain. A patient would be required to be willing to tolerate a risk of 1.06 additional revascularisation procedures at 3 years in exchange for being pain free at 1 month, in order to be 95% confident that the risk is worth the benefit in choosing PCI over CABG. Reprinted from EuroIntervention, Federspiel *et al*, Risk-benefit trade-offs in revascularisation choices. Copyright 2009, with permission from Europa Edition.[88]

The strengths of the risk model are that it was internally validated in the registry population and it retained its discriminatory power (c-statistic 0.90).

RISK—BENEFIT ANALYSIS

Undoubtedly, both CABG and PCI result in an improvement in the quality of life of the patient. One of the main drawbacks of using contemporary risk models for both CABG and PCI is that the role of the individual patient and their personal preferences and perception of risk may be underestimated. To address this issue, the novel concept of a clinical model that balances the risks and benefits of the proposed revascularisation procedure has recently emerged.[88]

Remaining active in their professional/personal lives may be vital for some people, and they would thus be more prepared to accept the longer-term risks of PCI (in particular an increased risk of repeat revascularisation) in order to remain at their present functional state, compared with the short-term morbidity effects associated with CABG, the latter being predominantly related to the intrinsically more invasive nature of the CABG procedure (eg, thoracotomy and vein harvesting and subsequent sternotomy and leg pain, etc).[89 90]

Individual patients may, however, value this risk—benefit trade-off differently. For some, exchanging the increased risk of repeat PCI or CABG to obtain short-term pain relief and a rapid return to full mobility will be acceptable, while others may prefer to endure short-term pain to obtain a higher probability of avoiding a subsequent revascularisation. Some patients may also prefer to risk undergoing multiple PCI procedures compared with a single CABG, or they may prefer to avoid the risk of requiring CABG subsequent to PCI and instead have CABG initially. Consequently, from the patient's perspective, the balance between these conflicting considerations plays a crucial role in selecting the preferred revascularisation strategy.

Federspiel *et al* recently applied this concept to the ARTS II population, by quantifying the trade-off between the risks and benefits of PCI versus CABG, such as freedom of chest pain and improvement in health-related quality of life measures, for patients with multivessel disease (figure 7).[83 88] Although this study was performed on data that were over 10 years old, in a population who had implantation of bare metal stents, the results nevertheless supported this concept and have allowed, for the first time, quantification of a level of risk that a patient would be able to accept in order to maintain their present functional state. Data from the SYNTAX Trial on this concept, reflecting more contemporary practice with drug-eluting stents, are forthcoming.

CONCLUSION

It would appear that a combination of clinical and anatomical variables is required for an effective, clinically useful risk model for patients. The SXscore, while prognostically useful in risk-stratifying patients proposing to undergo PCI, in itself appears to carry important information on clinical comorbidity and outcomes for the individual patient. However, this clearly is not the whole picture, and it is our view that the incremental value of adding clinical variables to the SXscore, as demonstrated with risk models such as Global Risk, will ultimately prove to be more clinically useful compared with the SXscore alone. Ongoing and future risk models may answer these questions. Novel concepts such as the Functional SXscore, performed invasively or non-invasively as discussed, and the patient-empowered risk—benefit trade-off are all further areas in current development where additional clinically relevant information may become available.

Acknowledgements VF thanks the Dickinson Trust Travelling Scholarship, Manchester Royal Infirmary, Manchester, England, UK.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1. **Serruys PW,** Morice MC, Kappetein AP, *et al*. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961—72.
2. **Kappetein AP,** Feldman TE, Mack MJ, *et al*. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: three-year follow-up of the SYNTAX trial. *Eur Heart J* 2011;**32**:2125—34.
3. **Ong AT,** Serruys PW, Mohr FW, *et al*. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006;**151**:1194—204.
4. **Serruys PW,** Onuma Y, Garg S, *et al*. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50—6.
5. **Wijns W,** Kolh P, Danchin N, *et al*. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010;**31**:2501—55.
6. **Nashef SA,** Roques F, Michel P, *et al*. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardio Thorac Surg* 1999;**16**:9—13.
7. **Roques F,** Michel P, Goldstone AR, *et al*. The logistic EuroSCORE. *Eur Heart J* 2003;**24**:881—2.
8. **Shahian DM,** O'Brien SM, Filardo G, *et al*. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg* 2009;**88**:S2—22.
9. **Mohr FW,** Rastan AJ, Serruys PW, *et al*. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. *J Thorac Cardiovasc Surg* 2011;**141**:130—40.
10. **Romagnoli E,** Burzotta F, Trani C, *et al*. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart* 2009;**95**:43—8.
11. **Kim YH,** Ahn JM, Park DW, *et al*. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol* 2006;**98**:1567—70.

12. **Kim Y-H,** Park D-W, Kim W-J, *et al*. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. *JACC Cardiovasc Interv* 2010;**3**:612—23.
13. **Applegate RJ.** Toward better stratification of patients with left main disease: value of clinical and angiographic-derived risk scores. *JACC Cardiovasc Interv* 2011;**4**:298—9.
14. **Topol EJ.** *Textbook of Interventional Cardiology*. 3rd edn. Philadelphia: WB Saunders, 1999.
15. **Khattab AA,** Hamm CW, Senges J, *et al*. Prognostic value of the modified American College of Cardiology/American Heart Association lesion morphology classification for clinical outcome after sirolimus-eluting stent placement (results of the prospective multicenter German Cypher Registry). *Am J Cardiol* 2008;**101**:477—82.
16. **Capodanno D,** Di Salvo ME, Cincotta G, *et al*. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. *Circ Cardiovasc Interv* 2009;**2**:302—8.
17. **Escaned J,** Serruys PW. *Coronary Stenosis Imaging, Structure and Physiology*. PCR Publishing, 2011. Europa Edition 2010. ISBN:978-2-913628-56-4.
18. **Valgimigli M,** Dawkins K, Macaya C, *et al*. Impact of stable versus unstable coronary artery disease on 1-year outcome in elective patients undergoing multivessel revascularization with sirolimus-eluting stents: a subanalysis of the ARTS II trial. *J Am Coll Cardiol* 2007;**49**:431—41.
19. **Chakravarty T,** Buch MH, Naik H, *et al*. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol* 2011;**107**:360—6.
20. **Garg S,** Sarno G, Girasis C, *et al*. A patient-level pooled analysis assessing the impact of the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. *JACC Cardiovasc Interv* 2011;**4**:645—53.
21. **Nam CW,** Mangiacapra F, Entjes R, *et al*. Functional SYNTAX Score for Risk Assessment in Multivessel Coronary Artery Disease. *Journal of the American College of Cardiology* 2011;**58**:1211—18.
22. **Califf RM,** Phillips HR 3rd, Hindman MC, *et al*. Prognostic value of a coronary artery jeopardy score. *J Am Coll Cardiol* 1985;**5**:1055—63.
23. **Graham MM,** Faris PD, Ghali WA, *et al*. Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. *Am Heart J* 2001;**142**:254—61.
24. **Alderman EL,** Stadius M. The angiographic definitions of the bypass angioplasty revascularization investigation. *Coron Artery Dis* 1992;**3**:1189—207.
25. **Singh M,** Rihal CS, Lennon RJ, *et al*. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. *Mayo Clin Proc* 2007;**82**:701—8.
26. **Singh M,** Peterson ED, Milford-Beland S, *et al*. Validation of the Mayo clinic risk score for in-hospital mortality after percutaneous coronary interventions using the national cardiovascular data registry. *Circ Cardiovasc interv* 2008;**1**:36—44.
27. **Singh M,** Gersh BJ, Li S, *et al*. Mayo Clinic Risk Score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. *Circulation* 2008;**117**:356—62.
28. **Valgimigli M,** van Mieghem CA, Ong AT, *et al*. Short- and Long-Term Clinical Outcome After Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease: Insights From the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH). *Circulation* 2005;**111**:1383—9.
29. **Parsonnet V,** Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 1989;**79**: I3—12.
30. **Rodes-Cabau J,** Deblois J, Bertrand OF, *et al*. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. *Circulation* 2008;**118**:2374—81.
31. **Peterson ED,** Dai D, DeLong ER, *et al*. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2010;**55**:1923—32.
32. **Wykrzykowska JJ,** Garg S, Onuma Y, *et al*. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. *Circ Cardiovasc Interv* 2011; **4**:47—56.
33. **Capodanno D,** Caggegi A, Miano M, *et al*. Global Risk Classification and Clinical SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) Score in Patients Undergoing Percutaneous or Surgical Left Main Revascularization. *J Am Coll Cardiol Intv* 2011;**4**:287—97.
34. **Ranucci M,** Castelvecchio S, Menicanti L, *et al*. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 2009;**119**:3053—61.
35. **Ranucci M,** Castelvecchio S. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. *EuroIntervention* 2010;**6**:549—53.
36. **Serruys PW,** Farooq V, Brugaletta S, *et al*. The SYNTAX Trial at 3 Years: a global risk approach to identify patients with 3-vessel and/or left main stem disease who could safely and efficaciously be treated with percutaneous coronary intervention. Part 1: the randomised population. *Presented at: TCT, San Francisco, USA*, 8 Nov 2011.
37. **Farooq V,** Serruys PW, Vranckx P, *et al*. The SYNTAX trial at 3 years: a global risk approach to identify patients with 3-vessel and/or left main stem disease who could safely and efficaciously be treated with percutaneous coronary intervention. Part 2: the all-comers population. *Presented at: TCT, San Francisco, USA*, 8 Nov 2011.
38. **de Mulder M,** Gitt A, van Domburg R, *et al*. EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2011;**32**:1398—408.
39. **Chen SL,** Chen JP, Mintz G, *et al*. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *J Am Coll Cardiol Intv* 2010;**3**:632—41.
40. **Garg S,** Sarno G, Garcia-Garcia HM, *et al*. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 2010;**3**:317—26.
41. **Wu C,** Hannan EL, Walford G, *et al*. A risk score to predict in-hospital mortality for percutaneous coronary interventions. *J Am Coll Cardiol* 2006;**47**:654—60.
42. **Madan P,** Elayda MA, Lee VV, *et al*. Predicting major adverse cardiac events after percutaneous coronary intervention: t. *Am Heart J* 2008;**155**:1068—74.
43. **Singh M,** Rihal CS, Selzer F, *et al*. Validation of Mayo Clinic risk adjustment model for in-hospital complications after percutaneous coronary interventions, using the National Heart, Lung, and Blood Institute dynamic registry. *J Am Coll Cardiol* 2003;**42**:1722—8.
44. **Leaman DM,** Brower RW, Meester GT, *et al*. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981;**63**:285—99.
45. **Smith SC Jr,** Feldman TE, Hirshfeld JW Jr, *et al*. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006;**47**:e1—121.
46. **Scanlon PJ,** Faxon DP, Audet AM, *et al*. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation* 1999;**99**:2345—57.
47. **Lefevre T,** Louvard Y, Morice MC, *et al*. Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv* 2000;**49**:274—83.
48. **Sianos G,** Morel MA, Kappetein AP, *et al*. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;**1**:219—27.
49. **SYNTAX Working-Group.** SYNTAX score calculator. http://www.syntaxscore.com (accessed 19 May 2009).
50. **Krone RJ,** Laskey WK, Johnson C, *et al*. A simplified lesion classification for predicting success and complications of coronary angioplasty. Registry Committee of the Society for Cardiac Angiography and Intervention. *Am J Cardiol* 2000;**85**:1179—84.
51. **Capodanno D,** Capranzano P, Di Salvo ME, *et al*. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2009;**2**:731—8.
52. **Serruys PW,** Daemen J, Morice MC, *et al*. Three-year follow-up of the ARTS-II# - sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. *EuroIntervention* 2008;**3**:450—9.
53. **Serruys PW,** Onuma Y, Garg S, *et al*. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 2010;**55**:1093—101.
54. **Okwuosa TM,** Greenland P, Ning H, *et al*. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol* 2011;**57**:1838—45.
55. **Fowkes FG,** Murray GD, Butcher I, *et al*. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197—208.
56. **Adams MR,** Nakagomi A, Keech A, *et al*. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. *Circulation* 1995;**92**:2127—34.
57. **Steinvil A,** Sadeh B, Arbel Y, *et al*. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol* 2011;**57**:779—83.
58. **Wykrzykowska JJ,** Garg S, Girasis C, *et al*. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol* 2010;**56**:272—7.
59. **Garg S,** Serruys PW, Silber S, *et al*. The prognostic utility of the SYNTAX score on 1-year outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial. *JACC Cardiovasc Interv* 2011;**4**:432—41.
60. **Garg S,** Sarno G, Serruys PW, *et al*. Prediction of 1-year clinical outcomes using the SYNTAX score in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a substudy of the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Acute Myocardial Infarction) and MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study) trials. *JACC Cardiovasc Interv* 2011;**4**:66—75.

61. **Koo BK,** Park KW, Kang HJ, *et al*. Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. *Eur Heart J* 2008;**29**:726—32.
62. **Tonino PA,** Fearon WF, De Bruyne B, *et al*. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;**55**:2816—21.
63. **Pijls NH,** Fearon WF, Tonino PA, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010;**56**:177—84.
64. **Reiber JH,** Serruys PW. Quantitative coronary angiography: methodologies. *Quantitative Coronary Angiography*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1991;98—102.
65. **Yong ASC,** Ng ACC, Brieger D, *et al*. Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. *Eur Heart J* 2011;**32**:345—53.
66. **Onuma Y,** Girasis C, Aben JP, *et al*. A novel dedicated 3-dimensional quantitative coronary analysis methodology for bifurcation lesions. *EuroIntervention* 2011;**7**:629—35.
67. **Cutlip DE,** Mehran R, Vranckx P. FAME and coronary stent investigations: is there a kink in the wire? *J Am Coll Cardiol* 2011;**57**:115—16; author reply 6.
68. **Park SJ,** Ahn JM, Kang SJ. Paradigm shift to functional angioplasty: new insights for fractional flow reserve- and intravascular ultrasound-guided percutaneous coronary intervention. *Circulation* 2011;**124**:951—7.
69. **Kern MJ,** Lerman A, Bech JW, *et al*. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation* 2006;**114**:1321—41.
70. **Kern MJ,** Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010;**55**:173—85.
71. **Koo BK.** *Discover Flow*. Paris, France: EuroPCR, 2011.
72. **Goto K,** Lansky AJ, Fahy M, *et al*. Predictors of outcomes in medically treated patients with acute coronary syndromes after angiographic triage: an Acute Catheterization And Urgent Intervention Triage Strategy (ACUITY) substudy. *Circulation* 2010;**121**:853—62.
73. **Perera D,** Stables R, Booth J, *et al*. The balloon pump-assisted coronary intervention study (BCIS-1): rationale and design. *Am Heart J* 2009;**158**:910—16.e2.
74. **Morton GDJ,** De Silva K, Ishida M, *et al*. Validation of the BCIS-1 myocardial Jeopardy score using cardiac MRI. *Heart* 2011;**97**:A71—2.
75. **Anon.** TCT-170: The BCIS-1 myocardial jeopardy score predicts mortality after percutaneous coronary intervention. *J Am Coll Cardiol* 2010;**56**:B40.
76. **Gogbashian A,** Sedrakyan A, Treasure T. EuroSCORE: a systematic review of international performance. *Eur J Cardiothorac Surg* 2004;**25**:695—700.
77. **Bhatti F,** Grayson AD, Grotte G, *et al*. The logistic EuroSCORE in cardiac surgery: how well does it predict operative risk? *Heart* 2006;**92**:1817—20.
78. **Grant SW,** Grayson AD, Jackson M, *et al*. Does the choice of risk-adjustment model influence the outcome of surgeon-specific mortality analysis? A retrospective analysis of 14,637 patients under 31 surgeons. *Heart* 2008;**94**:1044—9.
79. **Steyerberg EW,** Vickers AJ, Cook NR, *et al*. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;**21**:128—38.
80. **Farooq V,** Brugaletta S, Vranckx P, *et al*. A guide to interpreting and assessing the performance of prediction models. *EuroIntervention* 2011;**6**:909—12.
81. **Walter J,** Mortasawi A, Arnrich B, *et al*. Creatinine clearance versus serum creatinine as a risk factor in cardiac surgery. *BMC Surg* 2003;**3**:4.
82. **Cockcroft DW,** Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31—41.
83. **Serruys PW,** Ong AT, Morice MC, *et al*. Arterial Revascularisation Therapies Study Part II—Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention* 2005;**1**:147—56.
84. **Serruys PW.** Unprotected left main PCI: change in guidelines, change in practice? Systematic risk stratification for left main PCI: syntax, Euroscore, ACEF, NERS, NCDR, Parsonnet Scores. *Presented at: Amercian College of Cardiology, Scientific Session 2011, New Orleans, USA*, 3 Apr 2011.
85. **Min SY,** Park DW, Yun SC, *et al*. Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left main coronary disease: analysis from the MAIN-COMPARE study. *Circ Cardiovasc Interv* 2010;**3**:127—33.
86. **Serruys PW.** Integrating lessons from recent clinical trials into practice: beyond the SYNTAX score. *Presented at: Transcatheter Therapeutics (TCT) Asia Pacific*; 29 April 2010, Seoul, South Korea, 2010.
87. **Capodanno D,** Miano M, Cincotta G, *et al*. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J* 2010;**159**:103—9.
88. **Federspiel J,** Stearns SC, van Domburg R, *et al*. Risk-benefit trade-offs in revascularisation choices. *EuroInternvention* 2011;**6**:936—41.
89. **van Domburg RT,** Daemen J, Morice MC, *et al*. Short- and long-term health related quality-of-life and anginal status of the Arterial Revascularisation Therapies Study part II, ARTS-II; sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. *EuroIntervention* 2010;**5**:962—7.
90. **Cohen DJ,** Van Hout B, Serruys PW, *et al*. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 2011;**364**:1016—26.

PART II

Understanding the clinical impact of incomplete revascularisation

Chapter 2

The Negative Impact of Incomplete Angiographic Revascularization on Clinical Outcomes and Its Association With Total Occlusions: The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) Trial

Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Ståhle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E

J Am Coll Cardiol. 2013;61(3):282-94 (Impact Factor: 14.086)

The Negative Impact of Incomplete Angiographic Revascularization on Clinical Outcomes and Its Association With Total Occlusions

The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) Trial

Vasim Farooq, MBChB,* Patrick W. Serruys, MD, PhD,* Hector M. Garcia-Garcia, MD, PhD,* Yaojun Zhang, MD,* Christos V. Bourantas, MD, PhD,* David R. Holmes, MD,† Michael Mack, MD,‡ Ted Feldman, MD,§ Marie-Claude Morice, MD,‖ Elisabeth Ståhle, MD,¶ Stefan James, MD,¶ Antonio Colombo, MD,# Roberto Diletti, MD,* Michail I. Papafaklis, MD, PhD,** Ton de Vries MSc,†† Marie-angèle Morel, BSc,†† Gerrit Anne van Es, PhD,†† Friedrich W. Mohr, MD,‡‡ Keith D. Dawkins, MD,§§ Arie-Pieter Kappetein, MD, PhD,‖‖ Georgios Sianos, MD, PhD,¶ Eric Boersma, MSc, PhD*

Rotterdam, the Netherlands; Rochester, Minnesota; Dallas, Texas; Evanston, Illinois; Massy, France; Uppsala, Sweden; Milan, Italy; Boston and Natick, Massachusetts; and Leipzig, Germany

Objectives The study sought to evaluate the clinical impact of angiographic complete (CR) and incomplete (ICR) revascularization and its association with the presence of total occlusions (TO), after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in the "all-comers" SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial.

Background In patients with complex coronary artery disease undergoing PCI or CABG, the long-term prognostic implications of CR versus ICR is unsettled.

Methods In this post hoc study, consisting of randomized (n = 1,800) and nested PCI (n = 198) and CABG (n = 649) registries, 4-year clinical outcomes were compared in groups, with and without angiographic CR, in the PCI and CABG arms. Clinical outcomes were analyzed with Kaplan-Meier estimates, log-rank comparisons, and Cox regression analyses. Multivariate predictors of ICR were determined. Similar analyses were undertaken in the TO and non-TO treated groups of both study arms.

Results Angiographic CR was achieved in 52.8% of the PCI arm and 66.9% of the CABG arm. Within the PCI and CABG arms, ICR (compared with CR) seemed to be a surrogate marker of a greater burden of anatomical coronary complexity and clinical comorbidity and was associated with significantly higher frequencies of 4-year mortality, all-cause revascularization, stent thrombosis (PCI arm), and major adverse cardiac and cerebrovascular events. The presence of a TO was the strongest independent predictor of ICR after PCI (hazard ratio: 2.70, 95% confidence interval: 1.98 to 3.67, $p < 0.001$). Eight hundred and forty patients (PCI: 26.3%, CABG: 36.4%, $p < 0.001$) were identified to have 1,007 TOs, with 68.1% of TOs located in the proximal-mid coronary vasculature. The findings associating ICR (compared with CR) with higher frequencies of 4-year mortality and major adverse cardiac and cerebrovascular events remained consistent in the TO-treated groups in the PCI and CABG arms.

Conclusions Within the PCI and CABG arms of the all-comers SYNTAX trial, angiographically determined ICR has a detrimental impact on long-term clinical outcomes, including mortality. This effect remained consistent in patients with and without TOs. (J Am Coll Cardiol 2013;61:282–94) © 2013 by the American College of Cardiology Foundation

In patients with complex coronary artery disease—namely, unprotected left main coronary artery (ULMCA) or de novo 3-vessel disease—undergoing coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI), the long-term prognostic implications of complete (CR) versus incomplete (ICR) revascularization is unsettled (1–12). In addition, recent studies have suggested that angiographic CR after CABG revascularization might not be associated with a significant improvement in long-term clinical outcomes (6,7).

The impact of successful or unsuccessful treatment of total occlusion (TO) and its association with completeness of revascularization in PCI- or CABG-treated patients with ULMCA and/or multivessel disease also remains undefined. Although multiple registries have associated successful complete TO PCI with improved long-term mortality, these studies were conducted in patients with less complex coronary disease (13–17). Only 1 retrospective registry study has examined CTO PCI in patients with predominantly multivessel disease and associated successful CTO PCI in the context of CR with a survival advantage, compared with patients with ICR (18).

The purpose of this study was to report the long-term (4-year) clinical impact of complete and incomplete angiographic revascularization in the All-Comers SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) Trial. The All-Comers SYNTAX Trial provided an opportunity for the assessment of patients where selection bias in enrolling patients was minimal and therefore was potentially more representative of contemporary clinical practice. Secondly, the presence of TOs to influence the ability of PCI or CABG to achieve CR was examined, on the basis of the hypothesis that failure to treat TOs would have a significantly detrimental impact on long-term clinical outcomes in PCI- and CABG-treated patients.

From the *Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; †The Mayo Clinic, Rochester, Minnesota; ‡Medical City Dallas Hospital, Dallas, Texas; §Evanston Hospital, Evanston, Illinois; ‖Institut Jacques Cartier, Massy, France; ¶University Hospital Uppsala, Uppsala, Sweden; #San Raffaele Scientific Institute, Milan, Italy; **Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; ††Cardialysis BV, Rotterdam, the Netherlands; ‡‡Herzzentrum, Leipzig, Germany; §§Boston Scientific Corporation, Natick, Massachusetts; and the ‖‖Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands. The SYNTAX Trial was funded by Boston Scientific. Drs. Dawkins, Pereda, and Huang are all full-time employees in Boston Scientific. Dr. Dawkins holds stock in Boston Scientific. Dr. Mack has served on the Speakers' Bureau of Cordis and Medtronic and reports no financial disclosures. Dr. Feldman has received research grants and consulting fees from Abbott Vascular, Boston Scientific, and Edwards Lifesciences. Dr. Morice reported that her institution received a research grant from Boston Scientific. Dr. James has received institutional research grants from Medtronic, Inc., Vascular Solutions, Terumo, Inc., AstraZeneca, and Eli Lilly; and has served on the advisory board and received honoraria from AstraZeneca, Eli Lilly, Abbott Vascular, Boston Scientific, and Medtronic. Dr. Kappetein served as a member of the steering committee for the SYNTAX trial, sponsored by Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 15, 2012; revised manuscript received October 16, 2012, accepted October 30, 2012.

Methods

The All-Comers SYNTAX Trial is a randomized, prospective, multicenter trial (n = 3,075) investigating patients with ULMCA disease (isolated or associated with 1-, 2-, or 3-vessel disease) or de novo 3-vessel coronary artery disease and has previously been described (19–21). In brief, exclusion criteria were appropriately limited and consisted of patients with prior coronary revascularization, the requirement of concomitant cardiac surgery, or ongoing acute myocardial infarction. During the local Heart Team meeting, the interventional cardiologist and cardiac surgeon specified the number of coronary lesions requiring treatment and their angiographic location and characteristics with the SYNTAX Score as a tool to aid in this process (22–24). All patients considered as potentially achieving "equivalent anatomic" revascularization with percutaneous or surgical revascularization by the Heart Team were randomized on a 1:1 basis (n = 1,800) to either PCI with TAXUS Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Massachusetts) or CABG. Patients unsuitable for randomization were nested into PCI (CABG ineligible patients, n = 198) and CABG registries (PCI ineligible patients, n = 1,077) (Fig. 1). All randomized patients underwent planned follow-up. Within the nested registries, all PCI patients and 649 randomly allocated CABG patients underwent follow-up on the basis of the original study protocol (20,21).

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery

CI = confidence interval

CR = complete revascularization

CTO = chronic total occlusion

CVA = cerebrovascular accident

HR = hazard ratio

ICR = incomplete revascularization

LVEF = left ventricular ejection fraction

MACCE = major adverse cardiac and cerebrovascular events

PCI = percutaneous coronary intervention

TO = total occlusion

ULMCA = unprotected left main coronary artery disease

An independent Clinical Events Committee, including cardiologists, cardiac surgeons, and a neurologist reviewed all the primary clinical endpoints (20,21). Baseline and peri- and post-procedural data were prospectively collected by the individual participating centers. Pre-procedural left ventricular ejection fraction (LVEF) was defined as the percentage LVEF taken by transthoracic echocardiography or diagnostic coronary angiogram and was categorized as good (≥50%), moderate (30% to 49%), or poor (<30%). Four-year clinical outcomes were compared in groups with and without angiographic CR in the PCI and CABG arms, with analyses repeated in the respective TO/non-TO groups.

Clinical outcomes. Clinical outcomes included all-cause death, cardiac death, major adverse cardiac and cerebrovascular events (MACCE) (a composite of all-cause death, myocardial infarction, stroke, and all-cause revascularize-

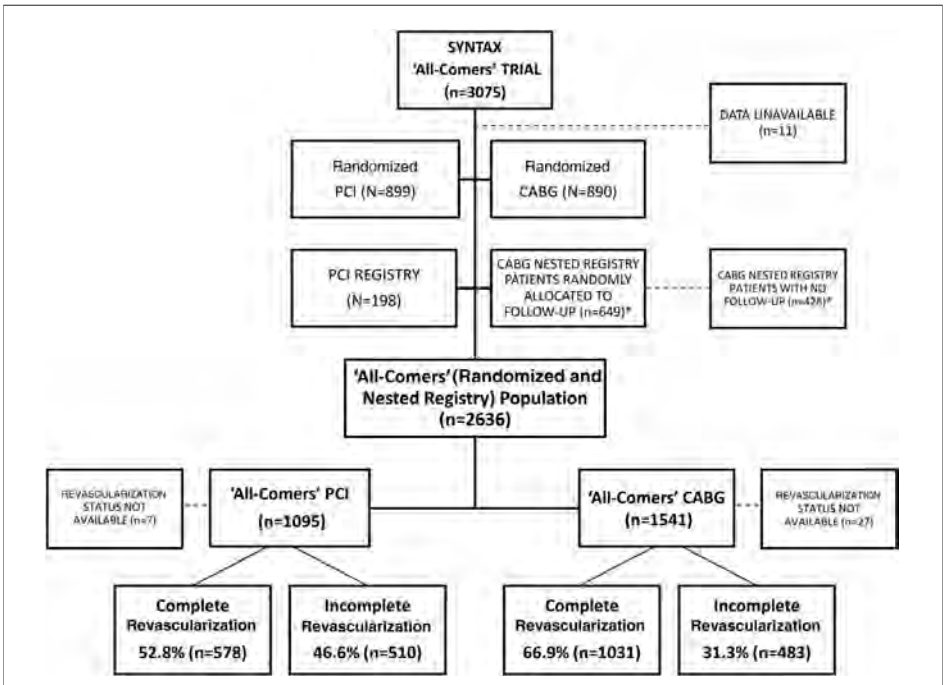


Figure 1 **Flow Chart of Frequency of CR versus ICR in PCI and CABG Arms of "All-Comers" SYNTAX Population**

The "All-Comers" population incorporates the randomized and nested registries of the percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) arms. *Of the 1,077 CABG patients, 649 were randomly allocated for follow-up on the basis of the original study protocol (21). CR = complete revascularization; ICR = incomplete revascularization.

tion) and its components, stent thrombosis, and graft occlusion. Direct comparisons between the All-Comers PCI and CABG arms were not undertaken due to the previously reported outcomes of the SYNTAX trial (19,20,25,26) and the presence of greater clinical comorbidity and more complex anatomical coronary disease in the nested PCI and CABG registries, respectively, which were the predominant reasons for entry (27,28).

SYNTAX score and TO. The calculation of the SYNTAX Score was undertaken by the study sites and an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) blinded to the treatment assignment (22–24). The age and angiographic characteristics of TOs were specified as part of the SYNTAX Score calculation. The definition of the TOs required that there was absolutely no flow through the lesion (Thrombolysis In Myocardial Infarction flow grade 0). Antegrade flow beyond the TO maintained by bridging collaterals and/or ipsi-collaterals was permitted. Core laboratory-calculated SYNTAX Scores are reported in this study. Procedural success rates of recanalization/bypass of TOs were available in the electronic case records of the randomized SYNTAX population and are reported.

Completeness of revascularization. Completeness of revascularization was prospectively determined after the revascularization procedure by the operator, on the basis of the intended "equivalent anatomic" revascularization agreed during the local Heart Team conference before revascularization. The degree of revascularization was angiographic, on the basis of segment numbering of vessels with a diameter ≥1.5 mm used in the calculation of the SYNTAX Score (22–24). The exact definition of CR defined in the original trial protocol (NCT00114972) is detailed in the following text.

> The interventional cardiologist and surgeon during the local Heart Team conference will specify the number of lesions and locations requiring treatment to achieve "equivalent anatomic" revascularization (decision). Complete revascu-

larization is defined as the treatment of any lesion with more than 50% diameter stenosis in vessels ≥1.5 mm as estimated on the diagnostic angiogram during the local Heart Team conference. Outcomes will be documented by the operator based on whether the intended equivalent anatomic revascularization was achieved.

Statistical analysis. The means ± SD for continuous variables were compared with the Student *t* test. Binary variables are reported as counts and/or percentages and compared with the chi-square test. Four-year clinical outcomes were compared in groups with and without angiographic CR and expressed as Kaplan-Meier estimates, with curves examined visually. Comparisons were made with Cox proportional hazard ratios (HRs) and the log-rank test. In addition, TO and non-TO group-specific HRs for all recorded 4-year clinical outcomes were obtained. The significance of the interaction effect between CR versus ICR in the PCI and CABG arms and the respective TO and

Table 1 Baseline and Procedural Characteristics for "All-Comers" CABG and PCI Populations Stratified by Completeness of Revascularization

	PCI (n = 1,095)			CABG (n = 1,541)		
	CR	ICR	p Value	CR	ICR	p Value
Baseline clinical characteristics						
Age (yrs)	65.7 ± 9.6	67.2 ± 10.5	0.01	64.9 ± 9.6	66.1 ± 9.7	0.020
Male	73.4%	77.8%	0.086	80.2%	79.5%	0.75
BMI (kg/m^2)	28.2 ± 5.0	28.0 ± 4.9	0.42	28.0 ± 4.6	27.8 ± 4.3	0.63
Diabetes	25.6%	34.1%	0.002	27.3%	31.1%	0.13
Hypertension	73.0%	75.9%	0.28	73.3%	79.7%	0.007
Hyperlipidemia	74.4%	79.0%	0.077	77.2%	76.3%	0.71
Peripheral vascular disease	8.1%	12.9%	0.009	10.7%	14.5%	0.032
Current smoker	18.6%	15.7%	0.21	22.5%	21.0%	0.54
Unstable angina	28.7%	32.4%	0.19	22.7%	31.5%	<0.001
Prior MI	33.4%	33.7%	0.93	31.8%	36.7%	0.063
LVEF						
Good (≥50%)	80.6%	71.4%	<0.001	76.5%	72.3%	0.073
Moderate (30%–49%)	15.6%	22.7%	0.003	18.1%	23.4%	0.017
Poor (<30%)	1.6%	2.7%	0.17	3.3%	3.1%	0.84
Baseline anatomical and clinical scores						
SYNTAX score	26.3 ± 10.5	32.0 ± 12.2	<0.001	32.2 ± 13.0	34.0 ± 12.7	0.011
Total Parsonnet score	8.8 ± 7.2	10.5 ± 8.3	<0.001	8.2 ± 6.6	9.6 ± 7.5	<0.001
Additive EuroSCORE	3.9 ± 2.7	4.4 ± 3.0	0.001	3.6 ± 2.6	4.2 ± 2.9	<0.001
Logistic EuroSCORE	4.0% ± 5.1	5.1% ± 6.4	0.002	3.6% ± 4.1	4.6% ± 5.0	<0.001
Anatomical characteristics						
TOs present	16.9%	36.8%	<0.001	35.0%	40.3%	0.048
Number of TOs	—	—	<0.001	—	—	0.085
1	15.9%	31.0%	—	27.3%	33.4%	—
2	0.9%	5.7%	—	6.8%	6.1%	—
≥3	0.2%	0.0%	—	0.9%	0.8%	—
Diffuse disease or small vessels	18.9%	26.9%	0.002	23.6%	30.0%	0.009
Number of lesions	3.4 ± 1.6	4.6 ± 1.5	<0.001	4.0 ± 1.7	5.0 ± 1.8	<0.001
Left main disease	45.2%	33.3%	<0.001	46.9%	34.0 %	<0.001
Bifurcation	58.3%	66.9%	0.004	63.4%	67.2%	0.15
Trifurcation	6.1%	9.2%	0.049	8.8%	10.6%	0.28
Aorto-ostial	16.8%	13.8%	0.19	16.9%	14.2%	0.18
Any thrombus	2.4%	2.8%	0.74	3.9%	2.3%	0.10
Heavy calcification	47.3%	54.0%	0.03	53.3%	56.2%	0.30
Any severe tortuosity	60.9%	72.3%	<0.001	67.8%	71.6%	0.14
Any lesion length >20 mm	48.5%	67.8%	<0.001	61.5%	74.7%	<0.001
Left arterial dominance	16.3%	20.6%	0.066	13.4%	19.5%	0.003
Procedural characteristics						
Total number of stents implanted	4.5 ± 2.4	4.2 ± 2.1	0.009	—	—	—
Total length of stents implanted (mm)	85.5 ± 51.5	76.4 ± 43.1	0.002	—	—	—
Post-procedural hospital stay (days)	3.6 ± 7.1	3.7 ± 6.0	0.71	8.7 ± 5.9	9.4 ± 9.3	0.13
Procedure time (h)	1.6 ± 0.9	1.7 ± 0.9	0.11	3.5 ± 1.1	3.4 ± 1.1	0.034

Values are mean ± SD or %.

BMI = body mass index; CABG = coronary artery bypass graft surgery; CR = complete revascularization; ICR = incomplete revascularization; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; TO = total occlusion.

non-TO groups were tested with the chi-square test. This was undertaken to assess whether the HR of all 4-year clinical outcomes for CR versus ICR was different across the TO and non-TO groups.

Binary logistic regression analyses were undertaken to identify univariate predictors of ICR with baseline characteristics (20) and components of the SYNTAX Score, respectively. The variables examined are detailed in Table 1. The SYNTAX Score was excluded from these analyses to allow for the appropriate identification of its components (e.g., TO, calcification) associated with ICR. Univariate predictors of ICR were entered into a multivariable model. The enter method was implemented to determine independent predictors, with a variable entry/stay criteria of 0.05/0.1. Similar analyses for ICR were repeated in the TO treated groups. A 2-sided p value < 0.05 was considered significant for all tests. Analyses were conducted with SPSS (version 19.0, SPSS, Inc., Chicago Illinois) and STATA (version 11.0, StataCorp, College Station, Texas).

Results

Baseline characteristics of the randomized and nested registry arms (All-Comers population) of the SYNTAX Trial have previously been described (20,28). Within the All-Comers population (n = 2,636), angiographic CR was

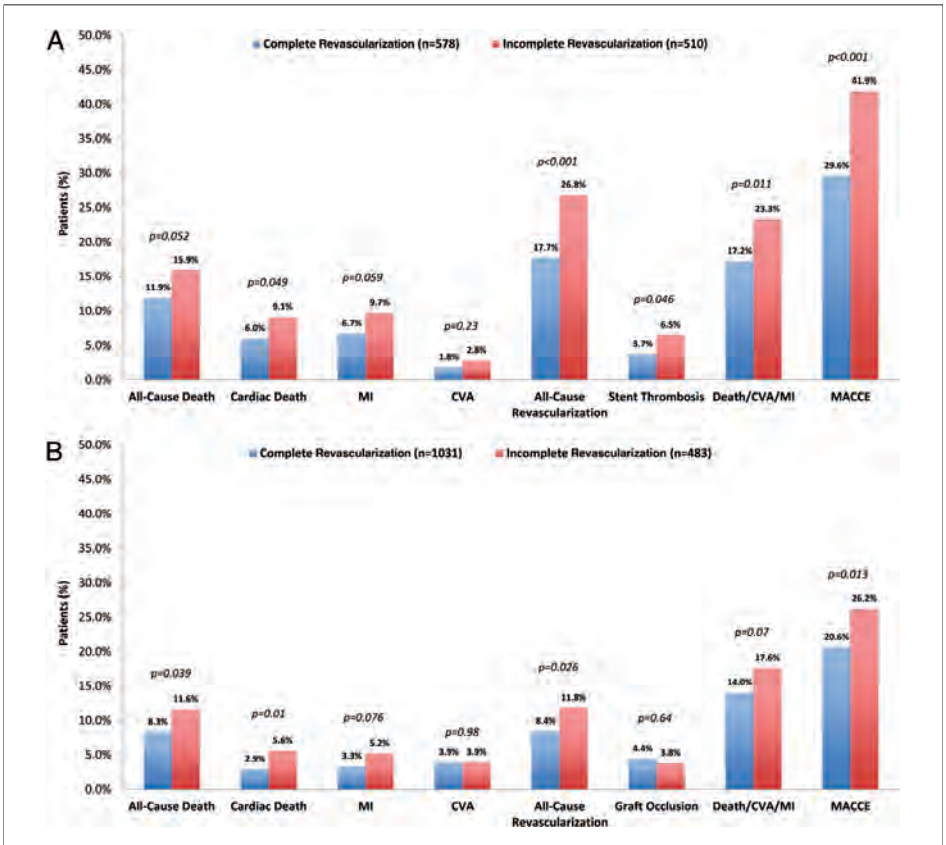


Figure 2 **Four-Year Clinical Outcomes in Patients by Complete Versus Incomplete Revascularization**

Comparisons (Kaplan-Meier analyses) of 4-year clinical outcomes by completeness of revascularization in the All-Comers PCI **(A)** and All-Comers coronary artery bypass grafting **(B)** populations. CVA = cerebrovascular accident; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction.

Table 2 Independent Predictors of ICR in All-Comers PCI and CABG Populations

Anatomical/Clinical Characteristic	OR (95% CI)	p Value
PCI-treated patients		
TO	2.70 (1.98–3.67)	<0.001
Any RCA lesion	2.12 (1.33–3.38)	0.002
Left arterial dominance	1.81 (1.26–2.60)	0.001
Additive EuroSCORE ≥6	1.58 (1.18–2.13)	0.002
Number of lesions*	1.44 (1.29–1.59)	<0.001
Hyperlipidemia	1.49 (1.08–2.06)	0.015
Any tortuosity	1.39 (1.04–1.86)	0.025
Total bifurcation/trifurcations*	1.32 (1.13–1.53)	<0.001
CABG-treated patients*		
Left arterial dominance	1.99 (1.45–2.73)	<0.001
Any RCA lesion	1.89 (1.16–3.06)	0.010
Unstable angina	1.59 (1.23–2.05)	<0.001
Peripheral vascular disease	1.34 (0.95–1.88)	0.092
Number of lesions*	1.30 (1.21–1.40)	<0.001
Parsonnet score*	1.02 (1.00–1.04)	0.027
Left main coronary artery disease	0.70 (0.55–0.90)	0.005

Independent predictors of ICR in the All-Comers PCI (n = 1095) and CABG (n = 1541) populations.
*Continuous variables/unit increase.
CI = confidence interval; OR = odds ratio; RCA = right coronary artery; other abbreviations as in Table 1.

achieved in 52.8% of the PCI arm (n = 1,095) and 66.9% of the CABG arm (n = 1,541) (Fig. 1).

Baseline and procedural characteristics on the basis of CR and ICR. Baseline and procedural characteristics of CR and ICR in the PCI (n = 1,095) and CABG (n = 1,541) arms are shown (Table 1). Within the PCI and CABG arms, more anatomically complex disease (higher SYNTAX Score)—including the presence of TOs, greater clinical comorbidity (higher EuroSCORE [29] and Parsonnet Score [30]), and a reduced prevalence of ULMCA disease—were evident in patients with ICR compared with CR.

Clinical outcomes on the basis of completeness of revascularization. Within the PCI and CABG arms, ICR (compared with CR) was associated with significantly higher frequencies of 4-year mortality, all-cause revascularization, stent thrombosis (PCI arm), and MACCE (Fig. 2).

Predictors of ICR. Multivariate analyses of ICR in the PCI and CABG arms are shown (Table 2). The strongest independent predictor of ICR in the PCI arm was the presence of a TO (HR: 2.70, 95% confidence interval [CI]: 1.98 to 3.67, $p < 0.001$). The strongest independent predictor of ICR in the CABG arm was left arterial dominance (HR: 2.19, 95% CI: 1.05 to 4.57, $p = 0.038$). Left arterial dominance, any right coronary artery lesion, number of lesions, and clinical variables (EuroSCORE/Parsonnet Score) were common independent predictors of ICR in the PCI and CABG arms.

TO. Baseline and procedural characteristics of patients with and without TOs in the PCI (n = 1,095) and CABG (n = 1,541) arms are shown (Table 3). Eight hundred and forty patients (PCI: 26.3%, CABG: 36.4%, $p < 0.001$) were identified to have 1,007 TOs. All patients with TOs (PCI and CABG arms) were significantly more likely to have had a previous myocardial infarction, a lower LVEF, diffuse or small vessel disease, more coronary lesions, lesion length >20 mm, and a reduced prevalence of ULMCA disease. Patients with TOs were less likely to achieve CR in the PCI and CABG arms (CR PCI: non-TO 59.8%, TO 34.3%, $p < 0.001$; CR CABG: non-TO 69.8%, TO 64.8%, $p = 0.048$).

Table 4 shows the baseline angiographic characteristics of the TOs in the entire SYNTAX population and PCI and CABG arms. The age of the TOs was documented as >3 months or unknown in 95.6% of the study population. Approximately two-thirds of TOs (68.1%) were located in the proximal-mid coronary vessels on coronary angiography (Fig. 3).

Procedural success rates of TO. Figure 4 demonstrates the procedural success rates of TOs (n = 543) on an intention to treat basis by the study sites in the randomized SYNTAX population. More TOs were successfully treated with CABG compared with PCI (68.1% vs. 49.4%, $p < 0.001$).

Clinical outcomes on the basis of completeness of revascularization in the TO groups. Figure 5 demonstrates comparisons of HRs for CR versus ICR in the PCI and CABG arms for all 4-year clinical endpoints in the respective TO and non-TO groups. The findings associating ICR (compared with CR) with higher frequencies of 4-year adverse clinical outcomes, as seen in the CABG and PCI arms of the SYNTAX population, remained consistent in the respective TO groups (nonsignificant p values for interaction), with a few notable exceptions.

Within the PCI arm (p value for interaction <0.001), CR in patients with TOs was associated with substantially fewer episodes of 4-year stent thrombosis compared with ICR (CR: 0%, n = 0; ICR: 4.6%, n = 7; no HR available as 0 events in patients with CR) (Fig. 5). Within the CABG arm (p value for interaction = 0.0008), CR in patients with TOs was related to a significantly lower risk of 4-year graft occlusion, compared with ICR (CR 2.7% vs. ICR 7.6%; HR: 0.34, 95% CI: 0.14 to 0.84, $p = 0.019$); conversely, in patients with CR without TOs, the risk of 4-year graft occlusion was substantially higher (CR 5.2% vs. ICR 0.86%; HR: 6.22, 95% CI: 1.49 to 26.07, $p = 0.012$).

Despite limitations of power in the TO groups, significant reductions in 4-year MACCE were evident in patients with TOs who achieved CR (vs. ICR) treated with either PCI or CABG (Fig. 6).

Predictors of ICR in TO groups. Table 5 lists independent predictors of ICR in the TO groups of PCI- and CABG-treated patients. Within the cohort of TO treated PCI patients, heavy calcification and long lesions were additional independent predictors of ICR compared with the main study findings (Table 2).

Table 3 Baseline and Procedural Characteristics for All-Comers PCI and CABG and Populations Stratified by the Presence of TOs

	PCI (n = 1,095)			CABG (n = 1,541)		
	Non-TO	TO	p Value	Non-TO	TO	p Value
Baseline clinical characteristics						
Age (yrs)	66.4 ± 9.9	65.9 ± 10.6	0.47	65.4 ± 9.4	64.9 ± 10.0	0.31
Male	74.6%	77.6%	0.31	76.8%	84.7%	<0.001
BMI (kg/m^2)	28.0 ± 4.8	28.5 ± 5.2	0.17	27.8 ± 4.5	28.3 ± 4.7	0.04
Diabetes	28.9%	31.5%	0.41	28.0%	30.9%	0.24
Hypertension	73.7%	75.7%	0.50	75.7%	75.0%	0.76
Hyperlipidemia	75.8%	79.4%	0.21	76.5%	78.3%	0.44
Peripheral vascular disease	9.9%	11.5%	0.43	10.2%	14.8%	0.008
Current smoker	17.9%	15.1%	0.29	21.7%	22.6%	0.67
Unstable angina	29.9%	31.8%	0.54	27.1%	22.6%	0.051
Prior MI	31.4%	39.4%	0.015	30.3%	39.7%	<0.001
LVEF						
Good (≥50%)	80.3%	65.0%	<0.001	81.6%	64.4%	<0.001
Moderate (30%–49%)	16.5%	25.9%	0.001	15.2%	27.1%	<0.001
Poor (<30%)	1.0%	5.2%	<0.001	2.2%	5.4%	0.001
Baseline clinical scores						
Total Parsonnet score	9.5 ± 7.8	9.9 ± 7.9	0.42	8.5 ± 7.0	8.9 ± 6.9	0.30
Additive EuroSCORE	4.1 ± 2.7	4.3 ± 3.1	0.27	3.8 ± 2.7	3.8 ± 2.7	0.96
Logistic EuroSCORE	4.2% ± 5.1	5.2% ± 7.4	0.047	3.9% ± 4.3	4.0% ± 4.6	0.72
Anatomical characteristics						
Number of TOs	—	—	—	—	—	—
1	—	87.8%	—	—	79.8%	—
2	—	11.9%	—	—	17.9%	—
≥3	—	0.3%	—	—	2.4%	—
Diffuse disease or small vessels	20.9%	26.9%	0.035	20.9%	33.0%	<0.001
Number of lesions	3.9 ± 1.7	4.2 ± 1.3	0.001	4.2 ± 1.9	4.7 ± 1.6	<0.001
Left main disease	44.1%	26.9%	<0.001	48.0%	32.9%	<0.001
Bifurcation	61.9%	63.6%	0.60	65.7%	63.4%	0.36
Trifurcation	8.4%	4.9%	0.055	10.0%	8.8%	0.45
Aorto-ostial	16.0%	15.0%	0.70	18.2%	12.5%	0.003
Any thrombus	2.5%	2.8%	0.79	3.9%	2.7%	0.21
Heavy calcification	49.4%	52.4%	0.37	52.7%	56.5%	0.16
Any severe tortuosity	65.5%	67.5%	0.54	68.7%	70.4%	0.48
Left dominance	17.8%	18.9%	0.37	15.9%	14.8%	0.16
Procedural characteristics						
Lesion length >20 mm	49.0%	80.8%	<0.001	53.1%	87.2%	<0.001
Total number of stents implanted	4.4 ± 2.3	4.4 ± 2.0	0.82	—	—	—
Total length of stents implanted (mm)	80.6 ± 49.1	84.2 ± 44.3	0.29	—	—	—
Post-procedural hospital stay (days)	3.6 ± 7.1	3.8 ± 5.2	0.63	8.8 ± 5.7	9.2 ± 9.1	0.30
Procedure time (h)	1.6 ± 0.9	1.7 ± 1.0	0.012	3.5 ± 1.1	3.6 ± 1.0	0.025
Completeness of revascularization						
Complete revascularization	59.8%	34.3%	<0.001	69.8%	64.8%	0.048

Values are mean ± SD or %.
Abbreviations as in Table 1.

Discussion

In this post hoc study of the All-Comers SYNTAX Trial, there were several notable findings. First, within the PCI and CABG arms, ICR (compared with CR) seemed to be a surrogate marker of a greater burden of anatomical coronary complexity and clinical comorbidity and was associated with a significant increase in 4-year mortality, all-cause revascularization, MACCE, and stent thrombosis (PCI arm). Second, the presence of a TO was less likely to result in CR in the PCI and CABG arms, with this effect being substantially more pronounced in the PCI arm, where the presence of a TO was shown to be the strongest independent predictor of ICR. Third, ICR (compared with CR) was associated with poorer clinical outcomes (4-year mortality and MACCE) across the TO and non-TO groups.

The low rate of CR in the PCI arm (34.3%) compared with the CABG arm (64.8%) was predominantly related to the lack of procedural success of TO PCI, as evident by a 49.4% recanalization rate in the randomized SYNTAX

Table 4 Baseline Angiographic Characteristics of TOs on the Basis of Parameters From SYNTAX Score Calculation From All-Comers SYNTAX Trial

SYNTAX Score Parameter for TO on Lesion Level in All-Comers SYNTAX Trial*	All Treated TOs (n = 1,007)	PCI-Treated TOs (n = 324)	CABG-Treated TOs (n = 683)
Age of TO			
>3 months/unknown	963 (95.6%)	304 (93.8%)	659 (96.5%)
≤3 months	44 (3.4%)	20 (6.2%)	24 (3.5%)
Blunt stump	231 (22.9%)	78 (24.1%)	153 (22.4%)
Bridging occlusion	105 (10.4%)	40 (12.3%)	65 (9.5%)
Ostial lesion	34 (3.4%)	12 (3.7%)	22 (3.2%)
Severe tortuosity	224 (22.2%)	77 (23.8%)	147 (21.5%)
Heavy calcification	241 (23.9%)	71 (21.9%)	170 (24.9%)
Thrombus	7 (0.7%)	2 (0.6%)	5 (0.7%)
Length >20 mm	647 (64.3%)	192 (59.3%)	455 (66.6%)
Non-visible segments beyond TO†	226 (22.4%)	85 (26.2%)	141 (20.6%)
Side-branch at the origin of the TO			
No	317 (31.5%)	110 (34.0%)	207 (30.3%)
Yes, side-branches <1.5mm	512 (50.8%)	158 (48.8%)	354 (51.8%)
Yes side-branches ≥1.5 mm	208 (20.7%)	66 (20.4%)	142 (20.8%)

Baseline angiographic characteristics of the TOs on the basis of parameters from the SYNTAX Score calculation from the All-Comers SYNTAX Trial (n = 2,636) (22–24). Lesion level data shown (n = 1,007). Percentages relate to proportions/column. *Analyzed lesions include serial stenoses (diameter stenosis ≥50% in vessels ≥1.5 mm) <3 vessel reference diameters apart. †Visualized by antegrade or retrograde contrast.
Abbreviations as in Table 1.

population (compared with procedural success rate of 68.1% in the CABG arm) on an intention-to-treat basis (Fig. 4). Furthermore, the clinical impact of failure to recanalize TOs by PCI would potentially have been greater, because two-thirds of TOs were located in the proximal-mid coronary major epicardial vessels (Fig. 3). Comparatively, other anatomical factors associated with ICR in the PCI and CABG arms might be of lesser importance, because the amount of jeopardized myocardium would have been lower compared with a TO—for example, a diseased side branch of a coronary bifurcation. Previous studies have shown that myocardial territory with >10% reversible ischemia derives the greatest clinical benefit from revascularization (31–33).

In the CABG arm, CR was achieved less frequently in patients with TOs compared with patients without TOs (non-TO: 69.8%, TO: 64.8%, p = 0.048). Notably, a similar phenomenon was reported in the ARTS (Arterial Revascularization Therapies Study) (34). A potential explanation for this finding might be related to the presence of a TO being associated with more diffuse or small vessel disease (non-TO: 20.9%, TO: 33.0%, p < 0.001) and consequently hindering the anastomosis of a bypass graft distally (Fig. 4).

Completeness of revascularization. One of the reasons the long-term prognostic implications of completeness of revascularization has historically remained controversial has been a lack of consistency in the definition of ICR (1,4–6,8,10,11). For example, variations in the size of coronary vessels included and diameter stenosis on the basis of coronary angiography have made results difficult to

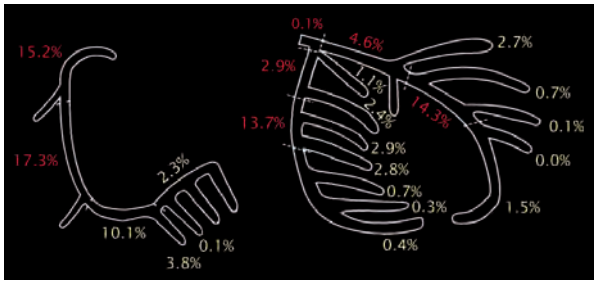


Figure 3 Location of Total Occlusions in All-Comers SYNTAX Population

Total occlusions (n = 1,007 lesions) in the All-Comers SYNTAX population (n = 2,636). Left main, proximal, and mid vessels (highlighted in **red**) accounted for over two-thirds (68.1%) of total occlusions.

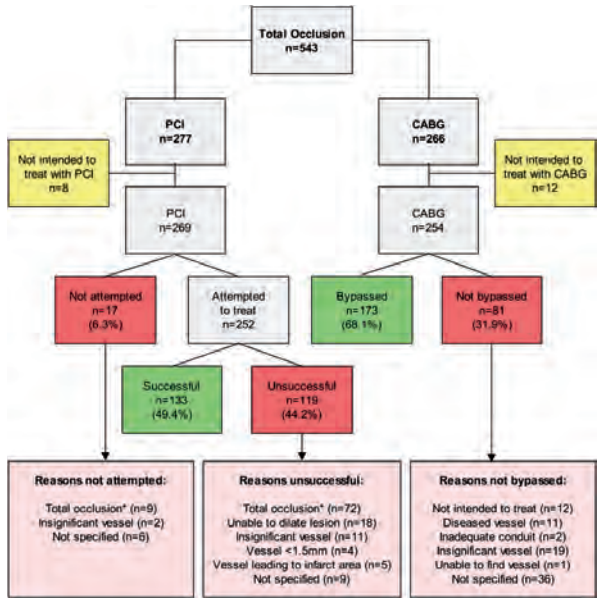


Figure 4 **Treatment of Total Occlusions on an Intention to Treat Basis by Study Sites in Randomized SYNTAX Population**

*Specified as "total occlusion" on the electronic case records without specific reason given for unsuccessful treatment of total occlusion.
Abbreviations as in Figure 1.

compare. Furthermore, inconsistencies in defining the clinical endpoints, quality of clinical endpoint monitoring and adjudication, and selection biases in observational registries have compounded this issue (1,5).

The strength of the present study was that the angiographic-based definition of CR/ICR was prospectively and rigorously systematically applied across all PCI- and CABG-treated patients in an All-Comers setting. Although more anatomically complex patients were enrolled into the nested CABG registry and more with clinical comorbidity were enrolled in the nested PCI registry (27,28), this is representative of contemporary clinical practice. Within the present study, the decision to use a 1.5-mm vessel as the minimum size of vessel that could be revascularized was devised during the design of the SYNTAX Trial to reflect the ability of the cardiac surgeon to anastomose bypass grafts to vessels of this size. To allow appropriate randomization of the patient, the interventional cardiologist was required to match this practice.

In patients treated with PCI or CABG, ICR seemed to be a surrogate marker of a greater burden of anatomical coronary complexity and clinical comorbidity and was associated with a poorer long-term prognosis in PCI- and CABG-treated patients. These findings are not unexpected, given the historical association of more extensive baseline preoperative coronary disease with reduced long-term survival in the CASS (Coronary Artery Surgery Study) (35) and Rotterdam (36) registries. Furthermore, within the BARI (Bypass Angioplasty Revascularization Investigation) trial (37)—consisting of patients treated with PCI or CABG who underwent entry and 5-year coronary angiographic follow-up—native coronary disease progression (and not the extent of initial revascularization) was shown to be the predominant determinant of recurrence of angina and jeopardized myocardium at 5 years. Notably in this study, two-thirds of the increase in myocardial jeopardy was in previously untreated coronary vessels.

Moreover, the findings of the present study directly contradict that reported from the 3-year randomized SYNTAX trial (7), where no differences in clinical outcomes between CR and ICR were seen in the CABG population. Similar findings were shown in the 4-year randomized data (unpublished data). The disparity in results seems to reflect the fact that the nested CABG registry

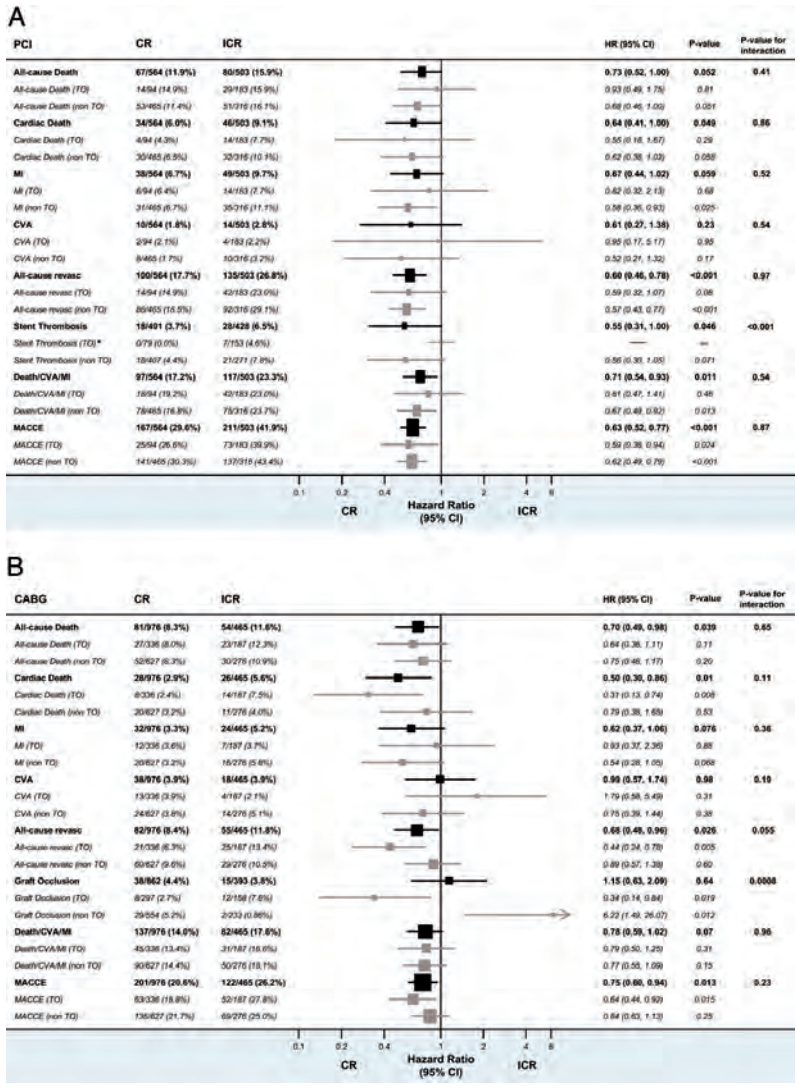


Figure 5 **Four-Year Clinical Outcomes in Patients Stratified by Presence of CR and ICR With and Without TOs**

Hazard ratios (HR) represent CR versus ICR for each 4-year clinical endpoint. A nonsignificant p value for interaction indicates that the HR of CR versus ICR in the PCI and CABG arms remained similar across the respective TO and non-TO groups. CI = confidence interval; Revasc = revascularization; TO = total occlusion; other abbreviations as in Figures 1 and 2.

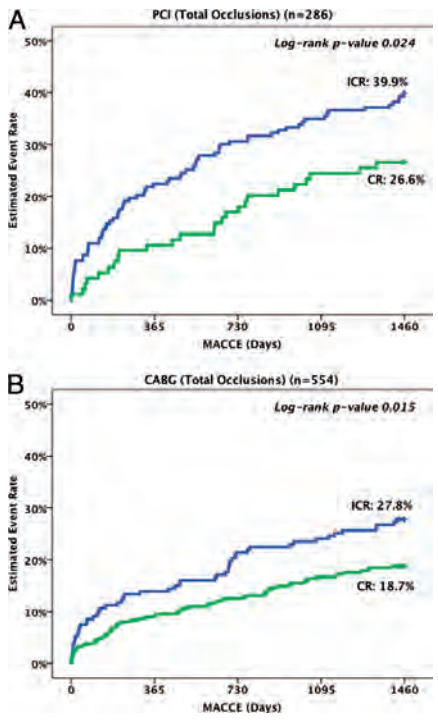


Figure 6 **Four-Year MACCE Stratified by Presence of ICR Versus CR in Patients With TOs**

A significant increase in MACCE was evident in PCI- and CABG-treated TO patients with ICR. These findings reflect the findings seen in both the PCI and CABG arms, where ICR was associated with poorer 4-year clinical outcomes compared with CR (Fig. 2). Abbreviations as in Figures 1 and 2.

contains more anatomically complex patients compared with the randomized CABG cohort (SYNTAX Score: nested CABG registry 37.8 ± 13.3, randomized CABG 29.1 ± 11.4, $p < 0.002$) (27,28). The ICR in the All-Comers CABG population therefore potentially resulted in more jeopardized myocardium, secondary to more anatomically complex coronary artery disease and greater clinical comorbidity (higher EuroSCORE and Parsonnet Scores) and their association with a likely increase in coronary atherosclerotic burden (4) and adverse long-term clinical outcomes as previously discussed. Within the PCI arm, potentially more jeopardized myocardium remained in patients with ICR compared with CABG, secondary to the failure to recanalize TOs or other (perhaps lesser important) anatomical factors, such as the presence of bifurcations, in addition to the similar factors associated with ICR in CABG patients.

Clinical impact of PCI- and CABG-treated TO. Beyond the main study findings of increased stent thrombosis associated with ICR in the PCI arm (CR 3.7%, ICR 6.5%, $p = 0.046$), further analyses indicated that there was a substantial increase in stent thrombosis in patients with TOs who had ICR (CR: 0 episodes [0%], ICR: 7 episodes [4.6%]). Notably, patients with ICR had fewer stents ($p = 0.009$) and shorter total length of stents implanted ($p = 0.002$) (Table 1). Attempting to understand the mechanisms underlying this possible phenomenon are speculative. As to whether episodes of stent thrombosis are secondary to neoatherosclerosis (38) related to the more adverse clinical comorbidity in patients with ICR: stent under-deployment due to greater coronary calcification associated with ICR, failure to fully expand a TO after successful coronary wire passage (Fig. 4), or the potential risk of delayed re-endothelialization—particularly if a subintimal technique of coronary wire passage is undertaken (39)—are all hypothetical mechanisms that require further study.

In the present study, the graft occlusion rate was substantially lower when CR was achieved in patients with TOs (and greater when CR was achieved in patients without TOs). These findings are consistent with previous studies, where early graft failure has been shown to be higher when anastomosed to functionally nonsignificant lesions or where competitive filling with the treated native vessel is seen (40–43).

Potential recommendations. Recently the concept of "reasonable" or "appropriate" ICR has been highlighted (1,3–5). This is either anatomically guided, on the basis of revascularizing most of the major epicardial vessels, or functionally/physiologically guided (on the basis of the burden of residual ischemia). The underlying principle is that, even if CR was technically possible and achievable (i.e., in all vessels >1.5 mm in diameter), this would not necessarily improve clinical outcomes—given the small territory a small side branch would, for example, supply. Future studies, possibly using a

Table 5 **Independent Predictors of ICR in TO Patients Within All-Comers PCI and CABG Populations**

Anatomical/Clinical Characteristic	OR (95% CI)	p Value
PCI-treated TO patients		
Left arterial dominance	2.19 (1.05–4.57)	0.038
Additive EuroSCORE ≥6	2.13 (1.16–3.88)	0.014
Any heavy calcification	2.02 (1.19–3.43)	0.009
Any lesion >20 mm	1.84 (0.96–3.53)	0.068
Total bifurcations/trifurcations*	1.37 (0.98–1.91)	0.067
Number of lesions*	1.36 (1.09–1.71)	0.006
CABG-treated TO patients		
Left arterial dominance	2.50 (1.53–4.09)	<0.001
Number of lesions*	1.25 (1.11–1.40)	<0.001
Parsonnet score*	1.03 (1.01–1.06)	0.013

PCI (n = 554) and CABG (n = 554) populations. *Continuous variables/unit increase. Abbreviations as in Tables 1 and 2.

noninvasive functional approach (44,45), might help best distinguish what acceptable level of revascularization is appropriate that would have a significant impact on long-term clinical outcomes. The newly devised Residual SYNTAX (46) and CABG SYNTAX (47) Scores each allows for more objective assessment of the degree of revascularization and residual anatomical disease complexity post-PCI or -CABG. Use of these methodologies might in the future aid in determining a "reasonable" threshold of revascularization.

Study limitations. The present study represents a post hoc analysis of the SYNTAX trial, and the results should be considered as hypothesis-generating. There was limited statistical power in the TO-treated patients and for the comparison of low-frequency events, such as stroke, graft occlusion, and stent thrombosis. The age of TOs could not be clearly defined, with most cases being unknown. Further procedural details of recanalization of TOs are not available beyond what is reported in the study. Core laboratory assessment of CR/ICR was not undertaken, because no post-operative (CABG) coronary angiograms were mandated in the SYNTAX trial. The possibility of other unmeasured adverse clinical characteristics to have confounded the data toward ICR cannot be excluded, although the intention of the study was to achieve CR in all study patients. The "All-Comers" concept of the SYNTAX trial, although more representative of contemporary clinical practice compared with the randomized approach, has been reported to potentially not result in the inclusion of consecutive patients, predominantly due to the inability to gain appropriate informed consent and refusal to participate (48,49). Although the SYNTAX trial was based on contemporary revascularization practice at the time, improvements in technology in PCI and CABG might yield differences in clinical outcomes in future trials.

Conclusions

Within the PCI and CABG arms of the All-Comers SYNTAX Trial, angiographically determined ICR seemed to be a surrogate marker of a greater burden of anatomical coronary complexity and clinical comorbidity and had a detrimental impact on long-term clinical outcomes, including mortality. This effect remained consistent in patients with and without TOs.

The impact of ICR on clinical outcomes is dependent on the complexity of coronary disease and risk profile of the study population, on the basis of the observations associating ICR with: 1) no effect on long-term clinical outcomes (randomized CABG population); and 2) more adverse long-term clinical outcomes (All-Comers CABG population).

Acknowledgements

The authors express their gratitude to all of the study centers and participants whose work made this study possible. Thanks are provided to Peggy Pereda and Jian Huang of Boston Scientific Corporation for their invaluable technical support in accessing the study database.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Professor of Medicine, Head of the Interventional Cardiology Department, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. De Bruyne B. Multivessel disease from reasonably incomplete to functionally complete revascularization. Circulation 2012;29:2557–9.
2. Schwartz L, Bertolet M, Feit F, et al. Impact of completeness of revascularization on long-term cardiovascular outcomes in patients with type 2 diabetes mellitus: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). Circ Cardiovasc Interv 2012;5:166–73.
3. Taggart DP. Incomplete revascularization: appropriate and inappropriate. Eur J Cardiothorac Surg 2012;41:542–3.
4. Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circulation 2012;125:2613–20.
5. Dauerman HL. Reasonable incomplete revascularization. Circulation 2011;123:2337–40.
6. Kim YH, Park DW, Lee JY, et al. Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. Circulation 2011;123:2373–81.
7. Head SJ, Mack MJ, Holmes DR Jr., et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. Eur J Cardiothorac Surg 2012;41:535–41.
8. Hannan EL, Wu C, Walford G, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. J Am Coll Cardiol Intv 2009;2:17–25.
9. Lange RA, Hillis LD. Coronary revascularization in context. N Engl J Med 2009;360:1024–6.
10. Rastan AJ, Walther T, Falk V, et al. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? Circulation 2009;120:S70–7.
11. Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. Circulation 2006;114:249–55.
12. Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. Circulation 2006;113:2406–12.
13. Jones DA, Weerackody R, Rathod K, et al. Successful recanalization of chronic total occlusions is associated with improved long-term survival. J Am Coll Cardiol Intv 2012;5:380–8.
14. Mehran R, Claessen BE, Godino C, et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. J Am Coll Cardiol Intv 2011;4:952–61.
15. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J 2010;160:179–87.
16. Aziz S, Stables RH, Grayson AD, Perry RA, Ramsdale DR. Percutaneous coronary intervention for chronic total occlusions: improved survival for patients with successful revascularization compared to a failed procedure. Catheter Cardiovasc Interv 2007;70:15–20.
17. Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992–2002. Eur Heart J 2005;26:2630–6.
18. Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. Eur Heart J 2008;29:2336–42.

19. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
20. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
21. Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151:1194–204.
22. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention: 2009;5:50–6.
23. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
24. SYNTAX score calculator. Available at: http://www.syntaxscore.com. SYNTAX working-group. Accessed July 2012.
25. Holmes DR, Vazales B, Cannon LA, et al. TCT-228: four-year follow-up of the SYNTAX trial: optimal revascularization strategy in patients with three-vessel disease and/or left main disease (abstr). J Am Coll Cardiol 2011;58 Suppl;B61.
26. Serruys PW, González-Santos JM, Mack MJ, et al. TCT-49: four-year follow-up of the SYNTAX trial: optimal revascularization strategy in patients with left main disease (abstr). J Am Coll Cardiol. 2011;58 Suppl:B15.
27. Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX trial at 3 years. J Am Coll Cardiol Intv 2012;5:606–17.
28. Mohr FW, Rastan AJ, Serruys PW, et al. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. J Thorac Cardiovasc Surg 2011;141:130–40.
29. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.
30. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79:I3–12.
31. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037–43.
32. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107: 2900–7.
33. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
34. van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. J Am Coll Cardiol 2002;39:559–64.
35. Myers WO, Blackstone EH, Davis K, Foster ED, Kaiser GC. CASS Registry long term surgical survival. Coronary Artery Surgery Study. J Am Coll Cardiol 1999;33:488–98.
36. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. Eur Heart J 2009;30:453–8.
37. Alderman EL, Kip KE, Whitlow PL, et al. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol 2004;44:766–74.
38. Park S-J, Kang S-J, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol 2012;59:2051–7.
39. Erlich I, Strauss BH, Butany J. Stent thrombosis following the STAR technique in a complex RCA chronic total occlusion. Catheter Cardiovasc Interv 2006;68:708–12.
40. Botman CJ, Schonberger J, Koolen S, et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. Ann Thoracic Surg 2007;83:2093–7.
41. Glineur D, D'Hoore W, El Khoury G, et al. Angiographic predictors of 6-month patency of bypass grafts implanted to the right coronary artery: a prospective randomized comparison of gastroepiploic artery and saphenous vein grafts. J Am Coll Cardiol 2008;51:120–5.
42. Nakajima H, Kobayashi J, Toda K, et al. A 10-year angiographic follow-up of competitive flow in sequential and composite arterial grafts. Eur J Cardiothorac Surg 2011;40:399–404.
43. Morice MC, Feldman TE, Mack MJ, et al. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with TAXUS express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). EuroIntervention 2011;7:670–9.
44. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989–97.
45. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;97:1902–13.
46. Genereux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012;59:2165–74.
47. Farooq V, Girasis C, Magro M, et al. The CABG SYNTAX score—an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. EuroIntervention 2012 Aug 25 [E-pub ahead of print].
48. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331–41.
49. de Boer SP, Lenzen MJ, Oemrawsingh RM, et al. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. Eur Heart J 2011;32:2161–7.

Key Words: angiographic incomplete revascularization ■ coronary artery bypass graft surgery ■ percutaneous coronary intervention ■ SYNTAX ■ total occlusion.

PART III

Quantifying incomplete revascularisation

Chapter 3.1

Quantification of Incomplete Revascularisation and its Association with Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial. Validation of the Residual SYNTAX Score

Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Ståhle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW

Circulation. 2013;128(2):141-51 (Impact Factor: 15.202)

Quantification of Incomplete Revascularization and its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score

Vasim Farooq, MBChB, MRCP; Patrick W. Serruys, MD, PhD; Christos V. Bourantas, MD; Yaojun Zhang, MD; Takashi Muramatsu, MD; Ted Feldman, MD; David R. Holmes, MD; Michael Mack, MD; Marie Claude Morice, MD; Elisabeth Ståhle, MD; Antonio Colombo, MD; Ton de Vries, MSc; Marie-angèle Morel, BSc; Keith D. Dawkins, MD; Arie-Pieter Kappetein, MD, PhD; Friedrich W. Mohr, MD

Background—The residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score is an objective measure of the degree and complexity of residual stenosis after percutaneous coronary intervention (PCI).

Methods and Results—In the randomized PCI cohort of the SYNTAX Trial (n=903), the baseline and residual SYNTAX Scores were calculated. Subjects with a residual SYNTAX Score of 0 were defined as having undergone complete revascularization (CR), and a residual SYNTAX Score >0 as incomplete revascularization (ICR). Five-year clinical outcomes were stratified by CR and ICR (tertiles of the residual SYNTAX Score: >0–4, >4–8, and >8). In the PCI cohort, the mean baseline and residual SYNTAX Scores were 28.4±11.5 and 4.5±6.9, respectively. The mean Δ SYNTAX Score (representative of the burden of disease removed by PCI) was 23.8±10.9. The residual SYNTAX Score was distributed as follows: CR, 0 (n=386, 42.7%); ICR, >0 to 4 (n=184, 20.4%), >4 to 8 (n=167, 18.5%), >8 (n=153, 16.9%). A progressively higher residual SYNTAX Score was shown to be a surrogate marker of increasing clinical comorbidity and anatomic complexity. Subjects with CR or residual SYNTAX Scores ≤8 had comparable 5-year mortality (CR, 8.5%; residual SYNTAX Score >0–4, 8.7%; >4–8, 11.4%; P=0.60). A residual SYNTAX Score >8 was associated with 35.3% all-cause mortality at 5-years (P<0.001). Stratified analyses in the predefined medical treated diabetic and left main subgroups yielded similar results.

Conclusions—The residual SYNTAX Score was shown to be a powerful indicator of 5-year mortality in the SYNTAX Trial. The residual SYNTAX Score may aid in determining a reasonable level of revascularization.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00114972. **(*Circulation*. 2013;128:141-151.)**

Key Words: coronary disease ■ drug-eluting stents ■ myocardial ischemia ■ percutaneous coronary revascularization ■ survival analysis

Incomplete revascularization (ICR) has recently been shown to be a surrogate marker of a greater burden of anatomic coronary complexity and clinical comorbidity in patients undergoing percutaneous or surgical based revascularization in a post hoc analysis[1] of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial.[2–5] In addition, ICR has been linked to adverse short- and longer term morbidity and mortality.[6–14] Recently, the concept of reasonable incomplete revascularization has been proposed,[7,8,11,13,15] the underlying principle being that an acceptable burden of obstructive coronary artery disease post revascularization to be associated with similar outcomes to subjects in whom complete revascularization (CR) was achieved.

Editorial see p 95
Clinical Perspective on p 151

Received June 28, 2012; accepted May 10, 2013.

From the Department of Interventional Cardiology, Erasmus University Medical Center, Thoraxcenter, Rotterdam, The Netherlands (V.F., P.W.S., C.V.B., Y.Z., T.M.); Evanston Hospital, Evanston, IL (T.F.); The Mayo Clinic, Rochester, MN (D.R.H.); Medical City Dallas Hospital, Dallas, TX (M.M.); Institut Jacques Cartier, Massy, France (M.C.M.); University Hospital Uppsala, Uppsala, Sweden (E.S.); San Raffaele Scientific Institute, Milano, Italy (A.C.); Cardialysis BV, Rotterdam, The Netherlands (T.d.V., M.-a.M.); Boston Scientific Corporation, Natick, MA (K.D.D.); Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands (A.-P.K.); and Herzzentrum, Leipzig, Germany (F.W.M.).

Correspondence to Patrick W. Serruys, MD, PhD, FESC, Professor of Medicine, Head of the Interventional Cardiology Department, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail p.w.j.c.serruys@erasmusmc.nl

The recently developed residual SYNTAX Score is an objective, quantitative measure of the degree and complexity of residual stenosis after percutaneous coronary intervention (PCI).[16] In a post hoc analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial,[16] consisting of subjects with moderate to high-risk acute coronary syndrome undergoing PCI, and substantially less complex coronary artery disease compared with the SYNTAX Trial, a residual SYNTAX Score of >8.0 after PCI was associated with adverse 1-year mortality. The purpose of this study was to assess the prognostic significance of the residual SYNTAX Score in the randomized all-comers SYNTAX Trial at the final 5-year follow-up.

Methods

The all-comers SYNTAX Trial is a randomized, prospective, multicenter trial investigating subjects with unprotected left main coronary artery (ULMCA) disease (isolated or associated with 1-, 2-, or 3-vessel disease), or de novo 3-vessel (3VD) coronary artery disease.[3,5] In total, 1800 patients were recruited and randomized in PCI (n=903) and coronary artery bypass graft (CABG; n=897) arms from 85 centres in 18 countries from Europe and the United States. Exclusion criteria were limited, and consisted of subjects with prior coronary revascularization, the requirement of concomitant cardiac surgery (eg, valve surgery or resection of aortic or left ventricular aneurysm), or on-going acute myocardial infarction (MI). During the local Heart Team meeting, the interventional cardiologist and cardiac surgeon specified the number of coronary lesions requiring treatment, and their angiographic location and characteristics using the anatomic SYNTAX Score—a quantitative measure of coronary artery complexity (http://www.syntaxscore.com)[17–20]—as a tool to aid in this process. All subjects considered as potentially achieving equivalent anatomic revascularization with percutaneous or surgical revascularization by the Heart Team were randomized on a 1:1 basis (n=1800) to either PCI with Taxus Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, MA) or CABG. Patients unsuitable for randomization were nested into registries.[5]

Randomization of subjects was stratified by clinical site, the absence or presence of ULMCA disease, and medically treated diabetes mellitus (requiring oral medications or insulin), to ensure approximately equal allocation to the 2 revascularization methods at each site and within each stratum.[5] The Parsonnet[21] and EuroSCORE[22,23] were assessed by the Heart Team before randomization. Baseline, peri-, and postprocedural data were prospectively collected by the individual participating centres.

Baseline, Residual, and Δ SYNTAX Scores

The calculation of the baseline SYNTAX Score[17–20] was carried out by the Heart Team before randomization and corroborated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) blinded to the treatment assignment. Baseline and procedural coronary angiograms were centrally stored. The baseline and procedural coronary angiogram were analyzed side by side by a panel of 3 interventional cardiologists blinded to the clinical outcomes. The baseline SYNTAX Score and its components, including anatomic location of all lesions, recorded by the core laboratory in calculation of the original SYNTAX Score, were used to identify all coronary lesions in the baseline and procedural coronary angiogram. The residual SYNTAX Score was calculated based on the remaining obstructive coronary disease after treatment with PCI. The intraobserver variability for calculation of the residual SYNTAX Score (quartile partitioning), based on reanalyzing 50 cases at a 3-month interval, indicated a high level of agreement (κ statistic=0.89; 95% confidence interval [CI], 0.79 – 0.99; $P<0.001$).[17,24] The high level of agreement was attributable to the panel having preknowledge of all coronary lesion locations before PCI. The Δ SYNTAX Score, representative of the burden of disease removed by PCI, was calculated by subtracting the residual from the baseline SYNTAX Score.[16]

Clinical Outcomes

Clinical outcomes included all-cause death, all-cause death/MI/cerebrovascular accident, major adverse cardiac and cerebrovascular events (MACCE; a composite of all-cause death, MI, cerebrovascular accident, and all-cause revascularization) and its components, and stent thrombosis using the Academic Research Consortium definition.[25] An independent Clinical Events Committee, including

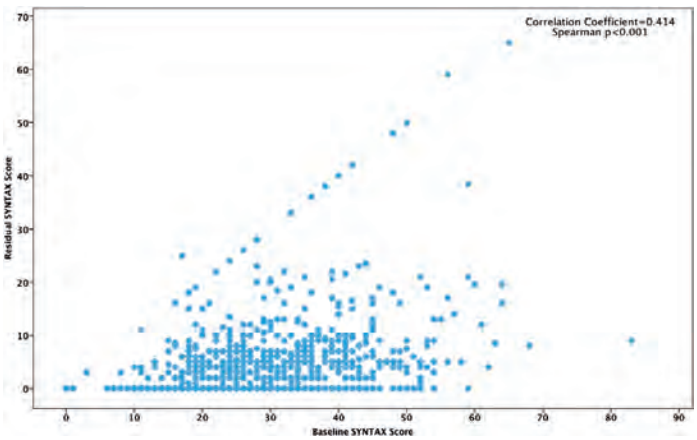


Figure 1. Correlation between the baseline and residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score. Relationship between the baseline (*x* axis) and residual (*y* axis) SYNTAX Score, for individual patients in the randomized percutaneous coronary intervention (PCI) arm of the SYNTAX Trial. Paired data were available in 886/903 subjects (98.1%). Each point can be used to assess the baseline and residual SYNTAX Scores for individual patients from the SYNTAX Trial. Each point may represent >1 value.

Table 1. Baseline and Procedural Characteristics According to Complete (Residual SYNTAX Score 0) and Incomplete Revascularization (Tertiles of the Residual SYNTAX Score)

	Residual SYNTAX Score (n=890)				
	0 (n=386)	>0–4 (n=184)	>4–8 (n=167)	>8 (n=153)	*P* Value for Linear Trends*
Clinical characteristics					
Age, y	64.6±9.8	64.8±8.7	66.0±9.8	66.7±9.8	0.015
Male	72.5%	81.0%	82.0%	73.9%	0.25
Diabetes mellitus	22.0%	31.0%	29.3%	39.9%	<0.0001
Medically treated diabetes mellitus (oral medications or insulin)†	20.5%	26.6%	26.3%	37.3%	0.0001
HbA1c ≥7%	13.6%	18.1%	7.3%	22.6%	0.24
Body mass index, kg/m^2	28.0±4.7	28.4±5.2	27.6±4.6	28.7±4.6	0.53
Hypertension	71.5%	77.6%	70.7%	80.8%	0.099
Hyperlipidemia	77.9%	75.8%	80.7%	82.7%	0.19
Peripheral vascular disease	8.3%	6.0%	9.6%	15.0%	0.025
Current smoker	20.5%	15.2%	16.2%	19.6%	0.54
Unstable angina	25.9%	34.8%	29.3%	28.8%	0.44
Previous myocardial infarction	29.8%	31.9%	28.8%	37.9%	0.17
History of GI bleeding/peptic ulcer disease	4.4%	1.6%	3.0%	7.3%	0.32
COPD	8.8%	6.0%	8.4%	7.8%	0.75
LVEF (continuous variable), %	60.3±12.2	59.8±12.9	57.4±13.9	56.5±13.4	0.0058
Good LVEF (≥50%)	82.6%	84.2%	73.1%	67.3%	<0.0001
Moderate LVEF (30%-49%)	13.2%	14.1%	22.2%	28.1%	<0.0001
Poor LVEF (<30%)	0.8%	0.5%	2.4%	2.6%	0.046
Creatinine clearance, ml/min‡	87.2±32.0	92.4±48.2	83.6±28.2	81.3±32.9	0.059
Baseline anatomical and clinical scores					
Baseline SYNTAX Score	23.6±10.0	29.0±10.2	31.7±9.8	35.9±12.4	<0.0001
Residual SYNTAX Score	0.0±0.0	3.0±1.0	6.2±1.1	15.7±9.4	<0.0001
Δ SYNTAX Score¶	23.6±10.0	26.0±10.1	25.4±9.9	20.1±13.7	0.04
Total Parsonnet Score	8.2±7.1	7.8±5.9	8.6±6.8	10.5±7.6	0.002
Additive EuroSCORE	3.6±2.7	3.6±2.4	3.8±2.5	4.2±2.6	0.02
Logistic EuroSCORE	3.8±5.5	3.3±2.9	3.7±3.6	4.3±4.2	0.34
Anatomical characteristics					
Left main disease§†	42.5%	34.8%	40.1%	39.2%	0.48
De novo 3VD	57.5%	65.2%	59.9%	60.8%	0.48
Number of lesions	3.5±1.7	4.1±1.6	4.3±1.6	4.5±1.6	<0.0001
Any total occlusions	12.3%	22.3%	28.3%	50.7%	<0.0001
Number of total occlusions					
1 TO	12.0%	22.3%	25.3%	42.8%	<0.0001
2 TO	0.3%	0.0%	3.0%	7.9%	<0.0001
Any bifurcation lesion	57.3%	66.3%	62.9%	70.6%	0.0056
Any trifurcation lesion	7.3%	6.0%	10.2%	6.5%	0.77
Any bifurcation or trifurcation	62.2%	68.5%	70.1%	71.9%	0.015
Diffuse or small vessel disease	18.4%	26.1%	20.4%	28.1%	0.034
Any aorto-ostial lesion	17.3%	13.6%	11.5%	17.1%	0.48
Any angiographically visible thrombus	2.6%	2.2%	2.4%	2.6%	0.97
Any heavy calcification	42.7%	47.3%	53.0%	64.5%	<0.0001
Any severe tortuosity	55.8%	74.5%	74.7%	71.7%	<0.0001
Left arterial dominance	16.8%	19.6%	19.8%	16.3%	0.85

(*Continued*)

Table 1. Continued

	Residual SYNTAX Score (n=890)				
	0 (n=386)	>0–4 (n=184)	>4–8 (n=167)	>8 (n=153)	*P* Value for Linear Trends*
Proximal LAD (segment 6) lesion	52.3%	62.0%	61.1%	64.7%	0.0047
Any circumflex lesion	77.7%	92.9%	88.0%	92.2%	<0.0001
Any right coronary artery lesion	74.9%	83.7%	87.4%	91.5%	<0.0001
Any lesion length >20 mm	46.1%	57.6%	62.1%	70.4%	<0.0001
Procedural characteristics					
Total number of stents implanted	4.5±2.4	4.9±2.2	4.7±2.0	4.6±2.1	0.73
Total length of stents implanted, mm	85.8±51.6	91.0±47.9	84.3±42.5	82.2±42.1	0.44
Stent length >100 mm	35.1%	36.1%	28.7%	29.6%	0.12
Postprocedural hospital stay, d	3.0±4.3	2.9±3.4	2.9±2.4	5.1±7.1	0.0001
Procedure time, h	1.6±0.9	1.7±0.8	1.9±0.9	1.9±1.0	<0.0001

3VD indicates 3-vessel disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HbA1c, hemoglobin A1c; LAD, left anterior descending artery; LVEF, left ventricular ejection function; MI, myocardial infarction; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and TO, total occlusion.

*Testing for (linear) trends was performed using generalized linear models with the residual SYNTAX Score class as a covariable for continuous variables and the Cochran-Armitage test for trends in categorical data.

†Prespecified patient subsets at randomization.

‡Cockcroft and Gault formula.

Δ SYNTAX Score represents the burden of disease removed by PCI.

§Isolated or associated with 1, 2, or 3VD.

cardiologists, cardiac surgeons, and a neurologist, reviewed all the primary clinical end points.[3,5] A separate independent Clinical Events Committee adjudicated the Academic Research Consortium stent thrombosis events.

Statistical Analysis

Analyses were performed by intention to treat. Binary variables are reported as counts or percentages, continuous data are expressed as means±SD. All variables were stratified according to a residual SYNTAX Score 0 (CR), and tertiles of the residual SYNTAX Score >0 (ICR). For the baseline characteristics, testing for linear trends across residual SYNTAX Score groups was performed using generalized linear models with the residual SYNTAX Score class as a covariable for continuous variables, and the Cochran-Armitage test for trends in categorical data. Time-to-event variables are presented as Kaplan–Meier curves and compared using Cox proportional hazard ratios (HR) and the log-rank test. Multivariable analyses were conducted with a Cox regression model using the forced enter method. Previously determined anatomic and clinical variables, shown to be independent predictors of long-term mortality in the SYNTAX Trial ($P<0.1$),[26] were entered into the model, with no exit criteria. There was no departure from the proportionality of hazards assumption using the global proportional hazards test based on Schoenfeld residuals.[27] Area under the curve for the baseline and residual SYNTAX Scores for 5-year all-cause death and 5-year MACCE were computed by logistic regression and compared using the nonparametric method of deLong et al.[28] Area under the curve performed with and without censored data removed had a negligible difference. A 2-sided probability value <0.05 was considered significant for all tests. All analyses were conducted using SPSS 20.0 (SPSS Inc, Chicago IL) and SAS System Software Version 9.2 (SAS Institute, Cary, NC)

Results

In the randomized PCI cohort (n=903), the baseline SYNTAX Score was available in 899/903 subjects (99.6%). The mean baseline SYNTAX Score was 28.4±11.5. The residual

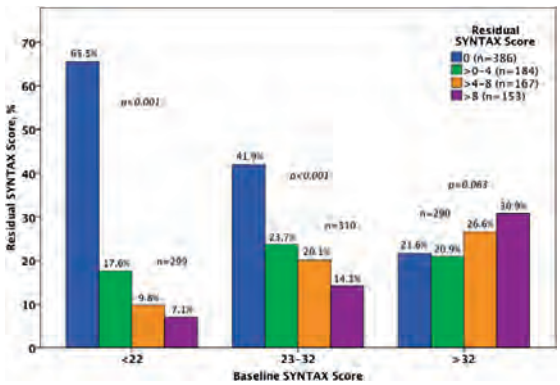


Figure 2. Complete (residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery [SYNTAX] Score 0) and incomplete (tertiles of the residual SYNTAX Score [residual SYNTAX Score >0]) revascularization, stratified according to tertiles of the baseline SYNTAX Score. Note the progressive increase in the frequency of a residual SYNTAX Score >8 across conventional tertiles of the baseline SYNTAX Score.

SYNTAX Score was available in 890/903 subjects (98.6%). The correlation (Spearman coefficient 0.414, *P*<0.001) and distribution of the baseline and residual SYNTAX Score is illustrated in Figure 1. CR (residual SYNTAX Score 0) was evident in 42.7% of the PCI arm (n=386), and ICR in 55.8% of the PCI arm (n=504) (residual SYNTAX Score: >0 to 4 (20.4% [n=184]), >4 to 8 (18.5% [n=167]), and >8 (16.9% [n=153]). The mean Δ SYNTAX Score (representative of the burden of disease removed by PCI) was 23.8±10.9. The mean residual SYNTAX Score was 4.5±6.9.

Baseline Characteristics

Baseline characteristics of CR (residual SYNTAX Score 0) and ICR (tertiles of the residual SYNTAX Score) are shown in Table 1. A higher residual SYNTAX Score was associated with progressively increasing clinical comorbidity; namely, older age (*P*=0.015), medically treated diabetes mellitus (*P*=0.0001), peripheral vascular disease (*P*=0.025), reduced left ventricular ejection fraction (*P*=0.0058), reduced creatinine clearance (*P*=0.059), greater Parsonnet Score (*P*=0.0020), and additive EuroSCORE (*P*=0.020). Similarly, a greater residual SYNTAX Score was associated with progressively higher baseline SYNTAX score (*P*<0.0001), with a residual SYNTAX Score of >8 associated with significantly more total occlusions (TO; 50.7%, *P*<0.0001), bifurcations (70.6%, *P*=0.0056), diffuse or small vessel disease (28.1%, *P*=0.034), heavy calcification (64.5%, *P*<0.0001), severe tortuosity (71.7%, *P*<0.0001), and long lesions (70.4%, *P*<0.0001). Stent length was not associated with an increase in the residual SYNTAX Score (*P*=0.44). Notably, the Δ SYNTAX Score was lower in subjects with a residual SYNTAX Score >8 (20.1±13.7) compared with CR (23.6±10.0, *P*=0.040).

Distribution of Residual SYNTAX Score per Tertiles of the Baseline SYNTAX Score

Figure 2 illustrates the distribution of the residual SYNTAX Score per tertile of the baseline SYNTAX Score. The frequency of subjects with a residual SYNTAX Score >8 progressively increased across tertiles of the baseline SYNTAX Score (0–22: 7.1% versus 23–32: 14.3% versus ≥33: 30.9%, *P* value for linear trend <0.0001).

5-Year Clinical Outcomes

Figure 3 illustrates the HRs for categories of the residual SYNTAX Score for differing clinical outcomes, using CR (residual SYNTAX Score 0) as a reference. Subjects with CR or lower residual SYNTAX Scores (≤8) had comparable 5-year mortality (CR [n=386]: 8.5%, residual SYNTAX Score >0–4 [n=184]: 8.7%, >4–8 [n=167]: 11.4%, *P*=0.60). At 5 years, a residual SYNTAX Score >8 was associated with significantly increased all-cause mortality (35.3%, *P*<0.001), MACCE (59.5%, *P*<0.001), MI (17.0%, *P*<0.001), all-cause revascularization (32.0%, *P*<0.001), and definite/probable stent thrombosis (16.0%, *P*=0.005) (Figure 4).

Tertiles of the Baseline SYNTAX Score

Figure 5 demonstrates the impact of ICR (tertiles of the residual SYNTAX Score) according to the conventional tertiles of the baseline SYNTAX Score. From low (0-22), to intermediate (23–32) and high (≥33) baseline SYNTAX Scores, there was an incremental rise in the 5-year mortality impact of a residual SYNTAX Score >8 (low: 23.8%, *P*=0.022; intermediate: 34.1%, *P*<0.001; high: 39.1%, *P*<0.001).

Stratified Analyses

Stratified analyses (Table 2) in the subgroups of medically treated diabetes mellitus (n=231/903 [26%], *P* value for interaction 0.84), ULMCA disease (n=357/903 [40%], *P* value for interaction 0.91), and impaired left ventricular function (n=172/903 [19%], *P* value for interaction 0.36) indicated that a residual SYNTAX Score >8 was similarly associated with adverse 5-year mortality. In the subgroup consisting of TOs (n=217/903 [24%]), a residual SYNTAX Score of >8 was associated with a more modest effect on mortality (HR, 2.17; 95% CI, 0.80–5.88; *P*=0.13), compared with a more pronounced effect in subjects without TOs (HR, 8.51; 95% CI, 5.20–13.94; *P*<0.0001; *P* value for interaction 0.015).

Discriminative and Predictive Value of the Baseline and Residual SYNTAX Scores

Compared with the baseline SYNTAX Score, the residual SYNTAX Score demonstrated greater discrimination for 5-year all-cause mortality (0.619 [95% CI, 0.568–0.671]

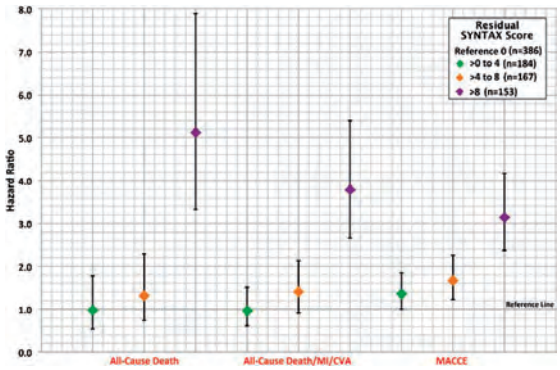


Figure 3. Five-year clinical outcomes stratified by tertiles of the residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score (incomplete revascularization, >0). Hazard ratios (HR) are relative to complete revascularization (Reference Line, residual SYNTAX Score 0). HR for tertiles of the residual SYNTAX Score (>0) are shown. The error bars represent 95% confidence intervals. A residual SYNTAX Score 10.0 was associated with a doubling of 5-year all-cause death. A residual SYNTAX Score of 10.7 and 11.3 respectively lead to a doubling of 5 year all-cause death/MI/CVA and 5 year MACCE. CVA indicates cerebrovascular accident; MACCE, major adverse cardiac and cerebrovascular events; and MI, myocardial infarction.

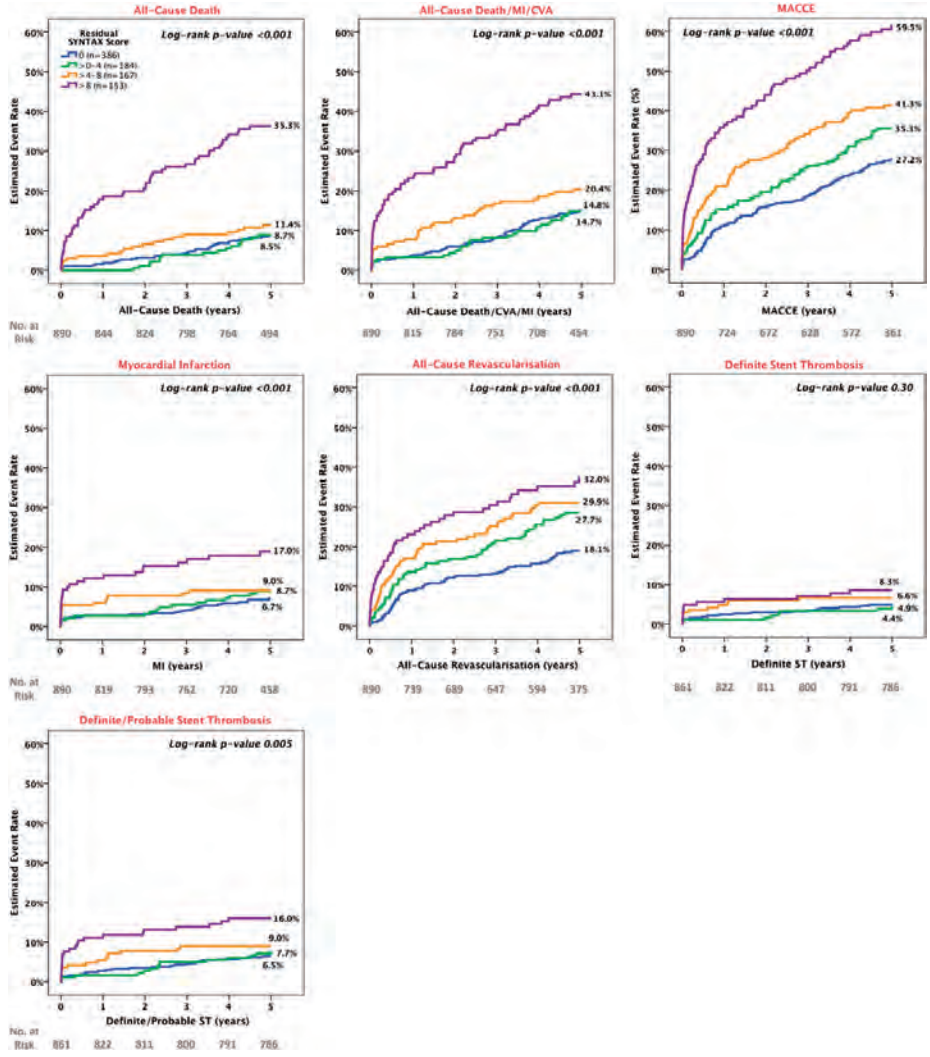


Figure 4. Kaplan–Meier curves showing cumulative event rates through to 5 years based on complete (residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery [SYNTAX] Score 0) and incomplete (tertiles of the residual SYNTAX Score) revascularization. All-cause death, all-cause death/myocardial infarction (MI)/cerebrovascular accident (CVA), major adverse cardiac and cerebrovascular events (MACCE), MI, all-cause revascularization, definite stent thrombosis and, definite/probable stent thrombosis, are illustrated. For all clinical outcomes, with the exception of definite stent thrombosis, a residual SYNTAX Score >8 was associated with adverse events. ST indicates stent thrombosis.

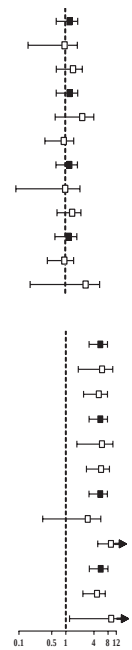
versus 0.687 [95% CI, 0.630–0.744]; *P*=0.024) and MACCE (0.570 [95% CI, 0.531–0.610] versus 0.634 [95% CI, 0.597–0.672]; *P*=0.0026). Notably, a residual SYNTAX Score >8 was highly specific in its association with 5-year clinical outcomes (specificity: all cause death, 88%; MACCE, 90%).

Multivariable Analysis

Multivariable analysis (Table 3) demonstrated the residual SYNTAX Score to be an independent predictor of 5-year all-cause death (HR, 1.65; 95% CI, 1.41–1.92; *P*<0.001)

Table 2. Stratified Analyses of Complete (Residual SYNTAX Score 0) Versus Incomplete Revascularization (Residual SYNTAX Score >0–8 and >8), for 5-Year All-Cause Death in Subjects With and Without Medically Treated Diabetes Mellitus, Unprotected Left Main Coronary Artery Disease, Total Occlusions, and Impaired Left Ventricular Ejection Fraction

	CR (rSS=0)	ICR (rSS>0)	Hazard Ratio (95% CI)	*P* Value	$P_{interaction}$
rSS 0 vs. rSS >0-8	rSS=0	rSS >0-8			
All-cause death	33/369 (9%)	35/348 (10%)	1.13 (0.71–1.83)	0.60	0.31
Medically treated diabetes mellitus*†	10/76 (13%)	9/91 (10%)	0.75 (0.31–1.85)	0.54	
No medically treated diabetes mellitus	23/293 (8%)	26/257 (10%)	1.30 (0.74–2.28)	0.36	
All-cause death	33/369 (9%)	35/348 (10%)	1.13 (0.71–1.83)	0.60	0.11
Unprotected left main†	11/157 (7%)	16/130 (12%)	1.83 (0.85–3.95)	0.12	
De novo 3VD	22/212 (10%)	19/218 (9%)	0.83 (0.45–1.53)	0.55	
All-cause death	33/365 (9%)	35/347 (10%)	1.12 (0.70–1.81)	0.63	0.32
Total occlusion	5/44 (11%)	7/88 (8%)	0.67 (0.21–2.11)	0.49	
No total occlusion	28/321 (9%)	28/259 (11%)	1.26 (0.75–2.13)	0.38	
All-cause death	32/356 (9%)	33/342 (10%)	1.08 (0.67–1.76)	0.76	0.20
LVEF Not Impaired (≥50%)	27/306	21/274 (8%)	0.86 (0.49–1.52)	0.61	
LVEF Impaired (<50%)	5/50 (10%)	12/68 (18%)	1.85 (0.65–5.26)	0.25	
rSS 0 vs. rSS >8	rSS=0	rSS >8			
All-cause death	33/369 (9%)	54/145 (37%)	5.12 (3.32–7.90)	<0.0001	0.84
Medically treated diabetes mellitus*†	10/76 (13%)	25/52 (48%)	5.01 (2.40–10.44)	<0.0001	
No medically treated diabetes mellitus	23/293 (8%)	29/93 (31%)	4.60 (2.66–7.95)	<0.0001	
All-cause death	33/369 (9%)	54/145 (37%)	5.12 (3.32–7.90)	<0.0001	0.91
Unprotected left main†	11/157 (7%)	17/58 (29%)	4.93 (2.31–10.53)	<0.0001	
De novo 3VD	22/212 (10%)	37/87 (43%)	5.16 (3.04–8.76)	<0.0001	
All-cause death	33/365 (9%)	54/144 (38%)	5.11 (3.31–7.88)	<0.0001	0.015
Total occlusion	5/44 (11%)	17/73 (23%)	2.17 (0.80–5.88)	0.13	
No total occlusion	28/321 (9%)	37/71 (52%)	8.51 (5.20–13.94)	<0.0001	
All-cause death	32/356 (9%)	54/142 (38%)	5.22 (3.37–8.09)	<0.0001	0.36
LVEF not impaired (<50%)	27/306 (9%)	31/98 (32%)	4.25 (2.53–7.12)	<0.0001	
LVEF impaired (<50%)	5/50 (10%)	23/44 (52%)	6.96 (2.64–18.34)	<0.0001	



Data are (n/N [%]). Interaction *P* value is for the test on the difference in HR between CR (rSS 0) vs ICR (rSS >0) in the respective diabetic/non diabetic groups, unprotected left main/non unprotected left main groups, total occlusion/non total occlusion groups and LVEF impaired/not impaired groups.

3VD indicates 3-vessel disease; CI, confidence interval; CR, complete revascularization; ICR, incomplete revascularization; LVEF, left ventricular ejection function; rSS, residual SYNTAX Score; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

*Insulin or oral hypoglycemics.

†Prestratified at randomization.

Discussion

The main findings of this study are the following, at 5 years: (1) A progressively higher residual SYNTAX Score was shown to be a surrogate marker of increasing clinical comorbidity and more anatomically complex disease; (2) a residual SYNTAX Score of ≤8 was associated with long-term mortality comparable with subjects with CR; (3) a residual SYNTAX Score of >8 was associated with progressively increasing adverse long-term clinical outcomes, including mortality—an effect that remained consistent across all conventional tertiles of the baseline SYNTAX Score; (4) The findings of a residual SYNTAX Score >8 to be associated with adverse long-term mortality were equally applicable in the predefined subgroups of ULMCA disease and medically treated diabetes mellitus, and the subgroup with impaired left ventricular ejection function; (5) In the TO subgroup, a residual SYNTAX Score >8 was associated with a more modest effect on long-term mortality, compared with a pronounced effect in subjects without TOs; and (6) the residual SYNTAX Score was shown to be a powerful indicator of long-term mortality and other clinical outcomes in subjects with ULMCA disease or de novo 3VD.

Previous predominantly registry studies investigating the clinical impact of CR and ICR have lacked standardized definitions. These studies have for example used the number of treated vessels/treated important vessels based on varying degrees of stenosis, and have analyzed IR with or without the presence of TOs, or on revascularization of all vessels with a size ≥1.5 mm.[1,6–14,29] Such varying definitions of ICR have made comparisons between studies problematic. In addition, the unavoidable selection bias inherent to all registries has added to the difficulties in interpreting these studies.[7,8] Even using multivariate and propensity score adjustments of baseline characteristics to control for selection bias would be potentially misleading, because ICR was

Table 3. Univariable and Multivariable Cox Regression Analyses, Incorporating the Residual SYNTAX Score, Using Clinical Variables Previously Shown to be Independent Predictors of Long-Term Mortality in the SYNTAX Trial[26]

	Univariable Analyses		Multivariable Analyses	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Residual SYNTAX Score (4 groups)*	1.76 (1.50, 2.06)	<0.001	1.65 (1.41, 1.92)	<0.001
Baseline SYNTAX Score (tertiles)†	1.50 (1.20, 1.88)	<0.001	—	—
Preprocedural poor (<30%) LVEF	5.60 (2.61, 12.02)	<0.001	5.04 (2.30, 11.04)	<0.001
Peripheral vascular disease	3.31 (2.15, 5.11)	<0.001	2.92 (1.88, 4.52)	<0.001
History of GI bleeding or peptic ulcer disease	2.08 (1.05, 4.09)	0.035	1.89 (0.95, 3.76)	0.069
Age per increase in 10 yr	1.79 (1.46, 2.20)	<0.001	1.61 (1.30, 1.99)	<0.001
Female sex	1.70 (1.17, 2.47)	0.006	1.57 (1.06, 2.33)	0.023

CI indicates confidence interval; CR, complete revascularization; GI, gastrointestinal; HR, hazard ratio; ICR, incomplete revascularization; LVEF, left ventricular ejection function; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

*Four groups comprising CR (residual SYNTAX Score 0) and ICR (tertiles of the residual SYNTAX Score >0 to 4, >4 to 8, >8).

†Conventional tertiles of the baseline SYNTAX Score (low 0–22, intermediate 23–32, high ≥33).[17]

*†Correlation of 0.4 precluded entry of baseline SYNTAX Score into multivariable model.

demonstrated to be a surrogate marker of sicker patients with more anatomically complex baseline coronary artery disease.[11]

Conversely, the residual SYNTAX Score allowed for an objective, quantitative assessment of the extent of ICR in PCI treated subjects in the randomized all-comers population of the SYNTAX Trial, in which selection bias would have been minimal. Furthermore, the residual SYNTAX Score allowed for a threshold value of ICR to be determined that would not have a negative impact on long-term mortality (ie, the concept of reasonable incomplete revascularization).[7,8,11,13,15] This concept, using the residual SYNTAX Score, has recently been described in the ACUITY Trial,[16] the main differences being that the ACUITY Trial recruited subjects solely presenting with non-ST elevation acute coronary syndrome, followed up for 1-year, and importantly, with substantially lesser complex coronary artery disease (primarily single or double vessel disease, median SYNTAX Score 9.0, interquartile range 5.0–16.0). Comparatively, the SYNTAX Trial recruited subjects with substantially more complex coronary artery disease (left main or de novo 3VD, median SYNTAX Score 28, interquartile range 20.0–36.0), and validated the findings of a residual SYNTAX Score >8 to be associated with adverse outcomes at up to 5 years, in an all-comers randomized population, and in several clinical and anatomic subgroups.

Reducing the Ischemia Burden

The residual SYNTAX Score is principally a marker of the residual ischemia burden, dependent on the location of the coronary lesion and the anatomic complexity (eg, calcification, bifurcation, long lesion, etc) associated with the obstructive disease. This is attributable to the fact that most of the points of the SYNTAX Score are accrued from the severity of luminal diameter narrowing and its weighting according to the usual blood flow to the left ventricle in each vessel or vessel segment.[17,18,30] More proximal coronary artery disease therefore scores more highly on the SYNTAX Score, particularly if the obstructive disease is more complex. From a prognostic perspective this is important because MIs have been shown to cluster in the proximal third of major epicardial vessels,[31] and a large plaque burden and small luminal area have both been linked to the highest risk of future cardiac events.[32,33]

Reducing the ischemia burden of the patient would undoubtedly improve long-term prognosis, as exemplified by previous studies associating a short- and long-term survival benefit in

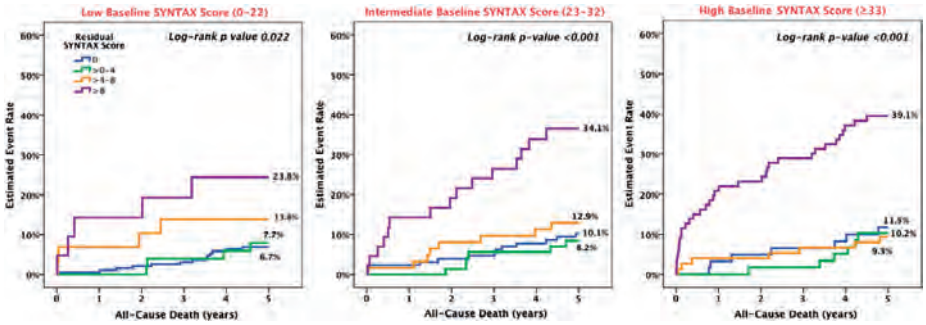


Figure 5. Completeness of revascularization stratified to conventional tertiles of the baseline Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score using the residual SYNTAX Score. Kaplan–Meier curves showing cumulative event rates through to 5 years, based on complete (residual SYNTAX Score 0) and incomplete (tertiles of residual SYNTAX Score) revascularization, in the low (0–22), intermediate (23–32), and high (≥33) baseline SYNTAX Scores. Note the progressive rise in the 5-year mortality impact of a residual SYNTAX Score >8 with increasing anatomic complexity.

patients with moderate to large amounts of inducible ischemia who were revascularized.[34–36] Specifically, in the nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial,[35] ≥10% reversible ischemia was associated with adverse 5-year mortality if treated medically.

Strikingly, the frequency of a high residual SYNTAX Score (ie, >8), and its association with more severe baseline anatomic complexity such as calcification, bifurcations, TOs, and tortuosity (Table 1), was shown to progressively increase across the conventional tertiles of the baseline SYNTAX Score (Figure 2), which in turn was linked to an incremental rise in 5-year all-cause mortality (Figure 5). In addition, the most pronounced effect of the long-term adverse prognostic effects of a residual SYNTAX Score >8 were in subjects without TOs (Table 2). These findings perhaps epitomize the need for appropriate myocardial viability testing to ensure that revascularization of the TO is clinically justified.[37–42]

Notably in the high baseline SYNTAX Scores, despite the greater anatomic complexity, the Δ SYNTAX Score (representative of burden of coronary disease removed by PCI) was less than that seen in subjects with CR. These results suggest the potential difficulties the interventional cardiologist may face in the treatment of highly complex coronary artery disease. Advances in PCI technology, with more deliverable newer generation drug-eluting stents, adjunctive devices to aid stent delivery, crossing and re-entry systems to aid TO revascularization, functional assessment of lesions, intravascular ultrasound guidance to ensure adequate stent expansion, and dedicated specialists for specific anatomic subsets, may improve long-term prognosis by ensuring major epicardial vessels are fully revascularized.[43–47]

Surrogate Marker of Anatomic Complexity and Clinical Comorbidity

The findings associating ICR with sicker patients, more anatomically complex coronary artery disease, and consequent poorer long-term clinical outcomes, are supported by the historical data as detailed below.

First, that very long term follow-up data (>10 years) of CABG treated patients in 2 separate registries[48,49] have associated more extensive baseline preoperative disease with adverse mortality. Second, in the Bypass Angioplasty Revascularization Investigation (BARI) Trial,[50] where jeopardized myocardium and recurrence of angina were shown to occur more frequently secondary to native coronary artery disease progression, a reflection of the clinical risk profile of the patient, compared with failed revascularization in both PCI- and CABG-treated subjects at 5 year follow-up. Findings that have also been observed in other studies,[51,52] with baseline comorbidities, such as diabetes mellitus, having been shown to be a predictor of native coronary disease progression. Third, that coronary artery calcification has been linked to adverse all-cause mortality at 10 years, independent of other risk factors.[53,54] Notably, heavy calcification was present in almost two-thirds (64.5%) of subjects with a residual SYNTAX Score >8 (Table 1).

Decision-Making Between CABG and PCI

The recently developed and validated SYNTAX Score II[55] combines anatomic (including the SYNTAX Score) and clinical variables that directly affect decision making between CABG and PCI. This is based on the provision that the cardiologist and cardiac surgeon agree, before revascularization, that equivalent anatomic revascularization could be achieved. Incorporation of quantitative factors of completeness of revascularization in the SYNTAX Score II would however have a limited role in decision-making between CABG and PCI, because this is a clinical outcome. This is typified in the SYNTAX Trial, where, despite the mandatory requirement of the interventional cardiologist and cardiac surgeon to agree that equivalent anatomic revascularization could be achieved to allow the patient to be randomized, CR was realized in 56.7% and 63.2% of the PCI and CABG arms, respectively.[29]

Study Limitations

The present study represents a post hoc analysis of the SYNTAX Trial, and the results should be considered as hypothesis-generating. Although a core laboratory undertook baseline SYNTAX Scores prospectively, the residual SYNTAX Score was retrospectively assessed by a panel of 3 interventional cardiologists. Despite this limitation, analyses were performed with the identification of the lesions recorded by the core-laboratory, with consequent excellent reproducibility (κ statistic 0.89). It is entirely plausible that the residual SYNTAX Score could be improved through enhanced identification of functionally significant lesions with fractional flow reserve[47,56] or viability assessment of the supplied myocardium.[37–42] Although multivariable adjustments were performed for significant confounders ($P<0.1$), the possibility of other unmeasured confounders to have affected the results cannot be excluded. Although the SYNTAX Trial was based on contemporary revascularization practice at the time, improvements in technology in PCI and CABG may yield differences in clinical outcomes in future trials.

Conclusions

The residual SYNTAX Score was shown to be a powerful indicator of 5-year clinical outcomes, including mortality, after PCI with drug-eluting stents in subjects with left main or de novo 3VD. The residual SYNTAX Score may aid determining a reasonable level of revascularization.

Acknowledgments

We are grateful to all of the study participants whose work made this study possible. Thanks also to Jian Huang for his invaluable technical support in accessing the study database.

Sources of Funding

The SYNTAX Trial was funded by Boston Scientific.

Disclosures

Drs Dawkins and Huang are all full-time employees in Boston Scientific. Dr Dawkins holds stock in Boston Scientific. Dr Mack has served on the Speaker's Bureau of Boston Scientific, Cordis, and Medtronic. Dr Feldman reported serving on the Speaker's Bureau of Boston Scientific, receiving grant support from Abbott, Atritech, BSC, Edwards, and Evalve, and consulting for Abbott, Coherex, Intervalve, Square One, and

WL Gore. Dr Morice reported that her institution received a research grant from Boston Scientific. The other authors report no conflicts.

References

1. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Ståhle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol*. 2013;61:282–294.
2. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381:629–638.
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–972.
4. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Ståhle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J*. 2011;32:2125–2134.
5. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J*. 2006;151:1194–1204.
6. Rosner GF, Kirtane AJ, Genereux P, Lansky AJ, Cristea E, Gersh BJ, Weisz G, Parise H, Fahy M, Mehran R, Stone GW. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circulation*. 2012;125:2613–2620.
7. De Bruyne B. Multivessel disease: from reasonably incomplete to functionally complete revascularization. *Circulation*. 2012;125:2557–2559.
8. Dauerman HL. Reasonable incomplete revascularization. *Circulation*. 2011;123:2337–2340.
9. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S, King SB 3rd. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. J Am Coll Cardiol. *Cardiovasc Interv*. 2009;2:17–25.
10. Kim YH, Park DW, Lee JY, Kim WJ, Yun SC, Ahn JM, Song HG, Oh JH, Park JS, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. *Circulation*. 2011;123:2373–2381.
11. Taggart DP. Incomplete revascularization: appropriate and inappropriate. *Eur J Cardiothorac Surg*. 2012;41:542–543.
12. Schwartz L, Bertolet M, Feit F, Fuentes F, Sako EY, Toosi MS, Davidson CJ, Ikeno F, King SB 3rd. Impact of completeness of revascularization on long-term cardiovascular outcomes in patients with type 2 diabetes mellitus: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). *Circ Cardiovasc Interv*. 2012;5:166–173.
13. Gössl M, Faxon DP, Bell MR, Holmes DR, Gersh BJ. Complete versus incomplete revascularization with coronary artery bypass graft or percutaneous intervention in stable coronary artery disease. *Circ Cardiovasc Interv*. 2012;5:597–604.
14. Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. *Circulation*. 2006;114:249–255.
15. Rastan AJ, Walther T, Falk V, Kempfert J, Merk D, Lehmann S, Holzhey D, Mohr FW. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? *Circulation*. 2009;120(11 Suppl):S70–S77.
16. Généreux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol*. 2012;59:2165–2174.
17. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention*. 2009;5:50–56.
18. Sianos G, Morel MA, A.P. K, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. The SYNTX Score: An angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005 1:219–227.
19. SYNTAX Score calculator: http://www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.
20. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart*. 2011;97:1902–1913.
21. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation*. 1989;79(6 Pt 2):I3–12.
22. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16:9–13.
23. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J*. 2003;24:881–882.
24. Généreux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, Lazar D, Jankovic I, Corral MD, Dressler O, Fahy MP, Parise H, Lansky AJ, Stone GW. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv*. 2011;4:553–561.
25. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.
26. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Ståhle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J*. 2012;33:3105–3113.
27. Schoenfeld d. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; 69:239–241.
28. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
29. Head SJ, Mack MJ, Holmes DR Jr, Mohr FW, Morice MC, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535–541.
30. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation*. 1981;63:285–299.
31. Wang JC, Normand SL, Mauri L, Kuntz RE. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation*. 2004;110:278–284.
32. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262–1275.
33. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235.
34. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–2907.
35. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR,

Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–1291.
36. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt C, Deanfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation*. 1997;95:2037–2043.
37. Baks T, van Geuns RJ, Duncker DJ, Cademartiri F, Mollet NR, Krestin GP, Serruys PW, de Feyter PJ. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. *J Am Coll Cardiol*. 2006;47:721–725.
38. Kwon DH, Hachamovitch R, Popovic ZB, Starling RC, Desai MY, Flamm SD, Lytle BW, Marwick TH. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: association with end-systolic volume and viability. *Circulation*. 2012;126(11 Suppl 1):S3–S8.
39. Gerber BL, Rousseau MF, Ahn SA, le Polain de Waroux JB, Pouleur AC, Phlips T, Vancraeynest D, Pasquet A, Vanoverschelde JL. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. *J Am Coll Cardiol*. 2012;59:825–835.
40. Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, Lammertsma AA, Liedtke AJ, Paternostro G, Vatner SF. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). *Circulation*. 1997;96:3205–3214.
41. Fiocchi F, Sgura F, Di Girolamo A, Ligabue G, Ferraresi S, Rossi R, D'Amico R, Modena MG, Torricelli P. Chronic total coronary occlusion in patients with intermediate viability: value of low-dose dobutamine and contrast-enhanced 3-T MRI in predicting functional recovery in patients undergoing percutaneous revascularisation with drug-eluting stent. *Radiol Med*. 2009;114:692–704.
42. Kirschbaum SW, Baks T, van den Ent M, Sianos G, Krestin GP, Serruys PW, de Feyter PJ, van Geuns RJ. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. *Am J Cardiol*. 2008;101:179–185.
43. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:254–265.
44. Zhang Y, Farooq V, Garcia-Garcia HM, Bourantas CV, Tian N, Dong S, Li M, Yang S, Serruys PW, Chen SL. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention*. 2012;8:855–865.
45. Werner GS, Schofer J, Sievert H, Kugler C, Reifart NJ. Multicentre experience with the BridgePoint devices to facilitate recanalisation of chronic total coronary occlusions through controlled subintimal re-entry. *EuroIntervention*. 2011;7:192–200.
46. Farooq V, Mamas MA, Fath-Ordoubadi F, Fraser DG. The use of a guide catheter extension system as an aid during transradial percutaneous coronary intervention of coronary artery bypass grafts. *Catheter Cardiovasc Interv*. 2011;78:847–863.
47. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF; FAME Study Investigators. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol*. 2011;58:1211–1218.
48. Myers WO, Blackstone EH, Davis K, Foster ED, Kaiser GC. CASS Registry long term surgical survival. Coronary Artery Surgery Study. *J Am Coll Cardiol*. 1999;33:488–498.
49. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. *Eur Heart J*. 2009;30:453–458.
50. Alderman EL, Kip KE, Whitlow PL, Bashore T, Fortin D, Bourassa MG, Lesperance J, Schwartz L, Stadius M; Bypass Angioplasty Revascularization Investigation. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol*. 2004;44:766–774.
51. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, Killip T, Sosa JA, Bourassa MG. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. *J Am Coll Cardiol*. 1993;22:1141–1154.
52. Bourassa MG, Fisher LD, Campeau L, Gillespie MJ, McConney M, Lespérance J. Long-term fate of bypass grafts: the Coronary Artery Surgery Study (CASS) and Montreal Heart Institute experiences. *Circulation*. 1985;72(6 Pt 2):V71–V78.
53. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007;49:1860–1870.
54. Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, Lloyd-Jones DM. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol*. 2011;57:1838–1845.
55. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639–650.
56. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.

CLINICAL PERSPECTIVE

Interpreting the long-term prognostic impact of incomplete revascularization (ICR) in patients with complex coronary artery disease has historically remained difficult. The lack of standardized definitions of ICR, lack of randomized data, unavoidable selection bias inherent to all registry studies, and quality of monitoring and adjudication of outcomes, have led to conflicting results in the literature. The residual Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score is based on the principle of being a measure of the myocardial ischemia burden, dependent on the location of the coronary disease, its importance in supplying blood to the myocardium, and the anatomic complexity associated with the obstructive disease. Importantly, the residual SYNTAX Score allowed for the determination of an objective level of reasonable ICR, whereby a threshold value of ICR could be determined (≤8) that would not have a negative impact on long-term mortality and other clinical outcomes. The residual SYNTAX Score was validated in a randomized, all-comers population, consisting of subjects with complex coronary artery disease (unprotected left main coronary artery or de novo 3-vessel-disease) who had undergone 5-year follow-up. Notably, progressively higher residual SYNTAX Scores were shown to be a surrogate marker of sicker patients, with greater baseline clinical comorbidity and anatomic complexity, with consequent adverse long-term clinical outcomes, including all-cause mortality. Results that were equally applicable in subjects with unprotected left main coronary artery disease and medically-treated diabetes mellitus. Such findings are of value in guiding the clinician to reduce the level of reversible myocardial ischemia by treating obstructive lesions to stay within the threshold of reasonable ICR.

Chapter 3.2

The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy

Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia Garcia HM, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Ståhle E, James S, Carrié D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW

EuroIntervention. 2013;8(11):1277-85 (Impact Factor: 3.173)

The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy

Vasim Farooq[1], MBChB, MRCP; Chrysafios Girasis[1], MD; Michael Magro[1], MD; Yoshinobu Onuma[1], MD; Marie Angèle Morel[7], BSc; Jung Ho Heo[1], MD; Hector Garcia-Garcia[1], MD; Arie Pieter Kappetein[2], MD, PhD; Marcel van den Brand[7], MD; David R. Holmes[3], MD; Michael Mack[4], MD; Ted Feldman[5], MD; Antonio Colombo[10], MD; Elisabeth Ståhle[8], MD; Stefan James[8], MD; Didier Carrié[12], MD; Gerard Fournial[12], MD; Gerrit-Anne van Es[7], PhD; Keith D. Dawkins[9], MD; Friedrich W. Mohr[11], MD; Marie-Claude Morice[6], MD; Patrick W. Serruys[1]*, MD, PhD, FESC

1. Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands; 2. Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands; 3. The Mayo Clinic, Rochester, MN, USA; 4. Medical City Dallas Hospital, Dallas, TX, USA; 5. Evanston Hospital, Evanston, IL, USA; 6. Institut Jacques Cartier, Massy, France; 7. Cardialysis BV, Rotterdam, The Netherlands; 8. University Hospital Uppsala, Uppsala, Sweden; 9. Boston Scientific Corporation, Natick, MA, USA; 10. San Raffaele Scientific Institute, Milano, Italy; 11. Herzzentrum, Leipzig, Germany; 12. Centre Hôpital Universitaire Rangueil, Toulouse, France

The references and also the accompanying supplementary data can be found in the online version of this paper at the following website: www.eurointervention.org

KEYWORDS

- CABG
- PCI
- SYNTAX Score
- CABG SYNTAX Score
- Leaman score

Abstract

Aims: The SYNTAX Score (SXscore) has established itself as an important prognostic tool in patients undergoing percutaneous coronary intervention (PCI). A limitation of the SXscore is the inability to differentiate outcomes in patients who have undergone prior coronary artery bypass graft (CABG) surgery. The CABG SXscore was devised to address this limitation.

Methods and results: In the SYNTAX-LE MANS substudy 115 patients with unprotected left main coronary artery disease (isolated or associated with one, two or three-vessel disease) treated with CABG were prospectively assigned to undergo a 15-month coronary angiogram. An independent core laboratory analysed the baseline SXscore prior to CABG. The 15-month CABG SXscore was calculated by a panel of three interventional cardiologists. The CABG SXscore was calculated by determining the standard SXscore in the "native" coronary vessels ("native SXscore") and deducting points based on the importance of the diseased coronary artery segment (Leaman score) that have a functioning bypass graft anastomosed distally. Points relating to intrinsic coronary disease, such as bifurcation disease or calcification, remain unaltered. The mean 15-month CABG SXscore was significantly lower compared to the mean baseline SXscore (baseline SXscore 31.6, SD 13.1; 15-month CABG SXscore 21.2, SD 11.1; $p<0.001$). Reproducibility analyses (kappa [k] statistics) indicated a substantial agreement between CABG SXscore measurements ($k=0.70$; 95% CI [0.50-0.90], $p<0.001$), with the points deducted to calculate the CABG SXscore the most reproducible measurement ($k=0.74$; 95% CI [0.53-0.95], $p<0.001$). Despite the limited power of the study, four-year outcome data (Kaplan-Meier curves) demonstrated a trend towards reduced all-cause death (9.1% vs. 1.8%, $p=0.084$) and death/CVA/MI (16.4% vs. 7.0%, $p=0.126$) in the low compared to the high CABG SXscore group.

Conclusions: In this pilot study the calculation of the CABG SXscore appeared feasible, reproducible and may have a long-term prognostic role in patients with complex coronary disease undergoing surgical revascularisation. Validation of this new scoring methodology is required.

**Corresponding author: Thoraxcenter, Ba583a, Erasmus MC , 's-Gravendijkwal 230, NL-3015 CE Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl*

Introduction

The SYNTAX Score (SXscore) (http://www.syntaxscore.com)[1-5] has established itself as an important prognostic tool in risk stratifying patients being considered for revascularisation, and has been validated in patients undergoing percutaneous coronary intervention (PCI) at one-year follow-up[6-11]. In addition, the SXscore has been applied to contemporary drug-eluting stent trials enrolling "all-comers" type populations, and has been shown to be an independent predictor of one-year mortality and major adverse cardiac events (MACE)[12-14].

As a consequence, the SXscore is now advocated in both the European and the US revascularisation guidelines in aiding the risk stratification of patients with complex coronary artery disease to the most appropriate revascularisation modality[15-17]. Furthermore, the US FDA (Food and Drug Administration) recommends the application of the SXscore in selecting low-intermediate SXscore patients with unprotected left main coronary artery disease in the ongoing EXCEL Trial (ClinicalTrials.gov Identifier: NCT01205776), and low SXscore patients suitable for transcatheter aortic valve implantation in the SURTAVI Trial (ClinicalTrials.gov Identifier: NCT01586910). However, a limitation of the SXscore is the inability to apply it usefully to patients who have previously undergone CABG.

Based on the principles first defined by Leaman et al (Leaman score)[18], the SXscore takes into account both the coronary anatomy and also the importance of the diseased coronary artery segment supplying the myocardium – termed "vessel-segment weighting". Although the baseline SXscore, calculated prior to surgical revascularisation, has been shown not to have any effect on the short to long-term prognosis after CABG[3,4,7,19,20], it was hypothesised that a suitably developed CABG SXscore that takes into account native coronary disease anatomy, including features such as calcification, bifurcation disease and the effects of surgical revascularisation on the vessel-segment weighting, may have potential clinical and research applications. The purpose of this pilot study is to examine the feasibility of the newly developed CABG SXscore in the SYNTAX-LE MANS angiographic substudy[21].

Methods

The overall study design of the all-comers SYNTAX Trial[3,5,22] and the SYNTAX-LE MANS substudy[21] have previously been described. In brief, SYNTAX-LE MANS was a predefined substudy of patients from the randomised SYNTAX Trial who provided a separate written, informed consent for the substudy entry[21]. Eligible patients were those with left main disease (isolated or associated with one, two or three-vessel disease) who did not have renal dysfunction (defined as creatinine >2.0 mg/dL [150 µmol/L]) or hypersensitivity to contrast agents that could not be adequately premedicated. Per protocol, the time window for the 15-month angiogram was set between 14 and 16 months post-allocation. Patients enrolled in the study who had a clinically driven angiogram from 9 to 13 months (inclusive) after treatment allocation were permitted to use the earlier coronary angiogram to fulfil the 15-month angiographic requirement.

CABG SYNTAX SCORE ANALYSIS

Baseline and 15-month coronary angiograms were analysed side by side by a panel of three interventional cardiologists to calculate the 15-month CABG SXscore. All reviewers were blinded to the clinical outcomes of the patient analyses and to the baseline SXscore, undertaken prior to CABG by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) as part of the original SYNTAX Trial[3].

The CABG SXscore calculation was repeated on 30 randomly selected cases at a three-month interval with the reviewers blinded to the original baseline and CABG SXscores. Intraobserver reproducibility analyses were undertaken.

CABG SYNTAX SCORE

The CABG SXscore is essentially the SXscore of the "native" coronary vessels ("native SXscore"), with points deducted based on the vessel-segment weighting of the bypassed coronary vessel as previously proposed by Leaman et al[18].

SYNTAX SCORE

In brief, the SXscore[1-4] was developed by combining the importance of a diseased coronary artery segment by the vessel-segment weighting (Leaman score)[18], adverse characteristics of such a lesion for revascularisation (ACC/AHA lesion classification)[23,24] and the Medina classification system for bifurcation lesions[25]. Each vessel segment, 1.5 mm in diameter or greater (**Figure 1**, labelled 1 to 16), with a ≥50% diameter stenosis by visual estimation, is awarded a multiplication factor related to coronary lesion location and severity **(Figure 2)**. Further characterisation of the coronary lesions leads to the addition of more points, which includes features of total occlusions (duration, length, blunt stump, presence of bridging collaterals or side branch), presence of bifurcation (based on the Medina classification) or trifurcation disease (number of diseased branches involved), side branch angulation, aorto-ostial lesion, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus and diffuse or small vessel disease. An online SXscore algorithm[1] automatically summates each of these features to calculate the final total SXscore.

LEAMAN SCORE

The Leaman score is based on the severity of luminal diameter narrowing, and is weighted according to the usual blood flow to the left ventricle (LV) in each vessel or vessel segment based on whether the coronary system is right or left dominant[18].

In a right dominant system the right coronary artery (RCA) supplies approximately 16% and the left coronary artery (LCA) approximately 84% of the blood flow to the LV. This 84% is normally directed 66% to the left anterior descending (LAD) and 33% to the left circumflex (LCx) vessels. Thus the LAD and LCx respectively carry approximately 3.5 times and 1.5 times as much blood as the RCA. In a left dominant system the LV receives all of its blood supply from the LCA; consequently, the RCA is not weighted and its value is assigned to the LCA, thereby leading to a heavier vessel-segment weighting of the LAD and LCx compared to a right dominant system[18,26-28]. These principles ultimately formed the basis of

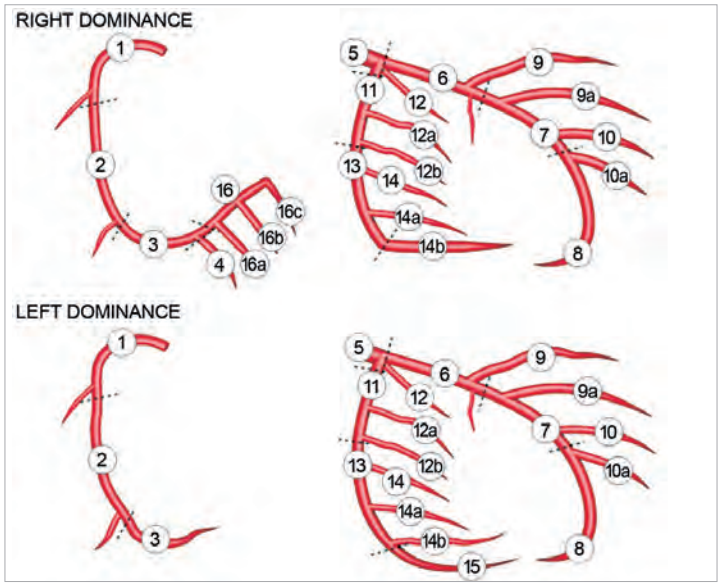


Figure 1. *The effect of right and left arterial dominance on the segment numbering – refer to Table 1 for the segment-weighting for the respective arterial segments. Anatomical description of the segment numbers has previously been described[2] and is included in the supplementary appendix.*

the segment-weighting factors that were incorporated into the SXscore **(Table 1)**[1-4].

CALCULATION OF THE CABG SYNTAX SCORE

In order to allow consistency and reproducibility in the application of the CABG SXscore, five rules were adhered to in calculating the CABG SXscore.

1. The SXscore of the native coronary vessels (native SXscore) was analysed using the standard methodology (http://www.syntaxscore.com)[1], utilising the bypass graft angiogram as necessary to allow visualisation of the entire vessel.
2. All the bypass grafts were analysed to establish the vessel-segment weighting of the "protection" conferred by the bypass grafts **(Figure 1, Table 1)**.
3. Based on the presence of obstructive or non-obstructive bypass disease by visual assessment, segment-weighting points were deducted from the native SXscore:
   a. Patent bypass graft to a significant coronary lesion: segment-weighting points for the coronary lesion were deducted, provided there was no intervening significant coronary disease **(Figure 3)**.

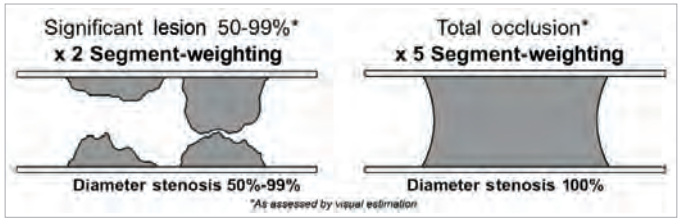


Figure 2. *Segment-weighting multiplication factors utilised in the SYNTAX Score – used to calculate the points required to deduct from the "native SXscore" to calculate the CABG SYNTAX Score.*

Table 1. Coronary vessel segment-weighting based on the principles first established by Leaman et al[18] and incorporated into the SYNTAX Score[2]. Refer to Figure 1 for location of segment numbers on the coronary tree based on arterial dominance.

Segment number	Right dominance	Left dominance
1 (RCA proximal)	1	0
2 (RCA mid)	1	0
3 (RCA distal)	1	0
4 (Posterior descending artery)	1	n/a
16 (Posterolateral branch from RCA)	0.5	n/a
16a (Posterolateral branch from RCA)	0.5	n/a
16b (Posterolateral branch from RCA)	0.5	n/a
16c (Posterolateral branch from RCA)	0.5	n/a
5 (Left main)	5	6
6 (LAD proximal)	3.5	3.5
7 (LAD mild)	2.5	2.5
8 (LAD apical)	1	1
9 (First diagonal)	1	1
9a (First diagonal)	1	1
10 (Second diagonal)	0.5	0.5
10a (Second diagonal)	0.5	0.5
11 (Proximal circumflex artery)	1.5	2.5
12 (Intermediate/anterolateral artery)	1	1
12a (Obtuse marginal)	1	1
12b (Obtuse marginal)	1	1
13 (Distal circumflex artery)	0.5	1.5
14 (Left posterolateral)	0.5	1
14a (Left posterolateral)	0.5	1
14b (Left posterolateral)	0.5	1
15 (Posterior descending artery)	n/a	1

RCA: right coronary artery; LAD: left anterior descending artery; n/a: not applicable

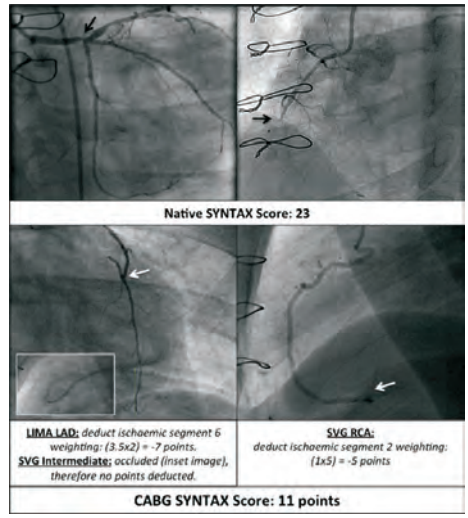


Figure 3. *Example of the calculation of the CABG SXscore in a patient with distal left main trifurcation disease and an occluded mid RCA. The native SXscore was 23 (upper images). A patent LIMA to the LAD with no intervening obstructive coronary disease (lower left image) led to the deduction of 3.5×2 points (x2 segment-weighting due to ischaemic LAD) from the native SXscore. An occluded SVG to the intermediate led to no points being deducted (inset lower left image). A patent SVG to the distal RCA led to 1×5 points (x5 segment-weighting due to occluded mid RCA) deducted from the native SXscore. Final CABG SXscore was therefore 23-7-5=11 points. LIMA: left internal mammary artery; SVG: saphenous vein graft; RCA: right coronary artery. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels*

b. Occluded bypass graft: native SXscore remained unaltered **(Figure 3)**.

c. Bypass graft with obstructive (50-99%) disease **(Figure 4)**:

i. obstructive native coronary lesion (50-99%): no segment-weighting points deducted;

ii. occluded native coronary lesion (100%, TIMI 0 flow): x3 segment-weighting points deducted.

With an obstructive native coronary lesion (50-99%), it is assumed that a significantly diseased graft (50-99%) would confer no additional benefit to the blood supply to the affected coronary vessel; consequently, there would be no net gain or loss in the segment-weighting points to the native SXscore. Conversely, if the coronary vessel was occluded, then a diseased graft (50-99%) would provide "ischaemic protection" to the territory supplied by the occluded lesion. Consequently, the segment-weighting factor would be reduced from x5 (occluded vessel) to x2 (non-occluded vessel with a significant lesion [50-99%]), i.e., a deduction of x3 segment-weighting factor from the native SXscore.

4. Any further native coronary disease clearly identified through the angiograms of the bypass grafts were added to the native SXscore. Lesions ≥3 reference vessel diameters were viewed as two separate lesions and within this distance as one lesion.
5. If an obstructive coronary lesion interferes with the blood flow to the vessel being protected by the bypass graft, then the points deducted were for the segment weighting of the lesion only **(Figure 5)**.

Points related to the lesion characteristics of the "native" coronary disease, such as calcification, bifurcation disease, total occlusion, etc., would remain unaltered as these reflect the native coronary anatomy. Further detail on the SXscore/Leaman score and applications of the CABG SXscore are provided in the Supplementary Appendix.

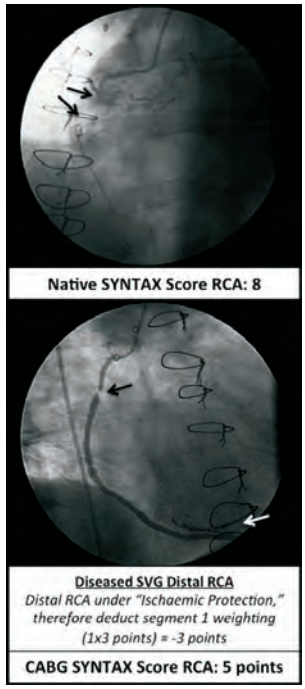


Figure 4. *Principle of "ischaemic protection" in the CABG SXscore. Upper image: occluded mid RCA (segment 2 - black arrows) with bridging collaterals: native SXscore for the RCA is 8. Lower image: SVG anastomosed to distal RCA (white arrow). If the SVG was free of obstructive disease then the CABG SXscore would be 8 minus (1×5)=3 points. If the SVG was diseased with an obstructive lesion as illustrated (lower image, black arrow) the distal RCA would be under "ischaemic protection". Consequently x2 weighting factor for the RCA should remain – therefore x3 weighting needs to be deducted leading to a CABG SXscore of 8 minus (1×3) points=5 points. If the SVG was occluded then the CABG SXscore would remain unaltered at 8 points. RCA: right coronary artery; SVG: saphenous vein graft*

STATISTICAL ANALYSIS

Continuous variables are expressed as means±SD. Comparisons of means and four-year outcomes (Kaplan-Meier curves) were performed with the paired t-test and log-rank test respectively. Intraobserver variability (tertile partitioning) was determined with kappa statistics (<0 none, 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-1.00 almost perfect) on the native SXscore, deducted points and CABG SXscore[4]. A two-sided p-value <0.05 was considered significant for all tests. Analyses were conducted with SAS System Software Version 8.0+ (SAS Institute, Cary, NC, USA) and SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 271 patients were enrolled in the SYNTAX-LE MANS study, 115 of whom were enrolled in the CABG arm. Available 15-month coronary angiograms were suitable for analysis in 113 of 115 (97.4%) CABG patients. No patients died in the CABG arm from baseline to undergoing the 15-month coronary angiogram. One patient had no angiographic films available and a further patient did not have native coronary vessels filmed. Baseline characteristics for the SYNTAX-LE MANS substudy have been published previously[21].

COMPARISONS OF THE BASELINE SYNTAX SCORE AND 15-MONTH CABG SYNTAX SCORE

Comparisons of the baseline SXscores and 15-month CABG SXscores demonstrated a significant decline in the mean value of the 15-month CABG SXscores **(Figure 6)**. Both the baseline SXscore and the 15-month CABG SXscore appeared to be broadly normally distributed with the mean 15-month CABG SXscore significantly moved to the left **(Figure 7)**. The mean 15-month CABG SXscore was significantly lower compared to the mean baseline SXscore (baseline SXscore 31.6, SD 13.1; 15-month CABG SXscore 21.2, SD 11.1; p<0.001) **(Figure 7)**.

Comparisons of the baseline SXscore and 15-month native SXscore did not demonstrate any significant statistical differences (baseline SXscore 31.6, SD 13.1; 15-month native SXscore 31.1, SD 12.2; p=0.50). The mean number of points deducted from the 15-month native SXscore to derive the CABG SXscore was 9.9 (SD 5.3) **(Figure 8)**.

REPRODUCIBILITY ANALYSES

The intraobserver variability for the 15-month native SXscore (k=0.70; 95% CI: 0.50-0.91, p<0.001), points deducted from the native SXscore to derive the 15-month CABG SXscore (k=0.74; 95% CI: 0.53-0.95, p<0.001) and the final 15-month CABG SXscore (k=0.70; 95% CI: 0.50-0.90, p<0.001) were all substantial. The number of points deducted to derive the 15-month CABG SXscore was the most reproducible measurement.

CLINICAL OUTCOMES

Due to limited power the present outcome analyses should be interpreted as exploratory and hypothesis-generating. The CABG SXscores were separated into two groups, divided by the median of the normally distributed 15-month CABG SXscores into low (0-21) (n=58) and high-risk groups (≥22) (n=55).

Four-year clinical outcome data demonstrated a trend towards an increased mortality in the high CABG SXscore group compared to the low CABG SXscore group (low CABG SXscore: 1.8%, high CABG SXscore: 9.1%, p=0.084) **(Figure 9)**. Furthermore, an increase in the composite of all-cause death/cerebrovascular accident (CVA)/ myocardial infarction (MI) at four years was also evident in the high CABG SXscore group compared to the low CABG SXscore group (low CABG SXscore: 7.0%, high CABG SXscore: 16.4%, p=0.126).

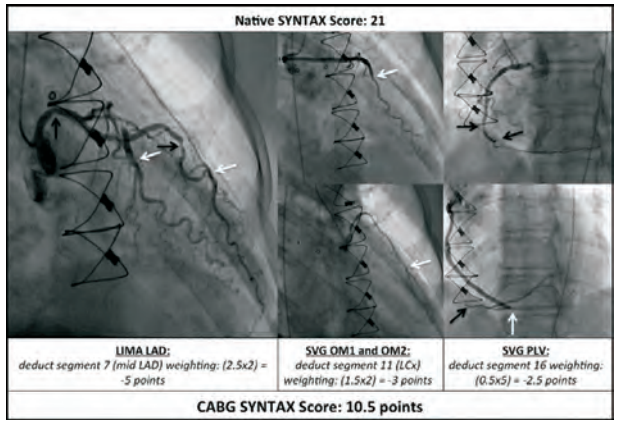


Figure 5. *Example of the calculation of the CABG SXscore in a patient with mid left main and two-vessel coronary disease. Native SXscore was 21. A patent LIMA anastomosed to the mid LAD, with upstream native mid LAD disease, and led to the segment-weighting (2.5×2 points) of the mid LAD (segment 7) being deducted from the native SXscore (left image). The LCx was protected by two OM SVGs leading to a deduction of 1.5×2 points from the native SXscore (middle image). The occluded PLV was protected by an SVG leading to the deduction of 0.5×5 points from the native SXscore (right image). Final CABG SXscore was therefore 21-5-3-2.5=10.5 points. LAD: left anterior descending artery; LCx: left circumflex; OM: obtuse marginal; RCA: right coronary artery; PLV: posterior left ventricular branch of the RCA; LIMA: left internal mammary artery; SVG saphenous vein graft. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels.*

Notably, the Kaplan-Meier curves for all clinical outcomes in the low and high CABG SXscores did not start to separate until after one year of follow-up, with continued separation of the curves up to four years of follow-up. A peak in the incidence of all-cause

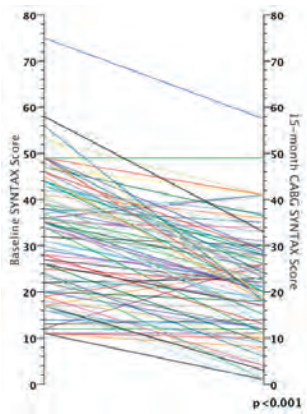


Figure 6. *Reduction in the CABG SYNTAX Score at scheduled coronary angiography at 15 months, compared to the baseline SYNTAX Score (n=113).*

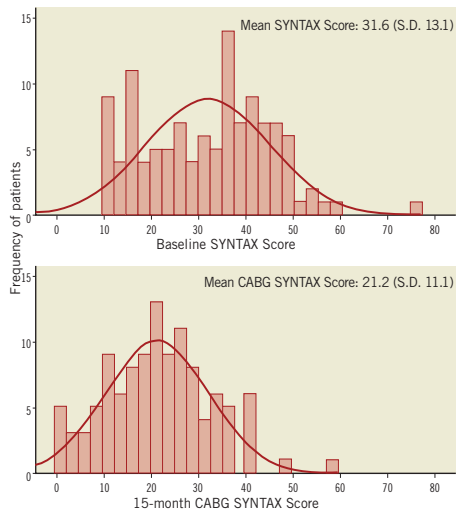


Figure 7. *Distribution of the baseline SYNTAX Scores and the 15-month CABG SYNTAX Scores (n=113). Note the significant decrease in the mean CABG SYNTAX Score compared to the mean baseline SYNTAX Score (p<0.001). SD: standard deviation.*

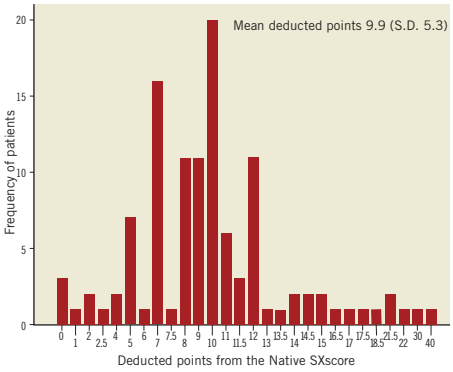


Figure 8. *Distribution of the deducted points from the native SXscore to calculate the CABG SXscore (n=113). SD: standard deviation.*

revascularisation was observed at approximately 15 months secondary to the scheduled study coronary angiogram triggering repeat revascularisation **(Figure 9)**.

Discussion

The main findings of this pilot study are: 1) that the application of the newly developed CABG SXscore appears feasible; 2) that the 15-month CABG SXscore demonstrated a significant decrease in value compared to the baseline SXscore (prior to CABG), secondary to a deduction in points attributed to the segment-weighting of the revascularised coronary vessels; 3) that the CABG SXscore appears to be a reproducible technique when performed by a panel of interventional cardiologists experienced in the reporting of the SXscore; 4) that the deduction of the segment-weighting related points due to the presence of bypass grafts was the most reproducible technique; and 5) that the CABG SXscore may have a long-term prognostic role. Further validation of this newly developed score is required.

The findings from this present study are consistent with the methodology adopted by Leaman et al when applying the Leaman score to patients pre and post CABG[18], namely that the segment-weighting for the treated vessel would be deducted if it had a functioning bypass graft anastomosed distal to the treated lesion. In comparison to the baseline SXscore, a clear and significant reduction in the 15-month CABG SXscore was evident. The main difference between the CABG SXscore and the Leaman score was that the points relating to lesion characteristics in the CABG SXscore remained.

One of the unavoidable limitations of the present study was that the coronary angiograms were taken 15 months post CABG and the results compared to the baseline SXscore taken prior to surgery. The mean baseline SXscore and the 15-month native SXscore did however not differ significantly (baseline SXscore 31.6, SD 13.1; 15-month native SXscore 31.1, SD 12.2; p=0.50), making the potential effects of native coronary disease progression at 15 months likely to be of lesser significance.

Conversely, as reported in the SYNTAX-LE MANS substudy, over a quarter of the CABG patients (27.2%) had a significantly diseased (≥50% to <100%) or obstructed (100%) bypass graft at 15 months[21]. These findings may have led to the underestimation of the 15-month CABG SXscore compared to if the CABG SXscore had been performed post CABG surgery. Although it has previously been reported that early bypass graft occlusion rates may be associated

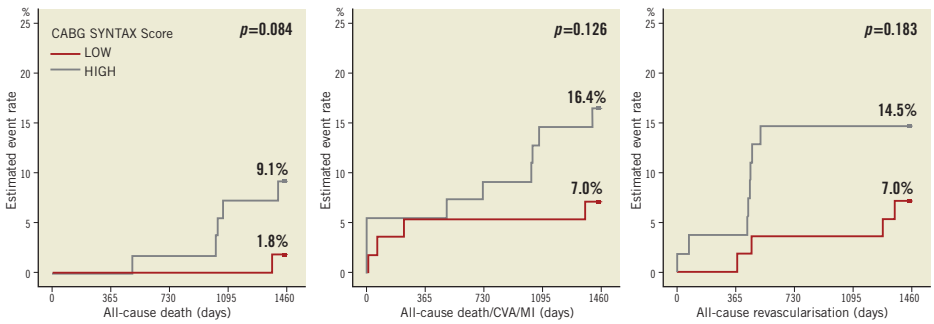


Figure 9. *Clinical outcomes separated by the median of the CABG SYNTAX Score into low (0-21) (n=58) and high (≥22) (n=55) score groups. A non-significant trend towards higher mortality (left image) and all-cause death/CVA/MI (middle image) were evident in the high CABG SYNTAX Score group at four years. The peak in repeat all-cause revascularisation between years one and two (right image) were secondary to patients undergoing scheduled coronary angiography, the findings of which triggered repeat revascularisation. CVA: cerebrovascular accident; MI: myocardial infarction*

with adverse clinical events[29-31], the reported loss of the bypass grafts in SYNTAX-LE MANS were not significantly associated with early MACCE[21].

It may be speculated that a proportion of these bypass grafts may potentially have been unnecessary. Early bypass graft patency rates for functionally significant native coronary lesions have been shown to be significantly higher compared to those for bypass grafts with functionally insignificant native coronary lesions[32-34]. Furthermore, angiographically defined percentage diameter stenoses or the minimum lumen diameter of native coronary vessels[29,35] and grafts that have competitive filling with the treated native vessel[36,37] have been shown to be predictors of insufficient flow and/or early graft failure. Consequently, despite the limitations, the 15-month CABG SXscore may potentially be representative of patients who have been surgically revascularised at baseline.

ASSOCIATION OF THE CABG SYNTAX SCORE WITH CLINICAL OUTCOMES

The SXscore taken prior to surgery has consistently been shown not to have any significant effect on the short to long-term prognosis after CABG[2-4,7,19,20]. It has previously been suggested that this observation may be related to the fact that bypass grafts are anastomosed distal to the proximal disease regardless of the complexity of the native coronary disease, providing there are suitable graftable targets[4,38]. With the CABG SXscore this concept is potentially challenged, with the observation of a non-significant trend towards a higher longer-term mortality and death/MI/CVA in the high (compared to the low) CABG SXscore group. MACCE was not examined as the 15-month scheduled coronary angiogram triggered repeat revascularisation **(Figure 9)**.

PREVIOUS STUDIES

Alderman et al[39] previously demonstrated in The Bypass Angioplasty Revascularisation Investigation (BARI) trial – consisting of patients treated with percutaneous or surgical revascularisation who underwent entry and five-year coronary angiographic follow-up – that native coronary disease progression (and not the extent of initial revascularisation) was the predominant determinant of the recurrence of angina and jeopardised myocardium at five years. Notably within the BARI Trial two thirds of the increase in myocardial jeopardy at five years was in previously untreated coronary vessels.

Although other studies have suggested that incomplete surgical revascularisation may be associated with short and long-term adverse outcomes[40,41], further predominantly more contemporary studies have suggested that "reasonable" incomplete surgical revascularisation does not have an adverse effect on long-term clinical outcomes[42-45]. Furthermore, the long-term survival of patients treated with surgical revascularisation in the CASS (Coronary Artery Surgery Study)[46] and Rotterdam[47] registries has been shown to be associated with more extensive preoperative coronary disease, which in turn was linked to the higher prevalence and severity of other clinical risk factors.

In addition, the Duke graft index[48] – an anatomical-based scoring system for patients who had previously undergone CABG – was demonstrated to be significantly more associated with long-term prognosis compared to the native coronary anatomy prior to CABG. Remarkably, the Duke graft index had a design concept that in principle was similar to the CABG SXscore, namely associating anatomical coronary disease (Duke Graft index: based on the number of diseased coronary territories; CABG SXscore: a more sophisticated assessment of the coronary anatomy as previously described) with the level of protection to the diseased territories conferred by bypass grafts in both scores.

IMPLICATIONS OF THE CABG SYNTAX SCORE FOR CLINICAL PRACTICE

The CABG SXscore may thus be regarded as both a marker of anatomical coronary disease complexity, and of the degree of revascularisation secondary to the deduction of segment-weighting points related to the bypass grafts. Furthermore, it may be speculated that the CABG SXscore consisting of anatomical characteristics of the coronary vessel – such as bifurcation disease, calcification, total occlusions, etc. – may reflect the clinical risk profile of the patient and the likelihood of native coronary (and possibly non-coronary as detailed below) atherosclerotic disease progression which, importantly, may actually target the bypass grafts.

It has previously been suggested that the SXscore is a marker of patients with a more adverse clinical risk profile who have evidence of systemic atherosclerotic disease, and are thus at greater longer-term cardiovascular and cerebrovascular risk[19,20,49]. This hypothesis is supported by the significant and direct relationship of the 10-year predicted Framingham risk scores with the prevalence and magnitude of coronary artery calcium scores[50]. In addition, the ankle-brachial index[51-54] and common carotid intima-media thickness[55-58], both markers of extra-cardiac disease, have been correlated with the severity of coronary artery disease and even clinical events.

Notably, the clinical outcomes in the present study did not start to separate until after one year, and continued to separate at up to four years **(Figure 9)**. It may be further hypothesised that the curves would continue to separate in the longer term where the clinical manifestations of continued native atherosclerotic coronary disease progression, and importantly bypass graft disease progression particularly with SVG, would become more apparent. Consistent with these hypotheses are the findings that SVGs have been shown to be protective in the first seven years, and that thereafter mortality increases significantly in parallel to the gradual loss of SVG patency[47,59].

POTENTIAL CLINICAL AND RESEARCH APPLICATIONS OF THE CABG SYNTAX SCORE

Potential clinical applications of the CABG SXscore include long-term risk stratification of patients who have previously undergone CABG to aid in the identification of a group at high risk for future clinical events and repeat revascularisation. Even without the use of a CABG SXscore, it may be further postulated that higher SXscore

patients may benefit more from undergoing revascularisation with more durable grafts that have a proven long-term patency (e.g., LIMA and RIMA) compared to SVG[60,61].

Although aggressive risk factor control would undoubtedly improve the prognosis of all these patients, perhaps future study may target patients with a higher SXscore/CABG SXscore who may potentially benefit from more aggressive risk factor control with established and emerging drugs that cause atherosclerotic disease regression.

Other potential applications of the CABG SXscore in a research setting include the allowance of the incorporation of CABG patients into contemporary stent trials measuring the SXscore, where such patients are at present excluded.

STUDY LIMITATIONS

As previously discussed, apart from the time frame at which the CABG SXscore was taken, the main limitation of this study is that there was limited power to examine long-term clinical outcomes. Despite this limitation, a non-significant trend towards more adverse clinical outcomes in the higher CABG SXscore group was seen, which is further supported by the concept of the Duke graft index, as previously discussed[48].

One other limitation is that the CABG SXscore does not account for the type of graft anastomosed and the characteristics of the graft disease (if present), except if there is obstructive graft disease or not. This is perhaps more notable with the LIMA bypass graft given its proven higher long-term patency rates compared to other types of bypass graft[60,61]. The hypothesis central to the CABG SXscore does, however, relate to the native SXscore and its apparent association with clinical comorbidity, with the additional "protection" conferred by the bypass grafts. Furthermore, reducing the CABG SXscore by an arbitrary number of points based on the type and numerous anatomical complexities of the bypass graft would substantially increase the complexity of the analyses, making this impractical.

FUTURE DIRECTIONS

Potentially, the integration of the CABG SXscore into an online algorithm, as is currently available with the SXscore[1], may serve to simplify the calculation of the CABG SXscore. The functional SYNTAX Score – a fractional flow reserve (FFR) guided SYNTAX scoring methodology – has recently been demonstrated to improve the diagnostic accuracy of the SXscore[62]. Furthermore, the feasibility of undertaking non-invasive anatomical and fractional flow measurements has since been proven, utilising computational fluid dynamics applied to coronary computed tomography (CT) angiography[63]. The application of this emerging technology to the CABG SXscore may improve the diagnostic accuracy and reproducibility of the CABG SXscore. In addition, the non-invasive combined coronary CT and FFR technology may potentially allow for the automatic adjustment of the vessel-segment weighting for coronary vessels based on actual measured blood flow, in order to calculate a more "physiological" functional CABG SXscore.

Conclusion

The calculation of the CABG SXscore is feasible, reproducible and may have a long-term prognostic role in the assessment of risk in patients undergoing coronary artery bypass grafting. Confirmation and validation of the findings from this pilot study are required in larger studies.

Acknowledgements

The authors express their gratitude to all of the study centres and participants whose work made this study possible. Furthermore, thanks go to Peggy Pereda and Jian Huang of Boston Scientific for their invaluable support in accessing the study database. The authors thank Ana Guimarães of Cardialysis for her technical support in producing the images.

Funding sources

The SYNTAX Trial was funded by Boston Scientific.

Conflict of interest statement

K.D. Dawkins is a full-time employee in Boston Scientific and holds stock in Boston Scientific. M. Mack has served on the Speakers' Bureau of Boston Scientific, Cordis and Medtronic. T. Feldman reported serving on the Speakers' Bureau of Boston Scientific, receiving grant support from Abbott, Atritech, BSC, Edwards, Evalve, and consulting for Abbott, Coherex, Intervalve, Square One, WL Gore. M. Morice reported that her institution received a research grant from Boston Scientific. M.A. Morel, M. van der Brand and G.A. van Es are employees of Cardialysis BV, The Netherlands. The other authors have no conflict of interest to declare.

References

The references can be found on the online version of the paper.

Online data supplement

Supplementary appendix. Detailed description of SYNTAX and Leaman scores, and further case examples applying the CABG SXscore.

Online data supplement

References

1. SYNTAX score calculator: http://www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.

2. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1:219-27.

3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-72.

4. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention.* 2009;5:50-6.

5. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Ståhle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J.* 2011;32:2125-34.

6. Park DW, Kim YH, Yun SC, Song HG, Ahn JM, Oh JH, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol.* 2011;57:2152-9.

7. Chakravarty T, Buch MH, Naik H, White AJ, Doctor N, Schapira J, Mirocha JM, Fontana G, Forrester JS, Makkar R. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol.* 2011;107:360-6.

8. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patané M, Tamburino C, Tolaro S, Patané L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv.* 2009;2:731-8.

9. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts outcome of surgery for left main disease. *Ann Thorac Surg.* 2009;87:1097-104; discussion 1104-5.

10. Lemesle G, Bonello L, de Labriolle A, Steinberg DH, Roy P, Pinto Slottow TL, Torguson R, Kaneshige K, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cardiovasc Interv.* 2009;73:612-7.

11. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G; ARTS II. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol.* 2007;99:1072-81.

12. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol.* 2010;56:272-7.

13. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. *J Am Coll Cardiol.* 2011;57:2389-97.

14. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Räber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient-level pooled analysis assessing the impact of the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. *JACC Cardiovasc Interv.* 2011;4:645-53.

15. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for

Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2010;31:2501-55.

16. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44-122.

17. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2011;58:e123-210.

18. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation.* 1981;63:285-99.

19. Serruys PW, Farooq V, Vranckx P, Brugaletta S, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Ståhle E, Colombo A, Pereda P, Huang J, Morel MA, van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. The SYNTAX Trial at 3 Years: a Global Risk approach to identify patients with 3-vessel and/or left main stem disease who could safely and efficaciously be treated with percutaneous coronary intervention. Part 1: the randomised population. Presented at: TCT, San Francisco, USA, 8 Nov 2011.

20. Farooq V, Serruys PW, Vranckx P, Brugaletta S, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Ståhle E, Colombo A, Pereda P, Huang J, Morel MA, van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. The SYNTAX trial at 3 years: a Global Risk approach to identify patients with 3-vessel and/or left main stem disease who could safely and efficaciously be treated with percutaneous coronary intervention. Part 2: The 'All-Comers' population. Presented at: TCT, San Francisco, USA, 8 Nov 2011.

21. Morice MC, Feldman TE, Mack MJ, Ståhle E, Holmes DR, Colombo A, Morel MA, van den Brand M, Serruys PW, Mohr F, Carrié D, Fournial G, James S, Leadley K, Dawkins KD, Kappetein AP. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with TAXUS express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). *EuroIntervention.* 2011;7:670-9.

22. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J.* 2006;151:1194-204.

23. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol.* 2006;47:e1-121.

24. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Cheitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation.* 1999;99:2345-57.

25. Medina A, Suárez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol.* 2006;59:183.

26. Kalbfleisch H, Hort W. Quantitative study on the size of coronary artery supplying areas postmortem. *Am Heart J.* 1977;94:183-8.

27. Dwyer EM Jr, Dell RB, Cannon PJ. Regional myocardial blood flow in patients with residual anterior and inferior transmural infarction. *Circulation.* 1973;48:924-35.

28. Ross RS, Ueda K, Lichtlen PR, Rees JR. Measurement of Myocardial Blood Flow in Animals and Man by Selective Injection of Radioactive Inert Gas into the Coronary Arteries. *Circ Res.* 1964;15:28-41.

29. Desai ND, Naylor CD, Kiss A, Cohen EA, Feder-Elituv R, Miwa S, Radhakrishnan S, Dubbin J, Schwartz L, Fremes SE. Impact of patient and target-vessel characteristics on arterial and venous bypass graft patency: insight from a randomized trial. *Circulation.* 2007;115:684-91.

30. Cho KR, Kim JS, Choi JS, Kim KB. Serial angiographic follow-up of grafts one year and five years after coronary artery bypass surgery. *Eur J Cardiothorac Surg.* 2006;29:511-6.

31. Alexander JH, Hafley G, Harrington RA, Peterson ED, Ferguson TB Jr, Lorenz TJ, Goyal A, Gibson M, Mack MJ, Gennevois D, Califf RM, Kouchoukos NT; PREVENT IV Investigators. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA.* 2005;294:2446-54.

32. Botman CJ, Schonberger J, Koolen S, Penn O, Botman H, Dib N, Eeckhout E, Pijls N. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg.* 2007;83:2093-7.

33. Bech GJ, Droste H, Pijls NH, De Bruyne B, Bonnier JJ, Michels HR, Peels KH, Koolen JJ. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart.* 2001;86:547-52.

34. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation.* 2009;120:1505-12.

35. Berger A, MacCarthy PA, Siebert U, Carlier S, Wijns W, Heyndrickx G, Bartunek J, Vanermen H, De Bruyne B. Long-term patency of internal mammary artery bypass grafts: relationship with preoperative severity of the native coronary artery stenosis. *Circulation.* 2004;110:II36-40.

36. Nakajima H, Kobayashi J, Toda K, Fujita T, Shimahara Y, Kasahara Y, Kitamura S. A 10-year angiographic follow-up of competitive flow in sequential and composite arterial grafts. *Eur J Cardiothorac Surg.* 2011;40:399-404.

37. Bezon E, Choplain JN, Maguid YA, Aziz AA, Barra JA. Failure of internal thoracic artery grafts: conclusions from coronary angiography mid-term follow-up. *Ann Thorac Surg.* 2003;76:754-9.

38. Mohr FW, Rastan AJ, Serruys PW, Kappetein AP, Holmes DR, Pomar JL, Westaby S, Leadley K, Dawkins KD, Mack MJ. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. *J Thorac Cardiovasc Surg.* 2011;141:130-40.

39. Alderman EL, Kip KE, Whitlow PL, Bashore T, Fortin D, Bourassa MG, Lesperance J, Schwartz L, Stadius M. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol.* 2004;44:766-74.

40. Buda AJ, Macdonald IL, Anderson MJ, Strauss HD, David TE, Berman ND. Long-term results following coronary bypass operation. Importance of preoperative actors and complete revascularization. *J Thorac Cardiovasc Surg.* 1981;82:383-90.

41. Kleisli T, Cheng W, Jacobs MJ, Mirocha J, Derobertis MA, Kass RM, Blanche C, Fontana GP, Raissi SS, Magliato KE, Trento A. In the current era, complete revascularization improves survival after coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* 2005;129:1283-91.

42. Kim YH, Park DW, Lee JY, Kim WJ, Yun SC, Ahn JM, Song HG, Oh JH, Park JS, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. *Circulation.* 2011;123:2373-81.

43. Rastan AJ, Walther T, Falk V, Kempfert J, Merk D, Lehmann S, Holzhey D, Mohr FW. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? *Circulation.* 2009;120:S70-7.

44. Srinivas VS, Selzer F, Wilensky RL, Holmes DR, Cohen HA, Monrad ES, Jacobs AK, Kelsey SF, Williams DO, Kip KE. Completeness of revascularization for multivessel coronary artery disease and its effect on one-year outcome: a report from the NHLBI Dynamic Registry. *J Interv Cardiol.* 2007;20:373-80.

45. Dauerman HL. Reasonable incomplete revascularization. *Circulation.* 2011;123:2337-40.

46. Myers WO, Blackstone EH, Davis K, Foster ED, Kaiser GC. CASS Registry long term surgical survival. Coronary Artery Surgery Study. *J Am Coll Cardiol.* 1999;33:488-98.

47. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. *Eur Heart J.* 2009;30:453-8.

48. Liao L, Kong DF, Shaw LK, Sketch MH Jr, Milano CA, Lee KL, Mark DB. A new anatomic score for prognosis after cardiac catheterization in patients with previous bypass surgery. *J Am Coll Cardiol.* 2005;46:1684-92.

49. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart.* 2011;97:1902-13.

50. Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, Lloyd-Jones DM. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol.* 2011;57:1838-45.

51. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008;300:197-208.

52. Otah KE, Madan A, Otah E, Badero O, Clark LT, Salifu MO. Usefulness of an abnormal ankle-brachial index to predict presence of coronary artery disease in African-Americans. *Am J Cardiol.* 2004;93:481-3.

53. Sukhija R, Aronow WS, Yalamanchili K, Peterson SJ, Frishman WH, Babu S. Association of ankle-brachial index with severity of angiographic coronary artery disease in patients with peripheral arterial disease and coronary artery disease. *Cardiology.* 2005;103:158-60.

54. Papamichael CM, Lekakis JP, Stamatelopoulos KS, Papaioannou TG, Alevizaki MK, Cimponeriu AT, Kanakakis JE, Papapanagiotou A, Kalofoutis AT, Stamatelopoulos SF. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. *Am J Cardiol.* 2000;86:615-8.

55. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med.* 1998;128:262-9.

56. Adams MR, Nakagomi A, Keech A, Robinson J, McCredie R, Bailey BP, Freedman SB, Celermajer DS. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. *Circulation.* 1995;92:2127-34.

57. Steinvil A, Sadeh B, Arbel Y, Justo D, Belei A, Borenstein N, Banai S, Halkin A. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol.* 2011;57:779-83.

58. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. *Eur Heart J.* 2012;33:113-9.

59. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol.* 1996;28:616-26.

60. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W; VA Cooperative Study Group #207/297/364. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol.* 2004;44:2149-56.

61. Ruttmann E, Fischler N, Sakic A, Chevtchik O, Alber H, Schistek R, Ulmer H, Grimm M. Second internal thoracic artery versus radial artery in coronary artery bypass grafting: a long-term, propensity score-matched follow-up study. *Circulation.* 2011;124:1321-9.

62. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF; FAME Study Investigators. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol.* 2011;58:1211-8.

63. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol.* 2011;58:1989-97.

Scores

LEAMAN SCORE

The Leaman Score[64] is based on the severity of luminal diameter narrowing and is weighted according to the usual blood flow to the left ventricle in each vessel or vessel segment. In a right dominant system, the right coronary artery (RCA) supplies approximately 16% and the left coronary artery approximately 84% of the blood flow to the left ventricle. This 84% is normally directed 66% towards the left anterior descending (LAD) and 33% to the left circumflex (LCx) vessels. Consequently, the LMS, LAD and LCx supply approximately x5, x3.5 (84/16 x0.66) and x1.5 respectively as much blood as the RCA to the left ventricle, the values of which are designated as the respective vessel's segment-weighting factors. In a left dominant system, the RCA does not contribute to the blood supply of the left ventricle, which is instead supplied by the LCx. Thus the LMS supplies 100% of the blood flow to the left ventricle. Hence the LAD provides 58% (segment-weighting factor x3.5) and the LCx 42% (segment-weighting factor x2.5) of the total blood flow to the LV. These concepts ultimately formed the basis of the segment-weighting factors that were incorporated into the now validated SXscore[65-73].

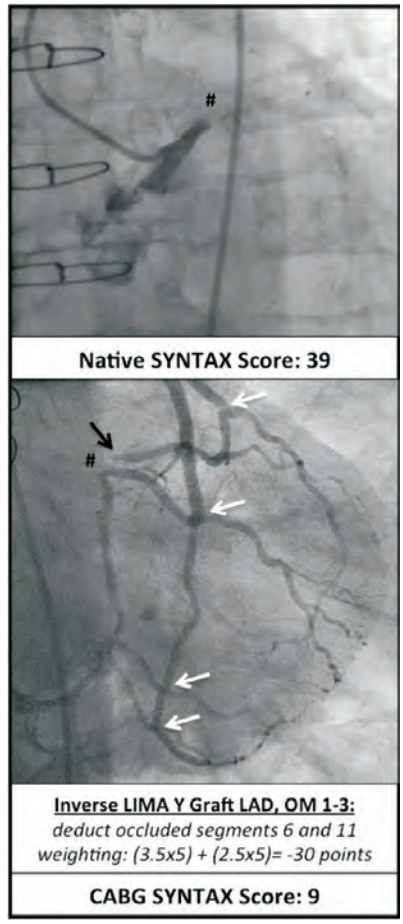
APPLICATION OF THE LEAMAN SCORE IN PATIENTS UNDERGOING CABG. Leaman et al previously applied the Leaman Score, derived from the segment-weighting factors, to patients at baseline and post CABG surgery[64]. This concept was based on the principle that the segment-weighting for the treated vessel would be deducted if it had a functioning bypass graft anastomosed distal to the treated lesion. For example, a significant mid RCA lesion would score a segment-weighting factor of 1x2 (2 points) if the lesion was significantly (non-total) diseased, or 1x5 (5 points) if the lesion was occluded. Post-surgery, if the graft to the RCA was patent, the respective segment-weighting points for the treated vessel would be deducted. Conversely, if the graft was occluded, the points would remain unaltered.

SYNTAX SCORE

The SXscore methodology has previously been described[74-77]. In brief, the SXscore was developed by combining the importance of a diseased coronary artery segment by the vessel-segment weighting (modified Leaman Score)[64], adverse characteristics of such a lesion for revascularisation (ACC/AHA lesion classification)[78,79] and the Medina classification system for bifurcation lesions[80,81].

Each vessel segment, 1.5 mm in diameter or greater, with a ≥50% diameter stenosis by visual estimation, is awarded a multiplication factor related to the location of the lesion, and the severity of the stenosis (non-total vs. total occlusion). Further characterisation of the coronary lesions leads to the addition of more points. These include features of total occlusions (duration, length, blunt stump, presence of bridging collaterals or side branch), the presence of bifurcation (based on the Medina classification) or trifurcation disease (number of diseased branches involved), side branch angulation, aorto-ostial lesion, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus and diffuse or small vessel disease. The above information is entered into the online available SXscore algorithm[75] which automatically sums each of these features to calculate the total SXscore.

DEFINITIONS OF VESSEL SEGMENTS. A table of vessel segments relating to the SYNTAX Score is detailed hereafter **(Online Table 1)**.



Online Figure 1. *Example of the calculation of the CABG SXscore in a patient with an occluded LMS. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels, # occluded LMS. LMS: left main stem; RCA: right coronary artery; LIMA: left internal mammary artery; OM: obtuse marginal; LAD: left anterior descending artery; SVG: saphenous vein graft*

Table 1. Definitions of segments.

1.	RCA proximal	From ostium to one half the distance to the acute margin of the heart.
2.	RCA mid	From end of first segment to acute margin of heart.
3.	RCA distal	From the acute margin of the heart to the origin of the posterior descending artery.
4.	Posterior descending artery	Running in the posterior interventricular groove.
16.	Posterolateral branch from RCA	Posterolateral branch originating from the distal coronary artery distal to the crux.
16a.	Posterolateral branch from RCA	First posterolateral branch from segment 16.
16b.	Posterolateral branch from RCA	Second posterolateral branch from segment 16.
16c.	Posterolateral branch from RCA	Third posterolateral branch from segment 16.
5.	Left main	From the ostium of the LCA through bifurcation into left anterior descending and left circumflex branches.
6.	LAD proximal	Proximal to and including first major septal branch.
7.	LAD mid	LAD immediately distal to origin of first septal branch and extending to to the point where LAD forms an angle (RAO view). If this angle is not identifiable this segment ends at one half the distance from the first septal to the apex of the heart.
8.	LAD apical	Terminal portion of LAD, beginning at the end of previous segment and extending to or beyond the apex.
9.	First diagonal	The first diagonal originating from segment 6 or 7.
9a.	First diagonal a	Additional first diagonal originating from segment 6 or 7, before segment 8.
10.	Second diagonal	Second diagonal originating from segment 8 or the transition between segment 7 and 8.
10a.	Second diagonal a	Additional second diagonal originating from segment 8.
11.	Proximal circumflex artery	Main stem of circumflex from its origin of left main to and including origin of (first and second) obtuse marginal branch(es).
12.	Intermediate/ anterolateral artery	Branch from trifurcating left main other than proximal LAD or LCx. Belongs to the circumflex territory.
12a.	Obtuse marginal a	First side branch of circumflex running in general to the area of obtuse margin of the heart.
12b.	Obtuse marginal b	Second additional branch of circumflex running in the same direction as 12.
13.	Distal circumflex artery	The stem of the circumflex distal to the origin of the most distal obtuse marginal branch and running along the posterior left atrioventricular grooves. Calibre may be small or artery absent.
14.	Left posterolateral	Running to the posterolateral surface of the left ventricle. May be absent or a division of obtuse marginal branch.
14a.	Left posterolateral a	Distal from 14 and running in the same direction.
14b.	Left posterolateral b	Distal from 14 and 14a and running in the same direction.
15.	Posterior descending	Most distal part of dominant left circumflex when present. Gives origin to septal branches. When this artery is present, segment 4 is usually absent.

Further illustrative examples of the application of the CABG SXscore

CASE 1

Occluded LMS (#) in a left dominant system gave a native SXscore of 39 (upper image). The ostial involvement of the LAD (black arrow) was regarded as part of the LMS lesion as it was located within ≥3 vessel reference diameters from the occluded LMS lesion. A patent LIMA inverse Y graft anastomosed to the mid LAD (upper white arrow), with sequential anastomoses to the 1st, 2nd and 3rd OM branches (lower three white arrows) are shown. Based on the segment-weighting 30 points were deducted from the native SXscore. Final CABG SXscore was therefore 39–17.5–12.5=9 points **(Online Figure 1)**.

CASE 2

Upper images: native SXscore was 35.5 with distal LMS disease (Medina 1.1.1), distal RCA disease, and an occluded ostial LCx (#). Lower images: distal RCA protected by SVG (left image), therefore 1x2 points were deducted from the native SXscore. Occluded ostial LCx is under "ischaemic protection" by the RIMA to the distal OM (middle image) secondary to disease more proximal to the anastomosis. Therefore 1.5x3 points are deducted from the native SXscore (no points are added for the OM disease as it is protected by the RIMA graft). The ostial LAD disease is protected by the LIMA (right image) anastomosed to the distal LAD with no intervening obstructive disease, so 3.5x2 points are deducted from the native SXscore. Final CABG SXscore was therefore 35.5–2–4.5–7=22 points **(Online Figure 2)**.

References

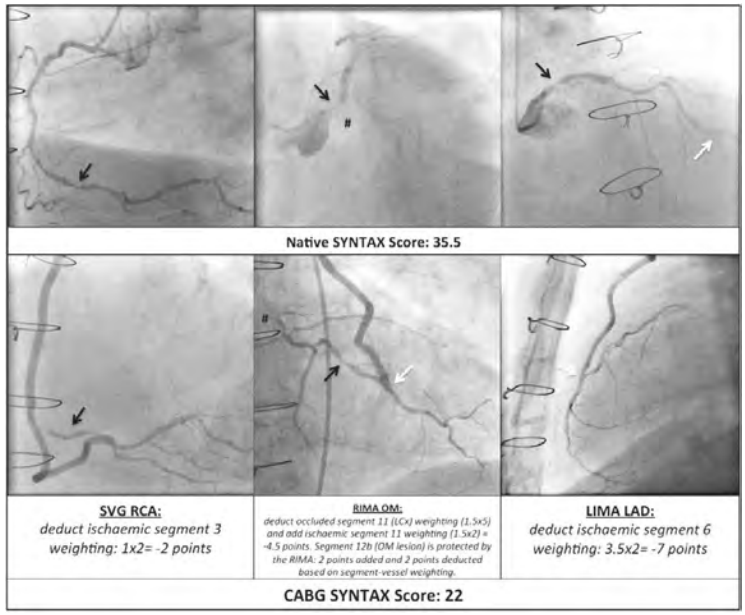
64. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation.* 1981;63:285-99.

65. Park DW, Kim YH, Yun SC, Song HG, Ahn JM, Oh JH, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol.* 2011;57:2152-9.

66. Chakravarty T, Buch MH, Naik H, White AJ, Doctor N, Schapira J, Mirocha JM, Fontana G, Forrester JS, Makkar R. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *J Am Coll Cardiol.* 2011;107:360-6.

67. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv.* 2009;2:731-8.

68. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts out-



Online Figure 2. *Example of the calculation of the CABG SXscore in a complex case. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels. LMS: left main stem; RCA: right coronary artery; LIMA: left internal mammary artery; RIMA: right internal mammary artery; LCx: left circumflex; OM: obtuse marginal; LAD: left anterior descending artery; SVG: saphenous vein graft*

come of surgery for left main disease. *Ann Thorac Surg.* 2009;87:1097-104; discussion 1104-5.

69. Lemesle G, Bonello L, de Labriolle A, Steinberg DH, Roy P, Pinto Slottow TL, Torguson R, Kaneshige K, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cardiovasc Interv.* 2009;73:612-7.

70. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G; ARTS II. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol.* 2007;99:1072-81.

71. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol.* 2010;56:272-7.

72. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. *J Am Coll Cardiol.* 2011;57:2389-97.

73. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Raber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient-level pooled analysis assessing the impact of the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. *JACC Cardiovasc Interv.* 2011;4:645-53.

74. Sianos G, Morel MA, A.P. K, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005; 1:219-27.

75. SYNTAX score calculator: http://www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.

76. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-72.

77. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention.* 2009;5:50-6.

78. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB, 3rd, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol.* 2006;47:e1-121.

79. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Cheitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation.* 1999;99:2345-57.

80. Topol EJ. Textbook of Interventional Cardiology, 3rd ed. Philadelphia: WB Saunders; 1999.

81. Medina A, Suarez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol.* 2006;59:183.

Chapter 3.3

The coronary artery bypass graft SYNTAX Score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy

Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia Garcia HM, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Ståhle E, James S, Carrié D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW

EuroIntervention. 2013;9(8):1009-1010 (Impact Factor: 3.173)

The coronary artery bypass graft SYNTAX Score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy

Vasim Farooq[1], MBChB, MRCP; Chrysafios Girasis[1], MD; Michael Magro[1], MD; Yoshinobu Onuma[1], MD; Marie-Angèle Morel[2], BSc; Jung Ho Heo[1], MD; Hector M. Garcia-Garcia[2], MD; Arie Pieter Kappetein[3], MD, PhD; Marcel van den Brand[2], MD; David R. Holmes[4], MD; Michael Mack[5], MD; Ted Feldman[6], MD; Antonio Colombo[7], MD; Elisabeth Ståhle[8], MD; Stefan James[8], MD; Didier Carrié[9], MD; Gerard Fournial[9], MD; Gerrit Anne van Es[2], PhD; Keith D. Dawkins[10], MD; Friedrich W. Mohr[11], MD; Marie-Claude Morice[12], MD; Patrick W. Serruys[1]*, MD, PhD

1. Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands; 2. Cardialysis BV, Rotterdam, The Netherlands; 3. Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands; 4. The Mayo Clinic, Rochester, MN, USA; 5. Medical City Dallas Hospital, Dallas, TX, USA; 6. Evanston Hospital, Evanston, IL, USA; 7. San Raffaele Scientific Institute, Milan, Italy; 8. University Hospital Uppsala, Uppsala, Sweden; 9. Centre Hôpital Universitaire Rangueil, Toulouse, France; 10. Boston Scientific Corporation, Natick, MA, USA; 11. Herzzentrum, Leipzig, Germany; 12. Institut Jacques Cartier, Massy, France

We recently reported the coronary artery bypass graft (CABG) SYNTAX Score, an objective measure of anatomical complexity and revascularisation post coronary artery bypass graft (CABG) surgery[1]. At four-year follow-up, a non-significant trend towards more adverse clinical outcomes, including all-cause death, was reported in the higher CABG SYNTAX group (≥22)[1]. The final five-year outcomes of the SYNTAX trial have recently been reported[2,3]. We report the five-year outcomes of the CABG SYNTAX Score from the CABG arm of the SYNTAX-LE MANS left main angiographic substudy.

At five years, significantly greater all-cause death was seen in the high CABG SYNTAX Score group (≥22) compared to the low CABG SYNTAX Score group (<22) (14.5% vs. 9.1%, log rank p-value=0.012) **(Figure 1)**. Similarly, significantly greater five-year all-cause death/cerebrovascular accident (CVA)/myocardial infarction (MI) (log rank p-value=0.025) and MACCE (major adverse cardiac and cerebrovascular events) (log rank p-value=0.050) were reported.

Incomplete revascularisation (ICR) has recently been hypothesised and shown to be a surrogate marker of a greater burden and complexity of coronary disease, other vascular disease, and clinical comorbidity, in both CABG and PCI (percutaneous coronary intervention) treated patients[4,5]. Specifically, in the all-comers CABG and PCI arms of the SYNTAX trial, adverse long-term (four-year) clinical outcomes – including mortality, all-cause revascularisation, and MACCE – were shown to occur more frequently in patients who were incompletely revascularised.

The CABG SYNTAX Score and its PCI equivalent, the residual SYNTAX Score[6], both provide objective measures of the complexity of the residual disease and level of revascularisation. These scores may aid in determining a level of "reasonable revascularisation" after undergoing surgical or percutaneous-based revascularisation[7], and may have a long-term prognostic role in identifying high-risk patients undergoing CABG or PCI. Validation studies are awaited.

**Corresponding author: Department of Interventional Cardiology, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl*

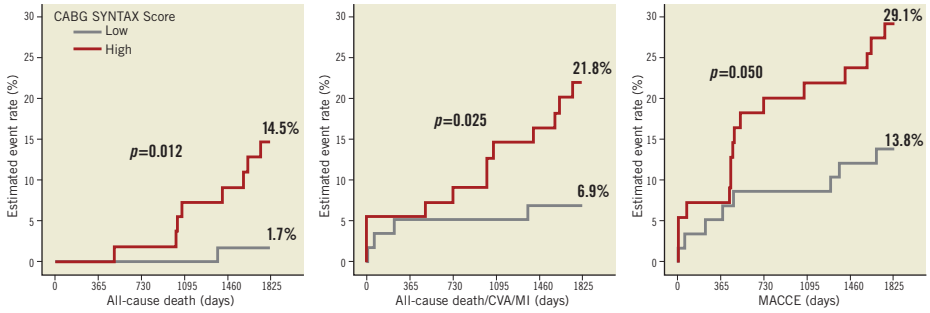


Figure 1. *Outcomes (Kaplan-Meier curves) separated by the median of the CABG SYNTAX Score into low (0-21) (n=58) and high (≥22) (n=55) score groups. At 5 years, significantly greater all-cause mortality (left image), significantly greater all-cause death/CVA/MI (middle image) and MACCE (right image) were evident in the high CABG SYNTAX Score group compared to the low CABG SYNTAX Score group. Note the peak in MACCE at approximately 18 months secondary to patients undergoing scheduled coronary angiography, the findings of which triggered repeat revascularisation. Log rank p-values are shown.*

Acknowledgements

The authors would like to thank all the study centres and participants.

Funding

The SYNTAX trial was funded by Boston Scientific.

Conflict of interest statement

K. Dawkins is a full-time employee of, and holds stock in, Boston Scientific. M. Mack has served on the speakers bureau of Boston Scientific, Cordis and Medtronic. T. Feldman has served on the speakers bureau of Boston Scientific; has received grant support from Abbott, Atritech, Boston Scientific Corporation, Edwards, and Evalve; and has worked as a consultant for Abbott, Coherex, Intervalve, Square One, and WL Gore. M-A. Morel's institution has received a research grant from Boston Scientific. M-A. Morel, H.M. Garcia-Garcia and G.A. van Es are employees of Cardialysis. The other authors have no conflicts of interest to declare.

References

1. Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia-Garcia HM, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Stahle E, James S, Carrie D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW. The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. *EuroIntervention.* 2013;8:1277-85.

2. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr., Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet.* 2013;381:639-50.

3. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629-38.

4. Taggart DP. Incomplete revascularization: appropriate and inappropriate. *Eur J Cardiothorac Surg.* 2012;41:542-3.

5. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol.* 2013;61:282-94.

6. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol.* 2012;59:2165-74.

7. De Bruyne B. Multivessel disease: from reasonably incomplete to functionally complete revascularization. *Circulation.* 2012;125:2557-9.

PART IV

Understanding the coronary bifurcation

Chapter 4.1

New insights into the coronary artery bifurcation hypothesis generating concepts utilizing 3-dimensional optical frequency domain imaging

Farooq V, Serruys PW, Heo JH, Gogas BD, Okamura T, Gomez-Lara J, Brugaletta S, Garcìa-Garcìa HM, van Geuns RJ

JACC Cardiovasc Interv. 2011;4(8):921-31 (Impact Factor: 6.552)

New Insights Into the Coronary Artery Bifurcation

Hypothesis-Generating Concepts Utilizing 3-Dimensional Optical Frequency Domain Imaging

Vasim Farooq, MBChB, Patrick W. Serruys, MD, PhD, Jung Ho Heo, MD, Bill D. Gogas, MD, Takayuki Okamura, MD, PhD, Josep Gomez-Lara, MD, Salvatore Brugaletta, MD, Hector M. Garcìa-Garcìa, MD, MSc, PhD, Robert Jan van Geuns MD, PhD

Rotterdam, the Netherlands

Coronary artery bifurcations are a common challenging lesion subset accounting for approximately 10% to 20% of all percutaneous coronary interventions. The provisional T-stenting approach is generally recommended as the first-line management of most lesions. Carina shift is suggested to be the predominant mechanism of side-branch pinching during provisional T-stenting and has been indirectly inferred from bench work and other intravascular imaging modalities. Offline 3-dimensional (3D) reconstructions of patients studied in the first-in-man trial of the high-frequency (160 frames/s) Terumo optical frequency domain imaging system were undertaken using volume-rendering software. Through a series of 3D reconstructions, several novel hypothesis-generating concepts are presented. (J Am Coll Cardiol Intv 2011;4:921–31) © 2011 by the American College of Cardiology Foundation

Coronary bifurcations are a challenging lesion subset accounting for approximately 10% to 20% of all percutaneous coronary interventions (PCI). Historically, they have been associated with lower rates of procedural success, higher restenosis rates, in particular at the ostium, and adverse events compared with the treatment of simpler, nonbifurcation lesions (1–3).

The current prevailing opinion in their management is one of a "simpler is better" approach, with provisional T-stenting recommended as the first-line strategy in most lesions (1,2). The traditional concept of plaque shift as the predominant mechanism in the pinching of the side branch (SideB) during this technique has recently been challenged and replaced by carina shift, with the suggestion that up to 30% of bifurcations have involvement of plaque shift, since atheroma is rarely seen at the carina alone because of it being a high wall shear stress area (2,4). The concept of carina shift has been indirectly inferred from bench work, in vivo longitudinal and cross-sectional intravascular ultrasound intravascular (IVUS) imaging, and computed tomography (CT) imaging modalities (1,4–8).

Both IVUS (image resolution: 100 to 150 μm) and CT (resolution: 300 to 500 μm) lack the imaging resolution to fully appreciate the complex architecture of the bifurcation compared with optical coherence tomography (OCT; image resolution: 10 to 20 μm). Fusion of CT and IVUS in obtaining 3D reconstructions of human coronary bifurcation have previously successfully been undertaken to allow for wall shear stress analyses; this system, however, lacks the resolution obtainable with OCT (9).

Current-generation Fourier-domain OCT (FD-OCT) allows rapid pullback speeds and has allowed visualization of the coronary bifurcation with 2-dimensional (2D) images in great detail (10–12). One of the major limitations of this technology, however, has been the lack of 3-dimensional (3D) images. Trying to mentally reconstruct a

From the ThoraxCenter, Erasmus University Medical Centre, Rotterdam, the Netherlands. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 4, 2011; revised manuscript received May 20, 2011, accepted June 3, 2011.

complex 3D structure from 2D images is difficult; 2D imaging may not allow a full appreciation of the anatomic features of the bifurcation and the effects of PCI.

Three-dimensional, offline FD-OCT reconstructions were first described by Tearney et al. (13) and more recently by Okamura et al. (14) in the assessment of jailed SideB by bioresorbable vascular scaffolds.

Prototypes of current-generation "real-time" (i.e., periprocedural) 3D FD-OCT are experimental, have not yet entered conventional clinical practice, and appear to have a limited resolution compared with the offline 3D optical frequency domain imaging (OFDI) reconstructions; this may be related to the lower frame rate of commercially available systems: the intracoronary Terumo OFDI system (Terumo Corporation, Tokyo, Japan) is currently the only system with a frame rate as high as 160 frames/s (11,14,15).

Abbreviations and Acronyms

2D = 2-dimensional
3D = 3-dimensional
CT = computed tomography
FD-OCT = Fourier-domain optical coherence tomography
IVUS = intravascular ultrasound intravascular
KBPD = kissing balloon post-dilation
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
MainB = main branch
OCT = optical coherence tomography
OFDI = optical frequency domain imaging
PCI = percutaneous coronary intervention
RV = right ventricular
SideB = side branch

Through a series of images demonstrating 3D OFDI reconstructions of coronary artery bifurcations, we aim to demonstrate several novel, hypothesis-generating concepts with regard to the anatomic characteristics of this complex structure.

Methodology

Three-dimensional reconstructions of patients who underwent conventional PCI from the original first-in-man study of the intracoronary Terumo OFDI system were undertaken (15). The high-speed Terumo OFDI system is capable of acquiring 160 frames/s during the catheter pullback up to a maximum speed of 40 mm/s; all images were acquired with a pullback speed of 20 mm/s. The 3D coronary angiography images were constructed from their respective biplane 2D images (CAAS 5.9, Pie Medical Imaging, Maastricht, the Netherlands) (16). All patients studied had stable angina; 3D reconstructions of coronary bifurcations and the consequent effects of provisional T-stenting were performed.

The methodology for the 3D reconstructions has previously been described (14). In brief, offline bitmap sequences (704 × 704 pixels) were generated from prior 2D OFDI imaging. Manual detection of every strut in each 2D cross section were undertaken, and 3D reconstructions of the coronary vessel pre- and post-intervention were performed using volume-rendering software (INTAGE Realia, KGT, Tokyo, Japan).

Nomenclature for 3D FD-OCT reconstructions. "Fly-through" views indicate a selected still image of an internal view of a vessel looking either downstream (proximal-to-distal vessel) or upstream (distal-to-proximal vessel). An "orientation" figure is located as an inset figure within the 3D reconstruction to best illustrate where the endoluminal point of view is electronically located, and in which direction it is pointing. In 3D reconstructions, the 3D rendering software provides x-, y-, and z-axes within the coronary vessel to allow precise assessment of the location of the endoluminal point of view. Longitudinal and, in some cases, cross-sectional 2D OFDI frames of the vessel and bifurcation, with a blue arrow superimposed on it, are used to orient the reader within the vessel: the base and direction of the blue arrow indicates from and in which direction, respectively, the 3D image is visualized from within the 2D plane(s).

3D Reconstructions

Anatomy of the left main stem, circumflex, left anterior descending, diagonal, and septal branches. Figure 1A demonstrates a fly-through view, looking downstream, from the distal left main stem showing the ostia of the left anterior descending coronary artery (LAD), circumflex, first diagonal (Fig. 1A, D1), and septal branches. Note the appearance of the opening of the diagonal vessel and its relationship to the LAD vessel opening. The main branch (MainB) and SideB appear to diverge parallel to each other at their respective origins, with the carina (labeled) appearing to be "interposed" between both vessel openings at this point of divergence.

Figure 1B demonstrates a close-up fly-through view of the same vessel looking downstream from the proximal LAD and aimed towards the diagonal ostium (upper right image); the left circumflex coronary artery (LCx) orifice appears between 12 and 3 o'clock in relation to the diagonal ostium. For comparison, note the corresponding 2D OFDI frames (lower image). The slit-like, elliptical appearance of the diagonal opening is clearly visible, and when bifurcation is viewed perpendicular to the vessel wall (inset left image—use the orientation figure to allow assessment of the endoluminal point of view), the carina is predominantly visualized, with the proximal course of the diagonal vessel appearing to be hidden behind the rim of the carina so that the diagonal orifice appears, in-depth, as a dead end. This is further suggestive of the proximal parallel course of the diagonal with the LAD at the point of divergence. The yellow arrows in the fly-through and perpendicular views are pointing in identical directions, namely, the direction of the opening of the diagonal vessel.

Figure 1C demonstrates a fly-through view looking further downstream into the same LAD (upper left image).

Observe the large septal branch orifice opening; when viewed perpendicular to the vessel wall (upper right image), and contrary to the observations made with the diagonal branch, the endoluminal opening of the septal branch is entirely visible and does not appear to be concealed behind the carina. This corresponds to the characteristic, almost perpendicular takeoff of the septal branch from the LAD. Corresponding 2D OFDI frames are displayed below the panel.

Anatomy of the proximal, mid, and distal LAD–diagonal branches. Figure 2A demonstrates downstream fly-through views of the LAD, looking distally (Image 1) and aimed towards the proximal diagonal ostium (Image 2). When the bifurcation is visualized perpendicular to the vessel wall (Image 3), the diagonal orifice appears to have a circular appearance with the rim of the carina appearing to be concealing the proximal course of diagonal, so that the diagonal orifice once again appears, in-depth, as a dead end. Yellow arrows (Images 2 and 3) point in identical directions at the opening of the same diagonal vessel. Corresponding 2D OFDI frames are shown below the panel for comparison.

Figure 2B demonstrates fly-through views (looking downstream) of the mid (D2, left image) and distal (D3, right image) LAD–diagonal bifurcations; yellow arrows point at the diagonal vessel openings. The corresponding 2D OFDI frames of each bifurcation are displayed below their respective 3D reconstructions.

All of these images are further suggestive of the proximal parallel course of the diagonal vessels relative to the LAD at their point of divergence.

Anatomy of diagonal branch originating perpendicular to the LAD. Figure 3 demonstrates a coronary angiogram (left image), suggesting the diagonal vessel (asterisk) originates almost perpendicular to the LAD at the point of divergence of both vessel origins. The 3D coronary angiography images (left inset figures) confirmed these findings with a bifurcation angle of 85°. A fly-through view of the LAD looking downstream (upper right image) demonstrates the diagonal vessel opening (asterisk), note the elliptical shape of the vessel opening and the observation that the diagonal vessel opening is fully visible, and not concealed by the carina, when visualized perpendicular to the vessel wall (lower right image). Observe how the stent is able to divide the opening of the diagonal vessel into at least 3 segments. Effectively, the diagonal branch with an almost perpendicular takeoff appears to have similar characteristics to the septal branch as described in Figure 1C.

The right ventricular branch of the right coronary artery. Figure 4 demonstrates how the right ventricular (RV) branch of the right coronary artery (RCA) appears to exhibit the phenomenon of a "parallel bifurcation" as described for the diagonal vessel. The downstream fly-through view of the proximal RCA demonstrates the opening of the RV branch (upper left image); note how the opening of the RV branch (yellow arrows) appears to be concealed behind the proximal rim of the carina in the perpendicular (upper middle image) and retrograde (upper right image) endoluminal point of views. In support of this concept is that the bifurcation angle is 57° on the corresponding 2D and 3D coronary angiograms (lower left images). Corresponding 2D OFDI frames are displayed (lower right images).

Bifurcation treated with provisional-T approach: comparing the diagonal and septal branches on 2D and 3D FD-OCT. Figure 5A demonstrates a long segment of disease in the proximal-mid LAD (upper left image) extending across the bifurcation with a diagonal branch. This was treated with 2 overlapping Xience V stents (Abbott Vascular, Abbott Park, Illinois) that lead to "pinching" of the SideB ostium with Thrombolysis In Myocardial Infarction flow grade 3 (middle left image with corresponding 3D coronary angiogram). Kissing balloon post-dilation (KBPD) was subsequently successfully performed with improvements in the pinched angiographic appearances (lower left image with corresponding 3D coronary angiograms) (Online Video 1). In the fly-through view (looking downstream) of the LAD post-intervention (right image), note the characteristic perpendicular and parallel takeoffs of the septal (asterisk) and diagonal (white arrow) branches at the point of divergence from the LAD lumen, respectively.

Figure 5B demonstrates fly-through views looking downstream at the diagonal and septal branches; note the differences between both branches as a more perpendicular view of the vessel wall is seen. Parallel yellow arrows represent the parallel courses of the diagonal and LAD vessels at their point of divergence. Medina et al. (6) have previously hypothesized the concept of carina shift pinching the SideB by the displacement of the carina so that it appears as an "eye-brow" sign on longitudinal 2D IVUS imaging (17). As shown on the 3D reconstruction, this effect can be more easily appreciated and may be hypothesized to have led to the near closure of the diagonal ostium following post-dilation of the MainB stent; subsequent KBPD may have reopened the SideB ostium by displacing the carina towards the lumen of the MainB. This principle may not be applicable to the septal branch because of the differing appearances of the carina.

Figure 5C demonstrates the corresponding 2D OFDI frames of the septal (asterisks) and diagonal branches (arrows). The almost parallel course of the diagonal vessel (yellow arrow indicates the diagonal vessel in cross-sectional view) in relation to the LAD lumen at the point of divergence appears to determine the 2D FD-OCT characteristics; without careful observation, the diagonal vessel may have been misinterpreted as an area of stent malapposition on the 2D FD-OCT imaging. With the septal branch, this appears to originate perpendicular to the vessel

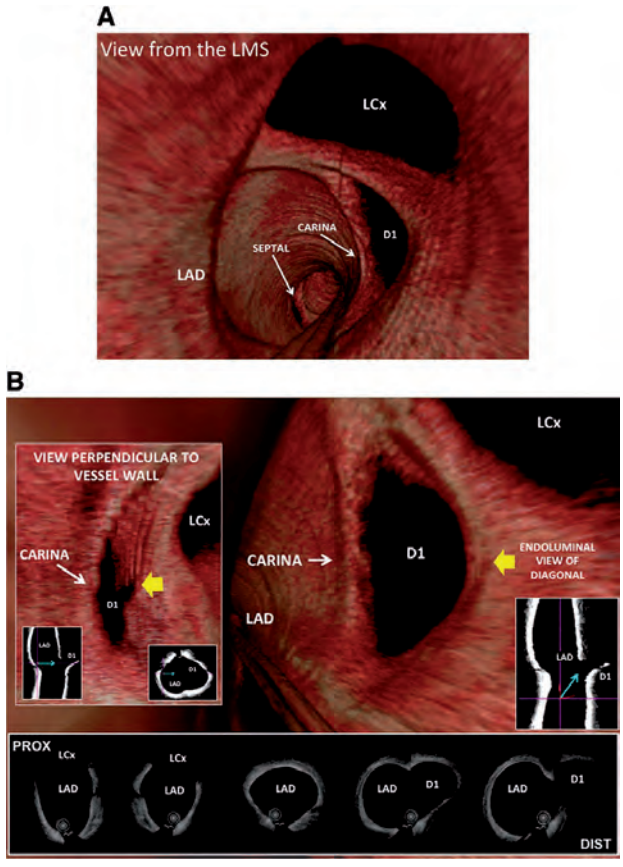


Figure 1. Anatomy of the Left Main Stem, Circumflex, Left Anterior Descending, Diagonal, and Septal Branches

(A) Fly-through view looking downstream from the distal left main stem (LMS). **(B)** Close-up view of the LAD–proximal diagonal "parallel bifurcation." Perpendicular **(left inset)** and downstream **(right)** fly-through views aimed at the first diagonal vessel opening (D1) are illustrated. Corresponding 2D OFDI frames are shown **below**.

Continued on the next page

wall giving its characteristic 2D FD-OCT appearances as shown (yellow asterisk).

Bifurcation treated with provisional-T approach: the concept of a parallel bifurcation and carina shift. Figure 6A demonstrates the concept of carina shift with pre- and post-intervention images: the solid line indicates the position of the carina pre-intervention (left image); broken lines demonstrate the position of the carina pre- (left image) and post- (right image) intervention. Two-dimensional (Online Video 2) and 3D coronary angiograms (inset images) demonstrate disease of the LAD with involvement of the diagonal ostium not evident on subsequent 3D reconstruction.

Implantation of a Xience V stent (Abbott Vascular) in the mid LAD led to angiographic "pinching" of the SideB ostium with Thrombolysis In Myocardial Infarction flow grade 3 maintained in the SideB. Post-dilation of the

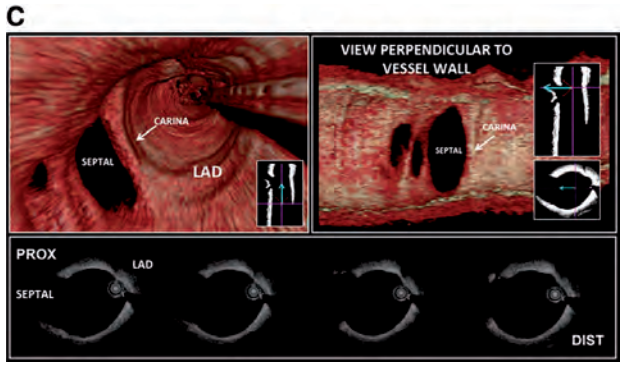


Figure 1. Continued

(C) Anatomy of the LAD–septal "perpendicular bifurcation." Downstream fly-through **(left)** and perpendicular **(right)** views are illustrated. Corresponding 2D OFDI frames are shown **below**. 2D = 2-dimensional; DIST = distal; LAD = left anterior descending artery; LCx = left circumflex; OFDI = optical frequency domain imaging; PROX = proximal.

MainB alone was performed with the deploying stent balloon; no KBPD was performed. The angiographic appearance of the pinching of SideB ostium improved (Online Video 2).

Figure 6B (upper images) demonstrates the appearance of the SideB opening when viewed perpendicular to the vessel wall (Image 3), illustrating the principle of a "parallel bifurcation" with the concealment of most of the opening of the diagonal vessel by the rim of the carina. It may be speculated that continued post-dilation of the MainB stent alone, especially with larger balloons, may have risked further carina shift and SideB closure.

Note how the MainB struts appear to overhang the carina over the SideB opening, especially evident in the perpendicular view (Image 3), because of the structure of the parallel bifurcation and carina. For comparison, the 2D OFDI frames (lower images) with the stent struts at the SideB ostium are illustrated. Asterisk indicates thrombus and the shadow it casts on the vessel wall, in both the 2D and 3D FD-OCT imaging.

Discussion

On the basis of the offline 3D OFDI reconstructions, we have proposed several hypothesis-generating concepts relating to bifurcation anatomy and the effects of PCI: 1) the concept of the parallel or perpendicular bifurcations and the corresponding 2D and 3D appearances—a reassessment of current interpretations of the 2D FD-OCT imaging of the bifurcation may be warranted; 2) the hypothesis that the angle of divergence between the MainB and SideB at their respective origins will ultimately determine the anatomic features of the carina and how it potentially interacts with the SideB vessel orifice during MainB stenting; and 3) the potential clinical application of instantaneous 3D FD-OCT in coronary bifurcation treatment.

Based on the appearances of the carina on the 3D reconstructions and the effects of PCI, a more perpendicular takeoff of the SideB from the MainB may be less prone to the effects of carina shift whereas a shallower angle of divergence appears to be more susceptible to the effects of carina shift. This concept is supported by a study suggesting a specific measure of SideB angulation on the coronary angiogram is associated with a higher incidence of SideB compromise (18). Asakaura et al. (19) also demonstrated, in a small case series, that a shallower angle, with a cutoff of 80°, between the LCx and LAD was predictive of LCx ostial impairment after stenting within the LAD ostial region—the authors had presumed at the time that the mechanism of SideB (LCx) closure was secondary to plaque shift or coronary dissection. Both of the aforementioned studies are, however, limited by a lack of 3D quantitative coronary angiography to calculate the bifurcation angulation (16). An awareness of the potential increased risk of SideB closure during MainB stenting of coronary bifurcations with a shallower bifurcation angle may be justified—further study into this phenomenon is required.

Angiographic appearances of the SideB ostium after MainB stenting has previously been demonstrated to be unreliable, with only a quarter (27%) of cases with a residual

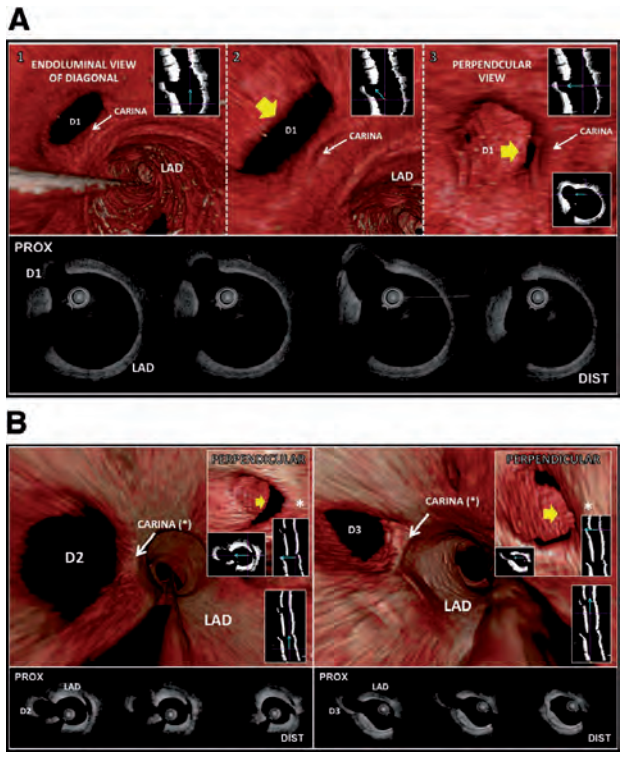


Figure 2. Anatomy of the Proximal, Mid, and Distal LAD–Diagonal Branches

(A) Further example of the LAD–proximal diagonal parallel bifurcation. Downstream fly-through **(top left)** aimed at the first diagonal **(top middle)** and perpendicular **(top right)** views are illustrated. Corresponding 2D OFDI frames are shown **below**. **(B)** Anatomy of the mid and distal LAD–diagonal parallel bifurcations. Downstream and perpendicular views of the mid **(upper left)** and distal **(upper right)** LAD–diagonal bifurcations are illustrated. Corresponding 2D OFDI frames are shown **below**. D2 = second diagonal; D3 = third diagonal; other abbreviations as in Figure 1.

angiographic narrowing of ≥75% in the SideB being found to have a functionally significant narrowing in pressure wire studies (1,8). The main limitation of this technique is the potential risk of dissecting the SideB ostium with a less flexible, less torquable, and less hydrophilic pressure wire and the increase in procedural time in rewiring the SideB through the MainB stent. As the 3D FD-OCT reconstructions can visualize the carina shift and the SideB vessel opening, quantification of the SideB opening as an area may allow the operator to assess whether the SideB ostium is hemodynamically compromised, without the need to perform a pressure wire study. The addition of quantitative measurements to the 3D software as well as the requirement for instantaneous online 3D FD-OCT availability of a high-enough resolution would, however, be necessary requirements.

Within the parallel bifurcation, the positioning and geometric relationship of the MainB stent over the SideB opening suggested "overhanging" of the struts over the edge of the carina (Fig. 7); this was especially evident in the views perpendicular to the vessel wall (Figs. 5B and 6B) and contrary to the appearances on the corresponding 2D images where a "jailed" appearance of the stent struts covering the SideB opening was suggested; the jailed appearance of the struts covering the SideB ostium was, however, evident with perpendicular bifurcations (Figs. 3 and 5).

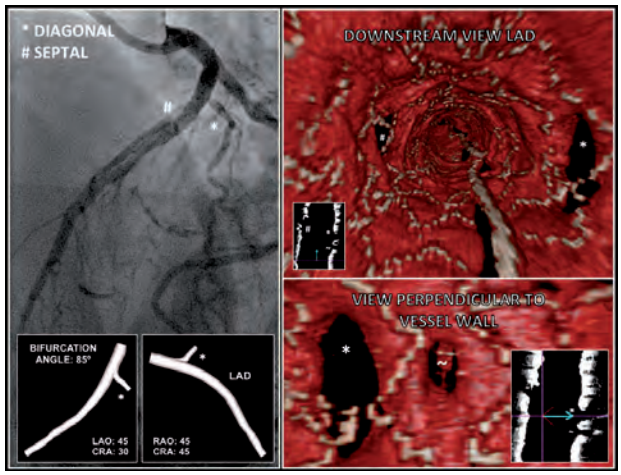


Figure 3. Anatomy of Diagonal Branch Originating Perpendicular to the LAD: Perpendicular Bifurcation

Two-dimensional and 3-dimensional (3D) coronary angiograms **(left)** and 3D reconstructions **(right)** are illustrated. An **asterisk** indicates the endoluminal opening of diagonal branch, a **tilde**, small diagonal branch, and a **hash mark**, septal branch. CRA = cranial; LAO = left anterior oblique; RAO = right anterior oblique.

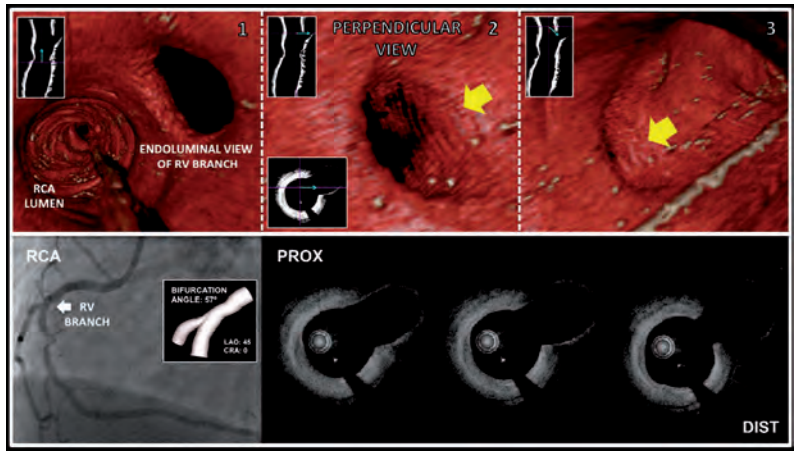


Figure 4. Anatomy of the RCA RV Branch Demonstrating a Parallel Bifurcation

Three-dimensional (3D) reconstructions **(top)** with the perpendicular view. Two-dimensional (2D) and 3D quantitative coronary angiography **(bottom left)** and corresponding 2D OFDI frames **(bottom right)**. RCA = right coronary artery; RV =right ventricular; other abbreviations as in Figures 1 and 3.

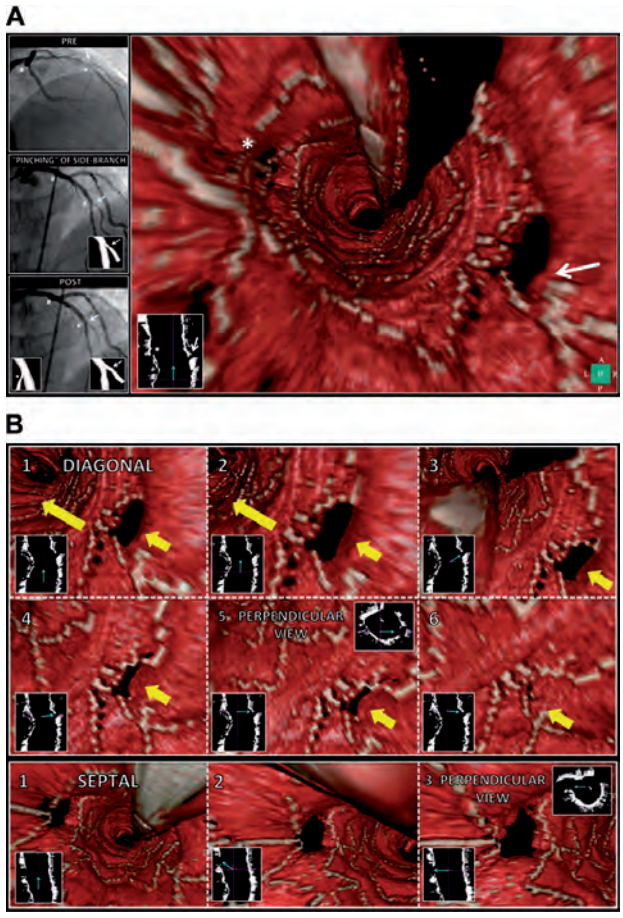


Figure 5. Bifurcation Treated With Provisional-T Approach: Comparing the Diagonal and Septal Branches on 2D and 3D FD-OCT

(A) LAD–diagonal bifurcation treated with the provisional-T approach. Angiographic findings **(left)** and downstream fly-through view of the LAD post-intervention **(right)** illustrating the septal **(white asterisks)** and diagonal **(white arrows)** vessel openings. **(B)** The differences between the septal and diagonal vessels based on perpendicular views. Progressively more perpendicular views of the diagonal **(top)** and septal **(bottom)** SideB openings. Parallel **yellow arrows** represent the parallel courses of the LAD–diagonal at their respective point of divergence.

Continued on the next page

Current recommendations during provisional T-stenting suggest the recrossing of the coronary wire (after MainB stenting) into the SideB through the most distal cell of the MainB stent covering the SideB opening (11,20,21). If the coronary wire is passed through a proximal cell into the SideB, this may potentially provide no scaffolding to the SideB ostium and leave many struts unopposed adjacent to the carina. The adoption of this principle to bifurcations with 3D FD-OCT has recently been shown to be potentially feasible in humans (11,22). To help further appreciate this potential appli-

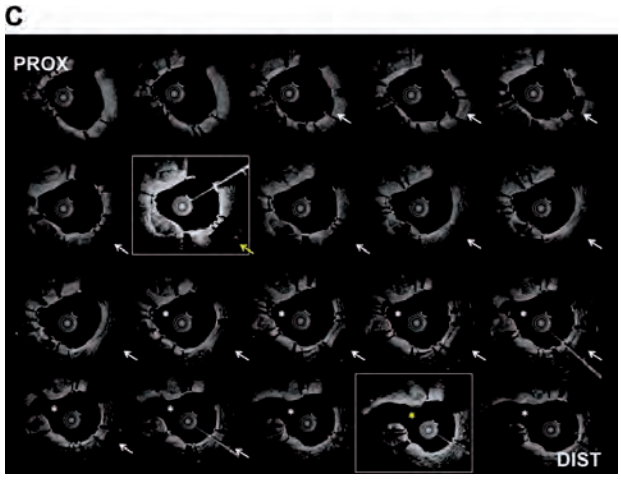


Figure 5. Continued

(C) Corresponding 2D OFDI images of the septal and diagonal branches. Highlighted OFDI frames demonstrate the diagonal **(yellow arrow)** and septal vessels (**yellow asterisk)** when viewed in cross section. Also see Online Video 1. SideB = side branch; other abbreviations as in Figure 1.

cation, a 3D OFDI reconstruction was performed in a patient separate from this study, utilizing the OFDI system from an ongoing trial (23): the case is of a proximal LCx–obtuse marginal bifurcation in the context of an acute coronary syndrome requiring manual aspiration thrombectomy; malapposition was evident immediately after MainB stent implantation requiring further post-dilation (not illustrated) (Fig. 7).

Based on the 3D reconstructions, the malapposed struts located in close vicinity to the proximal ostial rim (i.e., in the "takeoff" position) are overprojected on the true orifice of the SideB, giving the illusion that the SideB orifice is jailed when the orifice is viewed obliquely (Fig. 7A); this, however, appears to be the ideal endoluminal point of view to best select the distal cells of the stent over the parallel bifurcation to pass the coronary wire and perform KBPD (white arrow, Fig. 7A). When moving further downstream along the axis of the MainB, the optical visual perspective of overprojection on the orifice of the SideB is gradually reduced (Fig. 7B) and eliminated when a downstream endoluminal point of view at the level of the carina is selected (Fig. 7C). The struts located in front of the edge of the carina are now seen prominently as a metallic extension of the carina and not covering the SideB opening. The potential to advance a coronary wire beneath the malapposed struts in the proximal vicinity of the ostial rim appears to be very real, and if SideB dilation or stenting were performed, would result in multiple unappposed struts taking off from the carina.

Other properties of 3D FD-OCT reconstructions that may have a clinical application include the addition of tissue characterization; this has previously been performed offline (13,24,25). Tissue characterization within 3D FD-OCT imaging (25) or fusion imaging of 2D FD-OCT and IVUS virtual histology (26) would have the potential to aid in the identification of clinically useful areas of interest such as fibrocalcific plaque, lipid pools, and vulnerable plaque. A recent study utilizing longitudinal high-resolution intravascular ultrasound has suggested that that the effects of carina shift may be limited by the presence of fibro-calcific plaque at the carina, presumably because of resistance to expansion—using 3D FD-OCT, this concept appears easier to appreciate; tissue characterization of intravascular imaging may ultimately aid in identifying these areas (2,17).

Conclusions

The potential for the clinical application of 3D FD-OCT as a complementary tool to 2D imaging is demonstrated. A reassessment of the understanding of 2D FD-OCT imaging may be warranted in light of the 3D findings. Real-time, instantaneous, high-resolution 3D FD-OCT, with the

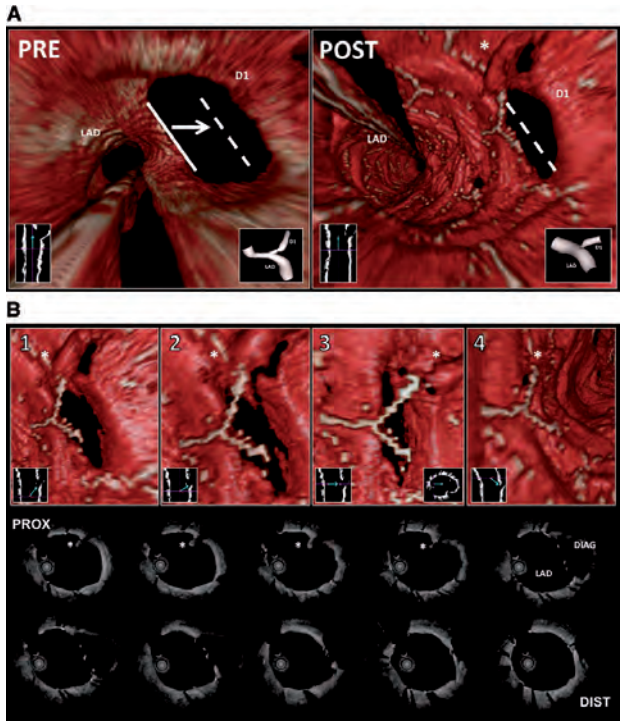


Figure 6. Bifurcation Treated With Provisional-T Approach: The Concept of a Parallel Bifurcation and Carina Shift

(A) The principle of carina shift. Downsteam fly-through views pre- **(left)** and post- **(right)** intervention of the LAD–diagonal bifurcation are demonstrated; 3D coronary angiograms are illustrated as **inset figures**. **(B)** Anatomy of the LAD–diagonal parallel bifurcation post-MainB (LAD) stenting. **Top** demonstrates a progressively more perpendicular view of the vessel. **Bottom** demonstrates the corresponding 2D OFDI images (Online Video 2). **White asterisk** indicates thrombus on corresponding 2D and 3D images. MainB = main branch; other abbreviations as in Figures 1 and 4.

addition of quantitative and possible tissue characterization properties, are required from industry to validate and apply this technology in conventional PCI practice. This may aid in the further understanding of the complexities of the coronary bifurcation.

Acknowledgments

The first author wishes to thank the Dickinson Trust Travelling Scholarship, Manchester Royal Infirmary, Manchester, England, UK. The authors wish to express their thanks to Evelyn Regar, MD, PhD, Carl Schultz, MD, PhD, Willem J. van der Giessen, MD, PhD, and Jurgen Ligthart, BSc, of the ThoraxCenter, Erasmus University Medical Centre, Rotterdam, the Netherlands, part of the team who undertook the original first-in-man study of the intracoronary Terumo optical frequency domain imaging (OFDI) system. The authors also thank Dr. Dragica Paunovic and Dr. Vladimir Borovicanin of Terumo Corporation and Terumo Europe N.V., and Glenda van Bochove, Ravindra Pawar, and Monique Schuijer of Cardialysis BV, Rotterdam, the Netherlands, for their invaluable technical support.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Interventional Cardiology Department, ThoraxCenter, Erasmus University Medical Centre,'s-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

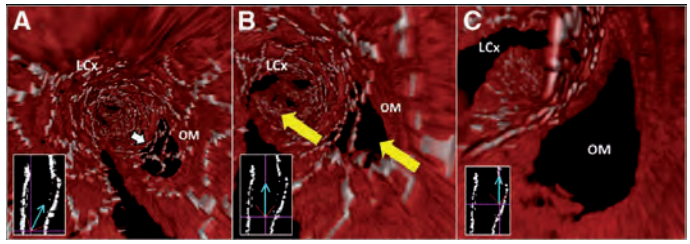


Figure 7. Provisional T-Stenting: The Principle of Recrossing the Coronary Wire (After MainB Stenting) Into the SideB Through the Most Distal Cell

Progressive downstream fly-through views culminating in the endoluminal point of view being located at the carina **(A to C)**. **White arrow** indicates the most distal cell where the coronary wire would be recommended to be passed; **yellow arrows** indicates the parallel courses of the left circumflex coronary artery (LCx) and obtuse marginal (OM) vessels at their point of divergence. Abbreviations as in Figures 5 and 6.

REFERENCES

1. Colombo A, Al-Lamee R. Bifurcation lesions: an inside view. Circ Cardiovasc Interv 2010;3:94–6.
2. Hildick-Smith D, Lassen JF, Albiero R, et al. Consensus from the 5th European Bifurcation Club meeting. EuroIntervention 2010;6:34–8.
3. Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. Circulation 2010;121:1235–43.
4. van der Giessen AG, Wentzel JJ, Meijboom WB, et al. Plaque and shear stress distribution in human coronary bifurcations: a multislice computed tomography study. EuroIntervention 2009;4:654–61.
5. Vassilev D, Gil R, Kwan T, Nguyen T, Nanjundappa A, Doganov A. Extension distance mismatch—an unrecognized factor for suboptimal side branch ostial coverage in bifurcation lesion stenting. J Interv Cardiol 2010;23:305–18.
6. Medina A, Martín P, Suárez de Lezo J, et al. Vulnerable carina anatomy and ostial lesions in the left anterior descending coronary artery after floating-stent treatment. Rev Esp Cardiol 2009;62:1240–9.
7. Koo BK, Waseda K, Kang HJ, et al. Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention. Circ Cardiovasc Interventions 2010;3:113–9.
8. Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol 2005;46:633–7.
9. van der Giessen AG, Schaap M, Gijsen FJ, et al. 3D fusion of intravascular ultrasound and coronary computed tomography for in-vivo wall shear stress analysis: a feasibility study. Int J Cardiovasc Imaging 2010;26:781–96.
10. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. J Am Coll Cardiol Intv 2009;2:1035–46.
11. Di Mario CII, van der Giessen WJ, Foin N, et al. Optical coherence tomography for guidance in bifurcation lesion treatment. EuroIntervention 2011;6 Suppl J:J99–106.
12. Gonzalo N, Garcia-Garcia HM, Regar E, et al. In vivo assessment of high-risk coronary plaques at bifurcations with combined intravascular ultrasound and optical coherence tomography. J Am Coll Cardiol Img 2009;2:473–82.
13. Tearney GJ, Waxman S, Shishkov M, et al. Three-dimensional coronary artery microscopy by intracoronary optical frequency domain imaging. J Am Coll Cardiol Img 2008;1:752–61.
14. Okamura T, Onuma Y, García-García HM, et al. 3-Dimensional optical coherence tomography assessment of jailed side branches by bioresorbable vascular scaffolds: a proposal for classification. J Am Coll Cardiol Intv 2010;3:836–44.
15. Okamura T, Onuma Y, Garcia-Garcia HM, et al. First-in-man evaluation of intravascular optical frequency domain imaging (OFDI) of Terumo: a comparison with intravascular ultrasound and quantitative coronary angiography. EuroIntervention 2011;6:1037–45.
16. Onuma Y, Girasis C, Aben JP, et al. A novel dedicated 3-dimensional quantitative coronary analysis methodology for bifurcation lesions. EuroIntervention 2011 Jan 6 [E-pub ahead of print].
17. Medina A, Pan M, Martin P, Suarez de Lezo J. Kissing in simple strategy. I prefer SMS. Paper presented at: 6th European Bifurcation Club; October 22-23, 2010; Budapest, Hungary. Available at: http://www.bifurc.net. Accessed March 1, 2011.
18. Gil RJ, Vassilev D, Formuszewicz R, Rusicka-Piekarz T, Doganov A. The carina angle-new geometrical parameter associated with periprocedural side branch compromise and the long-term results in coronary bifurcation lesions with main vessel stenting only. J Interv Cardiol 2009;22:E1–10.
19. Asakaura Y, Takagi S, Ishikawa S, et al. Favorable strategy for the ostial lesion of the left anterior descending coronary artery: influence on narrowing of circumflex coronary artery. Cathet Cardiovasc Diagn 1998;43:95–100.
20. Stankovic G, Darremont O, Ferenc M, et al. Percutaneous coronary intervention for bifurcation lesions: 2008 consensus document from the fourth meeting of the European Bifurcation Club. EuroIntervention 2009;5:39–49.
21. Ormiston JA, Webster MW, El Jack S, et al. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. Catheter Cardiovasc Interv 2006;67:49–55.
22. van Geuns RJ, Gogas BD, Farooq V, Regar E, Serruys PW. 3-Dimensional reconstruction of a bifurcation lesion with double wire after implantation of a second generation everolimus-eluting bioresorbable vascular scaffold. Int J Cardiol 2011 Mar 8. [E-pub ahead of print].
23. Serruys PW, Marco J. Primary PCI: step-by-step decision process. New optical imaging techniques to guide treatment Presented at: EuroPCR 2011; May 18, 2011; Paris, France.
24. Gonzalo N, Tearney GJ, van Soest G, et al. Witnessed coronary plaque rupture during cardiac catheterization. J Am Coll Cardiol Img 2011;4:437–8.
25. Waxman S, Freilich MI, Suter MJ, et al. A case of lipid core plaque progression and rupture at the edge of a coronary stent: elucidating the mechanisms of drug-eluting stent failure. Circ Cardiovasc Interv 2010;3:193–6.
26. Diletti R, Garcia-Garcia HM, Gomez-Lara J, et al. Assessment of Coronary Atherosclerosis Progression and Regression at Bifurcations Using Combined IVUS and OCT. J Am Coll Cardiol Img 2011;4:774–80.

Key Words: 3-dimensional ■ bifurcation ■ carina shift ■ FD-OCT.

APPENDIX

For supplementary videos, please see the online version of this article.

Chapter 4.2

Unravelling the complexities of the coronary bifurcation: is this raising a few eyebrows?

Farooq V, Okamura T, Onuma Y, Gogas BD, Serruys PW

EuroIntervention. 2012;7(10):1133-41 (Impact Factor: 3.173)

Unravelling the complexities of the coronary bifurcation: is this raising a few eyebrows?

Vasim Farooq[1], MBChB, MRCP; Takayuki Okamura[2], MD, PhD; Yoshinobu Onuma[1], MD; Bill D. Gogas[1], MD; Patrick W. Serruys[1]*, MD, PhD

1. Department of Interventional Cardiology, Erasmus MC, Thoraxcenter, Rotterdam, The Netherlands; 2. Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan

The coronary bifurcation has long proven to be a common but challenging lesion subset that the interventional cardiologist must face.[1-3] Despite the general consensus that the "simpler is better approach" to be the preferred treatment strategy[1,4] –as endorsed by the European Bifurcation Club[2]– practices amongst interventional cardiologists in certain bifurcation lesion subtypes differ, with the quote that "the simplest approach is not always the best approach."[1] Specifically that in selected cases an upfront 2 stent strategy may be preferable to the relatively simple provisional T-stenting approach.

Improvements to the provisional T-stenting approach are increasingly being reported in the literature: these range from the pressure wire assessment of jailed side branches (SideB);[5] the passage of the coronary wire into the distal cell covering the SideB ostium after main branch (MainB) stenting to allow for kissing balloon post-dilatation (KBPD) and subsequent clearance of over-hanging struts at the SideB ostium[6-10]; the proximal optimisation technique (POT)[2] to best avoid SideB compromise, facilitate coronary rewiring of the SideB and allow for appropriate stent apposition; fluoroscopic based assessment of stent expansion (such as Stent Boost)[11]; – the list continues to grow…

In this issue of EuroIntervention, two important papers are added to the expanding literature on undertaking the provisional T-stenting approach. Mylotte et al[12] describe the clinical application of the novel technique – first reported by the European Bifurcation Club 2010[2] – of utilising non-compliant balloons to undertake KBPD after MainB stenting. The use of non-compliant balloons to perform KBPD would theoretically minimise balloon over-expansion (a feature of compliant balloons) in the SideB with a consequent risk of vessel injury/restenosis, and stent under-expansion in the MainB stent. The lack of a control arm and the relatively small numbers (n=100) in this pilot study are obvious; the authors, however, do demonstrate the safety and feasibility of this technique, utilising the low profile Hiryu (Terumo Corporation, Tokyo, Japan) non-compliant balloon. The take-home message is very practical and can be incorporated with relative ease into clinical practice. One perhaps notable critique of this study is that angiographic criteria alone were used for assessing the need for SideB stenting – noting that only a quarter (27%) of cases with a residual angiographic narrowing of ≥75% in the SideB had a functionally significant narrowing in a previous classic pressure wire study.[5] Furthermore, the requirement to make an angiographic acceptable appearance of the SideB ostium may have driven the operators to use higher pressure balloon inflations or larger size balloons, with the consequent risk of inducing SideB ostial dissection and the need for two stents.

It is becoming increasingly clear that further adjunctive device(s) may be required to assess the ostium of the SideB. Two-dimensional axial intravascular ultrasound (IVUS), optical coherence tomography

*Corresponding author: Professor of Medicine, Head of the Interventional Cardiology Department, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl

(OCT) and pressure wire assessment have all proven feasible.[5,6,13-15] Furthermore, in this issue of EuroIntervention, Suárez de Lezo et al[16] elegantly demonstrate the use of longitudinal IVUS studies to describe the 'eyebrow' sign, "a powerful predictor of ostial SideB damage after stent implantation in the MainB in bifurcation coronary lesions without plaque involving the SideB."

Article see p 1147

The eyebrow sign is impressively illustrated in the figures accompanying the paper. The concept being that MainB stenting during the provisional T-stenting approach can lead to carina shift and pinching of the SideB ostium, with subsequent SideB compromise. Furthermore, when KBPD is performed, the authors demonstrate the repositioning – "endoluminal displacement" – of the carina so that the SideB is no longer compromised. The authors use the term "damage" to describe the eyebrow phenomenon which is helpfully defined as "an increase of the percentage of ostial stenosis by QCA ≥30%". Further adding to this novel concept is that plaque located at the carina –which most often can occur when it grows from the opposite lower shear stress wall to the higher shear stress carina[17]– was significantly less likely to be associated with the eyebrow sign. Presumably, the presence of more fibro-calcific plaque on the carina would make it more resistant to expansion and, subsequently, at a reduced risk of carina shift.

The authors then continue by associating the presence of the eyebrow sign with shallower bifurcation angles, and the lack of the eyebrow sign with a more perpendicular bifurcation angle (62°±23° vs. 76°±24° respectively, $p<0.05$). These absolute values of the bifurcation angle, although statistically supportive of this concept, should be viewed as a guide given the lack of 3-dimensional quantitative coronary angiography, which would have improved the accuracy of the SideB angulation measurements.[18,19]

Yet when we interpret the results of this study and its implications for clinical practice, can we now be sure we fully understand the mechanisms of SideB closure? Not until recently has the concept of carina shift as the predominant mechanism of SideB closure been widely accepted, with the previously long-held view that the so-called "snow-plough" effect, secondary to plaque shift, being the main aetiology. The latter does still occur, but to a substantially lesser degree than previously thought,[1,5,14,17,20,21] and rarely in this reported study by Suárez de Lezo et al[16].

3D-OCT

Recently 3-dimemsional OCT has demonstrated the potential application in improving our understanding of coronary bifurcations and the effects of the provisional T-stenting approach.[9,22-24] Firstly, a proposal of classification was made based on the number of compartments the SideB orifice was divided into by the jailed stent struts.[24] Secondly, hypotheses based on 3-OCT reconstructions during the provisional T-stenting approach were made, introducing concepts such as "parallel" **(Figure 1)** and "perpendicular" **(Figure 2)** bifurcations related to the SideB angulation with the MainB.[9,22,23] The results of Suárez de Lezo et al[16] further add to the evidence supporting these hypotheses. The eyebrow sign is related to shallower bifurcation angles, and fits into the concept of a parallel bifurcation, where the origin of the MainB and SideB take off parallel to each at the carina **(Figure 1)** until the SideB undergoes a change of direction. Consequently, MainB stenting in a parallel bifurcation may compromise the SideB (with the resultant eyebrow sign), whereas with the perpendicular bifurcation **(Figure 2)** this may not be so apparent because of the differing appearances of the carina. In support of this hypothesis are studies associating smaller bifurcation angles with more carina shift.[15,25-27] The implications of these findings may be that by simply assessing the bifurcation angle with QCA, a prediction could be made through which SideB may be at risk of carina shift and compromise, and thus need protecting with a coronary wire.

One interesting observation of the coronary bifurcation on 3D-OCT is the ellipsoid or oval appearances of the SideB opening, which is especially notable in the illustrated LAD diagonal bifurcation **(Figure 2)**, and appears to be evident in most bifurcations, especially after MainB stenting.[9,15,30] This observation perhaps warrants closer attention given the lack of any association between QCA and ostial SideB "lesions".[5,28,29,31] Once again, 3D-OCT may hold the answers to explaining this apparent paradox. It may be hypothesised that during coronary angiography, the plane of the angiography cuts the SideB in the narrower segment of the ellipsoid opening (which would be more likely to occur) rather than the longer segment given its oval shape, consequently the impression of angiographic SideB compromise is erroneously visualised.

Further adding to the potential appeal of 3D-OCT is the principle of passing the coronary wire into the distal cell of the struts covering the SideB after MainB stenting, during the provisional T-stenting approach. This is to reduce the likelihood of causing multiple malapposed struts if the coronary wire is passed into the more proximal cells and KBPD performed as illustrated **(Figure 3)**. If the coronary wire is passed into the most distal cell, then KBPD would subsequently displace the struts covering the SideB ostium so that they opposed the SideB vessel wall opposite the carina (akin to the "skirt" technique[30]).

In addition, 3D-OCT may potentially allow for the visualisation of the final result after a 2-stent bifurcation stent approach. This may guide the need for passage of the coronary wire into the appropriate cell to allow for further post-dilatation to clear any malapposed struts, guide the size of the angioplasty balloons needed to clear malapposed struts and ensure adequate ostial expansion, even if KBPD had already been performed as illustrated **(Figure 4)**.

The technology of 3D-OCT is rapidly progressing. If features like real-time 3D-OCT to allow for its immediate use in the catheterisation laboratory to assess the results of the bifurcation intervention, the introduction of quantitative measurements to allow for a more objective assessment of the SideB ostium and the need for further intervention, then the potential for the research and clinical application of 3D-OCT would be very promising.[22] Perhaps then, 3D-OCT may be seen more as an important adjunctive tool in the catheterisation laboratory, rather than an instrument to create visually appealing images.

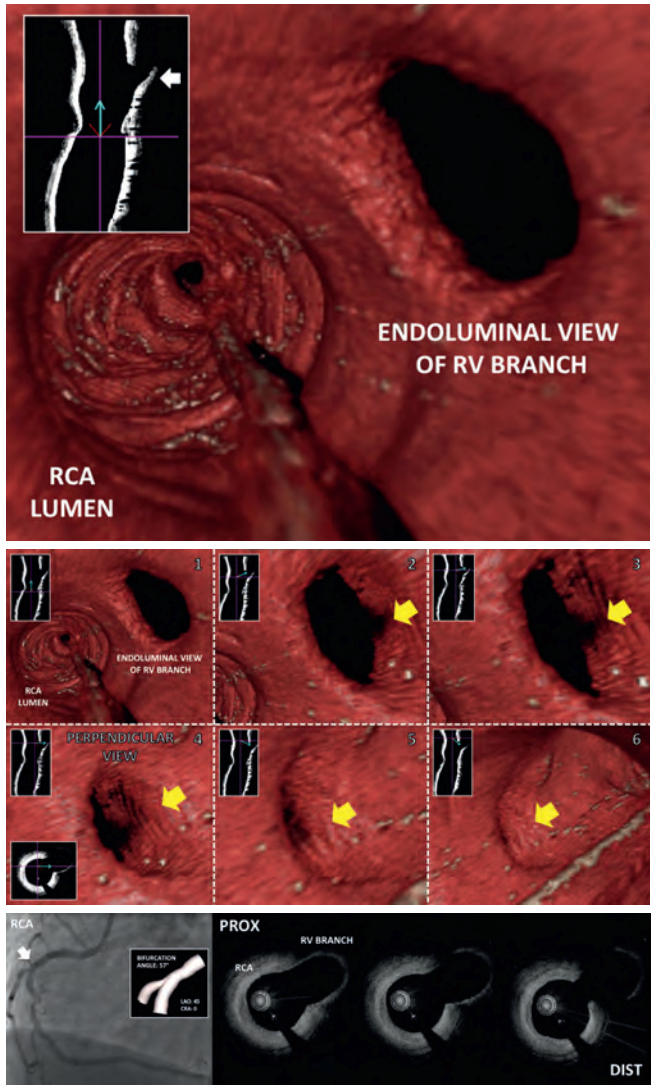


Figure 1. *Principle of a "parallel bifurcation". Downstream (proximal to distal) fly-through view of the right coronary artery (RCA) – right ventricular (RV) branch bifurcation (upper image). Note the characteristics of the carina interposed between the parallel origins of the MainB and SideB. Further note the progressive more perpendicular endoluminal views of the RV branch opening (middle image: numbers 1-4) culminating in the almost apparent concealment of the RV branch opening behind the proximal rim of the carina. With more retrograde endoluminal views (middle image: numbers 5-6), this leads to the apparent "disappearance" of the RV branch opening. The bifurcation angle is 57° on the corresponding 3-dimensional QCA (CAAS 5.9, Pie Medical Imaging, Maastricht, The Netherlands) (lower images). Longitudinal and cross-sectional 2D OCT images of the bifurcation, with a blue arrow superimposed on it are used to orientate the reader within the vessel – the base and direction of the blue arrow indicates from and in which direction respectively the 3D image is visualised from in 2D plane(s). Adapted and reproduced from Farooq et al.[9] (with kind permission from Elsevier)*

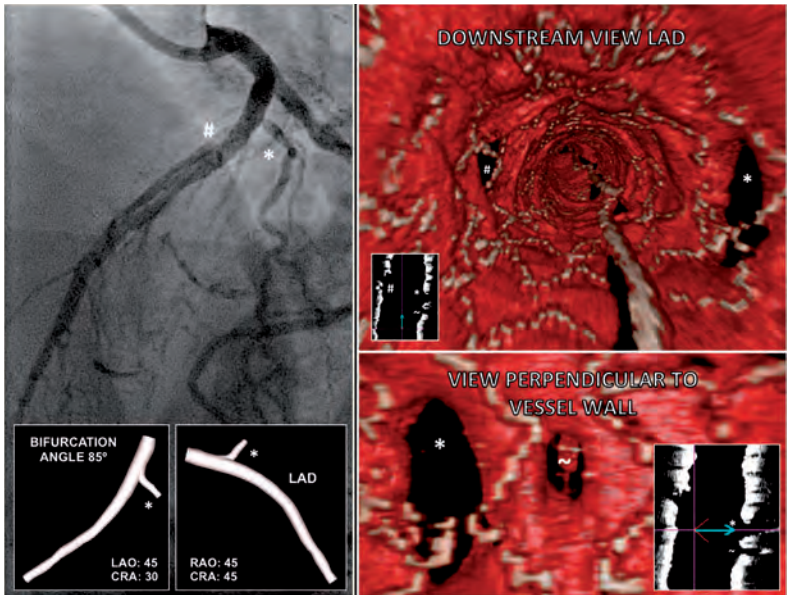


Figure 2. *Principle of a "perpendicular bifurcation". The take-off the SideB (diagonal vessel) from the MainB (left anterior descending artery - LAD) originates perpendicular to the LAD at the point of divergence of both vessel origins, with a bifurcation angle of 85° demonstrated on 3-dimensional QCA.[19] A downstream fly-through view (proximal to distal) of the LAD (upper right image) demonstrates the diagonal vessel opening (asterisked), note the elliptical shape of the vessel opening and the observation that the diagonal vessel opening is fully visible, and not concealed by the carina, when visualised perpendicular to the vessel wall (lower right image). Reproduced from Farooq et al.[9] *indicates diagonal branch, ~ small diagonal branch, # septal branch.*

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Colombo A, Al-Lamee R. Bifurcation lesions: an inside view. *Circ Cardiovasc Interv* 2010;3:94-6.

2. Hildick-Smith D, Lassen JF, Albiero R, Lefevre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y. Consensus from the 5th European Bifurcation Club meeting. *EuroIntervention* 2010;6:34-8.

3. Hildick-Smith D, de Belder AJ, Cooter N, Curzen NP, Clayton TC, Oldroyd KG, Bennett L, Holmberg S, Cotton JM, Glennon PE, Thomas MR, Maccarthy PA, Baumbach A, Mulvihill NT, Henderson RA, Redwood SR, Starkey IR, Stables RH. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation* 2010;121:1235-43.

4. Routledge HC, Morice MC, Lefevre T, Garot P, De Marco F, Vaquerizo B, Louvard Y. 2-year outcome of patients treated for bifurcation coronary disease with provisional side branch T-stenting using drug-eluting stents. *JACC Cardiovasc Interv* 2008;1:358-65.

5. Koo BK, Kang HJ, Youn TJ, Chae IH, Choi DJ, Kim HS, Sohn DW, Oh BH, Lee MM, Park YB, Choi YS, Tahk SJ. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol* 2005;46:633-7.

6. Di Mario C, van der Giessen WJ, Foin N, Adrianssens T, Tyczynski P, Ghilencea L, Viceconte N, Lindsay AC. Optical coherence tomography for guidance in bifurcation lesion treatment. *EuroIntervention* 2011;6:J99-J106.

7. Stankovic G, Darremont O, Ferenc M, Hildick-Smith D, Louvard Y, Albiero R, Pan M, Lassen JF, Lefevre T. Percutaneous coronary intervention for bifurcation lesions: 2008 consensus document from the fourth meeting of the European Bifurcation Club. *EuroIntervention* 2009;5:39-49.

8. Ormiston JA, Webster MW, El Jack S, Ruygrok PN, Stewart JT, Scott D, Currie E, Panther MJ, Shaw B, O'Shaughnessy B. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. *Catheter Cardiovasc Interv* 2006;67:49-55.

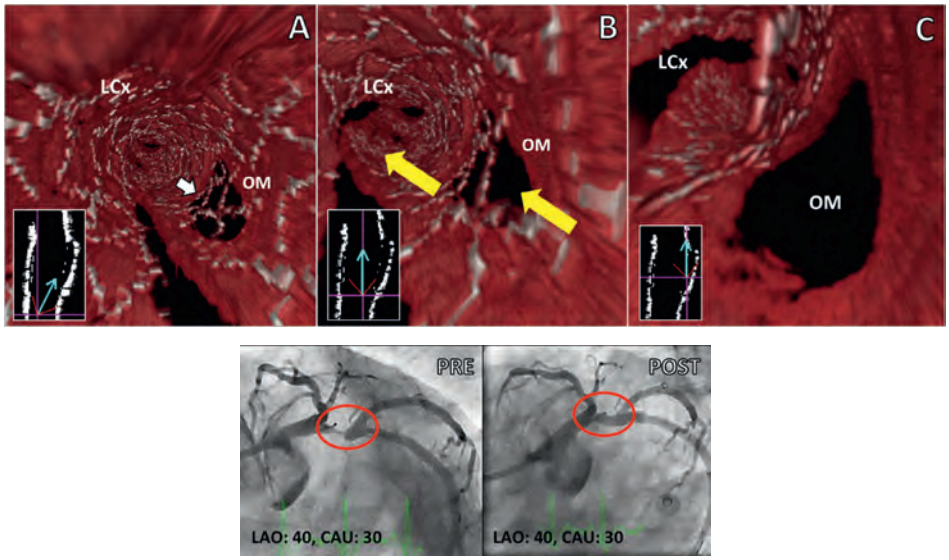


Figure 3. *Provisional T-stenting: the principle of re-crossing the coronary wire (after MainB stenting) into the SideB through the most distal cell in a parallel bifurcation. Progressive downstream fly-through views culminating in the endoluminal point of view being located at the carina (A to C). White arrow indicates the most distal cell where the coronary wire would be recommended to be passed; yellow arrows indicates the parallel courses of the left circumflex coronary artery (LCx) and obtuse marginal (OM) vessels at their point of divergence. Use the orientation figures (inset lower left images) in A-C to locate the endoluminal point-of-view (base of blue arrow). In this parallel bifurcation, the struts located in front of the carina (A) are actually a prominent metallic extension of the carina and not covering the SideB opening (B-C). The potential to advance a coronary wire beneath the malapposed struts in the proximal vicinity of the ostial rim appears to be very real, and if SideB dilatation were performed, would result in multiple unappposed struts taking-off from the carina. Corresponding coronary angiograms are illustrated below. Adapted and reproduced from Farooq et al.[9] (with kind permission from Elsevier)*

9. Farooq V, Serruys PW, Heo JH, Gogas BD, Okamura T, Gomez-Lara J, Brugaletta S, Garcia-Garcia HM, van Geuns RJ. New insights into the coronary artery bifurcation hypothesis-generating concepts utilizing 3-dimensional optical frequency domain imaging. *JACC Cardiovasc Interv* 2011;4:921-31.

10. Okamura T, Yamada J, Nao T, Suetomi T, Maeda T, Shiraishi K, Miura T, Matsuzaki M. Three-dimensional optical coherence tomography assessment of coronary wire re-crossing position during bifurcation stenting. *EuroIntervention* 2011;7:886-7.

11. Tanaka N, Pijls NH, Koolen JJ, Botman KJ, Michels HR, Brueren BR, Peels K, Shindo N, Yamashita J, Yamashina A. Assessment of optimum stent deployment by stent boost imaging: comparison with intravascular ultrasound. *Heart Vessels.* 2011 Oct 29. [Epub ahead of print]

12. Mylotte D, Hovasse T, Ziani A, Lefèvre T, Dumonteil N, Louvard Y, Carrie D. Non-compliant balloons for final kissing inflation in coronary bifurcation lesions treated with provisional T-stenting: a pilot study. *EuroIntervention* 2012;7:1162-1169 .

13. Nam CW, Yoon HJ, Cho YK, Park HS, Kim H, Hur SH, Kim YN, Chung IS, Koo BK, Tahk SJ, Fearon WF, Kim KB. Outcomes of percutaneous coronary intervention in intermediate coronary artery disease: fractional flow reserve-guided versus intravascular ultrasound-guided. *JACC Cardiovasc Interv* 2010;3:812-7.

14. Koo BK, Waseda K, Kang HJ, Kim HS, Nam CW, Hur SH, Kim JS, Choi D, Jang Y, Hahn JY, Gwon HC, Yoon MH, Tahk SJ, Chung WY, Cho YS, Choi DJ, Hasegawa T, Kataoka T, Oh SJ, Honda Y, Fitzgerald PJ, Fearon WF. Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2010;3:113-9.

15. Kang SJ, Mintz GS, Kim WJ, Lee JY, Oh JH, Park DW, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Changes in left main bifurcation geometry after a single-stent crossover technique: an

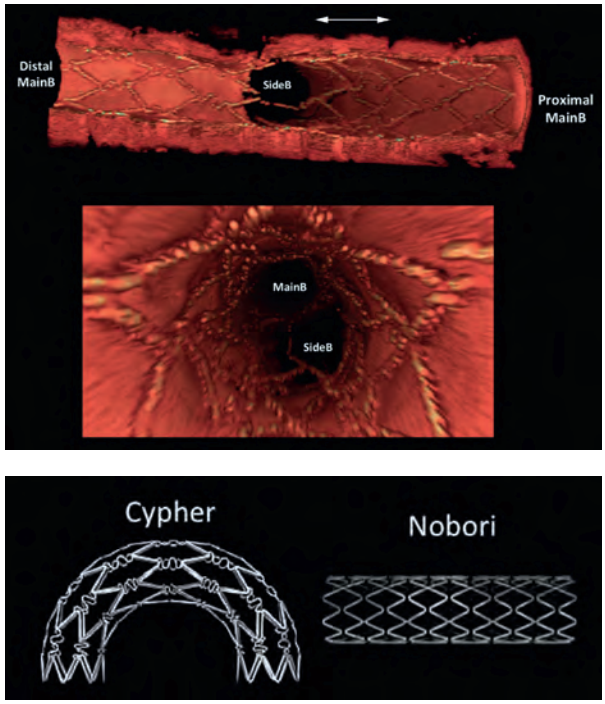


Figure 4. *3D-OCT of a two-stent approach to bifurcation stenting. Complex stenting was performed in a parallel bifurcation in a non-diseased porcine model. Firstly a Nobori® stent (Terumo Corporation, Tokyo, Japan) was deployed from the proximal MainB into the SideB. A Cypher® stent (Cordis Corporation, Johnson & Johnson, Miami Lakes, FL, USA) was subsequently implanted in the MainB – the area of overlap between the SideB and Main B stent was minimal (double white arrow) – followed by kissing balloon post-dilatation (KBPD). Note the malapposed struts straddling the coronary ostium and dividing it into compartments in the oblique longitudinal (upper image) and downstream fly-through views (middle image), presumably secondary to balloon under-sizing during KBPD. If this occurred in the catheterisation laboratory with the availability of on-line 3D-OCT, this may have triggered the operator to ensure the coronary wire was passed into the largest cell in the SideB ostium and to perform KBPD with a larger angioplasty balloon in the SideB. Images of actual Cypher and Nobori stents are displayed below.*

intravascular ultrasound study using direct imaging of both the left anterior descending and the left circumflex coronary arteries before and after intervention. *Circ Cardiovasc Interv.* 2011;4:355-61.

16. Suárez de Lezo J, Medina A, Martín P, Novoa J, Suárez de Lezo J, Pan M, Caballero E, Melián F, Mazuelos F, Quevedo V. Predictors of ostial side branch damage during provisional stenting of coronary bifurcation lesions not involving the side branch origin: an ultrasonographic study. *EuroIntervention* 2012;7:1147-1154.

17. van der Giessen AG, Wentzel JJ, Meijboom WB, Mollet NR, van der Steen AF, van de Vosse FN, de Feyter PJ, Gijsen FJ. Plaque and shear stress distribution in human coronary bifurcations: a multislice computed tomography study. *EuroIntervention* 2009;4: 654-61.

18. Girasis C, Schuurbiers JC, Onuma Y, Serruys PW, Wentzel JJ. Novel bifurcation phantoms for validation of quantitative coronary angiography algorithms. *Catheter Cardiovasc Interv.* 2011;77:790-7.

19. Onuma Y, Girasis C, Aben JP, Sarno G, Piazza N, Lokkerbol C, Morel MA, Serruys PW. A novel dedicated 3-dimensional quantitative coronary analysis methodology for bifurcation lesions. *EuroIntervention* 2011;7:629-35.

20. Vassilev D, Gil R, Kwan T, Nguyen T, Nanjundappa A, Doganov A. Extension distance mismatch--an unrecognized factor for suboptimal side branch ostial coverage in bifurcation lesion stenting. *J Interv Cardiol.* 2010;23:305-18.

21. Medina A, Martin P, Suarez de Lezo J, Amador C, Pan M, Melian F, Hernandez E, Burgos L, Ojeda S, Ortega JR, Garcia A.

Vulnerable carina anatomy and ostial lesions in the left anterior descending coronary artery after floating-stent treatment. *Rev Esp Cardiol.* 2009;62:1240-9.

22. Farooq V, Gogas BD, Okamura T, Heo JH, Magro M, Gomez-Lara J, Onuma Y, Radu MD, Brugaletta S, van Bochove G, van Geuns RJ, Garcia-Garcia HM, Serruys PW. Three-dimensional optical frequency domain imaging in conventional percutaneous coronary intervention: the potential for clinical application. *Eur Heart J.* 2011 Nov 21. [Epub ahead of print]

23. Gogas BD, van Geuns RJ, Farooq V, Regar E, Heo JH, Ligthart J, Serruys PW. Three-Dimensional Reconstruction of the Post-Dilated ABSORB Everolimus-Eluting Bioresorbable Vascular Scaffold in a True Bifurcation Lesion for Flow Restoration. *JACC Cardiovasc Interv* 2011;4:1149-50.

24. Okamura T, Onuma Y, Garcia-Garcia HM, Regar E, Wykrzykowska JJ, Koolen J, Thuesen L, Windecker S, Whitbourn R, McClean DR, Ormiston JA, Serruys PW. 3-Dimensional optical coherence tomography assessment of jailed side branches by bioresorbable vascular scaffolds: a proposal for classification. *JACC Cardiovasc Interv* 2010;3:836-44.

25. Vassilev D, Gil RJ. Relative dependence of diameters of branches in coronary bifurcations after stent implantation in main vessel--importance of carina position. *Kardiol Pol.* 2008;66:371-8; discussion 379.

26. Gil RJ, Vassilev D, Formuszewicz R, Rusicka-Piekarz T, Doganov A. The carina angle-new geometrical parameter associated with periprocedural side branch compromise and the long-term results in coronary bifurcation lesions with main vessel stenting only. *J Interv Cardiol.* 2009;22:E1-E10.

27. Asakaura Y, Takagi S, Ishikawa S, Asakura K, Sueyoshi K, Sakamoto M, Takatsuki S, Oda T, Nakagawa M, Furukawa Y, Oyamada K, Iwanaga S, Ogawa S, Hinohara T. Favorable strategy for the ostial lesion of the left anterior descending coronary artery: influence on narrowing of circumflex coronary artery. *Cathet Cardiovasc Diagn.* 1998;43:95-100.

28. Koo BK, De Bruyne B. FFR in bifurcation stenting: what have we learned? *EuroIntervention.* 2010;6:J94-8.

29. Farooq V, Heo JH, Raber L, Brugaletta S, Radu M, Gogas BD, Diletti R, Onuma Y, Garcia-Garcia HM, Serruys PW. Tools & techniques: risk stratification and diagnostic tools in left main stem intervention. *EuroIntervention.* 2011;7:747-53.

30. Iakovou I, Ge L, Colombo A. Contemporary stent treatment of coronary bifurcations. *JACC* 2005;46:1446-55.

31. Koh JS, Koo BK, Kim JH, Yang HM, Park KW, Kang HJ, Kim HS, Oh BH, Park YB. Relationship Between Fractional Flow Reserve and Angiographic and Intravascular Ultrasound Parameters in Ostial Lesions: Major Epicardial Vessel vs. Side Branch Ostial Lesions.*JACC Cardiovasc Interv* In Press 2011.

Chapter 4.3

Impact of Three-Dimensional Bifurcation Angle on Five-year Outcome of Patients after Percutaneous Coronary Intervention for Left Main Coronary Artery Disease: a Substudy of the SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery (SYNTAX) Trial

Girasis G, Farooq V, Diletti R, Muramatsu T, Bourantas CV, Onuma Y, Holmes DR, Feldman TE, Morel MA, van Es GA, Dawkins KD, Morice MC, Serruys PW

JACC Cardiovasc Interv. 2013;6(12):1250-60 (Impact Factor: 6.552)

Impact of 3-Dimensional Bifurcation Angle on 5-Year Outcome of Patients After Percutaneous Coronary Intervention for Left Main Coronary Artery Disease

A Substudy of the SYNTAX Trial (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery)

Chrysafios Girasis, MD,* Vasim Farooq, MBCHB,* Roberto Diletti, MD,* Takashi Muramatsu, MD,* Christos V. Bourantas, MD, PHD,* Yoshinobu Onuma, MD,* David R. Holmes, MD,† Ted E. Feldman, MD,‡ Marie-Angele Morel, BSC,§ Gerrit-Anne van Es, PHD,§ Keith D. Dawkins, MD,‖ Marie-Claude Morice, MD,¶ Patrick W. Serruys, MD, PHD*

Rotterdam, the Netherlands; Rochester, Minnesota; Evanston, Illinois; Natick, Massachusetts; and Massy, France

Objectives This study sought to investigate the impact of left main coronary artery (LMCA) 3-dimensional (3D) bifurcation angle (BA) parameters on 5-year clinical outcomes of patients randomized to LMCA percutaneous coronary intervention (PCI) in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial.

Background BA can affect outcome after bifurcation PCI; 3D angiographic analysis provides reliable BA measurements.

Methods The diastolic distal BA (between left anterior descending and left circumflex) and its systolic-diastolic range were explored. A stratified post-hoc survival analysis was performed for 5-year major adverse cardiac and cardiovascular events (MACCE) (all-cause death, cerebrovascular accident, myocardial infarction, or repeat revascularization), a safety endpoint (all-cause death, cerebrovascular accident, or myocardial infarction), and repeat revascularization. Analysis was performed in patients where 3D BA was available pre- and post-PCI.

Results Of 266 patients eligible for analysis, 185 underwent bifurcation PCI (group B); 1 stent was used in 75 patients (group B1), whereas ≥2 stents were used in 110 patients (group B2). Stratification across pre-PCI diastolic distal BA tertiles (<82°, 82° to 106°, ≥107°) failed to show any difference in MACCE rates either in the entire study population ($p = 0.99$) or in group B patients ($p = 0.78$). Group B patients with post-PCI systolic-diastolic range <10° had significantly higher MACCE rates (50.8% vs. 22.7%, $p < 0.001$); repeat revascularization and safety endpoint rates were also higher (37.4% vs. 15.5%, $p = 0.002$, and 25.4% vs. 14.1%, $p=0.055$, respectively). Post-PCI systolic-diastolic range <10° was an independent predictor of MACCE (hazard ratio: 2.65; 95% confidence interval: 1.55 to 4.52; $p < 0.001$) in group B patients.

Conclusions A restricted post-procedural systolic-diastolic distal BA range resulted in higher 5-year adverse event rates after LMCA bifurcation PCI. Pre-PCI BA value did not affect the clinical outcome. (J Am Coll Cardiol Intv 2013;6:1250–60)

Percutaneous coronary intervention (PCI) for unprotected left main coronary artery (LMCA) disease is emerging as a reasonable treatment option alternative to coronary artery bypass graft surgery, especially when concomitant coronary artery disease is limited and comorbidities are present (1,2). Data from major randomized trials (3–7) and many registries have led to the upgrade of PCI as a means of revascularization for LMCA ostial and/or shaft stenosis to a class IIa recommendation. However, bifurcation LMCA PCI was assigned a class IIb recommendation; it was deemed to be of considerably higher risk for adverse clinical outcomes than surgery (1,2). Issues such as the choice of (drug-eluting) stent, the number of stents used and individual techniques, SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score, and plaque distribution have all been addressed (8). However, whereas the impact of bifurcation angle (BA) on immediate post-procedural and especially the long-term outcome has been studied in non-LMCA lesions (9–11), its relation to the LMCA PCI is unclear. The studies reporting on this subject were largely on the basis of BA measurements derived from 2-dimensional (2D) quantitative coronary angiography (QCA) and therefore were prone to error; moreover, these studies had a small sample size and/or limited outcome data (12–14).

See page 1261

We have previously explored the 3-dimensional (3D) QCA-based distribution of the LMCA BA variables (diastolic and systolic values, pre- and post-PCI) in a report on the basis of patients that were randomized to PCI in the context of the SYNTAX trial; furthermore, we have provided 12-month outcome data stratified across the distal BA tertile values (15). At that time, the analysis did not show enough evidence to support 3D BA as a potential predictor of outcome; however, there was a weak trend indicating higher adverse event rates in patients with wider distal LMCA angles when ≥2 stents were implanted in the LMCA bifurcation. Now having 5-year outcome data available (16), we investigate once more the topic to attempt to get conclusive evidence on the impact of 3D BA on very long-term outcome after LMCA PCI and, if possible, to gain insight into the possible mechanisms whereby this effect is mediated.

Methods

Study population. This is a substudy of the SYNTAX trial (4), which was a randomized, prospective, multicenter, all-comers clinical trial with the overall goal of assessing the optimum revascularization treatment for patients with de novo 3-vessel disease or LMCA disease (either isolated or in combination with 1-, 2-, or 3-vessel disease). Patients (N = 1,800) amenable to either treatment option were randomized to PCI with polymer-based, paclitaxel-eluting Taxus Express (Boston Scientific Corporation, Natick, Massachusetts) stents or coronary artery bypass graft surgery; they were also stratified according to the presence or absence of LMCA disease. For the purpose of this study, we reviewed the cineangiograms of the 354 patients who actually underwent PCI of the LMCA stem (5). Patients with both distal and nondistal LMCA lesions were evaluated; the ones in whom 3D angiographic reconstruction could be performed to derive the LMCA BA parameters both pre- and post-procedure constituted our original study population (Fig. 1) (15). This study was not pre-specified in the SYNTAX trial protocol and was not subsidized by the official sponsor of the trial, Boston Scientific Corporation. Nevertheless, previous permission was sought and granted by the steering committee to access and analyze this dataset.

Abbreviations and Acronyms

BA = bifurcation angle
CI = confidence interval(s)
HR = hazard ratio(s)
LMCA = left main coronary artery
MACCE = major adverse cardiac and cardiovascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
SB = side branch
SDR = systolic-diastolic range
2D = 2-dimensional
3D = 3-dimensional

Treatment. Procedures were performed according to local practice and at the investigator's discretion. In the Taxus arm, clopidogrel was mandated for at least 6 months after the procedure, whereas patients were advised to maintain aspirin therapy indefinitely. Recommended procedural techniques included complete coverage of lesions with stent overlapping (where required) at both margins by ~4 mm and use of final kissing balloons inflation after bifurcation stenting (5).

Endpoints and definitions. The primary endpoint of the SYNTAX trial was a composite of major adverse cardiac and

From the *Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands; †Department of Cardiovascular Disease and Internal Medicine, Mayo Clinic, Rochester, Minnesota; ‡Division of Cardiology, Evanston Hospital, Evanston, Illinois; §Cardialysis B.V., Rotterdam, the Netherlands; ||Boston Scientific Corporation, Natick, Massachusetts; and the ¶Department of Cardiology, Institut Cardiovasculaire Paris Sud, Massy, France. Dr. Feldman has received grant support and consulting and/or lecture fees from Abbott Vascular, Boston Scientific, and Edwards Lifesciences. Dr. Dawkins is an employee and stockholder of Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 2, 2013; accepted August 14, 2013.

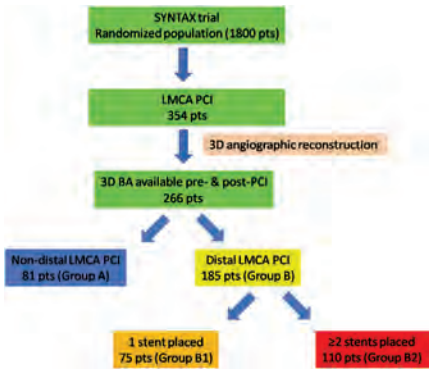


Figure 1. Flow Diagram Indicating the Entire Study Population Synthesis and Subgroups

Out of the entire randomized study population of 1800 patients, 354 patients actually underwent PCI of the LMCA stem; however, 3D angiographic reconstruction could be performed both pre- and post-PCI in only 266 patients. Thereof, 185 patients underwent distal LMCA PCI, wherein 2 stents or more were placed in 110 patients. LMCA = left main coronary artery; PCI = percutaneous coronary intervention; pts = patients; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; 3D = 3-dimensional.

cardiovascular events (MACCE) (all-cause death, cerebrovascular accident, myocardial infarction [MI], or repeat revascularization) throughout the 12-month period following treatment allocation. Definitions of clinical events have been previously described in detail (4,17). All adverse events were adjudicated by an independent clinical events committee; stent thrombosis has been adjudicated according to the study protocol. Patient follow-up has been conducted on an annual basis until 5 years after treatment allocation.

Angiographic analysis. 3D reconstruction was performed offline by 2 experienced operators (C.G. and Y.O.), who were blinded to individual patient data and clinical outcome, with a validated program for 3D QCA (CardiOp-B system, version 2.1.0.151, Paieon Medical Ltd., Rosh Ha'ayin, Israel). The distal BA was measured between the left anterior descending and the left circumflex coronary arteries designated as the distal main vessel and the side branch (SB), respectively; 3D reconstructions were performed at end diastole and end systole, both pre- and post-procedure. In this study, the diastolic distal BA and its systolic-diastolic range (SDR) were explored pre- and post-procedure. The latter variable (SDR) was defined as the absolute difference between diastolic and systolic distal BA values. On occasion, systolic values exceeded the diastolic ones; however, only absolute (positive) terms were studied. To prospectively grade the complexity of coronary artery disease, the Angiographic Core Laboratory (Cardialysis BV, Rotterdam, the Netherlands) scored the angiograms according to the SYNTAX score algorithm (18). LMCA bifurcation lesion type was adjudicated according to Medina; [1,1,1], [1,0,1], and [0.1,1] lesion types are summarily called true bifurcation lesions. Because the staff of the angiographic core laboratory was blinded to site information, adjudicated lesions for the SYNTAX score derivation could not be matched between core laboratory and site; we chose to report bifurcation type per site to be concordant with the choice of stenting technique.

Study design. Tertile and/or median values of the aforementioned angulation variables were used to stratify clinical outcomes. Pre-procedural values were explored over the entire study population, that is patients with nondistal (group A) and distal LMCA PCI (group B) (Fig. 1). However, regarding the post-procedure values and the change in LMCA bifurcation geometry conferred by PCI, it was deemed more meaningful to study their association with clinical outcomes only for patients in group B, whether they had 1 stent (group B1) or ≥2 stents (group B2) placed across the LMCA bifurcation.

Statistical analysis. Statistical analysis was performed using SPSS for Windows (version 19.0, SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD and compared between groups by the unpaired Student *t* test; paired Student *t* test was employed for within-group comparisons. Categorical variables are presented as counts and/or percentages; comparisons were performed with the chi-square test and the Fisher exact test as appropriate.

Cumulative 5-year event rates for MACCE, a safety composite endpoint (all-cause death, cerebrovascular accident, or MI) and stent thrombosis were calculated according to the Kaplan-Meier method. Event rates were compared according to the Cox proportional hazards model. Independent predictors of 5-year MACCE, repeat revascularization, and the safety endpoint were sought among variables significant beyond the level of $p = 0.10$ in univariable analysis. Potential predictors were checked for collinearity before entering a Cox regression multivariable backward stepwise model; variables with a variance inflation factor >2.5 were disqualified. Crude and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported for qualifying variables. All statistical tests were 2-sided and a p value of <0.05 was considered statistically significant.

Results

Five-year clinical follow-up was attained for 259 (97.4%) patients (median: 1,826 days, range: 4 to 2,082 days); 7 patients were lost to follow-up and were censored at days 389, 1,105, 1,442, 1,462, 1,462, 1,473, and 1,489,

Table 1. Baseline Clinical Characteristics in Patients With LMCA PCI (n = 266)

	Nondistal LMCA Group A, (n = 81)	Distal LMCA Group B, (n = 185)	p Value	Distal 1 Stent Group B1, (n = 75)	Distal ≥2 Stents Group B2, (n = 110)	p Value
Age, yrs	64.9 ± 9.4	65.3 ± 10.0	0.76	64.2 ± 10.3	66.1 ± 9.7	0.21
Male	54 (66.7)	142 (76.8)	0.10	61 (81.3)	81 (73.6)	0.29
BMI, kg/m^2	28.3 ± 5.2	28.1 ± 4.9	0.72	28.0 ± 4.7	28.2 ± 5.1	0.81
Diabetes mellitus	22 (27.2)	41 (22.2)	0.43	15 (20.0)	26 (23.6)	0.59
Hypertension	55/79 (69.6)	126 (68.1)	0.89	52 (69.3)	74 (67.3)	0.87
Hyperlipidemia	65 (80.2)	149 (80.5)	1.00	59 (78.7)	90 (81.8)	0.71
Current smoker	18 (22.2)	36 (19.5)	0.62	19 (25.3)	17 (15.5)	0.13
Prior myocardial infarction	25 (30.9)	47 (25.5)	0.37	20 (26.7)	27 (24.8)	0.86
Unstable angina	25 (30.9)	54 (29.2)	0.77	21 (28.0)	33 (30.0)	0.87
LVEF <30%	1 (1.2)	4 (2.2)	1.00	3 (4.0)	1 (0.9)	0.31
Prior TIA	5 (6.2)	9 (4.9)	0.77	3 (4.0)	6 (5.5)	0.74
Creatinine >200 μmol/l	0 (0.0)	5 (2.7)	0.33	2 (2.7)	3 (2.7)	1.00
Emergent revascularization priority	3 (3.7)	5 (2.7)	0.70	0 (0.0)	5 (4.5)	0.08
Additive EuroSCORE	3.7 ± 2.3	3.8 ± 2.9	0.79	3.6 ± 3.1	4.0 ± 2.8	0.39
SYNTAX score*	23.5 ± 10.5	32.6 ± 13.5	<0.001	30.6 ± 12.4	34.0 ± 14.1	0.10
Lesion number	2.6 ± 1.6	3.0 ± 1.8	0.23	3.1 ± 1.7	2.9 ± 1.8	0.76
Isolated LMCA	20 (24.7)	12 (6.5)	<0.001	5 (6.7)	7 (6.3)	1.00
LMCA + 1 vessel	27 (33.3)	22 (11.9)	<0.001	13 (17.3)	9 (8.2)	0.07
LMCA + 2 vessels	20 (24.7)	86 (46.5)	0.001	32 (42.7)	54 (49.1)	0.45
LMCA + 3 vessels	14 (17.3)	65 (35.1)	0.003	25 (33.3)	40 (36.4)	0.75

Values are mean ± SD or n (%). *Calculated by the core laboratory.

BMI = body mass index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIA = transient ischemic attack.

respectively. The baseline characteristics of the study population are shown in Table 1 stratified according to LMCA lesion location and bifurcation stenting technique (1 or ≥2 stents). Compared with group A patients, in group B patients, coronary artery disease was significantly more extensive as indicated by the increased SYNTAX score (32.6 ± 13.5 vs. 23.5 ± 10.5, $p < 0.001$) and percentage of patients with LMCA plus 2- or 3-vessel disease (81.6% vs. 42.0%, $p < 0.001$). Complete revascularization rates were comparable between groups A and B (67.9% vs. 64.3%, $p = 0.68$); 3.0 ± 1.9 stents with a total length of 51.0 ± 39.0 mm were used in the former, whereas 4.2 ± 2.4 stents with a total length of 77.7 ± 47.9 mm were used in the latter ($p < 0.001$ for both).

Complex stenting techniques were applied to patients with more complex bifurcation disease; 85 of 108 true bifurcation lesions were treated with ≥2 stents (Table 2). However, in 19 cases of a [1,1,1] bifurcation lesion, provisional T stenting was performed; in 14 of these cases, the procedure was finished with a kissing balloon inflation. Overall, final kissing balloon inflation was employed more frequently after complex bifurcation stenting ($p < 0.001$).

BA variables. Angulation variables for patients with LMCA bifurcation PCI are shown in Table 3. There is a significant post-procedural decrease in the diastolic distal BA ($\Delta = -6.3°$, $p < 0.001$), whereas SDR is only slightly decreased ($\Delta = -0.5°$, $p = 0.50$). On average, SDR is slightly increased after single-stenting ($\Delta = 0.7°$, $p = 0.45$), whereas moderately decreased by complex stenting ($\Delta = -1.3°$, $p = 0.17$); however, direction and extent of change vary significantly among 2-stent techniques ($p < 0.01$) (Fig. 2).

Impact on outcome. Stratification across pre-PCI diastolic distal BA tertiles (<82°, 82° to 106°, ≥107°) failed to show any difference in MACCE rates either in the entire study population (37.1%, 37.7%, and 35.6%, respectively, $p = 0.99$), or in group B patients (33.7%, 40.3%, and 35.6%, respectively, $p = 0.78$). Kaplan-Meier curves slightly diverged for patients in group B2 ($p = 0.41$), mainly due to relatively increased safety endpoint rates for patients in the middle tertile; this was not the case for group B1 (Fig. 3). Repeat revascularization rates did not show any significant differences across tertiles ($p = 0.42$ and 0.77 for groups B1 and B2, respectively) (Fig. 3); on the other hand, there was a strong trend for increased MI rates for patients with BA <82° in group B2 (17.5%, 16.8%, and 0.0% for low, mid-, and high tertiles, respectively, $p = 0.06$) that was not seen in group B1 (5.3%, 4.2%, and 6.6%, respectively, $p = 0.91$).

Stratification across post-PCI diastolic distal BA tertile values (<79°, 79° to 98°, ≥99°) did not show any significant difference in MACCE rates in group B (37.1%, 31.0%, and 42.0%, respectively, $p = 0.29$). There was a trend for increased safety endpoint rates in patients in the third tertile (13.5%, 17.7%, and 27.7% for low, mid-, and high tertiles, respectively, $p = 0.12$); however, this was not the case for

Table 2. Baseline Angiographic and Procedural Characteristics for Patients With LMCA Bifurcation PCI (n = 185)

	Distal 1 Stent Group B1, (n = 75)	Distal ≥2 Stents Group B2, (n = 110)	p Value
Bifurcation type per LMCA lesion			<0.001
Medina 1,1,1	19 (25.3)	71 (64.5)	<0.001
Medina 1,1,0	21 (28.0)	8 (7.3)	<0.001
Medina 1,0,1	4 (5.4)	14 (12.7)	0.13
Medina 1,0,0	31 (41.3)	17 (15.5)	<0.001
True bifurcation lesions	23 (30.7)	85 (77.3)	<0.001
Nontrue bifurcation lesions	52 (69.3)	25 (22.7)	<0.001
Bifurcation stenting technique			N/A
Provisional T-stenting	75 (100.0)	0 (0.0)	
Classic T-stenting, main vessel first	0 (0.0)	36 (32.7)	
Classic T-stenting, side branch first	0 (0.0)	12 (10.9)	
Modified T-stenting	0 (0.0)	6 (5.5)	
Crush technique	0 (0.0)	18 (16.4)	
Culotte technique	0 (0.0)	23 (20.9)	
V stenting, kissing stents	0 (0.0)	13 (11.8)	
Y stenting, touching stents	0 (0.0)	2 (1.8)	
Final kissing balloon inflation	46 (61.3)	97 (88.2)	<0.001
Complete revascularization	54 (72.0)	65 (59.1)	0.09
Total stents per patient	3.5 ± 2.2	4.8 ± 2.4	<0.001
Total stent length per patient, mm	65.4 ± 43.1	86.1 ± 49.4	0.004

Values are n (%) or mean ± SD.
N/A = not applicable; other abbreviations as in Table 1.

Table 3. BA Variables for Patients With LMCA Bifurcation PCI

	Distal 1 Stent Group B1, (n = 75)	Distal ≥2 Stents Group B2, (n = 110)	p Value
Pre-PCI distal BA, diastolic °	99.2 ± 23.7	93.3 ± 23.3	0.10
Post-PCI distal BA, diastolic °	92.7 ± 21.2	87.2 ± 21.2	0.09
Pre-PCI SDR °	11.0 ± 7.1	11.1 ± 8.8	0.92
Post-PCI SDR °	11.7 ± 7.8	9.8 ± 7.6	0.12

Values are mean ± SD.
BA = bifurcation angle; SDR = systolic-diastolic range (of distal BA); other abbreviations as in Table 1.

repeat revascularization rates (31.5%, 23.5%, and 23.8%, respectively, p = 0.55).

Systolic-diastolic BA range both pre- and post-procedure had a median value of 10°. There was no significant difference in MACCE rates for patients in group B with pre-PCI SDR ≥10° (40.6% vs. 32.5%; HR: 1.25; 95% CI: 0.77 to 2.02; p = 0.37). Conversely, patients with post-PCI SDR <10° showed significantly higher MACCE rates for group B (50.8% vs. 22.7%; HR: 2.65; 95% CI: 1.58 to 4.44; p < 0.001), group B1 (46.9% vs. 16.4%; HR: 3.47; 95% CI: 1.41 to 8.55; p = 0.01) and group B2 (52.8% vs. 28.0%; HR: 2.16; 95% CI: 1.15 to 4.07; p = 0.02). The event rates for all different endpoints for the entire group B are reported in Table 4 stratified across the post-PCI SDR median value. Moreover, in both subgroups, higher event rates were recorded for patients with post-PCI SDR <10° regarding repeat revascularization (p = 0.07 and 0.02 for groups B1 and B2) and the safety endpoint (p = 0.08 and 0.35 for groups B1 and B2) (Fig. 4). Finally, group B patients with even minimally increased SDR post-procedure (ΔSDR = post-PCI SDR minus pre-PCI SDR) showed significantly lower MACCE rates (28.6% vs. 43.9%; HR: 0.60; 95% CI: 0.37 to 0.99, p = 0.045), compared with patients with ΔSDR ≤0.

Stent thrombosis. Per protocol, stent thrombosis was adjudicated in 13 patients in the entire study population (4.9%). Of those 13, 9 had LMCA bifurcation PCI (4.9%); thereof 8 belonged to group B2. Among these 9 patients, 5 events occurred early (≤30 days), 1 event late (day 318), and 3 events very late (days 598, 835, and 1,594). If stratified across diastolic distal BA, there was a trend for higher stent thrombosis rates in the lowest angle tertiles (8.5%, 5.4%, and 1.6%, p = 0.23, and 8.5%, 3.5%, and 3.3%, p = 0.33, pre- and post-PCI, respectively); however, difference was mainly driven by early events (3 events each in the lowest angle tertiles). There was also a trend for higher event rates for patients with narrower post-PCI SDR (8.0% vs. 2.2%; HR: 3.75; 95% CI: 0.78 to 18.2, p = 0.10) (Table 4), which reflected a similar trend among group B2 patients with post-PCI SDR <10° (12.2% vs. 2.0%; HR: 6.21; 95% CI: 0.77 to 50.0, p = 0.09).

Multivariable analysis. In group B, next to a post-PCI SDR of the distal BA <10°, a number of variables were significantly associated with or showed a strong trend for (p < 0.10 in univariable analysis) higher MACCE rates (Table 5). Total stent length was eliminated from analysis due to collinearity with the total number of stents. The narrow post-PCI SDR emerged as an independent predictor of MACCE (HR: 2.65; 95% CI: 1.55 to 4.52, p < 0.001) next to poor left ventricular ejection fraction (HR: 7.53; 95% CI: 2.63 to 21.6, p < 0.001) and the total number of stents placed in a patient (HR: 1.13; 95% CI: 1.03 to 1.24, p < 0.01). Following a similar analysis, a narrow post-PCI SDR independently predicted increased rates for both repeat revascularization (HR: 2.39; 95% CI: 1.26 to 4.52, p < 0.01) next to the total number of stents (HR: 1.16; 95% CI: 1.05 to 1.29, p < 0.01) and for the safety endpoint (HR: 2.06; 95% CI: 1.03 to 4.12, p = 0.04) next to previous MI (HR: 2.93; 95% CI: 1.50 to 5.71, p < 0.01) and poor left ventricular ejection fraction (HR: 4.78; 95% CI: 1.37 to 16.6, p = 0.01).

Discussion

The following are the main findings of this study. 1) The pre-procedural 3D QCA-derived diastolic distal BA of the

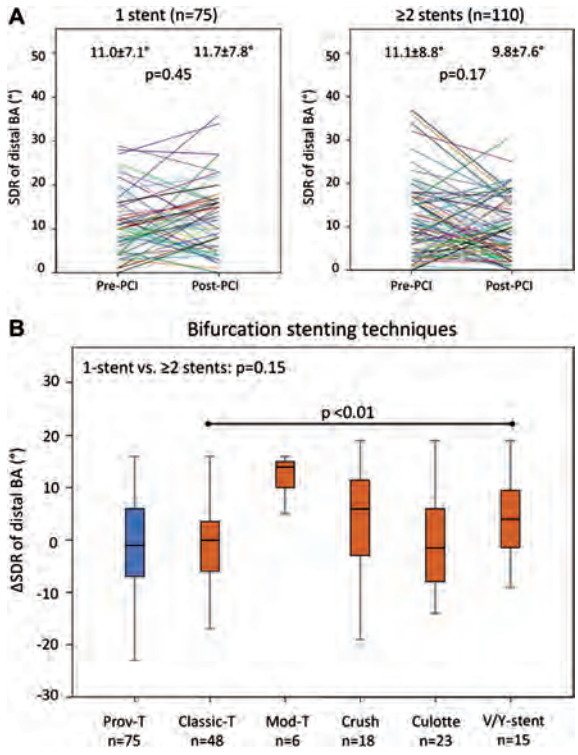


Figure 2. Effect of Bifurcation Stenting on the SDR of the Distal BA

(A) Periprocedural change in systolic-diastolic range (SDR) according to the number of stents implanted. **(B)** Difference in SDR (ΔSDR = post-PCI SDR – pre-PCI SDR) according to bifurcation stenting technique. BA = bifurcation angle; Mod-T = modified T-stenting; PCI = percutaneous coronary intervention; Prov-T = provisional T-stenting; V = kissing stenting; Y = touching stenting.

LMCA bifurcation could not predict long-term clinical outcomes after PCI for LMCA coronary artery disease. Even when patients with LMCA bifurcation PCI were examined separately, there was still no significant impact of this parameter on long-term clinical outcomes. 2) A narrow (<10°) post-PCI systolic-diastolic range of this angle was shown to be significantly associated with worse 5-year clinical outcomes in patients undergoing LMCA bifurcation PCI. Adjusted for various clinical, angiographic (including extent of concomitant disease), and procedural variables, it still proved an independent predictor of 5-year MACCE.

To our knowledge, this is the first study ever to report on such long-term clinical outcomes of LMCA PCI stratified across BA parameters exclusively derived from 3D angiographic bifurcation analysis. The relative merits of 3D angiography have already been stressed (15); regarding the BA derivation, 3D angiographic analysis is of apparent importance as the bifurcation is a 3D structure, and therefore its maximal opening can be accurately appreciated only in a 3D space (19). Moreover, on the basis of a phantom validation study, 3D QCA has recently been shown to provide more accurate and precise BA measurements than 2D software does (20).

Effect of SDR. The idea that a decreased post-PCI systolic-diastolic range of movement of the LMCA (or any) bifurcation is associated with higher event rates may on first

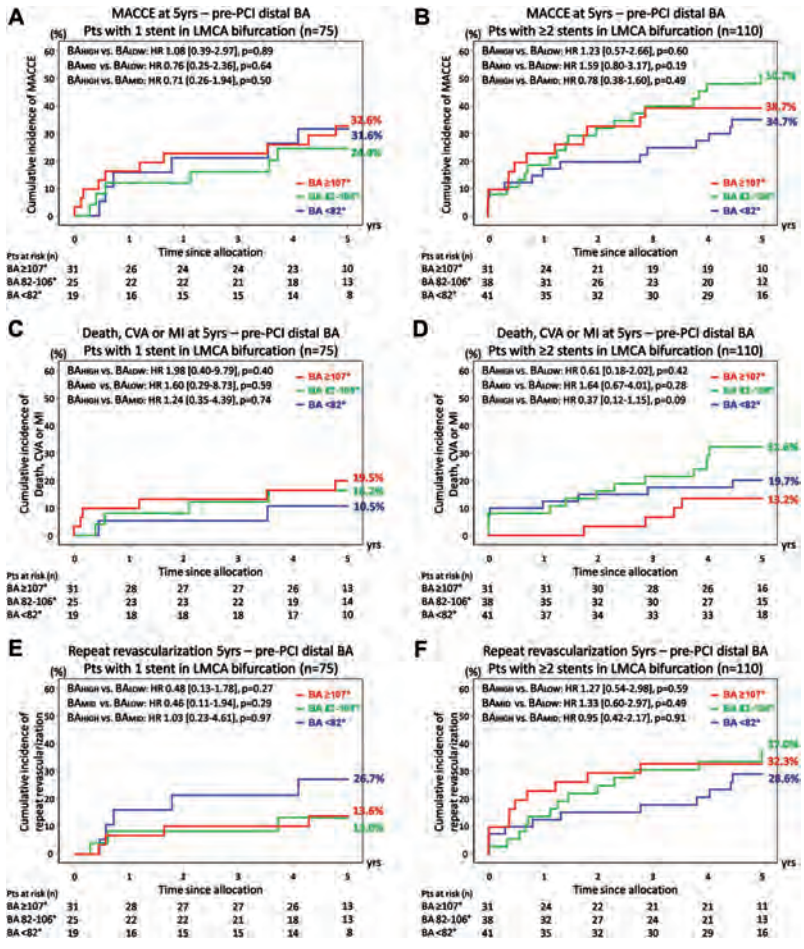


Figure 3. Impact of Pre-PCI Diastolic Distal BA on 5-Year MACCE, All-Cause Death, CVA, or MI (Safety Endpoint), and Repeat Revascularization

Kaplan-Meier curves shown for group B1 **(A, C, E)** and group B2 **(B, D, F)**. CVA = cerebrovascular accident; HR = hazard ratio; LMCA = left main coronary artery; MACCE = major adverse cardiac and cardiovascular events; MI = myocardial infarction; other abbreviations as in Figures 1 and 2.

print & web 4C/FPO

inspection sound like a paradox. It would be assumed that in the long term an increased range of torsion, flexion, and stretching of any metallic structure would lead to metal fatigue and eventually strut fracture (21,22). The premise we are making is the same, only seen in a different perspective. The diminished range of movement after the procedure, even more pronounced after complex stenting (Fig. 2), implies that the bifurcation has been "stiffened" by the stents and forced into an unnatural configuration. Therefore, the myocardium and hence the epicardial coronary arteries strive

Table 4. Five-Year Clinical Outcomes Stratified Across Post-PCI SDR in Patients With LMCA Bifurcation PCI (Univariable Analysis)

	SDR $<10^{\circ}$ (n = 92)	SDR $\geq 10^{\circ}$ (n = 93)	$<10^{\circ}$ vs. $\geq 10^{\circ}$	p Value
MACCE	50.8	22.7	2.65 (1.58–4.44)	<0.001
Death, CVA, or MI	25.4	14.1	1.95 (0.99–3.85)	0.055
Death	17.7	7.6	2.48 (1.02–6.02)	0.045
Repeat revascularization	37.4	15.5	2.70 (1.44–5.05)	0.002
MI	12.4	6.6	1.98 (0.73–5.35)	0.18
Stent thrombosis, per protocol	8.0	2.2	3.75 (0.78–18.2)	0.10

Values are % or hazard ratio (95% confidence interval).
CVA = cerebrovascular accident; MACCE = major adverse cardiac and cardiovascular events; MI = myocardial infarction; other abbreviations as in Tables 1 and 3.

to revert to the previous geometry (23,24), thereby exerting increased and repetitive strain on the metallic scaffolds. It has been reported that the Taxus Express metallic platform is not prone to strut fractures at least to the same extent as the Cypher stent (Cypher, Cordis, Johnson and Johnson Corporation, Miami, Florida) (22). This has been attributed to the Taxus Express open-cell design, which is said to enhance its conformability around bends (23) as well as to its diminished radiopacity, which makes fractures more difficult to detect angiographically. Stent strut fractures have been mostly explored in straight vessel segments; even there, high vessel tortuosity and excessive vessel angulation during the heart cycle were reported to be precipitating factors (24–26), especially in the presence of long overlapping stents. Even so, stent strut fractures seldom translate into stent thrombosis, MI, or sudden death (22), but rather in a hinge motion associated with in-stent restenosis (26); however, when seen in the context of the LMCA bifurcation, otherwise occult restenotic lesions could very well lead to catastrophic outcomes.

Effect of distal BA. Intuitively, the distal BA has been associated with the risk of SB occlusion during stent implantation in the main vessel (27); a shallow distal BA makes a carina shift more probable, thereby resulting in considerable residual stenosis (28). Moreover, for BA $\leq 70^{\circ}$, classic T stenting cannot fully scaffold the SB ostium without stent struts protruding into the main vessel (29); dedicated techniques, such as the crush and the culotte, that fully cover the SB ostium have been developed to address this issue. However, a shallow angle necessitates an increased stent cell size to avoid jailing the SB ostium after the crush or causing a napkin ring stenosis in the ostium of the distal main vessel after a culotte. Theoretically, for BA $\sim 60^{\circ}$, a distal main vessel diameter of 3 mm and an SB diameter of 2.75 mm, a stent cell diameter of ~ 3.3 mm would be required (30), which could be achieved with the Taxus Express metallic stent platform (31).

Moving to steeper angles, bench studies have shown that for BA $>80^{\circ}$, full stent strut apposition cannot be achieved with the crush (32,33) or the culotte techniques despite sequential kissing balloon inflations (34); straightening of the LMCA curvature could cause added distortion. Thereby, gaps in support and drug application are left at the SB ostium, which probably translate into higher adverse event rates for highly angulated bifurcations (9–12). At the same time, increasing BA have been associated with decreasing lower wall shear stress values and increased oscillatory flow at the lateral walls opposite the carina (35,36), which facilitate plaque proliferation and eventually restenosis; contrary to sirolimus, paclitaxel cannot modify the effect of low wall shear stress on neointima formation (37). Expectedly, all these phenomena are exacerbated in the presence of multiple stent strut layers, metallic neo-carinas, and protruding and malapposed struts.

Implementation and clinical implications. A single 3D angiographic reconstruction of a bifurcation requires 2 adequate images 30° apart with the least possible amount of foreshortening and vessel overlap. For a given bifurcation, there is usually 1 optimal view, whereas in any other direction certain features, usually the SB ostium, may be obscured; retrospective collection of 2 adequate images can be challenging. However, new software algorithms can retrieve missing information even from 2 suboptimal images, whereas the optimal view, if not among the images initially acquired, can be suggested by a provisional 3D reconstruction on the basis of 2 suboptimal views (20). Moreover, dedicated computation algorithms implemented in commercially available 2D and 3D bifurcation QCA software allow for accurate and reproducible BA calculation; time requirements (<10 s for reconstruction of 2 images, <60 s for 3 images) are not an issue.

The interventional cardiologist can do little to change the geometrical configuration of the LMCA bifurcation after the stent implantation, as long as this is done according to sound clinical practice facilitating free access to SB and good stent strut apposition to the vessel wall. Our findings may suggest a lesser degree of bifurcation stiffening with single bifurcation stenting; however, no solid recommendation could be issued on the basis of a single study. Nevertheless, in those cases where a decreased post-procedural range of movement can be manifested, there would probably be a need for potent and prolonged platelet inhibition and increased clinical surveillance.

Study limitations. This study was not pre-specified in the SYNTAX trial protocol and therefore was probably underpowered regarding the detection of a plausible effect of pre-PCI angulation parameters on clinical outcomes. Our analysis may have been further confounded by marked heterogeneity in bifurcation techniques, the number of stents used, the bifurcation type, the extent of final kissing balloon inflation, and other unforeseen and possibly unaccounted for periprocedural phenomena. In addition, data on maintenance of dual antiplatelet therapy were not available. On the

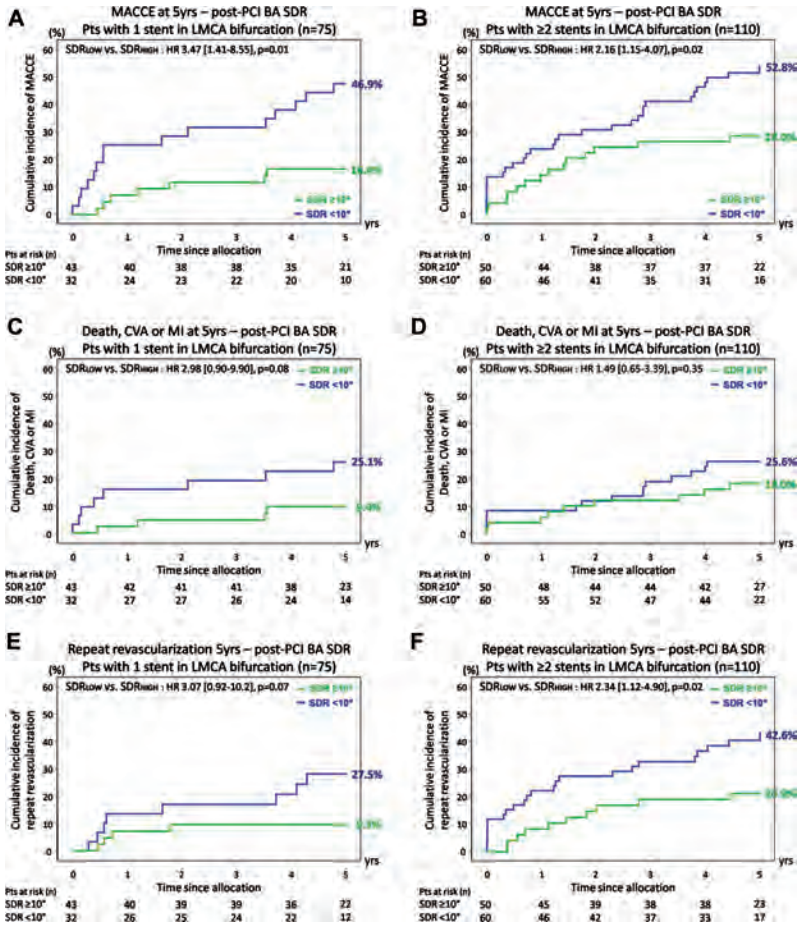


Figure 4. Impact of Post-PCI SDR of the Distal BA on 5-Year MACCE, All-Cause Death, CVA, or MI (Safety Endpoint), and Repeat Revascularization

Kaplan-Meier curves shown for group B1 **(A, C, E)** and group B2 **(B, D, F)**. Abbreviations as Figures 1 to 3.

other hand, per SYNTAX trial design, repeat revascularization events have not been adjudicated as to their anatomic location (5); therefore, clinical events cannot be necessarily ascribed to the LMCA lesion treatment. However, specifically for SDR analysis, events have been adjusted in multivariable analysis for individual patient characteristics, including additional vessel disease. Finally, Medina classification according to visual assessment is less precise in stratifying bifurcation lesion complexity; thus, detailed subsegmental angiographic analysis would be warranted for a better understanding of lesion complexity and possible association with outcomes. As already mentioned, 3D QCA analysis was not pre-specified in the SYNTAX trial protocol; therefore, such detailed results are not available

Table 5. Predictors of 5-Year MACCE in Patients With LMCA Bifurcation PCI

	Crude	p Value	Adjusted	p Value
Prior myocardial infarction	1.99 (1.21–3.27)	0.007		
Unstable angina	1.85 (1.13–3.03)	0.014		
Diabetes mellitus	1.69 (1.00–2.85)	0.050		
LVEF <30%	5.26 (1.90–14.6)	0.001	7.53 (2.63–21.6)	<0.001
Additive EuroSCORE*	1.07 (1.001–1.15)	0.046		
Total stents per patient*	1.17 (1.06–1.28)	0.001	1.13 (1.03–1.24)	0.009
Total stent length per patient*	1.005 (1.00–1.01)	0.04		
Post-PCI SDR <10°	2.65 (1.58–4.44)	<0.001	2.65 (1.55–4.52)	<0.001

Values are hazard ratio (95% confidence interval). *Per unit increase.
Abbreviations as in Tables 1, 3, and 4.

from the current analysis. Angiographic analysis including prospective collection of BA data in the ongoing EXCEL (Evaluation of Xience Prime Everolimus Eluting Stent System [EECSS] or Xience V EECSS or Xience Xpedition EECSS of Xience Pro EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial on ~3,100 patients undergoing LMCA PCI could help us shed more light on this subject.

Conclusions

This study assessed the impact of 3D distal BA parameters on 5-year clinical outcomes after LMCA PCI on the basis of the largest randomized trial to date. A restricted post-procedural systolic-diastolic distal BA range translated into significantly higher adverse event rates 5 years after LMCA bifurcation PCI; on the contrary, pre-procedural distal BA did not affect the long-term clinical outcomes. It is possible that this study provides us with new insights into the biomechanics of stent failure in bifurcation lesions, the LMCA bifurcation being the most important of all in the human coronary tree.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Department of Cardiology, Erasmus Medical Center Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Wijns W, Kolh P, Danchin N, et al., for the Task Force on Myocardial Revascularization of the ESC, EACTS, and EAPCI. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
2. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.
3. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008;51:538–45.
4. Serruys PW, Morice MC, Kappetein AP, et al., for the SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360:961–72.
5. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial. Circulation 2010;121:2645–53.
6. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011; 364:1718–27.
7. Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol 2011;57:538–45.
8. Capodanno D, Calvi V, Tamburino C. A focused update on emerging prognostic determinants in distal left main percutaneous coronary intervention. Int J Cardiol 2012;160:4–7.
9. Dzavik V, Kharbanda R, Ivanov J, et al. Predictors of long-term outcome after crush stenting of coronary bifurcation lesions: importance of the bifurcation angle. Am Heart J 2006;152:762–9.
10. Adriaenssens T, Byrne RA, Dibra A, et al. Culotte stenting technique in coronary bifurcation disease: angiographic follow-up using dedicated quantitative coronary angiographic analysis and 12-month clinical outcomes. Eur Heart J 2008;29:2868–76.
11. Collins N, Seidelin PH, Daly P, et al. Long-term outcomes after percutaneous coronary intervention of bifurcation narrowings. Am J Cardiol 2008;102:404–10.
12. Chen S, Zhang J, Ye F, et al. Final kissing balloon inflation by classic crush stenting did not improve the clinical outcomes for the treatment of unprotected left main bifurcation lesions: the importance of double-kissing crush technique. Catheter Cardiovasc Interv 2008;71:166–72.
13. Onuma Y, Girasis C, Piazza N, et al., for Interventional Cardiologists at Thoraxcenter 2000–2005. Long-term clinical results following stenting of the left main stem: insights from RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. J Am Coll Cardiol Intv 2010;3:584–94.
14. Dvir D, Assali A, Lev EI, Ben-Dor I, Battler A, Kornowski R. Percutaneous interventions in unprotected left main lesions: novel three-dimensional imaging and quantitative analysis before and after intervention. Cardiovasc Revasc Med 2010;11:236–40.
15. Girasis C, Serruys PW, Onuma Y, et al. 3-Dimensional bifurcation angle analysis in patients with left main disease: a substudy of the SYNTAX trial (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery). J Am Coll Cardiol Intv 2010;3:41–8.
16. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.
17. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
18. SYNTAX Score. Calculator. Available at: www.syntaxscore.com. Accessed May 19, 2009.
19. Onuma Y, Girasis C, Aben JP, et al. A novel dedicated 3-dimensional quantitative coronary analysis methodology for bifurcation lesions. EuroIntervention 2011;7:629–35.
20. Girasis C, Schuurbiers JC, Muramatsu T, et al. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. EuroIntervention 2013;8:1451–60.

21. Sianos G, Hofma S, Ligthart JM, et al. Stent fracture and restenosis in the drug-eluting stent era. Catheter Cardiovasc Interv 2004;61:111–6.
22. Canan T, Lee MS. Drug-eluting stent fracture: incidence, contributing factors, and clinical implications. Catheter Cardiovasc Interv 2010;75:237–45.
23. Chung WS, Park CS, Seung KB, et al. The incidence and clinical impact of stent strut fractures developed after drug-eluting stent implantation. Int J Cardiol 2008;125:325–31.
24. Umeda H, Gochi T, Iwase M, et al. Frequency, predictors and outcome of stent fracture after sirolimus-eluting stent implantation. Int J Cardiol 2009;133:321–6.
25. Popma JJ, Tiroch K, Almonacid A, Cohen S, Kandzari DE, Leon MB. A qualitative and quantitative angiographic analysis of stent fracture late following sirolimus-eluting stent implantation. Am J Cardiol 2009;103: 923–9.
26. Ino Y, Kubo T, Kitabata H, et al. Impact of hinge motion on in-stent restenosis after sirolimus-eluting stent implantation. Circ J 2011;75: 1878–84.
27. Louvard Y, Lefèvre T, Morice MC. Percutaneous coronary intervention for bifurcation coronary disease. Heart 2004;90:713–22.
28. Kang SJ, Mintz GS, Kim WJ, et al. Changes in left main bifurcation geometry after a single-stent crossover technique: an intravascular ultrasound study using direct imaging of both the left anterior descending and the left circumflex coronary arteries before and after intervention. Circ Cardiovasc Interv 2011;4:355–61.
29. Colombo A, Stankovic G, Orlic D, et al. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. Catheter Cardiovasc Interv 2003;60:145–51.
30. Mortier P, Van Loo D, De Beule M, et al. Comparison of drug-eluting stent cell size using micro-CT: important data for bifurcation stent selection. EuroIntervention 2008;4:391–6.
31. Ormiston JA, Webster MW, El Jack S, et al. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. Catheter Cardiovasc Interv 2006;67:49–55.
32. Ormiston JA, Currie E, Webster MW, et al. Drug-eluting stents for coronary bifurcations: insights into the crush technique. Catheter Cardiovasc Interv 2004;63:332–6.
33. Murasato Y. Impact of three-dimensional characteristics of the left main coronary artery bifurcation on outcome of crush stenting. Catheter Cardiovasc Interv 2007;69:248–56.
34. Ormiston JA, Webster MW, Webber B, Stewart JT, Ruygrok PN, Hatrick RI. The "crush" technique for coronary artery bifurcation stenting: insights from micro-computed tomographic imaging of bench deployments. J Am Coll Cardiol Intv 2008;1:351–7.
35. Nakazawa G, Yazdani SK, Finn AV, Vorpahl M, Kolodgie FD, Virmani R. Pathological findings at bifurcation lesions: the impact of flow distribution on atherosclerosis and arterial healing after stent implantation. J Am Coll Cardiol 2010;55:1679–87.
36. Moore JE Jr., Timmins LH, Ladisa JF Jr. Coronary artery bifurcation biomechanics and implications for interventional strategies. Catheter Cardiovasc Interv 2010;76:836–43.
37. Papafaklis MI, Bourantas CV, Theodorakis PE, et al. The effect of shear stress on neointimal response following sirolimus- and paclitaxel-eluting stent implantation compared with bare-metal stents in humans. J Am Coll Cardiol Intv 2010;3:1181–9.

Key Words: 3-dimensional ■ bifurcation angle ■ clinical outcomes ■ left main coronary artery ■ percutaneous coronary intervention.

PART V

Understanding mechanisms of drug eluting stent and bypass graft failure

Chapter 5.1

Short-Term and Long-Term Clinical Impact of Stent Thrombosis and Graft Occlusion in the SYNTAX Trial at 5 Years Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial

Farooq V, Serruys PW, Zhang Y, Mack M, Ståhle E, Holmes DR, Feldman T, Morice MC, Colombo A, Dawkins KD, Kappetein AP, Mohr FW

J Am Coll Cardiol. 2013;62(25):2360-69 (Impact Factor: 14.086)

Short-Term and Long-Term Clinical Impact of Stent Thrombosis and Graft Occlusion in the SYNTAX Trial at 5 Years

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial

Vasim Farooq, MBChB,* Patrick W. Serruys, MD, PhD,* Yaojun Zhang, MD,* Michael Mack, MD,† Elisabeth Ståhle, MD,‡ David R. Holmes, MD,§ Ted Feldman, MD,‖ Marie-Claude Morice, MD,¶ Antonio Colombo, MD,# Christos V. Bourantas, MD,* Ton de Vries, MSc,** Marie-angèle Morel, BSc,** Keith D. Dawkins, MD,†† Arie Pieter Kappetein, MD, PhD,‡‡ Friedrich W. Mohr, MD§§

Rotterdam, the Netherlands; Dallas, Texas; Uppsala, Sweden; Rochester, Minnesota; Evanston, Illinois; Massy, France; Milan, Italy; Natick, Massachusetts; and Leipzig, Germany

Objectives The aim of this study was to report the short-term and long-term clinical impact of stent thrombosis (ST) and graft occlusion (GO) in the final 5-year outcomes of the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial.

Background The clinical effect of newer-generation drug-eluting stents and operative factors in complex coronary artery disease is uncertain.

Methods The incidence of 5-year ST and GO, and their association with clinical outcomes, were analyzed in the randomized percutaneous coronary intervention and coronary artery bypass graft cohorts. ST and GO were defined by the SYNTAX protocol definitions (clinical presentation with acute coronary syndrome and angiographic/pathological evidence), the Academic Research Consortium (ARC) definition for ST, and the newly devised "ARC-like" definition of GO (i.e., definite, probable, or possible GO).

Results At 5 years, 871 of 903 patients (96.5%) in the percutaneous coronary intervention cohort and 805 of 897 patients (89.7%) in the coronary artery bypass graft cohort completed follow-up. As compared with other vessel locations, protocol ST (72 lesions) occurred more frequently in the left main (14 of 72; 19%) and proximal coronary vasculature (37 of 72; 51%) and protocol GO (41 lesions) with grafts anastomosed to the distal right coronary artery (17 of 41; 42%). The incidence of 5-year ARC definite ST and ARC-like definite GO did not significantly differ (7% [n = 48] vs. 6% [n = 32], log rank p = 0.34); landmark analyses indicated significantly increased ARC definite ST within 30 days (3% [n = 19] vs. 1% [n = 6], log rank p = 0.033) but not >30 days to 5 years (4.2% [n = 29] vs. 4.5% [n = 26], log rank p = 0.78). At presentation, ARC definite ST (n = 48) and ARC-like definite GO (n = 32) were adjudicated to be linked to 4 (8%) and 0 deaths, respectively. At 5 years, ARC definite ST (n = 48) and ARC definite/probable ST (n = 75) were associated with 17 (17 of 48, 35.4%; median days to death: 0 days; interquartile range: 0 to 16 days; maximum: 321 days) and 31 (31 of 75, 41.3%; median: 0 days; interquartile range: 0 to 9 days; maximum: 721 days) cardiac deaths, respectively. At 5 years, ARC-like definite GO (n = 32) and ARC-like definite/probable GO (n = 53) were associated with 0 and 12 (12 of 52, 23.1%; median: 0 days; interquartile range: 0 to 14 days; maximum: 257 days) cardiac deaths, respectively.

Conclusions Although the incidence of ST and GO was similar at 5 years, the clinical impact of ST appeared greater, with a negative impact on short-term to long-term mortality. (J Am Coll Cardiol 2013;62:2360–9) © 2013 by the American College of Cardiology Foundation

From the *Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; †Medical City Dallas Hospital, Dallas, Texas; ‡University Hospital Uppsala, Uppsala, Sweden; §Mayo Clinic, Rochester, Minnesota; ‖Evanston Hospital, Evanston, Illinois; ¶Institut Jacques Cartier, Massy, France; #San Raffaele Scientific Institute, Milan, Italy; **Cardialysis BV, Rotterdam, the Netherlands; ††Boston Scientific Corporation, Natick, Massachusetts; ‡‡Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; and the §§Herzzentrum, Leipzig, Germany. The SYNTAX trial was funded by Boston Scientific. Dr. Mack has served on the Speakers' Bureau of Boston Scientific, Cordis, and Medtronic. Dr. Feldman has served on the Speakers' Bureau of Boston Scientific; received grant support from Abbott Laboratories, Atritech, Boston Scientific, Edwards, and Evalve; and served as a consultant for Abbott Laboratories, Boston Scientific, Coherex, Edwards, InterValve, Square One, and W. L. Gore and Associates. Dr. Morice's institution has received a research grant from Boston Scientific. Dr. Dawkins is a full-time employee and stockholder of Boston Scientific. All other authors have reported that they have no relationships relevant to the content of this paper to disclose.

Manuscript received March 1, 2013; revised manuscript received June 3, 2013, accepted July 2, 2013.

The final 5-year reporting of the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial showed that coronary artery bypass graft (CABG) surgery remained the standard of care for patients with complex (left main or 3-vessel) coronary artery disease compared with percutaneous coronary intervention (PCI) with first-generation drug-eluting stents (1,2). In subjects with lesser complex coronary artery disease undergoing PCI, using the anatomic SYNTAX Score to assess coronary artery complexity (3) or the SYNTAX Score augmented with clinical factors (SYNTAX Score II), (4,5) were shown to be an acceptable alternative to CABG.

The clinical impact of stent thrombosis (ST) and graft occlusion (GO) in the SYNTAX trial is unreported. The purpose of the study was to report the incidence, timing, predictors, and clinical impact of ST and GO in the SYNTAX trial.

Methods

The SYNTAX trial is a randomized, prospective, multicenter, "all-comers" trial investigating subjects with unprotected left main coronary artery (ULMCA) disease (isolated or associated with 1-, 2-, or 3-vessel disease) or de novo 3-vessel disease and has previously been described (1,2). In total, 1,800 subjects were randomized on a 1:1 basis to either PCI with Taxus Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Massachusetts) or CABG.

An independent clinical events committee (CEC), including cardiologists, cardiac surgeons, and a neurologist, reviewed all the primary clinical endpoints and ST/GO events. All deaths were subdivided into cardiovascular and noncardiovascular deaths by the CEC. Cardiac deaths were classified as related or unrelated to a cardiac procedure by the CEC.

ST and GO. Because the SYNTAX trial began before publication of the Academic Research Consortium (ARC) definition, (6) the SYNTAX trial instigated a protocol definition for ST and GO (Table 1). Subsequently, the ARC criteria (6) for ST were implemented and reported by a separate CEC (see the Acknowledgments section). To allow comparisons of ARC ST events to GO, "ARC-like" definitions were formulated for GO (i.e., definite, probable, or possible GO) using adapted ARC definitions (Table 1).

Abbreviations and Acronyms

ARC = Academic Research Consortium
CABG = coronary artery bypass graft
CEC = clinical events committee
GO = graft occlusion
KM = Kaplan-Meier
LAD = left anterior descending artery
LIMA = left internal mammary artery
MI = myocardial infarction
PCI = percutaneous coronary intervention
RIMA = right internal mammary artery
ST = stent thrombosis
ULMCA = unprotected left main coronary artery

Table 1 SYNTAX Protocol and ARC/ARC-Like Definitions of ST and GO

Stent Thrombosis	Graft Occlusion
SYNTAX protocol definition The occurrence of any of the following: 1. Clinical presentation of acute coronary syndrome with ST confirmed by angiography, multi-slice CT, or autopsy a. Angiographic documentation of a complete occlusion (TIMI flow grade 0 or 1) of a previously successfully treated artery (TIMI flow gade 2 to 3 immediately after stent placement and diameter stenosis ≤30) and/or b. Documentation by angiography, multi-slice CT, or autopsy of flow-limiting thrombus or complete luminal obstruction within or adjacent to a previously successfully treated lesion 2. Q-wave MI in the territory of one or more of the treated vessels (LAD, LCX, RCA) within the first 30 days (acute or subacute)	SYNTAX protocol definition The occurrence of any of the following: 1. Clinical presentation of acute coronary syndrome with GO confirmed by angiography, multi-slice CT, or autopsy a. Angiographic documentation of occlusion (TIMI flow grade 0 or 1) of a vascular graft and/or b. Documentation by angiography, multi-slice CT, or autopsy of flow-limiting thrombus or complete luminal obstruction within a bypass graft or a flow limiting thrombus adjacent to the anastomosis of previously bypassed coronary artery 2. Q-wave MI in the territory of one or more of the treated vessels (LAD, LCX, RCA) within the first 30 days (acute or subacute)
ARC definite ST 1. Angiographic or pathological confirmation of partial or total thrombotic occlusion within the peri-stent region and at least one of the following additional criteria: a. Acute ischemic symptoms b. Ischemic electrocardiographic changes c. Elevated cardiac biomarkers	ARC-like definite GO* 1. SYNTAX protocol definition as stated in the preceding text
ARC probable ST 1. Any unexplained death within 30 days of stent implantation 2. Any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST	ARC-like probable GO† 1. Any unexplained death within 30 days of graft 2. Any MI that is related to documented acute ischemia in the territory of the anastomosed graft without angiographic confirmation of GO
ARC possible ST 1. Any unexplained death beyond 30 days	ARC-like possible GO‡ 1. Any unexplained death beyond 30 days

*The definitions of protocol GO and ARC-like definite GO were identical. †Because subjects had left main or de novo 3-vessel disease, it was assumed that an MI in any of the 3-vessel territories for 3-vessel disease or the left coronary system for unprotected left main coronary artery disease without subsequent angiographic confirmation of graft patency was classified as probable GO. ‡ARC possible GO was identical to ARC-like possible ST.

ARC = Academic Research Consortium; CT = computed tomography; GO = graft occlusion; MI = myocardial infarction; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; ST = stent thrombosis; TIMI = Thrombolysis in Myocardial Infarction.

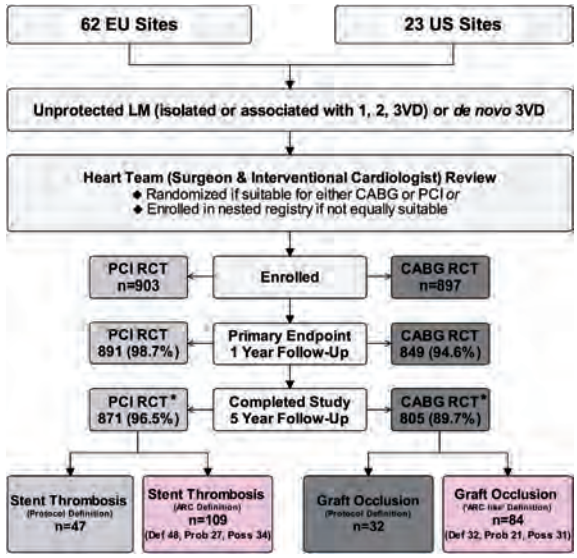


Figure 1 Flow Chart

SYNTAX trial design indicating the number of GO and ST cases using the protocol and ARC/ARC-like definitions. *In the PCI arm, 871 patients remained in the study at 5 years (11 withdrew consent and 21 were lost to follow-up/other; in the CABG arm, 805 patients remained in the study at 5 years (50 withdrew consent and 41 were lost to follow-up/other) (1). ARC = Academic Research Consortium; CABG = coronary artery bypass graft; Def = definite; EU = Europe; GO = graft occlusion; LM = left main; PCI = percutaneous coronary intervention; Poss = possible; Prob = probable; RCT = randomized controlled trial; ST = stent thrombosis; US = United States; 3VD = 3-vessel disease.

like definitions for GO were retrospectively assessed in conjunction with the safety reporting data obtained by the CEC.

Statistical analysis. Continuous variables are expressed as mean ± SD and binary variables as counts and/or percentages. Time-to-event variables are presented as Kaplan-Meier (KM) estimates and compared using the log-rank test. Corrected KM curves were constructed by removing the ST adjudicated clinical event from the KM curves (7). Multivariable analyses (Cox regression) were conducted using the baseline characteristics (Online Appendix) and the forced enter method (entry criteria 0.05, no exit criteria). There was no departure from the proportionality of hazards assumption using the global proportional hazards test based on Schoenfeld residuals (8). Variables were screened for correlation before entry into the multivariable model, and none were sufficiently correlated to warrant removal. A 2-sided p value <0.05 was considered significant for all tests. All analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, Illinois) and SAS system software version 9.2 (SAS Institute, Cary, North Carolina).

Results

Figure 1 shows the study design and frequency of ST and GO using the SYNTAX protocol and ARC/ARC-like definitions. At 5 years, 871 of 903 patients (96.5%) in the PCI cohort and 805 of 897 patients (89.7%) in the CABG cohort completed follow-up.

Antiplatelet compliance. Use of aspirin therapy was significantly lower after CABG compared with PCI post-procedurally (88.5% vs. 96.3%, $p < 0.001$) and at 1 year (84.3% vs. 91.2%, $p < 0.001$) but not at 5 years (85.0% vs. 87.1%, $p = 0.24$). Use of thienopyridine therapy was significantly lower for CABG post-procedurally (19.4% vs. 96.7%, $p < 0.001$) and at 1 year (15.0% vs. 71.1%, $p < 0.001$) and 5 years (12.1% vs. 32.0%, $p < 0.001$). Dual antiplatelet use at 5 years was significantly higher with PCI compared to CABG (9.1% vs. 27.4%, $p < 0.001$).

Anatomic location of ST and GO at 5 years of follow-up. Protocol ST was confirmed in 47 subjects with 72 lesions (Fig. 2). Forty-three of 47 subjects had documented protocol ST confirmed by angiography (62 lesions), 3 subjects had documented protocol ST confirmed by

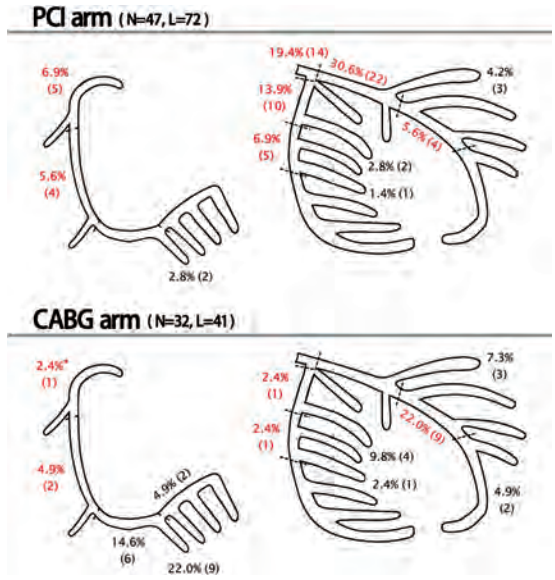


Figure 2 **Coronary Anatomic Location Sites of Protocol ST and Anastomosis Sites of Protocol GO Until 5 Years**

The location of per-protocol (clinical presentation with acute coronary syndrome and angiographic/pathological evidence) ST **(upper panel)** and GO **(lower panel)** on a lesion-level basis is shown. ST pertains to the anatomic location in coronary arteries, and GO pertains to the anastomosis site of bypass graft to native coronary arteries. Percentages are provided, and actual numbers are stated in parentheses. *Denotes ST (listed in the CABG arm on an intention-to-treat basis). N = number of patients; L = number of lesions; other abbreviations as in Figure 1.

autopsy (7 lesions), and this was not recorded in one subject (3 lesions). Protocol ST occurred more frequently in the left main (14 of 72; 19.4%) and proximal (37 of 72; 51.4%) coronary vasculature.

Protocol GO was confirmed in 32 subjects with 41 lesions (Fig. 2). All 32 subjects had documented protocol GO confirmed by angiography (41 lesions). Protocol GO occurred more frequently with grafts anastomosed to the distal right coronary artery (17 of 41; 42%) compared with other vessel locations.

ARC/ARC-like definitions of ST and GO: incidence and timing. The incidence and timing of ARC/ARC-like ST and ARC/ARC-like GO are shown in Figures 3 and 4. At 5 years (KM estimates), there was no significant difference between ARC definite ST and ARC-like definite GO (ARC ST: 6.8% [n = 48]; ARC-like GO: 5.5% [n = 32]; p = 0.34), ARC definite/probable ST and ARC-like definite/probable GO (p = 0.48), and ARC definite/probable/possible ST and ARC-like definite/probable/possible GO (p = 0.69).

Landmark analyses (Fig. 4) indicated significantly more ARC definite ST within 30 days (ARC definite ST: 2.7% [n = 19]; ARC-like definite GO: 1.0% [n = 6]; p = 0.033) but not >30 days to 5 years (ARC definite ST: 4.2% [n = 29]; ARC-like definite GO: 4.5% [n = 26]; p = 0.78).

Comparisons of ARC definite/probable ST and ARC-like definite/probable GO showed no significant differences at intervals of 0 to 30 days (p = 0.38), 30 days to 5 years (p = 0.12), and 5 years (p = 0.48). Comparisons of ARC definite/probable/ possible ST and ARC-like definite/probable/possible GO showed no significant differences at 30 days to 5 years (p = 0.33) and 5 years (p = 0.69).

ARC/ARC-like definitions of ST and GO: adjudicated clinical outcomes. ARC definite ST (n = 48) was adjudicated by the CEC to be linked to 4 deaths (4 of 48; 8.3%), 11 myocardial infarctions (MIs) (11 of 48; 22.9%), 23 cases of all-cause revascularization (23 of 48; 47.9%), and 10 cases with no clinical event (10 of 48; 20.8%). Corrected KM curves with the clinical events, adjudicated to be associated with the ARC definition of ST by the CEC, removed are shown (Fig. 5). Notably, removal of ARC definite/probable ST-related events would have led to a reduction of 5.1% in cardiac death/MI/all-cause revascularization and a 1.5% reduction in cardiac death at 5 years.

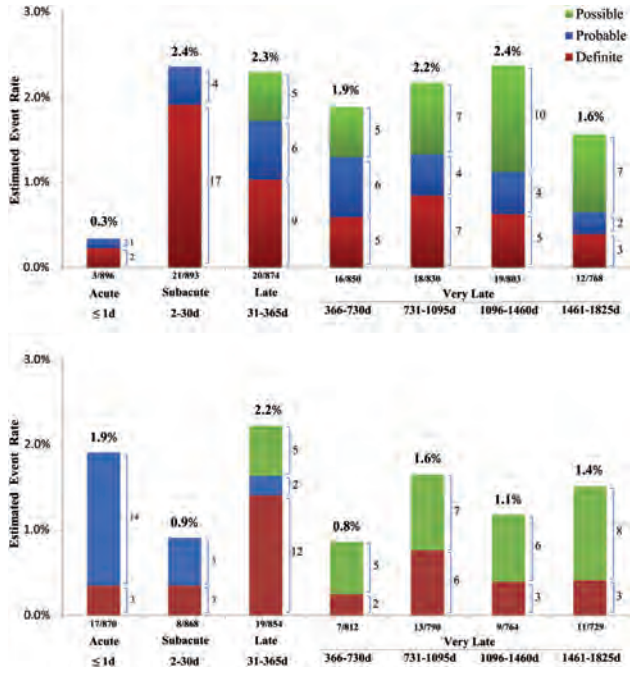


Figure 3 Comparison of Incidence of ARC Definition ST and ARC-Like Definition of GO Until 5 Years

ARC definite, probable, and possible ST **(upper panel)** and ARC-like definite, probable, and possible GO **(lower panel)** are illustrated. Patient-level data are shown. Abbreviations as in Figure 1.

ARC-like definite GO (n = 32) was adjudicated by the CEC to be linked to 0 deaths, 7 MIs (7 of 32; 21.9%), 21 cases of all-cause revascularization (21 of 32; 65.6%), and 4 cases with no clinical event (4 of 32; 12.5%).

Long-term cardiac mortality associated with the index ARC/ARC-like ST/GO events. The 5-year relationship of cardiac mortality to the index ARC ST or ARC-like GO events is shown (Table 2). At 5 years, ARC definite ST was associated with 17 cardiac deaths (17 of 48; 35.4%) (median number of days to cardiac death: 0; interquartile range: 0 to 16 days; maximum: 321 days) and ARC definite/probable ST (n = 75) with 31 cardiac deaths (31 of 75; 41.3%) (median number of days to death: 0; interquartile range: 0 to 9 days; maximum: 721 days).

Comparatively, at 5 years, ARC-like definite GO was not associated with any deaths and ARC-like definite/probable GO (n = 53) with 12 cardiac deaths (12 of 52; 23.1%) (median number of days to death: 0; interquartile range: 0 to 14 days; maximum: 257 days).

Multivariable predictors of the ARC definition of ST. Table 3 shows multivariable analyses of ARC definite/probable ST. Model 1 incorporated components of the SYNTAX Score and clinical- and procedural-related variables. Model 2 incorporated the SYNTAX Score and EuroSCORE. Stent length (in millimeters) and number of stents implanted were not univariable predictors of early or late/very late ST.

EARLY ARC ST (WITHIN 30 DAYS). The presence of ULMCA disease was not a univariable predictor of early ARC ST ($p = 0.84$). Lack of post-procedural antiplatelet therapy was the strongest independent predictor of early ST ($p < 0.001$), followed by peripheral vascular disease ($p = 0.054$), heavy calcification ($p = 0.054$), and prior MI ($p = 0.037$). Both the SYNTAX Score ($p = 0.086$) and additive EuroSCORE ($p = 0.006$) were predictors of early ST.

LATE/VERY LATE ARC ST (BEYOND 30 DAYS). The presence of ULMCA disease showed a trend toward being protective

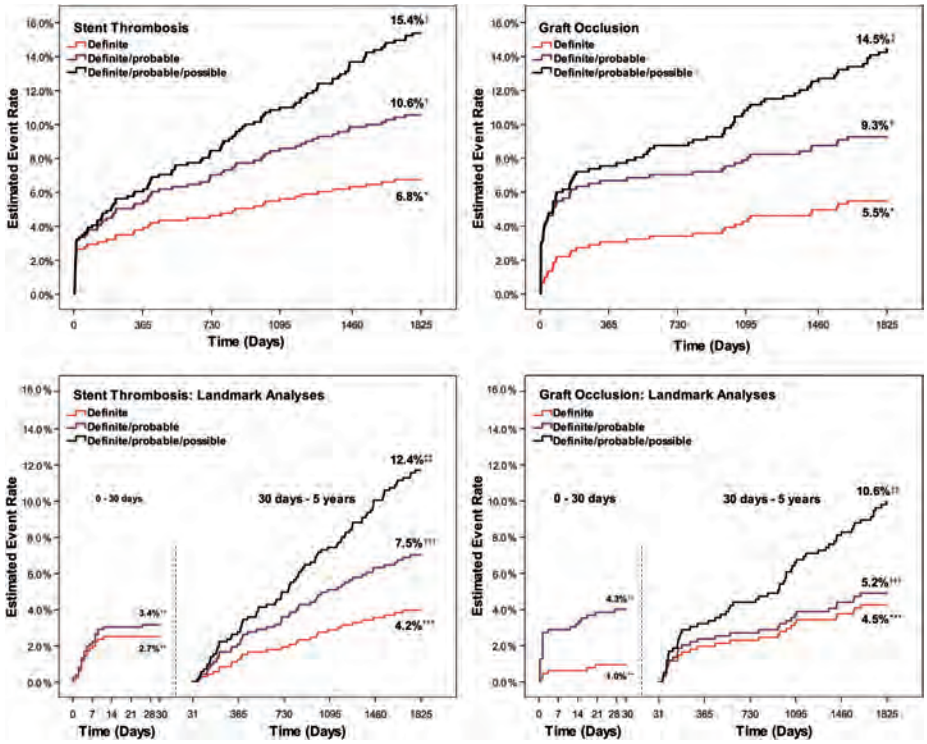


Figure 4 Kaplan-Meier Estimates of ARC Definition ST and ARC-Like Definition GO Until 5 Years

Five-year outcomes **(upper panels)** and landmark analyses at 0 to 30 days and 31 days to 5 years **(lower panels)** are illustrated. Log-rank comparisons between ARC and ARC-like definitions of ST and GO are shown. Definite: *p = 0.34, **p = 0.033, ***p = 0.78. Definite/probable: †p = 0.48, ††p = 0.38, †††p = 0.12. Definite/probable/possible: ‡p = 0.69, ‡‡p = 0.33. Abbreviations as in Figure 1.

against late/very late ARC ST on univariable analyses (hazard ratio: 0.61; 95% confidence interval: 0.33 to 1.12; p = 0.10). The SYNTAX Score was not a univariable predictor of late/very late ARC ST (p = 0.71). Any baseline angiographically visible thrombus (p = 0.003) and trifurcation lesion (p = 0.048) were the strongest independent predictors.

In total, 23 of 903 subjects (2.5%) in the PCI cohort were reported to have a baseline angiographically visible thrombus, of which 7 of 23 subjects had ARC ST beyond 30 days (ARC definite ST: n = 3; ARC possible ST: n = 3; ARC probable ST: n = 1). Sixty-six of 903 subjects (7.3%) in the PCI cohort were reported to have trifurcation lesions, of which 12 of these 66 subjects had ARC ST (ARC definite ST: n = 5; ARC probable ST: n = 5; ARC possible ST: n = 2). Three of the 12 cases of ARC ST occurred in <30 days (2 in subjects with ULMCA disease), and 7 occurred in >30 days (6 in subjects with ULMCA disease).

Multivariable predictors of ARC-like definite GO. In the CABG cohort, double left internal mammary artery (LIMA)/right internal mammary artery (RIMA) and complete arterial revascularization were reported to be used in 236 of 897 subjects (26.3%) and 161 of 897 subjects (17.9%), respectively. On univariable analyses, double LIMA/RIMA (hazard ratio: 0.86; 95% confidence interval: 0.35 to 2.10; p = 0.74), complete arterial revascularization (hazard ratio: 0.81; 95% confidence interval: 0.31 to 2.11; p = 0.67), and ULMCA disease (p = 0.66) were not statistically associated with a reduction in ARC-like

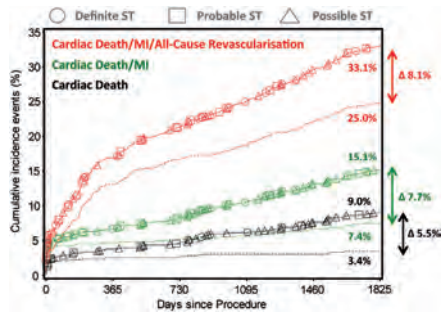


Figure 5 **Corrected Kaplan-Meier Curves for ARC Definition ST**

Kaplan-Meier estimates of cardiac death **(black)**, cardiac death or MI **(green)**, and cardiac death, MI, or all-cause revascularization **(red)** according to the ARC definition (6). **Broken lines** indicate corrected Kaplan-Meier curves after ST-related clinical events were excluded. ARC definite ST is superimposed on the Kaplan-Meier curves as **circles**, ARC probable ST as **squares**, and ARC possible ST as **triangles**. Removal of ARC ST-related events would lead to a reduction in cardiac death/MI/all-cause revascularization (ARC definite ST: Δ2.9%; ARC definite/probable ST: Δ5.1%; ARC definite/probable/possible ST: Δ8.1%), cardiac death/MI (ARC definite ST: Δ1.3%; ARC definite/probable ST: Δ3.8%; ARC definite/probable/possible ST: Δ7.7%), and cardiac death (ARC definite ST: Δ0.5%; ARC definite/probable ST: Δ1.5%; ARC definite/probable/possible ST: Δ5.5%). MI = myocardial infarction; other abbreviations as in Figure 1.

definite GO. Any baseline angiographically visible thrombus (n = 31) (p = 0.41) was not statistically associated with a reduction in ARC-like definite GO.

Multivariable analyses indicated that other arterial/venous conduits (i.e., no LIMA) to the left anterior descending artery (LAD) (p = 0.050) and the number of grafts (p = 0.017) were independent predictors of ARC-like definite GO (Table 3). Of subjects with ARC-like definite GO (n = 32), 8 had no LIMA to the LAD and 25 were not on pre-procedural aspirin therapy.

Discussion

In this post-hoc study of the randomized, all-comers SYNTAX trial, the main findings were as follows. First, although the incidence of ST and GO at 5 years was similar using the ARC/ARC-like definitions, the clinical impact of ST appeared greater, with a negative impact on short-term to longer-term mortality. Second, independent predictors of ST and GO were diverse and related to anatomic or procedural- or clinical-related factors.

Stent thrombosis. The findings of ST in the SYNTAX trial are notable in that early (<30 days) and late/very late ARC definite ST (>30 days) were associated with short-term and long-term mortality. It is important to emphasize that the actual causes of death are multifactorial and not easily directly attributed to ST. For example, although lack of post-procedural antiplatelet therapy was the strongest independent predictor of ST (Table 3), a recent substudy of the SYNTAX trial showed that this was of multifactorial origin (9). Factors precluding antiplatelet administration were reported to include gastrointestinal bleeding, retroperitoneal bleeding from procedure-related femoral vascular access, coronary perforation, or following surgical bailout for PCI-related complications. Consequently, directly attributing ST to mortality is difficult, although it is clear there was a strong causal link.

In addition, ST most frequently occurred in the left main and proximal vasculature (>70% of cases). Accordingly, the impact of ST on mortality is not only related to the acute consequences of abrupt closure of the treated vessel but also the short-term to longer-term complications of MI, including heart failure, arrhythmias, or mechanical complications (10). Indeed, previously reported analyses of PCI-treated patients who had post-procedural creatine kinase levels >2 times the upper limit of normal (with corroborating elevation of creatine kinase MB fraction) in the SYNTAX trial were shown to be associated with short-term (<3 months) and longer-term (2 to 4 years) mortality (11). Even selecting a time window (e.g., 1 day, 1 week, or 1 month) associating mortality with ST is arbitrary because, as shown in this study, the interquartile range of cardiac death after ARC definite ST ranged from 0 to 16 days, with a maximum duration of 321 days, and cardiac death was often of multifactorial origin. Consequently, determining the potential impact on mortality of newer-generation drug-eluting stents with proven reductions in ST (12,13) is difficult to determine in the SYNTAX trial. Comparatively, potential reductions in ST-related MI and all-cause revascularization were easier to determine, as highlighted in Figure 5.

Graft occlusion. The present study confirms the established supremacy of the long-term durability of LIMA to the LAD (14). Notably, double LIMA/RIMA was not associated with a reduced risk of GO on univariable analyses, despite being undertaken in more than one-fourth (27.6%) of randomized patients undergoing CABG. It is important to emphasize that the data related to double LIMA/RIMA were underpowered to draw any firm conclusions and are in contrast to the data in published reports (14,15). Ten-year follow-up data from a large ongoing randomized trial are awaited (16).

The finding of the number of grafts to be an independent predictor of GO is consistent with reported studies in that too extensive surgical revascularization has been associated with the occurrence of major perioperative complications and acute MI (17,18). Conversely, the 15-month angiographic substudy of the SYNTAX trial (19) showed that more than one-fourth (27.2%) of subjects undergoing CABG had at least one significantly diseased (≥50% to <100%) or occluded bypass graft at 15 months. Notably, the reported angiographic loss of the bypass grafts

Table 2 Association of First ARC ST or ARC-Like GO Event With 5-Year Cardiac Death

	Incidence at 5 Yrs (%)	No. of Cardiac Deaths Post-Event Until 5 Yrs (%)	Time From Index Event to Cardiac Death (Days)		
			Median	Interquartile Range	Minimum to Maximum
SYNTAX trial PCI arm (n = 903)					
ST ARC definition					
Classification					
Definite	48 (5.3)	17/48 (35.4)	0	0–16	0–321
Probable	27 (3.0)	14/27 (51.9)	0	0–4	0–721
Definite or probable	75 (8.3)	31/75 (41.3)	0	0–9	0–721
Possible	27 (3.0)	27/27 (100)	—	—	—
Time frame (definite)					
Acute/subacute (≤30 days)	19 (2.1)	8/19 (42.1)	0	0–6	0–17
Late (31 days to 1 yr)	9 (1.0)	2/9 (22.2)	173	—	25–321
Very late (>1 yr)	20 (2.2)	7/20 (35.0)	0	0–14	0–17
Time frame (definite/probable)					
Acute/subacute (≤30 days)	24 (2.7)	12/24 (50.0)	0	0–17	0–721
Late (31 days to 1 yr)	15 (1.7)	7/15 (46.7)	0	0–44	0–87
Very late (>1 yr)	36 (4.0)	12/36 (33.3)	0	0–7	0–17
SYNTAX trial CABG arm (n = 897)					
GO ARC-like definition					
Classification					
Definite	32 (3.6)	0/31 (0)	—	—	—
Probable	21 (2.3)	12/21 (57.1)	0	0–14	0–257
Definite or probable	53 (5.9)	12/52 (23.1)	0	0–14	0–257
Possible	31 (3.5)	31/31 (100)	—	—	—
Time frame (definite)					
Acute/subacute (≤30 days)	6 (0.7)	0/6 (0)	—	—	—
Late (31 days to 1 yr)	12 (1.3)	0/12 (0)	—	—	—
Very late (>1 yr)	14 (1.6)	0/13 (0)	—	—	—
Time frame (definite/probable)					
Acute/subacute (≤30 days)	25 (2.8)	10/25 (40.0)	0	0–6	0–15
Late (31 days to 1 yr)	14 (1.6)	2/14 (14.3)	214	—	170–257
Very late (>1 yr)	14 (1.6)	0/14 (0)	—	—	—

Binary values are given.

Abbreviations as in Table 1. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

was not significantly associated with early clinical events (19), in contrast to GO in the current study (defined in the context of clinical presentation with acute coronary syndrome). Reasons to account for the "clinically silent" loss of bypass grafts have included that they were anastomosed to functionally insignificant lesions, with resultant competitive filling to the native vessel, and were therefore unnecessary (20).

Study limitations. The present study represents a post-hoc analysis, and the results should be considered hypothesis generating. Because ST and GO were defined in the context of clinical presentation, the true occurrence is likely to be higher, particularly if the ST occurs in a distal vessel (19). In addition, saphenous vein grafts have been shown to be protective in the first 7 years; thereafter, mortality and repeat revascularization have been reported to increase significantly, secondary to a gradual loss of graft patency (21). Given that operative factors were linked to ARC-like probable GO, ARC-like definite GO was used for the multivariable analyses to identify long-term predictors of GO. As exists with ARC possible ST, ARC-like possible GO is likely to have a low specificity in identifying GO. The exact anatomic segment number of the ST using the ARC definite criteria is not available, because this was not recorded by the CEC. There was limited statistical power for further subanalyses in patients with ST or GO. Although multivariable adjustments were performed for significant confounders ($p < 0.1$), the possibility of other unmeasured confounders cannot be excluded. The possibility of overfitting in the multivariable analyses cannot be excluded. Because the confidence intervals of these correlates were relatively narrow, the risk would have been limited (22). Given the unavoidable differences in follow-up between the CABG and PCI cohorts, we cannot exclude the possibility that this may have affected the results.

Conclusions

Although the incidence of ST and GO was similar at 5 years, the clinical impact of ST appeared greater, with a negative impact on short-term to longer-term mortality.

Table 3 Multivariable Cox Regression Analyses of Early (<30 Days) and Late/Very Late (30 Days to 5 Years) ARC Definite/Probable ST and ARC-Like Definite GO at 5 Years

	Univariable Predictors		Multivariable Predictors	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Early ST (<30 days) (n = 24)				
Model 1				
Lack of post-procedural antiplatelet therapy (4 of 24, 16.7%)	22.30 (7.61–65.31)	<0.001	15.38 (5.20–45.62)	<0.001
Peripheral vascular disease (5 of 24, 20.8%)	2.84 (1.06–7.59)	0.038	2.68 (0.98–7.32)	0.054
Any heavy calcification* (18 of 24, 75.0%)	3.07 (1.22–7.75)	0.017	2.51 (0.98–6.39)	0.054
Prior MI (13 of 24, 54.2%)	2.60 (1.16–5.79)	0.020	2.38 (1.05–5.40)	0.037
Model 2				
SYNTAX Score (per 10-point increase)	1.42 (1.05–1.92)	0.025	1.31 (0.96–1.79)	0.086
Additive EuroSCORE†	1.22 (1.08–1.38)	0.001	1.20 (1.05–1.36)	0.006
Late/very late ST (>30 days) (n = 51)				
Model 1				
Any baseline angiographically visible thrombus‡ (4 of 51, 7.8%)	3.74 (1.35–10.37)	0.011	4.86 (1.73–13.65)	0.003
Any circumflex lesion (49 of 51, 96.1%)	4.27 (1.04–17.55)	0.044	3.08 (0.73–13.01)	0.13
Any trifurcation lesion (7 of 51, 13.7%)	2.00 (0.90–4.43)	0.089	2.27 (1.01–5.12)	0.048
Any right coronary artery lesion (47 of 51, 92.2%)	2.72 (0.98–7.53)	0.055	2.18 (0.76–6.23)	0.15
Unstable angina (21 of 51, 41.2%)	1.85 (1.07–3.21)	0.028	1.49 (0.77–2.87)	0.23
Prior MI (24 of 51, 47.1%)	2.04 (1.19–3.52)	0.01	1.68 (0.94–2.99)	0.079
Additive EuroSCORE†	1.09 (0.99–1.20)	0.076	1.02 (0.91–1.16)	0.72
Model 2				
SYNTAX Score (per 10-point increase)	0.96 (0.75–1.21)	0.71	—	—
Additive EuroSCORE†	1.09 (0.99–1.20)	0.076	—	—
ARC-like definite GO (n = 32)				
No LIMA to LAD (8 of 32, 25.8%)	2.68 (1.20–5.98)	0.017	2.30 (1.00–5.28)	0.050
Number of grafts per patient†	1.78 (1.08–2.93)	0.023	1.87 (1.12–3.12)	0.017
Lack of pre-procedural aspirin (25 of 32, 78.1%)	2.34 (1.01–5.41)	0.047	1.87 (0.79–4.40)	0.15
Peripheral vascular disease (6 of 32, 18.8%)	2.58 (1.06–6.27)	0.036	1.47 (0.54–4.00)	0.45
Body mass index† (kg/m^2)	0.92 (0.84–1.00)	0.062	0.93 (0.85–1.02)	0.13
Previous MI (5 of 32, 15.6%)	0.38 (0.15–0.98)	0.046	0.38 (0.15–1.01)	0.052

Incidence of variables is provided in parentheses. *Multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion. †Continuous variables per unit increase. ‡Spheric, ovoid, or irregular intraluminal filling defect or lucency surrounded on 3 sides by contrast medium seen just distal or within the coronary stenosis in multiple projections or a visible embolization of intraluminal material downstream.

CI = confidence interval; HR = hazard ratio; LIMA = left internal mammary artery; other abbreviations as in Table 1.

Acknowledgments

The authors thank the study centers whose work made this study possible; Kristine Roy, Jian Huang, and Vicki Houle of Boston Scientific Corporation for their invaluable technical support in accessing the study database; and the members of the separate CEC: Dr. E. W. L. Jansen (Universitair Medisch Centrum Utrecht, Utrecht, the Netherlands), Dr. C. Hanet (Clinique Universitaire de Saint-Luc, Brussels, Belgium), the late Prof. Dr. O. M. Hess (Swiss Cardiovascular Center, University Hospital, Bern, Switzerland), and his replacement, Dr. E. P. McFadden (Cork University Hospital, Cork, Ireland).

Reprint requests and correspondence: Dr. Patrick W. Serruys, Interventional Cardiology Department, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, Zuid Holland 3015 GD, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.
2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
3. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50–6.
4. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50.
5. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW. SYNTAX score II? Authors' reply. Lancet 2013;381:1899–900.
6. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
7. Serruys PW, Onuma Y, Garg S, et al. 5-Year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–101.
8. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–41.
9. Farooq V, Serruys PW, Bourantas C, et al. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. Eur Heart J 2012;33:3105–13.

10. Windecker S, Meier B. Late coronary stent thrombosis. Circulation 2007;116:1952–65.
11. Farooq V, Serruys PW, Vranckx P, et al. Incidence, correlates, and significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous based revascularisation: A substudy from the Synergy between Percutaneous Coronary Interventions with Taxus and Cardiac Surgery (SYNTAX) Trial. Int J Cardiol 2013;168:5287–92.
12. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393–402.
13. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254–65.
14. Taggart DP, Banning AP. Stents and failing vein grafts: are we any wiser after ISAR? Lancet 2011;378:1054–5.
15. Dorman MJ, Kurlansky PA, Traad EA, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts. Circulation 2012;126:2935–42.
16. Taggart DP, Altman DG, Gray AM, et al. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010;31:2470–81.
17. Rastan AJ, Walther T, Falk V, et al. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? Circulation 2009;120: S70–7.
18. Alamanni F, Dainese L, Naliato M, et al. On- and off-pump coronary surgery and perioperative myocardial infarction: an issue between incomplete and extensive revascularization. Eur J Cardiothorac Surg 2008;34:118–26.
19. Morice MC, Feldman TE, Mack MJ, et al. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with Taxus express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). EuroIntervention 2011; 7:670–9.
20. Farooq V, Girasis C, Magro M, et al. The CABG SYNTAX Score, an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. EuroIntervention 2013;8:1277–85.
21. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. Eur Heart J 2009;30:453–8.
22. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503–10.

Key Words: graft occlusion ■ mortality ■ stent thrombosis ■ SYNTAX.

APPENDIX

For an expanded Methods section as well as supplemental tables and figures, please see the online version of this article.

APPENDIX

Expanded Methods

The SYNTAX Trial is a randomized, prospective, multicenter, 'all-comers' trial investigating subjects with unprotected left main coronary artery (ULMCA) disease (isolated or associated with 1-, 2-, or 3-vessel disease [3VD]) or de novo 3VD, and has previously been described. (1,2) In total, 1800 subjects were recruited and randomized from 85 centers in 18 countries from Europe and the United States. Exclusion criteria were minimal, consisting of subjects with prior coronary revascularization, planned need for concomitant cardiac surgery (e.g. valve surgery or resection of aortic or left ventricular aneurysm), or on-going acute MI.

During the local Heart Team meeting, the interventional cardiologist and cardiac surgeon specified the number of coronary lesions requiring treatment, and their angiographic location and characteristics utilizing the anatomical SYNTAX Score as a tool to aid in this process. (1-3) All subjects considered by the Heart Team as potentially achieving *"equivalent anatomic"* revascularization with percutaneous or surgical revascularization were randomized on a 1:1 basis (n=1800) to either PCI with TAXUS Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Mass), or CABG. Patients unsuitable for randomization were nested into registries.

The calculation of the anatomical SYNTAX Score, and recording of its individual components, were carried out by the Heart Team prior to randomization, and corroborated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands), blinded to the treatment assignment. An independent Clinical Events Committee (CEC), including cardiologists, cardiac surgeons, and a neurologist, reviewed all the primary clinical end points and ST/GO events. All deaths were subdivided into cardiovascular or non-cardiovascular

deaths by the CEC. Cardiac deaths were classified as related or unrelated to a cardiac procedure by the CEC. In the event of any uncertainty arising in the classification of a clinical event, the CEC assisted the investigator in reaching his/her final classification. The CEC decision was able to overrule the investigator's classification.

Stent Thrombosis and Graft Occlusion

As the SYNTAX Trial was commenced prior to the publication of the Academic Research Consortium (ARC) Definition, (4) the SYNTAX Trial instigated a protocol definition for ST. To allow direct comparison between ST and GO, a similarly defined protocol definition of GO was devised (**Table 2a**). The protocol definitions of ST/GO required clinical presentation with acute coronary syndrome, and confirmation by coronary angiography, multislice computerized tomography or autopsy.

Subsequently, the ARC criteria (4) for ST was implemented and reported by a separate CEC (see *Acknowledgements*), and is reported in the study. To allow comparisons of ARC ST events to GO, 'ARC like' definitions were formulated for GO (i.e. definite, probable or possible GO), using adapted ARC definitions (**Table 2b**). The definition of definite GO was identical to the protocol definition. Since subjects had left main or de novo 3VD, the assumption was made that a MI in any of the 3 vessel territories for 3VD, or the left coronary system for ULMCA disease, without subsequent angiographic confirmation of graft patency, was classified as a probable GO. Possible GO was identical to the ARC definition of possible ST (unexplained death beyond 30 days). 'ARC like' definitions for GO were retrospectively assessed in conjunction with the safety reporting data performed by the CEC.

Statistical Analysis

Continuous variables are expressed as means (±SD), binary variables as counts and/or percentages. Time-to-event variables are presented as Kaplan-Meier (KM) estimates, and

compared using the log-rank test. Corrected KM curves were constructed by removing the ST adjudicated clinical event from the KM curves, in line with that previously reported. (5) Multivariable analyses were conducted with Cox regression using the forced enter method (variable entry criteria 0.05, and no exit criteria). The variables examined are detailed in the baseline characteristics (**Table 1**). There was no departure from the proportionality of hazards assumption using the global proportional hazards test based on Schoenfeld residuals. (6) Variables were screened for correlation before entering into the multivariable model, none were sufficiently correlated to warrant removal. A 2-sided p-value <0.05 was considered significant for all tests. All analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago IL, USA) and SAS System Software Version 9.2 (SAS Institute, Cary, North Carolina, USA).

Expanded Results

Online Table 1

Baseline characteristics of patients with and without definite stent thrombosis or definite graft occlusion.

	Stent Thrombosis (ARC)			Graft Occlusion ('ARC like')		
	Definite ST (n=48)	No Definite ST (n=855)	p-value	Definite GO (n=32)	No Definite GO (n=865)	p-value
Clinical Characteristics						
Age (years)	64.4±11.2	65.3±9.5	0.51	64.1±9.3	65.0±9.8	0.61
Male	75.5%	76.4%	0.89	78.1%	79.0%	0.91
BMI	27.6±5.2	28.2±4.8	0.42	26.3±3.6	28.0±4.6	0.042
Diabetes	28.6%	28.0%	0.93	31.2%	28.4%	0.73
Medically treated diabetes*†	26.5%	25.2%	0.84	25.0%	24.6%	0.96
Hypertension	58.3%	74.7%	0.012	76.7%	77.0%	0.97
Hyperlipidemia	73.5%	78.9%	0.37	78.1%	77.1%	0.90
Peripheral vascular disease	12.2%	8.5%	0.37	18.8%	10.3%	0.13
Current smoker	24.5%	17.4%	0.21	31.2%	21.7%	0.20
Unstable angina	38.8%	28.1%	0.11	34.4%	27.7%	0.41
Previous myocardial infarction	46.9%	30.6%	0.017	15.6%	34.5%	0.027
GI Bleeding/Peptic ulcer disease	6.1%	4.0%	0.48	3.1%	4.3%	0.74
COPD	8.2%	7.8%	0.93	9.4%	9.2%	0.98
LVEF (%)	54.1±14.2	54.9±11.8	0.65	60.7±12.1	58.1±13.2	0.35
Creatinine clearance (ml/min)‡	88.3±35.5	86.5±35.6	0.74	83.2±24.5	86.7±28.7	0.52
Total Parsonnet Score	8.1±6.6	8.6±7.0	0.65	7.3±6.3	8.5±6.9	0.35
Additive EuroSCORE	4.3±2.6	3.7±2.6	0.15	3.4±2.2	3.8±2.7	0.42
Logistic EuroSCORE	4.1±3.1	3.7±4.6	0.55	2.9±2.0	3.9±4.5	0.011
Anatomical Characteristics						
SYNTAX Score	29.3±11.2	28.4±11.4	0.59	27.5±12.5	29.2±11.3	0.41
Left Main Disease§†	34.7%	40.1%	0.46	43.8%	38.7%	0.56
Number of lesions	4.0±1.4	4.0±1.7	0.70	3.9±1.8	4.0±1.7	0.69
Any total occlusions	20.4%	24.2%	0.55	28.1%	22.0%	0.42
Any bifurcation lesion	69.4%	62.5%	0.33	62.5%	64.6%	0.81
Any trifurcation lesion	10.2%	7.3%	0.45	6.2%	7.1%	0.86
Diffuse or small vessel disease	22.4%	22.0%	0.95	21.9%	20.9%	0.97
Any aorto-ostial lesion	12.2%	15.8%	0.50	21.9%	14.8%	0.27
Any angiographically visible thrombus	6.1%	2.2%	0.084	6.2%	3.4%	0.39
Any heavy calcification	61.2%	49.0%	0.095	43.8%	48.8%	0.57
Any severe tortuosity	65.3%	66.9%	0.82	56.2%	68.2%	0.16
Left arterial dominance	12.2%	18.4%	0.28	6.2%	16.6%	0.29
Proximal LAD (Segment 6) lesion	61.2%	58.3%	0.69	65.6%	57.4%	0.36
Any circumflex lesion	93.9%	85.3%	0.094	90.6%	83.4%	0.28
Any right coronary artery lesion	87.8%	81.5%	0.27	81.2%	81.1%	0.99
Any lesion length >20 mm	69.4%	55.0%	0.048	65.6%	56.4%	0.30
Peri-/Post- Procedural Characteristics						
Procedure Time (hours)	1.9±1.0	1.7±0.9	0.22	3.5±1.0	3.4±1.1	0.92
Intra-aortic balloon pump	0.0%	2.3%	0.28	3.1%	0.9%	0.22
Complete Revascularization‖	42.9%	57.2%	0.050	78.1%	62.6%	0.075
Lack of pre-procedural antiplatelet therapy#	2.0%	0.7%	0.32	21.9%	35.4%	0.11
Lack of post-procedural antiplatelet therapy#	6.1%	0.9%	0.001	3.1%	8.6%	0.27
One post-procedural antiplatelet therapy**	4.1%	4.3%	0.95	-	-	-

Total number of stents	4.8±2.1	4.6±2.3	0.62	-	-	-
Stent length (mm)	90.3±50.3	86.3±47.9	0.58	-	-	-
Stent length >100 mm	29.2%	34.0%	0.50	-	-	-
Off pump	-	-	-	25.0%	13.9%	0.20
Blood cardioplegia	-	-	-	43.8%	47.7%	0.76
Grafts per patient	-	-	-	2.7±0.7	3.0±0.7	0.024
LIMA LAD	-	-	-	74.2%	88.8%	0.013
LIMA/RIMA	-	-	-	19.4%	21.4%	0.79
Complete arterial revascularization	-	-	-	16.1%	18.7%	0.72
Complete venous revascularization	-	-	-	3.2%	2.7%	0.85
At least one jump graft	-	-	-	29.0%	31.2%	0.80
At least one Y graft	-	-	-	9.7%	11.9%	0.71
Small/unsatisfactory vessel at anastomosis site	-	-	-	29.0%	27.4%	0.84
Calcification at anastomosis site	-	-	-	29.0%	24.7%	0.58
Endarterectomy performed	-	-	-	3.2%	2.9%	0.92

*Medically treated diabetes is defined as diabetic patients requiring oral medications or insulin for glycemic control.
†Prespecified patient subsets
‡Cockcroft and Gault formula
§Isolated or associated with 1, 2 or 3VD
||SYNTAX protocol definition
Aspirin nor thienopyridine. Pre-procedurally, the study protocol mandated aspirin (>70 mg per day) at least 12 hours pre-CABG, aspirin (>70 mg per day) at least 12 hours pre-PCI, and clopidogrel (300+ mg 24 hours pre-PCI) or ticlopidine (2x250 mg daily 48 hours pre-PCI).(7)
**Aspirin or thienopyridine. Post-procedurally, aspirin (>70 mg per day) was mandated in the CABG and PCI arms, and clopidogrel or ticlopidine (2 x 250 mg) for at least 6 months in the PCI arm.(7)

Abbreviations: Abbreviations: ARC, Academic Research Consortium;(4) BMI body mass index; Def definite; LAD left anterior descending artery; LIMA left internal mammary artery; LVEF left ventricular ejection fraction; MI myocardial infarction; ml millimeter; mm millimeter; min minute; PCI percutaneous coronary intervention; Poss possible; Prob probable; RIMA right internal mammary artery; ST stent thrombosis; TO total occlusion

Online Table 2

Association of adjudicated first ST event (Protocol definition) (a), or GO event (Protocol definition) (b) to 5-year cardiac death. Time frame (median, IQR, range) from ST /GO to cardiac death are also detailed. Binary values are given.

a) Stent Thrombosis (Protocol Definition)

SYNTAX Trial PCI Arm (n=903)	Incidence of Stent Thrombosis at 5 Years	No. of Cardiac Deaths Post ST Until 5 years	Time Elapsing From Index ST to Cardiac Death (Days)		
			Median	IQR	Min-Max
SYNTAX Protocol Definition	47 (5.2%)	15/47 (31.9%)	0	0-17	0-321
Time Frame					
Acute/subacute (≤30 days)	19 (2.1%)	8/19 (42.1%)	1	0-19	0-321
Late (31 days to 1 year)	8 (0.9%)	2/8 (25.0%)	-	-	-
Very Late (>1 year)	20 (2.2%)	5/20 (25.0%)	0	0-12	0-17

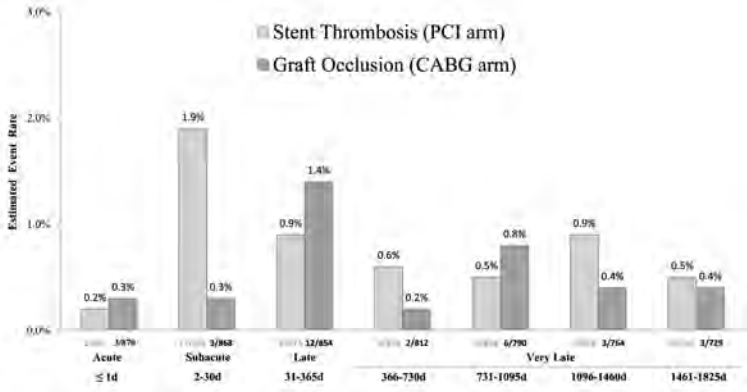
b) Graft Occlusion (Protocol Definition)

SYNTAX Trial CABG Arm (n=897)	Incidence of Graft Occlusion at 5 Years	No. of Cardiac Deaths Post ST Until 5 years	Time Elapsing from Index GO to Cardiac Death (Days)		
			Median	IQR	Min-Max
SYNTAX Protocol Definition	32 (3.6%)	0/31 (0%)	-	-	-
Time Frame					
Acute/subacute (≤30 days)	6 (0.7%)	0/6 (0%)	-	-	-
Late (31 days to 1 year)	12 (1.3%)	0/12 (0%)	-	-	-
Very Late (>1 year)	14 (1.6%)	0/13 (0%)	-	-	-

Abbreviations: ARC, Academic Research Consortium; MI, myocardial infarction; IQR, interquartile range; and ST, stent thrombosis.

Online Figure 1. Comparison of incidence of protocol defined stent thrombosis and graft occlusion at 5 years

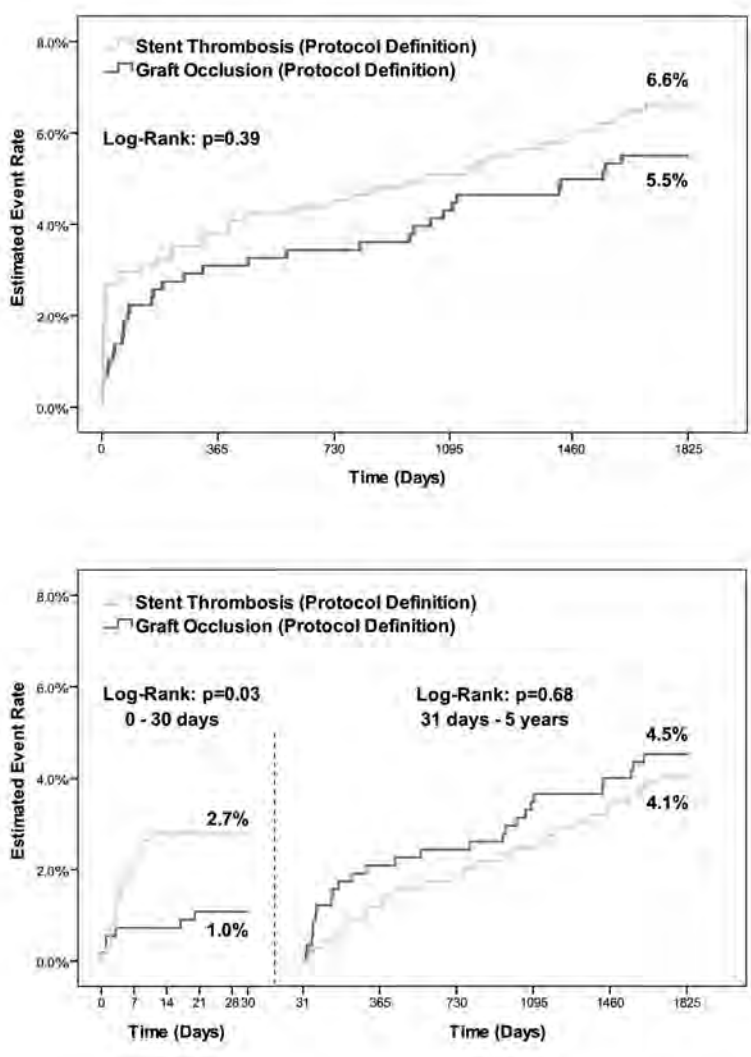
Patient level data shown.



Abbreviations: ARC Academic Research Consortium(4), CABG coronary artery bypass graft surgery, PCI percutaneous coronary intervention, d days

Online Figure 2. Kaplan-Meier estimates of protocol defined stent thrombosis and protocol defined graft occlusion at 5 years

5 year outcomes are illustrated (upper) with landmark analyses at 30 days and 31 days - 5 years (lower).



References

1. Serruys PW, Morice MC, Kappetein AP et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
2. Mohr FW, Morice MC, Kappetein AP et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.
3. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;97:1902-13.
4. Cutlip DE, Windecker S, Mehran R et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
5. Serruys PW, Onuma Y, Garg S et al. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. J Am Coll Cardiol 2010;55:1093-1101.
6. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982; 69:239-241.
7. Ong AT, Serruys PW, Mohr FW et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. American Heart Journal 2006;151:1194-204.

Chapter 5.2

In-stent restenosis (expanded version of original paper*)

Farooq V, Raber L, Gogas BD, Serruys PW

Percutaneous Interventional Cardiovascular Medicine. The PCR EAPCI Textbook. Volume II. Part III. Chapter 26.

*Restenosis: delineating the numerous causes of drug-eluting stent restenosis

Farooq V, Gogas BD, Serruys PW

Circ Cardiovasc Interv. 2011;4(2):195-205 (Impact Factor: 6.543)

In-stent restenosis

VASIM FAROOQ, LORENZ RÄBER, BILL D. GOGAS, PATRICK W. SERRUYS

SUMMARY

Despite the enormous progress made in reducing the incidence of restenosis with first and second-generation drug-eluting stents (DES), the incidence of in-stent restenosis (ISR) requiring target vessel revascularisation (TVR), so-called "DES failure", is approximately 5-10%, with one estimate suggesting approximately 200,000 repeat revascularisations performed in the US alone. Emerging evidence is now challenging the traditionally held view that ISR is a benign phenomenon with between 30-60% of cases presenting with acute coronary syndrome. The underlying mechanisms of DES restenosis are complex and can be broadly divided into 4 main causes, namely biological, arterial, stent and implantation factors. Evolving concepts concerning mechanisms relating to late restenosis and "neoatherosclerosis" are also discussed. The treatment of ISR and the determinant factors involved in the development of late stent thrombosis are well described elsewhere and are outside the scope of this review. In this review the numerous causes of DES restenosis are delineated to help identify the potentially controllable and non-controllable factors from the perspective of the interventional cardiologist intending to implant a DES.

KEYWORDS

- **Drug-eluting stents**
- **In-stent restenosis**
- **Mechanisms**
- **Percutaneous coronary intervention**

This chapter also includes supplementary data which can be found in the online version of this Textbook at **www.pcronline.com**

INTRODUCTION

In the last decade, tremendous progress has been made in reducing the incidence of restenosis with the advent of the drug-eluting stent (DES). With "plain old balloon angioplasty" (POBA), rates of acute and chronic vessel restenosis were unacceptably high at approximately 30-60%, secondary to acute and chronic recoil and constrictive remodelling [1-3]. The advent of bare metal stents (BMS) appeared to eliminate the issue of acute and chronic recoil but introduced a new entity – neointimal hyperplasia (NIH) with classical manuscripts unequivocally demonstrating a strong and linear relationship between NIH formation and late lumen loss (LLL) [4]. The restenosis rates with BMS were reported to be between 16-44% with higher rates of stenosis attributable to several risk factors, in particular long lesion length and small vessel calibre [3,5-7].

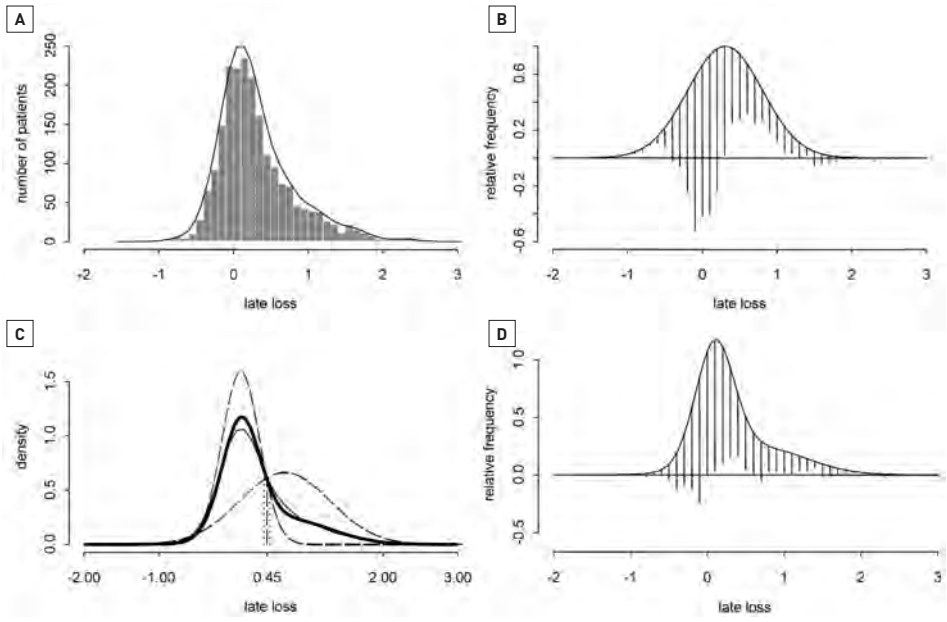
Consequently, attempts were made to limit the neointimal response after stent implantation with endovascular coronary brachytherapy. This involved the use of either catheter based endovascular delivery of radiation or radioactive stents. The technology initially appeared feasible in leading to dose-dependent reductions in restenosis. This technology resulted in an increased risk of stent thrombosis, and a significant edge vascular response leading to an "edge effect" or "candy-wrapper" phenomenon - secondary to the radioactive dose fall-off at the transition zones (proximal and distal stent edges) - precluding its widespread clinical use [8-10].

DES were thus conceived as the next step in tackling this iatrogenic entity of NIH, with large-scale reductions in restenosis rates reported at 0% in highly selective lesions and up to 16% in a broader range of patients and lesions with first-generation DES [3,6,11].

In contrast to POBA [12] and BMS [13],where an almost classical Gaussian (normal) distribution of late loss is broadly seen post-procedurally, the distribution of LLL after DES implantation has been shown to follow a bimodal pattern of distribution with both paclitaxel- (PES) and sirolimus- (SES) eluting stents (» Figure 1) [14].

FIGURE 1

The bimodal distribution of late lumen loss (LLL) **(A, B)** and percentage diameter stenosis **(C, D)** after Cypher (left) and Taxus (right) implantation. LLL indicates late lumen loss. Reproduced with permission from Byrne et al. [14] In each panel the observed frequency distribution curve (thin solid line), two subpopulations' normal distribution curves (dashed lines) and the composite distribution curve (thick solid line) are displayed; the vertical dashed line denotes the intersection point between the two subpopulation distribution curves.



Despite the significant advances in the technology to reduce restenosis, conservative estimates would, however, still suggest the incidence of ISR requiring repeat revascularisation, so-called "DES failure," to be approximately 5-10%, with one estimate suggesting approximately 200,000 repeat revascularisations in the United States alone [15].

CLASSIFICATION SYSTEM OF IN-STENT RESTENOSIS

In 1999, Mehran et al [16] first described a classification system for the patterns of restenosis seen with coronary stents. Two broad categories were described, namely focal and diffuse restenosis, with multiple subtypes within each group. The pattern of restenosis seen with DES is usually focal, in contrast to BMS which is primarily diffuse. In one series, over 60% of in-stent restenosis (ISR) cases with both PES and SES were focal, with the most common location for focal restenosis appearing to be at the proximal DES edge [17]. Despite this, over one fifth of cases of ISR remains diffuse and approximately 10-20% of cases are even occlusive (» Figure 2).

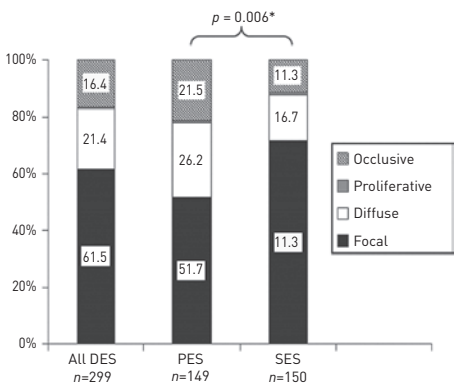
RISK FACTORS ASSOCIATED WITH IN-STENT RESTENOSIS

In 2004, there was the first reported description of the risk factors associated with DES restenosis in patients with the unrestricted use of SES since approval of its CE mark [18,19]. Despite the apparent differences in the distribution of LLL between BMS and DES as previously described, the main message of these and subsequent findings was that the usual patient characteristics, lesion types and procedural factors incriminated with restenosis in BMS were equally responsible with DES, with diabetes mellitus being implicated as one of the strongest risk factors for the development of restenosis [17-21]. It should, however, be emphasised that the distribution of restenosis with DES appears more attenuated compared with BMS, especially in long lesions and small vessels, highlighting the importance of drug elution in potentially diminishing the NIH response.

FIGURE 2

The patterns of restenosis in SES and PES

The predominant pattern of restenosis is a focal pattern of restenosis, although diffuse and proliferative restenosis are still seen with DES. *P-value calculated for the overall observed difference in the pattern of restenosis in PES and SES groups. SES indicates sirolimus- eluting stent; PES: paclitaxel-eluting stent; DES: drug-eluting stent. Reproduced with permission from Corbett et al [17].



HISTOPATHOLOGICAL BASIS OF IN-STENT RESTENOSIS

The inflammatory reaction which occurs after arterial injury is a critical factor that influences the extent of neointimal response, with the persistence of this inflammatory response beyond 90 days being strongly associated with an increased level of neointimal thickness and consequent restenosis [3,22,23]. In keeping with these findings, it has been demonstrated that restenotic lesions have a higher number of chronic inflammatory cells compared to non-restenotic lesions [22]. Histopathological analyses of ISR, involving samples taken by directional atherectomy at the time of reintervention, have been shown to be remarkably similar between BMS and DES. This is almost exclusively composed of proteoglycan-rich smooth muscle cells (SMC) and fibrolipidic areas rich in collagen and reticular fibres. A more "immature" restenotic process, as evidenced by differences in SMC phenotypes, however, has been shown potentially to exist with certain types of DES compared with BMS [24,25]. Fibrinoid tissue, indicative of a persistent inflammatory and incomplete healing response, has also been reported with DES [26-30] and implicated in the subsequent risk of late stent thrombosis (LST) [28].

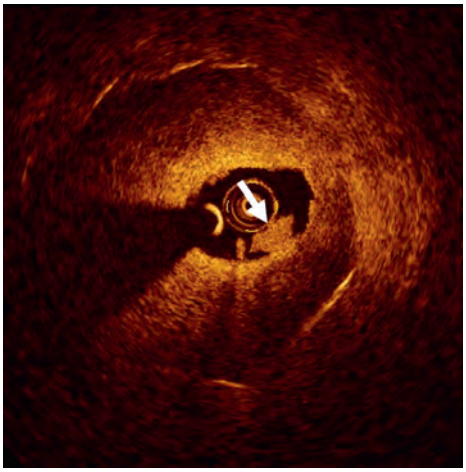
IN-STENT RESTENOSIS: A BENIGN ENTITY?

ISR has traditionally been suggested as being potentially less benign with the recurrence of anginal symptoms alone. Emerging evidence now suggests that between 30-60% of ISR cases perhaps present with an acute coronary syndrome (ACS), with unstable angina being the most common presentation (» Figure 3) [31-41], and up to 5% of patients even being reported as presenting with an ST-elevation myocardial infarction (STEMI) [36,38-41].

Furthermore, as to whether a total vessel occlusion presenting with acute ischaemia is related to a stent thrombosis or a subtotal restenosis is often difficult to differentiate

FIGURE 3

The presence of intraluminal material (white arrow), most probably thrombus, visualised in a restenotic segment. The OCT images were obtained from a patient referred for coronary angiography for unstable angina. Reproduced with permission from Gonzalo et al [229].



solely based on the clinical presentation and the angiographic findings. The consideration of the angiographic appearances, the behaviour of the lesion during balloon inflation and the patient history (such as the type of stent previously implanted) can potentially aid in identifying the aetiology of the ischaemic event. Intravascular imaging can serve as an additional supportive diagnostic tool, although the differentiation between thrombus and neointimal tissue is not always readily possible with currently available intravascular imaging techniques (intravascular ultrasound [IVUS] and optical coherence tomography [OCT]). This rapidly evolving concept is discussed in the *Late restenosis* section of *Arterial factors*.

OVERVIEW OF CHAPTER

The treatment of ISR and the determinant factors involved in the development of late stent thrombosis (LST) are well described elsewhere and are outside the scope of this chapter [42-44]. The underlying mechanisms of restenosis with DES can broadly be divided into 4 main causes (» Table 1), namely biological, arterial, stent and implantation factors, accepting that this classification is somewhat arbitrary with mechanisms of restenosis being attributable to more than one factor. In this chapter we explore these 4 main mechanisms and identify the potentially controllable and non-controllable factors from the perspective of the interventional cardiologist intending to implant a DES.

BIOLOGICAL FACTORS

Resistance to antiproliferative drugs

The underlying mechanisms of action and causes of resistance to paclitaxel or sirolimus are well documented in the cancer literature and can either be present in genetically predetermined individuals or be acquired, following cytotoxic exposure to the drug [45,46].

The so-called "drug resistance gene expression programme," described for paclitaxel resistance from the cancer literature, best exemplifies the complex pathways involved in the aetiology of drug resistance [45]. Essentially, the cellular context determines the genes that are expressed which contribute to drug resistance either in genetically predetermined cells or primed for expression following the cytotoxic insult after exposure to the drug. These genes may operate in conventional pathways that are well known (drug delivery and metabolism, apoptosis regulation, DNA repair), but the temporal (i.e., pro- and anti-apoptotic gene activity) and spatial regulation (i.e., cell survival signalling pathways) of these gene products after exposure to the drug also appear to be important.

As examples, polymorphisms in the genes that encode mTOR or proteins involved in paclitaxel or sirolimus metabolism have been shown to confer drug resistance both *in vitro* and *in vivo* [10,11] : decreased binding of sirolimus to

FOCUS BOX 1

- Drug-eluting stents (DES) were conceived as the next step - after balloon angioplasty and bare metal stents (BMS) - in tackling the iatrogenic entity of neointimal hyperplasia
- The distribution of late lumen loss (LLL) after drug-eluting stent implantation has been shown to follow a bimodal pattern of distribution with both paclitaxel (PES) and sirolimus (SES) eluting stents
- "DES failure" equates to approximately 5-10% of cases, with one estimate suggesting approximately 200,000 repeat revascularisations in the US alone [15]
- The pattern of restenosis seen with DES is usually focal. By contrast, the pattern of restenosis with BMS is primarily diffuse
- Persistence of the inflammatory response beyond 90 days after arterial injury is strongly associated with an increased level of neointimal thickness and consequent restenosis
- In-stent restenosis (ISR) may not be as "benign" as once originally thought with 30-60% of ISR cases presenting with an acute coronary syndrome (ACS)

TABLE 1

The underlying mechanisms of restenosis with DES

BIOLOGICAL FACTORS	ARTERIAL FACTORS	STENT FACTORS	IMPLANTATION FACTORS
Resistance to Antiproliferative drugs Hypersensitivity reaction (polymer) Hypersensitivity reaction (metallic stent platform) Inflammatory biomarkers Genetics	Wall shear stress "Thromborestenosis" Vessel remodelling Small vessels Late restenosis - Decreasing drug dose - Chronic inflammatory reactions - and persistent fibrin deposition - Neoatherosclerosis	Polymer drug release kinetics Type of DES? Type of drug? Stent gap, Non-uniform strut distribution and drug deposition Stent strut thickness "On" and "off" label use of DES Polymer disruption, peeling and cracking Stent fractures	Incomplete stent expansion Geographical miss Edge effect Barotrauma to Unstented Segments Incomplete lesion coverage Deployment of DES in a clot-laden arterial segment

mTOR due to mutations in FK-B12 and mTOR and mutations of downstream effector molecules of mTOR may all cause resistance to sirolimus [11].

Potentially overcoming drug resistance through the delivery of higher doses of antiproliferative agent to the implantation site

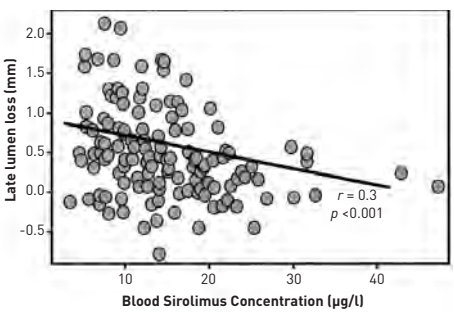
Given the possibility that drug resistance is one potential mechanism of restenosis, attempts have been made to give much higher doses of oral sirolimus to patients with refractory ISR in the theoretical attempt of overcoming drug resistance and delivering increased amounts of drug to the implantation site. The OSIRIS study [47] investigated the administration of higher doses of oral sirolimus to patients with refractory ISR and demonstrated a significant correlation between the level of sirolimus concentration in the bloodstream and rates of further late lumen loss (» Figure 4). Given that the patients received a short duration of oral sirolimus (7 days), it was unclear if these findings would be maintained at longer-term follow-up. It has been anecdotally reported that courses of sirolimus given for 30 days after POBA to the restenotic lesion, in the theoretical attempt to cover the injury period following POBA, can reduce restenosis in refractory restenosis cases [48]. Larger-scale studies are required to establish if this is feasible or practical.

Furthermore, evidence has suggested that the concomitant administration of steroids to patients implanted with BMS, particularly in patients with a persistent inflammatory state, as indicated by elevated C-reactive protein, may reduce the incidence of ISR [49-53]. Further trials are needed, however, to assess the clinical utility of steroid therapy for the treatment of ISR after prior DES implantation.

FIGURE 4

The patterns of restenosis in SES and PES

The association of sirolimus blood concentrations at the time of repeat intervention and the angiographic late lumen loss at 6-month angiographic follow-up from the OSIRIS study. Higher serum levels of sirolimus were found to correlate with the degree of 6-month angiographic late lumen loss. Reproduced with permission from Hausleiter et al [47].



Hypersensitivity reactions (the polymer)

Polymer layers in DES are used as both drug reservoirs and non-drug-coated external films to allow optimal drug release kinetics, as described in Stent Factors. As examples with the first-generation DES, the Cypher® (SES) stent (Cordis Corporation, Johnson & Johnson, Warren, NJ, USA) consists of a stainless steel platform covered with a basecoat formulation (67%) consisting of the polymers PEVA (polyethylene vinyl acetate) and PBMA (poly n-butyl methacrylate) mixed with sirolimus (33%); a drug-free PBMA topcoat is also applied over the polymer drug mixture to control drug release kinetics. The Taxus® (PES) stent (Boston Scientific, Natick, MA, USA) consists of a stainless steel platform with Translute™ (poly [styrene-b-isobutylene-b-styrene]) polymer combined with paclitaxel without a primer or topcoat layer.

The inflammatory reaction that occurs after arterial injury is a critical factor which influences the extent of neointimal response, with the persistence of this inflammatory response beyond 90 days being strongly associated with delayed healing and implicated in an increased risk of LST and restenosis long term [13,14].

The inflammatory and potential hypersensitivity response

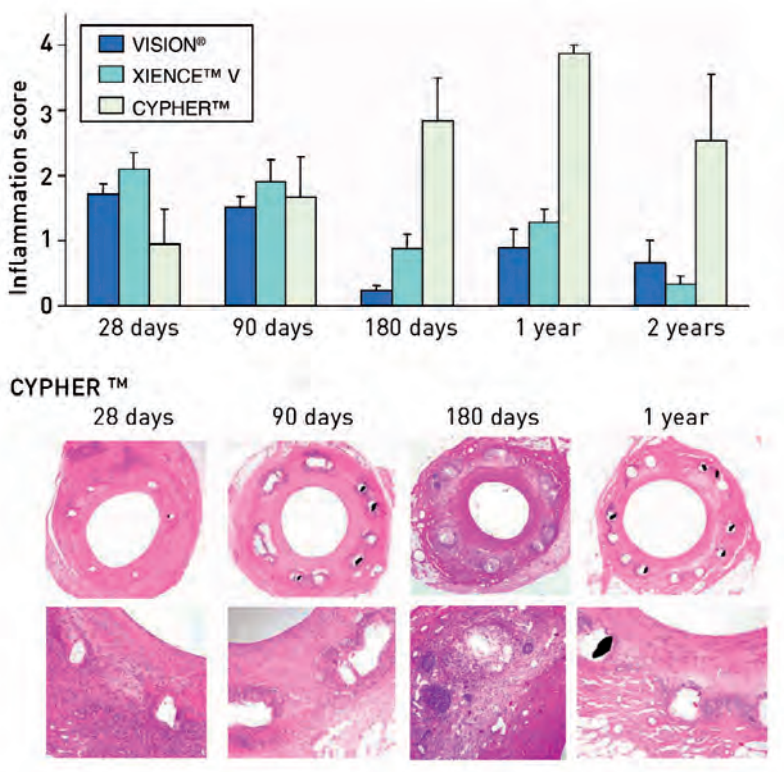
Both PES and SES have been demonstrated to provoke distinctive inflammatory responses in animal models beyond 90 days, with SES triggering giant cell infiltrations and PES causing eosinophilic reactions around stent struts [26-30]. The inflammatory responses associated with SES have been shown to persist beyond 180 days and up to 2 years (» Figure 5). This phenomenon has also been shown to be potentially further exacerbated at sites of overlapping DES [28]. This is in contrast to BMS and the second-generation everolimus-eluting stent (EES; Xience V; Abbott Vascular, Santa Clara, CA, USA) with a more biocompatible polymer, where the inflammatory responses have been demonstrated to be limited to a period of 90 days and 12 months, respectively (» Figure 5) [54].

Evidence of persistent inflammatory responses in humans have also been reported both in autopsy cases, with one case reported to involve up to one third of struts in first-generation DES at 3 months, and demonstrating signs of persistent inflammation characterised by granuloma formation and extensive eosinophilic infiltration as seen in the animal models. Furthermore, evidence of persistent inflammation has been demonstrated from thrombus aspirates taken at the time of emergency PCI in patients presenting with very LST [55].

FIGURE 5

The persistent inflammatory response to Cypher stents for a period of up to 2 years

The panels below show the persistent granulomatous inflammatory response to Cypher stents in sections at low and high power at various time points. Reproduced with permission from Nakazawa et al [54].



Further details related to this "late restenosis" phenomenon are described in *Arterial factors*.

Hypersensitivity reactions (metallic stent platform)

Koster et al [56] first reported an apparent association between the risk of restenosis and metal allergy, namely nickel and molybdenum, with BMS. This study has been controversial, however, and the research methodology subjected to criticism, in particular the methodology of identifying nickel allergy [57-59]. Small-scale, predominantly retrospective studies have failed to show an association between metal allergy in BMS and restenosis [60,61]. Saito et al [62] did, however, report nickel allergy as being an independent predictor for refractory ISR in BMS (odds ratio 5.1, p=0.0033), with almost one fifth of patients with refractory ISR having a documented true allergy to nickel (24 of 128 patients). Of note is the fact that the nickel allergy assessment was performed by an independent dermatologist blinded to the study results. Conversely, Lijima et al [63] suggested an association between nickel allergy by patch test and the recurrence of ISR, in patients treated with POBA for ISR after BMS implantation. Within their study no association was found with BMS implantation and first presentation of ISR.

The issue of ISR has also been linked to gold-coated stents, where several studies have associated these with contact allergy and a considerable increase in the risk of ISR [64-68]. Consequently, the use of gold in coronary stents has been abandoned.

Whether the issue of nickel hypersensitivity is a potential issue with DES is both speculative and theoretical. To date, only one small study (Nakazawa et al [69]) has examined this issue and found no association between the risk of ISR and SES implantation.

Inflammatory biomarkers and genetics

Inflammatory biomarkers

The inflammatory status, as assessed by C-reactive protein levels, has consistently failed to demonstrate any association with ISR after DES implantation, despite being associated with ISR after BMS implantation; C-reactive protein levels have, however, been implicated in the risk of stent thrombosis [70,71].

Circulating matrix metalloproteinases (MMP) have been shown to be potentially useful in identifying patients at a greater risk of developing ISR following DES implantation [72]. It is well established that both MMP-2 and MMP-9 play fundamental roles in the migration of vascular SMCs and matrix remodelling during wound healing and are produced by vascular SMCs, endothelial cells, macrophages, lymphocytes and mast cells in response to mechanical injury [73-75]. Significant elevations in MMP-9 levels at baseline and 24 hours post PCI, and MMP-2 levels 24 hours post PCI, have all proven to be strongly associated with the development of ISR following DES implantation [72].Conversely, in the same study, low and near-normal MMP-2 and MMP-9 levels were strongly associated with a lack of a significant restenotic response.

Furthermore, other inflammatory biomarkers such as serum levels of PAI-1 [76] and complement components (C3a and C5a) [77] have also been implicated with ISR after DES implantation.

Genetics

It would also appear that the effects of ISR are perhaps not immune from genetics. As to whether this is due to the resistance (predetermined or acquired) to the drug as previously described, or due to biological mechanisms, in particular the inflammatory response of the restenosis process itself, is presently unclear. Inflammatory gene polymorphisms in 4 differing genes have been previously demonstrated to be associated with ISR [78]. For example, homozygosity of the 16/glycine variant in the beta2-adrenergic receptor (ADRB2), a mediator of nitrous oxide synthetase, has been associated with ADRB2 receptor down-regulation and an increased risk of restenosis [78].Vogiatzi et al [79] have previously described a powerful association, by a factor of over 15-fold, between two functional polymorphisms of interleukin-8 (a strong mediator of inflammation) and the subsequent risk of restenosis. These latter gene polymorphisms were relatively rare, which subsequently limited any clinical application. Other gene mutations have also previously been described as being associated with restenosis [80,81]. Conversely, genetic markers such as angiotensin-converting enzyme (ACE), despite showing initial promise, have failed to demonstrate a clinical role – perhaps due to the multifactorial nature of ISR [82].

Potential clinical application

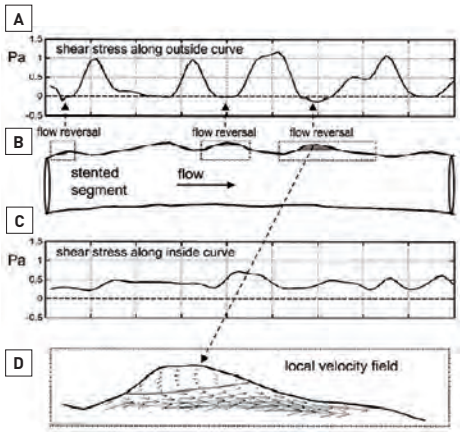
The prospect of potentially being able to identify patients with a greater propensity to develop ISR after DES implantation may perhaps allow a more "personalised revascularisation" with, for example, DES which deliver higher drug concentrations to the vessel or even the prospect of considering surgical revascularisation in this cohort of patients. This individualised approach to revascularisation based on individual genetic risk factor profiling is still in its infancy and extensive preclinical and clinical investigations are required before this can even be considered to enter conventional clinical practice.

FOCUS BOX 2

- Biological factors related to in-stent restenosis (ISR) can be secondary to resistance to antiproliferative drugs, hypersensitivity reactions to the polymer or metallic stent platform, and inflammatory biomarkers and genetics
- ISR secondary to antiproliferative drugs can either be present in genetically predetermined individuals or be acquired following cytotoxic exposure to the drug. Limited evidence exists for using oral sirolimus to overcome drug resistance – further trials are required to establish if this is feasible or practical
- Hypersensitivity to the polymer is well documented and has been associated with late restenosis (see *Arterial factors*) and stent thrombosis
- Hypersensitivity to the metallic platform of drug-eluting stents remains hypothetical and unproven with nickel. Gold-coated stents have a proven association with contact allergy and have been linked to restenosis: consequently, coronary stents are no longer manufactured from gold
- The identification of biomarkers (e.g., MMP) and genes associated with ISR is in its infancy – at the time of writing the clinical application is awaiting to be defined

FIGURE 6

Two-dimensional axial cross-section of a slightly curved stented coronary segment **(B)**. The results of a computation of velocity and shear stress distribution in this segment at follow-up show regions with low shear stress **(A)** that coincide with the shallow pits in **(B)**. Along the inner curve, the region with lower shear stress, the pits are virtually absent and shear stress distribution is much more homogeneous **(C)**. In some of the pits along the outside curve, flow reversal can be observed (inset and **D**). The areas containing negative axial velocity are indicated by the shaded boxed regions in **(B)**. Reproduced (Figure and Figure legend) with permission from Gijsen et al [89].



ARTERIAL FACTORS

Wall shear stress

Wall shear stress refers to the principle that fluid dynamics and vessel geometry may play a potential role in the cause of focal plaque or neointimal formation [83]. The concept of wall shear stress is that fluid (i.e., blood) does not move at the same velocity at every point within the vessel, with blood flowing fastest in the vessel centre (i.e., a high shear stress area) and slowest when closest to the vessel wall (i.e., a low shear stress area) due to frictional forces exerted by the vessel endothelium. For example, in coronary bifurcations this phenomenon becomes more notable with a lower shear stress occurring at the ostium of a side branch [83-85]. This may subsequently lead to the accumulation of growth factors, mitogenic cytokines and platelets, which may promote either atherosclerosis or neointimal formation if the side branch undergoes "vessel injury," such as after angioplasty or stenting [83,85-89]. Conversely, the carina of the side branch is a high shear stress area and atherosclerosis or restenosis rarely occurs here: indeed, animal models have shown that high shear stress areas can potentially directly inhibit SMC proliferation [90]. Other examples include differences in the shear stress in the inner and outer curvatures of a stented vessel (» Figure 6) [89].

Clinical implications of wall shear stress

In a novel experiment in an animal model, Carlier et al [91] demonstrated that, through the implantation of a "flow divider" into the centre of a stent implanted in the iliac arteries, they were able to modulate the local wall shear stress and the subsequent growth of NIH. The flow divider significantly increased the local wall shear stress and was consequently found to lead to a local reduction in inflammation and injury, with reduced NIH growth and subsequent late lumen loss. The closest human model of this example has been the use of the principle of simultaneous V-stenting (so-called "shotgun stenting") with the formation of a metallic neo-carina in the left main stem or other suitably sized vessels [92,93].Kim et al [92] demonstrated that in 36 consecutive patients (29 with left main stem interventions) using this technique with SES implantation, a 14% (5 patients) restenosis rate occurred over an average follow-up period of over 2 years. Interestingly, a "membranous diaphragm" at the carina was identified in 14 patients (47%) with restenosis occurring in just one of these patients. Conversely, Stinis et al [94] showed that, in 74 consecutive patients with predominantly left anterior descending-diagonal lesions, the target lesion revascularisation rate was more than twice as high in the simultaneous V-stenting group (14 patients, 40%), compared with the crush group (5 patients, 12.8%) at

a follow-up of >3 years. Whether lesion location played a role in the disparity of these results remains unclear. Robust, randomised controlled trials are therefore required to evaluate the feasibility of this technique.

The issue as to whether the actual presence of the stent in the vessel wall negatively alters the wall shear stress sufficiently to promote restenosis has proven to be controversial, with conflicting evidence existing in the literature. In a more recent, larger, well-designed trial, Papafaklis et al [95] demonstrated the presence of significant numbers of "pockets" of low shear stress within stented segments, secondary to local geometric factors such as angulation or curvature, and showed that these pockets were significantly associated with NIH formation at 6-month follow-up with BMS and PES. Interestingly, this was not seen with SES, suggesting that sirolimus significantly attenuated the neointimal response to low shear stress. Paclitaxel was unable to do this, perhaps because of its differing pharmacological mode of action or even its shorter drug-release kinetics as discussed in Stent factors [3].

"Thromborestenosis" phenomenon

"Thromborestenosis" is a term first described by Oikawa et al [96] to describe a novel theory in which chronic thrombus formation may play an integral part in the development of ISR following DES implantation. The uniqueness of this study was the combined use of intravascular ultrasound (IVUS), coronary angioscopy and histopathological analyses (taken by direct coronary atherectomy) in all patients who had presented with ISR following SES implantation. The major findings of this study were that, in patients presenting with ISR, the incidence of thrombus and fibrin deposition were substantially more frequently observed within ISR lesions associated with SES implantation (12 of 13 cases), as compared to BMS (2 of 8 cases), and that the thrombus seen was not only located at uncovered stent strut sites (if present) but also, more importantly, on covered stent strut sites (» Figure 7). A theory to explain the presence of neointimal thrombus put forward by the authors was that the neointima covering a SES strut site was potentially more thrombogenic.

Joner et al [26] have previously described evidence to support the concept of "thromborestenosis." In 2 of 14 autopsy cases of patients who died of LST, evidence of ISR with superimposed thrombus was seen [26]. Further support comes from, Cook et al [55] who demonstrated evidence of the widespread presence of chronic thrombi, as evidenced by the presence of a chronic inflammatory response, within all thrombus aspirates taken at the time of emergency percutaneous coronary intervention (PCI) in patients presenting with very LST. This was in addition to the acute thrombus seen in all samples and "hypereosinophilia" (likely to be secondary to polymeric hypersensitivity) observed in a proportion of aspirates [55].

Conversely, Rittersma et al [97] also showed evidence of chronic thrombi which was days to weeks old in at least 50% of 211 consecutive STEMI patients who had thrombus aspirates taken within 6 hours of onset of symptoms. Only 4 patients (2%) within the study group had prior PCI to the infarct-related artery, with the theory for the presence of older thrombi being speculated to be related to "clinically silent non-occlusive atherothrombotic events" in the preceding days to weeks prior to the clinical presentation of occlusive thrombosis.

As to whether "clinically silent non-occlusive atherothrombotic events" is also an explanation for the presence of chronic thrombi seen with ISR, or if this is related to "thromborestenosis", is presently unclear.

Vessel remodelling

Implantation of DES in vessels that have previously undergone positive remodelling (the "Glagov" phenomenon [98]) secondary to a large plaque burden have been shown to be a significant predictor of restenosis (» Figure 8) [98-100]. Theoretically, the level of NIH formation would be the same between a non-remodelled and a remodelled vessel following stent implantation; however, the phenomenon of where the NIH would potentially grow post stent implantation would be significantly different between the two vessels. In vessels without positive remodelling, the NIH can be partially accommodated between the stent and the external elastic membrane (EEM), thereby limiting neointimal growth within the vessel lumen. Conversely, in a fully remodelled vessel, this process cannot occur to the same extent, and the bulk of the NIH growth would therefore preferentially occur within the stented lumen with a subsequent greater likelihood of restenosis.

Small vessels

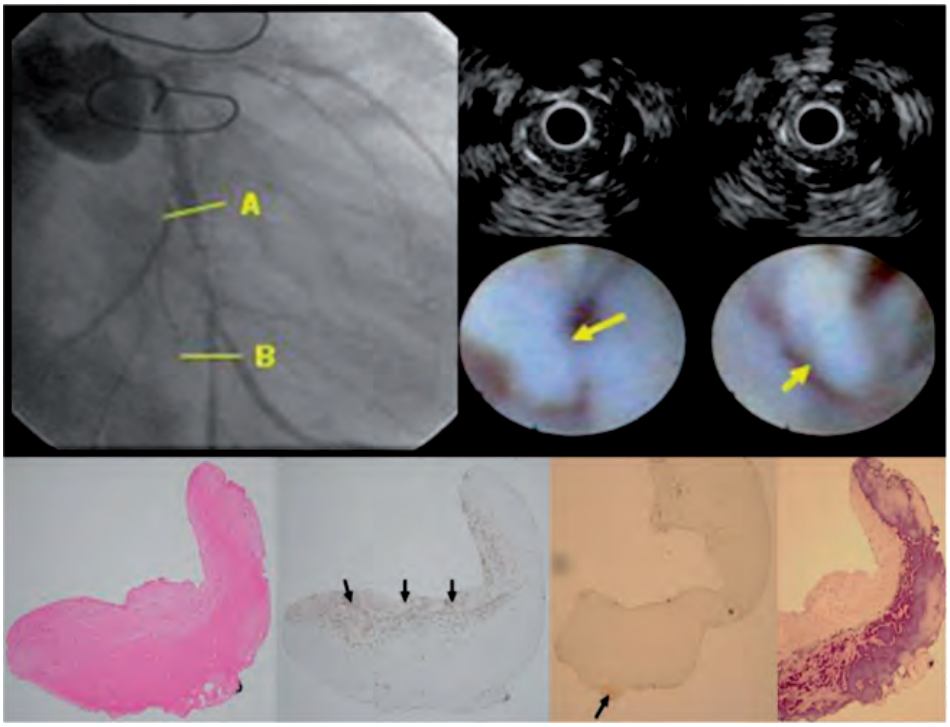
This is discussed in *Stent factors* with strut thickness.

FOCUS BOX 3

- Wall shear stress refers to the principle that blood flow is fastest (high shear stress) in the vessel centre and slowest (low shear stress) when closest to the vessel wall due to frictional forces exerted by the vessel endothelium. Low shear stress areas lead to the local accumulation of growth factors, mitogenic cytokines and platelets which may promote either atherosclerosis or neointimal formation after vessel injury
- SES, but not PES, are able to effectively inhibit the neointimal response in low shear stress areas
- "Thromborestenosis" describes the theory in which chronic thrombus formation may play an integral part in the development of ISR

FIGURE 7

Evidence of the "Thromborestenosis" theory?
Upper image: in a patient with a diffuse long ISR in the mid circumflex (A-B), IVUS shows homogeneous isoechoic restenotic lesions **(upper right images)** and coronary angioscopy reveals flapping white thrombus attached to the restenotic segment (middle right images: yellow arrows).
Lower image: histopathology of restenotic tissue taken by direct atherectomy from the restenotic site reveals **(from left to right)**, homogeneous tissue and collagen matrix (seen on haematoxylin and eosin stain), smooth muscle cells in collagen matrix (black arrows) (α-SMA stain), few proteoglycans (versican and decorin stain) and rich fibrin corresponding to the homogeneous tissue. Reproduced with permission from Oikawa et al [96].



Late restenosis

Whereas parallel neointimal proliferation and healing with BMS have been shown to be complete after 3 to 6 months [101], potentially followed by a late lumen enlargement beyond one year, a different pattern of healing has emerged with early-generation DES. This has been characterised by delayed healing with an ongoing neointimal growth beyond 30 days in experimental studies [102] as previously described (» Figure 5), and beyond 6 months in clinical studies [103].

Different mechanisms have been identified in the mechanisms of delayed neointimal growth and these are elaborated in the following paragraphs.

Decreasing drug dose

The antiproliferative drug concentration diminishes over time according to the individual elution profile of the different DES (see *Stent factors*): with decreasing drug dose, the antiproliferative inhibitive effect progressively declines. If the arterial healing is not terminated at the point in time when the drug elution has ceased, neointimal growth may continue to accrue (» Figure 9).

Chronic inflammation

Chronic inflammation is a trigger for late neointimal growth. Animal studies have suggested that the inflammatory response among different DES is clearly distinct in terms of the pro-

FIGURE 8

The phenomenon of the increased likelihood of restenosis occurring in positively remodelled vessels. Red arrow indicates position where NIH can potentially grow since the NIH cannot be accommodated between the stent and the external elastic membrane (EEM). Adapted and reproduced with permission from Spanos et al. [230].

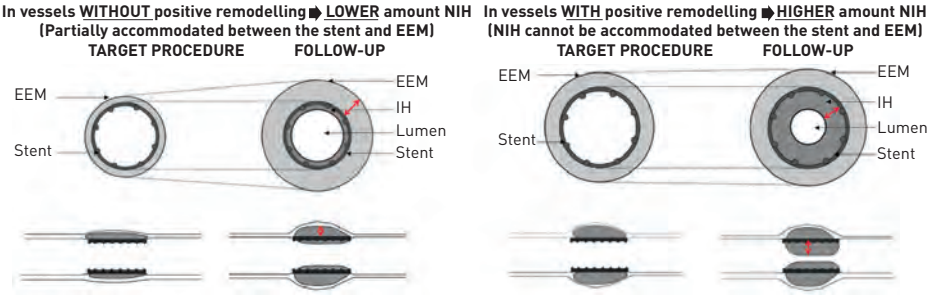
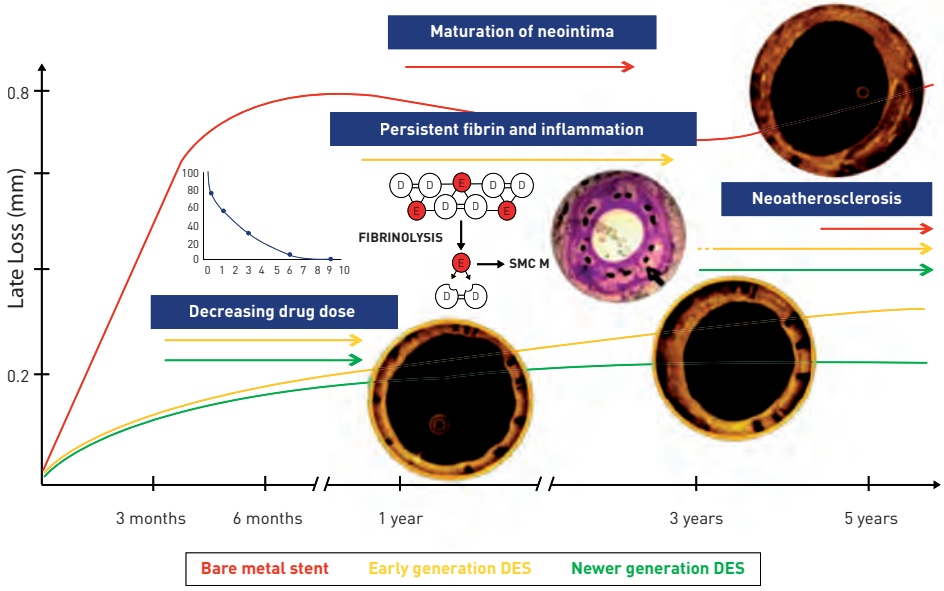


FIGURE 9

The different time courses of the neointimal growth (indicated by late lumen loss) for BMS, early and newer-generation DES are shown over a five-year period. Different mechanisms contributing to the late neointimal growth in DES are presented. In addition, a case example of a sirolimus-eluting stent showing delayed neointimal growth is depicted. SMC M: smooth muscle cell migration into neointima. D and E: D and E domains of fibrinogen. Arrow in histological cross-section depicts peri-strut inflammatory cell infiltrates. Reproduced (Figure and Figure legend) with permission from Räber et al [231].



portion of giant cells, granulomas, eosinophils, lymphocytes and fibrin deposition as previously described [26-30]. Carter et al compared SES and BMS in a porcine coronary artery model and found late neointimal formation between 30 and 90 days, which resulted in a similar amount of neointimal area at 90 days between SES and BMS, thus mitigating the initial suppression achieved with SES at 30 days [102]. Histological data documented a progressive increase in injury and inflammation scores between 30 and 180 days, probably representative of a chronic inflammatory response with a predominantly lymphocytic reaction with giant cells.

The presence of inflammatory reactions during the long-term time course following SES implantation was further corroborated by Virmani et al [104]. Histological evaluation of stented porcine coronary arteries demonstrated an intense circumferential granulomatous, eosinophil-rich inflammatory response during long-term follow-up (90 and 180 days) in SES, and to a lesser extent PES; conversely, inflammation was absent with BMS. PES as opposed to SES was further characterised by an increase in fibrin deposition. The presence of fibrin - which has been described in the vicinity of stent struts in experimental [104] and autopsy studies [105] is an initiator of smooth muscle cell migration and proliferation [106]. Porcine coronary models have demonstrated an increasing amount of fibrin in the long-term course (90 days), [104] which is analogous to delayed wound healing and excessive scarring. Delayed fibrinolysis is a stimulus to smooth muscle cell proliferation and excessive collagenous matrix deposition, leading to late restenosis.

The most likely culprits for the prolonged inflammatory reactions of the vessel wall are hypersensitivity reactions to the durable polymer. Durable polymers serve as a standard component of early-generation DES and are of importance as they facilitate drug delivery over a certain time (see *Stent factors*) [107]. Animal data have demonstrated that a peak in hypersensitivity reactions occurs only after the complete release of the drug (>60 days), supporting the notion that the durable polymer may be the more important cause [28].

Taken together, early-generation SES and PES showed distinct long-term vessel responses, which have not been described in BMS. Whereas SES may cause a granulomatous and eosinophilic reaction, PES is mainly characterised by fibrin deposition. Both of these inflammatory reactions may trigger a continued neointimal proliferation and thereby potentially cause late restenosis (» Figure 9). Inflammatory reactions are most likely caused by the durable polymers which have made them the consequent targets for improving stent designs. Whether the strategy of more biocompatible polymers or biodegradable polymers will result in a lower inflammatory response and consequent lower late neointimal proliferation has yet to be demonstrated.

Neoatherosclerosis

Neoatherosclerosis is defined as the presence of atherosclerotic disease within the neointima of a stented segment, ranging from pathological intimal thickening with presence of intercellular lipid accumulations to ruptured/unruptured thin-cap fibroatheroma. It has been speculated that the presence of neoatherosclerosis, namely ruptured thin-cap fibroatheromas, may be responsible for the acute clinical presentation of patients suffering from late restenosis.

Nakazawa et al described in a pathology registry the incidence of neoatherosclerosis within 142 BMS, 81 SES and 76 PES post-mortem specimens [108]. The incidence of neoatherosclerosis was higher in DES (31%) as compared to BMS (16%, $p<0.001$), whereas no meaningful differences were observed between the two early-generation DES. An important difference between BMS and early-generation DES was that the first occurrence of neoatherosclerosis occurred earlier with first-generation DES compared to BMS. Vulnerable plaques, namely thin-cap fibroatheroma (TCFA), were found in 1-4% of lesions without differences among stent types, but with a delayed occurrence in BMS as compared to early-generation DES.

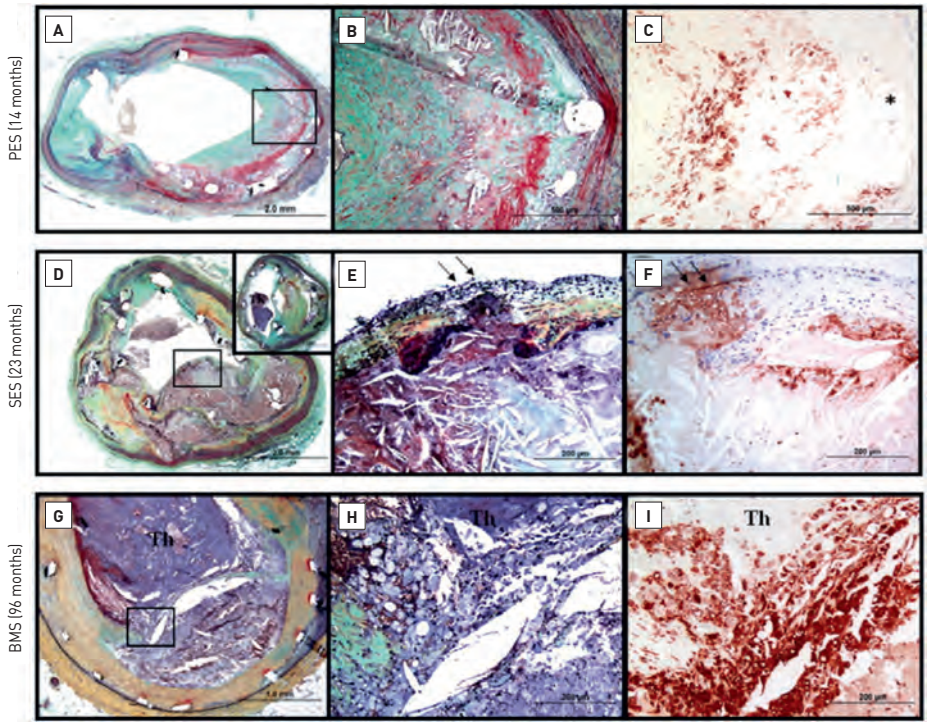
The underlying reason for the difference in the occurrence of neoatherosclerosis is currently speculative. The mechanisms of neoatherosclerosis in DES are likely to be different from the ones observed in BMS. DES have been associated with impaired re-endothelialisation and with a disturbed functionality of the neoendothelium. This potentially leads to the initialisation of the atherosclerotic cascade commencing with monocyte adhesion and migration into the neointima and an increased permeability of the endothelium for circulatory lipid migrating into the subendothelial matrix. Conversely, re-endothelialisation is faster and the endothelium exhibits a preserved functionality in BMS-treated segments, suggesting different mechanisms involved in the genesis of neoatherosclerosis. Nakazawa et al [108] speculated whether shear stress may be a major contributing explanatory factor, as evidenced by some differences in the longitudinal distribution of neoatherosclerosis, in particular an increased occurrence in the proximal part of BMS-treated segments.

Illustrative examples of histological cross-sections depicting neoatherosclerosis are provided in » Figure 10 and two examples of OCT cross-sections displaying neoatherosclerotic lesions are shown in » Figure 11.

To date, two *in vivo* studies have corroborated the aforementioned histopathological findings. Takano et al compared the appearances of neointimal tissue in BMS-treated lesions at 6 months and separate BMS-treated lesions more than 5 years previously [109]. Whereas neoatherosclerosis was absent in the early group, a transformation of the neointima during

FIGURE 10

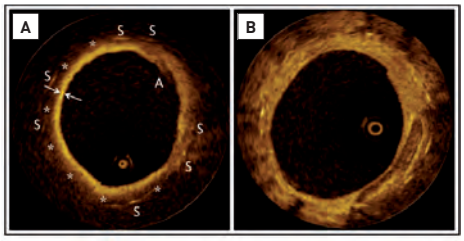
(A) Foamy macrophage clusters in the peri-strut region of sirolimus-eluting stents (SES) implanted for 13 months ante mortem are seen. **(B)** Fibroatheroma with foamy macrophage-rich lesion and early necrotic core formation in SES of 13 months' duration. **(C)** Fibroatheroma with peri-strut early necrotic core, cholesterol clefts, surface foamy macrophages, and early calcification (arrows) in SES at 13 months. **(D)** Peri-strut late necrotic core in the neointima characterised by large aggregates of cholesterol cleft in SES at 17 months. **(E)** Fibroatheroma with calcification in the necrotic core in SES of 10 months' duration. **(F)** A peri-strut calcification (arrows) with fibrin in SES of 7 months' duration. (**G** and **H**) A low-power magnification image **(H)** of a severely narrowed bare metal stent (BMS) implanted 61 months with a thin-cap fibroatheroma. Note macrophage infiltration and a discontinuous thin fibrous cap in a high-power magnification image **(G)**. **(I)** A low-power magnification image shows a plaque rupture with an acute thrombus that has totally occluded the lumen in BMS implanted for 61 months ante mortem. **(J)** A high-power magnification image shows a discontinuous thin-cap with occlusive luminal thrombus. Reproduced (Figure and Figure legend) with permission from Nakazawa et al [232].



long-term follow-up was noted with lipid-rich intima (68%), calcifications (10%), intimal disruptions (38%), thrombi, and neovascularisation (52%). These results were confirmed in another OCT study by Habara et al who evaluated the neointimal composition in BMS-treated patients presenting with early (<1 year) versus late (>1 year) clinical restenosis [110]. Whilst the neointima appeared to be relatively normal in the early restenosis group, a significant proportion of late restenosis lesions presented with atherosclerotic changes, thrombi or neointimal tears. An extension of these findings to DES was obtained by Kang et al [111] in 50 patients presenting with clinical restenosis who underwent optical coherence tomography (OCT), intravascular ultrasound (IVUS) and IVUS-VH (IVUS-virtual histology) after a mean duration of 32 months post DES implantation. The main finding was that 90% of all patients exhibited a lipid-rich intima, indicating that atherosclerotic transformation was indeed highly predominant in delayed restenotic lesions. Whilst a majority of patients with stable angina presented with a structurally intact intima, more than 50% of patients presenting with unstable clinical symptoms showed evidence of a ruptured and thrombosed thin-cap fibroatheroma.

FIGURE 11

This figure depicts 2 OCT cross-sections obtained 5 years following implantation of a sirolimus-eluting stent (Panel A) and a paclitaxel-eluting stent (Panel B). **In Panel A**, a signal-poor region between 4 and 1 o'clock is noted, suggestive of a lipid pool/necrotic core that is covered by a thick fibrous cap with a high signal intensity (100 microns at the location indicated by arrows). Due to the high attenuation of the lipid pool/necrotic core (*), the underlying stent struts are displaying an unusual low signal without shadowing (S). Taken together, the image suggests the presence of a thick-cap fibroatheroma within neointimal tissue. Note the artefact (A) at 2 o'clock.
In Panel B, the stent struts are displaying a much more intense signal with a typical shadowing. Between three and 6 o'clock, a sharply delineated region with low backscattering and low attenuation is noted, suggesting a calcific pool within the neointimal tissue.
Note that, in both images, there is no significant narrowing of the lumen, which refers to the fact that neoatherosclerosis does not necessarily lead to late restenosis. Image courtesy of Dr Lorenz Räber and Professor S. Windecker, Bern, Switzerland.



Taken together, the evidence derived from histology and *in vivo* imaging studies suggests that neoatherosclerosis occurs during the long-term time course after both BMS and DES implantation and can contribute to late restenosis.

Furthermore, neoatherosclerosis seems to be more prevalent in lesions causing symptomatic restenosis. The neoatherosclerotic transformation of the neointima potentially leads to the formation of (neo) thin-cap fibroatheromas, which can rupture and trigger an unstable clinical presentation. Therefore, in-stent neoatherosclerosis should also be considered as a differential diagnosis in patients presenting with stent thrombosis.

Angiographic and intravascular imaging data on late neointimal growth and restenosis in humans

Longitudinal angiographic and angioscopic follow-up series in patients implanted with BMS have observed late improvements in lumen diameter and an increased transparency (defined according to the visibility of the majority of the stent) respectively at three years of follow-up, suggesting late lumen remodelling on the basis of fibrotic maturation and regression of the neointima. Kimura et al reported a significant improvement in MLD from 1.94±0.48mm at 6 months to 2.09±0.48 ($p \leq 0.001$) at 3 years [112]. A longitudinal angioscopic evaluation in 12 patients following BMS implantation exhibited a change in neointimal appearance from 6 months to 3 years characterised by an increase in transparency [113]. A prolongation of the angiographic follow-up of the above-mentioned study by Kimura et al demonstrated late re-narrowing beyond 4 years, [114] suggesting a triphasic pattern following BMS implantation: 1) pronounced neointimal proliferation within the first 6 months, followed by 2) a lumen enlargement with maturation of the neointima, and finally 3) leading to a re-narrowing, probably paralleled by an atherosclerotic transformation as previously described (» Figure 9).

In contrast to BMS, angiographic and IVUS studies of early-generation DES documented a continued increase in neointimal formation beyond the time point at which neointimal proliferation is halted in BMS. » Table 2 provides an overview of IVUS studies that assessed serial changes in neointimal volumes among different stent types. Whereas in BMS no increase in neointimal volume was observed, early-generation DES have been associated with an on-going growth up to 4 years. Notably, all of these studies have only provided a snapshot within the first year after implantation, and at a single time point beyond one year (e.g., at 2, 3, or 4 years). In view of this methodological limitation, there is no definite answer in respect to the exact dynamics of late neointimal growth, and presently it remains unclear whether

TABLE 2

Serial intravascular ultrasound (IVUS) assessment of neointimal volume in patients treated with BMS or DES during long-term follow-up

TRIAL OR FIRST AUTHOR	STENT TYPE	PATIENT NUMBER	4-6 MONTHS (MM3)	1 YEAR (MM3)	2 YEARS (MM3)	4 YEARS (MM3)	P-VALUE
TAXUS II [216]	BMS	77	28.7±33.2	na	23.9±25.1	na	0.02
Aoki et al [217]	SES	23	2.1±1.7	3.8±3.3	7.0±6.7	8.4±5.8	<0.0001
TAXUS II [216]	PES-SR	43	9.4±12.1	na	13.6±11.3	na	0.018
TAXUS II [216]	PES-MR	41	10.7±15.8	na	16.9±17.3	na	0.013
Collet et al [218]	SES	12	na	2.5±3.7	na	7.7±6.7	na
Collet et al [218]	BES	13	1.2±2.0	na	na	1.2±4.9	na

BMS: bare metal stent; SES: sirolimus-eluting stent; PES-SR: paclitaxel-eluting stent slow release; PES-MR: paclitaxel-eluting stent moderate release; BES: biolimus-eluting stent using biodegradable polymer; na=not applicable.

the continued growth is halted at 2, 3, or 4 years, or whether it continues beyond 4 years. Furthermore, serial IVUS data on newer-generation DES are, to date, scarce.

Angiographic data

Table 3 provides an overview of angiographic long-term studies investigating delayed late loss, namely the difference in late loss between 6-12 months and at long-term follow-up beyond one year.

In SIRTAX LATE, 293 patients underwent serial angiography at baseline, 8 months and 5 years (SES=142, PES=151) [103]. Overall, an ongoing reduction of the minimal lumen diameter was noted between 8 months and 5 years, resulting in a late loss of 0.33±0.66 mm. Whilst SES was superior in terms of late loss at 8 months, differences between PES and SES were balanced at five years. This was explained by a late catch-up observed with SES, namely a numerically higher delayed late loss with SES (SES 0.37±0.73 mm, PES 0.29\0.59 mm, p=ns). In keeping with the findings from SIRTAX LATE, Byrne et al demonstrated in a large, unpaired angiographic patient cohort that the late loss at 6-8 months further accrued with first-generation DES (PES and SES) [115]. A numerically higher increase of late loss was consistently shown with SES (0.17±0.50 mm) compared to PES (0.13±0.50 mm). As the absolute increase in late loss from 8 months to 2 years observed by Byrne et al was numerically lower than the increase from 8 months to 5 years in SIRTAX LATE, one may speculate that neointimal growth continued beyond 2 years. Interestingly, a third group in the study of Byrne et al, composed of polymer-free DES, exhibited only a minimal delayed late loss of 0.01±0.42 mm, suggesting that polymer-free stents may be less affected.

Newer-generation drug-eluting stents

Histological data comparing the long-term inflammatory responses of newer-generation DES using durable polymer are to date scarce. As they relate to devices using biodegradable polymer technology for drug delivery, it will be of interest to investigate how the bio-absorption process, which is

TABLE 3

Serial angiographic assessment of late loss following BMS or DES implantation during long-term follow-up

FIRST AUTHOR	STENT TYPE	NUMBER OF LESIONS	LATE LOSS SHORT TERM (BL-FUP1) (MM)	LATE LOSS LONG TERM (BL-FUP 2) (MM)	DELAYED LATE LOSS/GAIN (MM)
Asakura et al [113]	BMS	12	6 mo 0.74 ± 0.32	3 yrs 0.51 ± 0.26	gain : 0.23
Kimura et al [112]	BMS	72	6 mo 0.61	3 yrs 0.46	gain : 0.15
Byrne et al [115]	PF- RES SES PES	375 704 501	6-8 mo 0.46 ± 0.57 0.25 ± 0.50 0.46 ± 0.59	2 yrs 0.47 ± 0.59 0.37 ± 0.60 0.55 ± 0.66	loss : 0.01 ± 0.42 loss : 0.17 ± 0.50 loss : 0.13 ± 0.50
Räber et al [219]	SES PES	179 203	8 mo 0.09 ± 0.18 0.13 ± 0.22	5 yrs 0.45 ± 0.73 0.42 ± 0.62	loss : 0.37 ± 0.73 loss : 0.29 ± 0.59
Kyung Woo Park et al [220]	SES PES	24 23	6-9 mo* 0.24 0.55	2 yrs* 0.50 0.65	loss : 0.26 loss : 0.10
Duk-Woo Park et al [221]	BMS LD-PES HD-PES	17 18 20	6 mo* 0.80 0.50 0.30	2 yrs* 2 yrs* 0.70 0.90	gain : 0.40 loss : 0.20 loss : 0.60
Sousa et al [222]	FR-SES SR-SES	13 13	1 yr 0.08 ± 0.31 0.08 ± 0.23	4 yrs 0.41 ± 0.49 0.09 ± 0.23	loss : 0.33 loss : 0.01

PF: polymer free; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; BMS: bare metal stent; LD: low dose; HD: high dose; FR: fast release; SR: slow release; mo: months; yrs: years ; where SD is missing, values have been calculated using MLD.

a known trigger for at least a transient inflammation, may enhance neointimal proliferation during the long-term follow-up [116]. With polymer-free DES, few animal studies have reported a decrease in both inflammatory reactions and fibrin deposition up to 180 days, with a subsequent lower extent of angiographically defined delayed late loss [115].

Clinical significance of late catch-up

The most relevant question emerging from the angiographic and intravascular imaging data is whether delayed neointimal proliferation translates into a clinically meaningful need for target lesion revascularisation (TLR) during long-term follow-up, reducing the early efficacy benefit of DES. Long-term results from randomised controlled trials of early and newer-generation DES consistently show a yearly TLR rate of less than 2% beyond one year, without meaningful differences compared to BMS (» Table 4). After subtraction of stent-thrombosis-related TLR - which are at least in part not related to restenosis - the annual TLR rate is as low as 1–1.5%. This relatively low frequency of late TLR is explainable by the magnitude of the delayed late loss (between 1 and 5 years = 0.30-0.40 mm), which is below the threshold that usually causes clinically significant restenosis. Against this backdrop it is reasonable to conclude that early-generation DES delay neointimal formation and healing during the long-term course, but without significantly compromising the early benefit in efficacy. Prolonged neointimal proliferation, however, may be a useful marker to assess the delay in healing. The presence of delayed healing

TABLE 4

Target lesion and stent thrombosis rates beyond one year in BMS, early and newer-generation DES

TRIAL ACRONYM	STENT TYPE AND NUMBER OF PATIENTS	CLINICAL SETTING	FOLLOW-UP PERIOD (YEARS)	INCIDENCE OF TLR UP TO LATEST FOLLOW-UP (%)	INCIDENCE OF TLR BETWEEN 1-5 YEARS (%)	ANNUAL TLR RATE BETWEEN 1 YEAR AND MAXIMUM FOLLOW-UP (%)	ARC DEFINITION VLST UP TO MAXIMUM FOLLOW-UP (%)	ANNUAL VLST INCIDENCE (%)
EARLY-GENERATION DES (RCTS WITH 5-YEAR FOLLOW-UP)								
RAVEL [223]	SES (n=120) vs. BMS (n=118)	Stable CAD	5		10.3 vs. 1.7*†	2.6 vs. 0.4*	0.8 vs. 0.8 p=1.0	0.2 vs. 0.2*
SIRIUS [224]	SES (n=533) vs. BMS (n=525	Stable CAD	5	9.4 vs. 24.2 p<0.001	4.5 vs. 4.0 p=0.76	1.1 vs. 1.0*	0.8 vs. 0.4 p=0.56	0.2 vs. 0.1*
TAXUS IV-SR [225]	PES (n=651) vs. BMS (n=643)	Stable and unstable CAD	5	16.4 vs. 4.3 p<0.001	6.0 vs. 8.0*	1.5 vs. 2.0 p=0.26	0.8 vs. 0.4*	0.2 vs. 0.1 p=0.49
SIRTAX LATE [103]	SES (n=503) vs. PES (n=509)	Allcomers	5	13.1 vs. 15.1 p=0.29	7.4 vs. 4.9 p=0.16	2.0 vs. 1.4 p=0.17	2.6 vs. 2.4 p=0.83	0.7 vs. 0.6 p=0.85
NEWER-GENERATION DES (RCTS WITH AT LEAST 3 YEARS OF FOLLOW-UP)								
LEADERS (Wykrzykowska, 2011 #30)	BES (n=857) vs. SES (n=850)	Allcomers	3	7.6 vs. 8.8 p=0.38	2.7 vs. 3.4 p=0.41	1.3 vs. 1.7 p=0.56	0.3 vs. 0.9 p=0.09	0.1 vs. 0.4 p=0.12
ENDEAVOR pooled [226]	ZES (n=2,132)	Stable and unstable CAD	3	6.7	1.3	0.65*	0.8‡	0.4‡
SPIRIT II, III pooled [227]	EES (n=892) vs. PES (n=410)	Stable CAD	3	5.4 vs. 9.1	2.5 vs. 3.7 p=0.27	1.3 vs. 1.9*	0.2 vs. 0.5 p=0.59	01. vs. 0.3*

TLR is ischaemia-driven if available. *Unpublished data that was calculated using outcomes at 1 year and at the time point of the maximal follow-up, therefore no p-values † TLR between 9 months and 5 years. ‡ARC definite or probable stent thrombosis.
BMS: bare metal stent; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; ZES: zotarolimus-eluting stent; na: not applicable; VLST: very late stent thrombosis; TLR: target lesion revascularisation; ENDEAVOR: randomised controlled trials of the Medtronic Endeavor drug-eluting coronary stent system. LEADERS: limus eluted from a durable versus erodible stent coating. RAVEL: a randomised comparison of a sirolimus-eluting stent with a standard stent for coronary revascularisation. SIRIUS: sirolimus-eluting stent in de novo native coronary lesions. TAXUS II-SR: treatment of de novo coronary disease using a single paclitaxel-eluting slow release stent. SPIRIT: a clinical evaluation of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions. SIRTAX LATE: sirolimus versus paclitaxel-eluting stent for coronary revascularisation LATE trial.

may contribute to a mechanistic explanation of the ongoing risk of very late stent thrombosis as it has been identified as the principal pathological finding in an autopsy study distinguishing late thrombosed from patent early-generation DES [117].

Newer-generation DES, such as an everolimus-eluting stent, have shown superior clinical safety and efficacy outcomes when compared to PES up to 2 years [118,119]. The annual incidence of late (>1 year) TLR in patients included in SPIRIT IV amounted to 2.1% in EES and 2.9% in PES. Patients included in the allcomers study COMPARE showed 0.9% late TLR in the EES and 1.5% in the PES-treated patient group, respectively. Although there was no significant statistical difference in late TLR in both studies, it is important to note the continued separation of the TLR curves beyond 1 year. This continued separation suggests a potential decrease in late TLR with the use of newer-generation DES as compared to the early-generation PES, potentially due to a less extensive inflammatory reaction.

Functional stent coverage by endothelium and vasomotor response

As a consequence of stent implantation, there is a substantial reduction in the integrity of the vessel endothelium within the treated vessel segment. Furthermore, histological studies have confirmed that recovery of the endothelial cellular layer is significantly delayed following DES compared to BMS implantation [120]. It is commonly accepted that the delay in the recovery of the endothelial cellular layer following DES implantation is a consequence of the applied antiproliferative drug, which non-selectively inhibits mitosis of smooth muscle cells, fibroblasts and endothelial cells. The endothelial cell layer of the vessel wall has, however, a vital role in mediating vasomotion of the vessel wall by the excretion of nitric oxide (NO).

Notably, several studies have associated a lower vasoreactivity in the vessel segments adjacent to implanted early-generation DES compared to BMS [121-123]. Within these studies different methodologies have been used to induce vasomotion of the vessel segment edges, namely physical stress (e.g., bicycle stress test), rapid atrial pacing, and high dose acetylcholine infusion. Newer-generation DES, integrating features such as reduced strut thickness, lower drug dose and a more biocompatible polymer, have allowed for less traumatic delivery and improved biocompatibility of the stent. These features may be the reasons why further studies have shown an improvement in the vasoreactivity of the adjacent vessel segments in implanted newer-generation DES, compared to earlier-generation DES [124,125].

To date, the magnitude of the correlation between endothelial restoration within the stented segment of DES and the vasomotor response in the adjacent vessel segment remains unclear. The introduction of intravascular optical coherence tomography (OCT) technology has permitted the assessment of vessel stent strut coverage, as an indicator of endothelial integrity. Fuji et al [126] assessed strut coverage 3 months after zotarolimus-eluting stent implantation and demonstrated a correlation between the degree of stent coverage and the vasomotor response assessed by acetylcholine infusion. Furthermore, an inverse correlation of the rate of uncovered struts with the vasomotor capacity of the vessel wall was shown, thus supporting the hypothesis of a relationship between restoration of the stent vessel endothelialisation and vasomotor response following DES implantation.

FOCUS BOX 4

- Three principal factors may be responsible for the formation of late restenosis: 1) decreasing drug dose; 2) chronic inflammatory reactions and persistent fibrin deposition; 3) neoatherosclerosis
- Early-generation SES and PES, but not BMS, have been associated with chronic inflammation and fibrin deposition during the long-term time course
- Neoatherosclerosis occurs earlier and more frequently in DES compared to BMS
- Incomplete re-endothelialisation and impaired functionality of the endothelium may be the source of neoatherosclerosis in DES, whereas shear stress has been suggested to be a relevant contributor in BMS
- Lipidic transformation of the neointima can lead to the formation of thin-cap fibroatheroma, which can be responsible for unstable presentations of restenosis
- Early-generation SES and PES have been associated with a delayed late loss of 0.3-0.4 mm between 1-5 years in angiographic long-term studies without significant differences between the two devices. Data on newer-generation DES are scarce
- The small magnitude of delayed late loss observed with early-generation DES does not translate into clinically significant late TLR rates (incidence <1.5% per annum) and does not compromise the early benefit in efficacy achieved with the introduction of DES
- Angiographic and clinical data suggest that some of the newer-generation DES (e.g., polymer-free DES) may be less vulnerable to late restenosis

STENT FACTORS

Polymer release kinetics

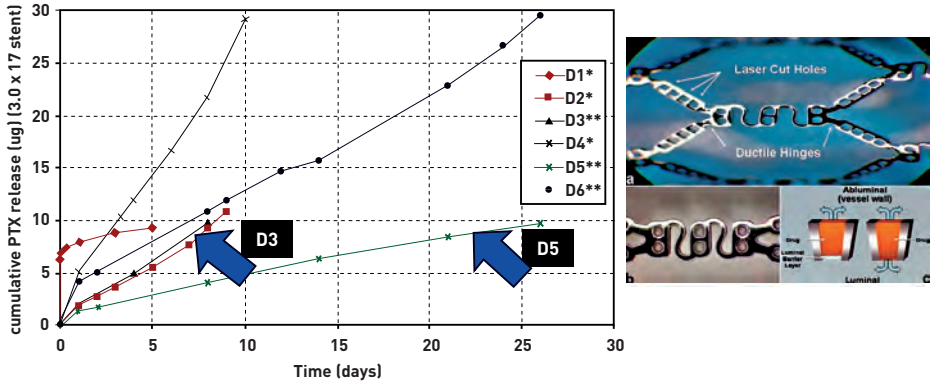
Polymer release kinetics play a key and fundamental role in the prevention of restenosis with the suggestion that it is not necessarily the total dosage of the antiproliferative drug delivered to the vessel wall that is important but more the kinetics

FIGURE 12

The PISCES trial involving the use of the Conor stent and six different polymer-drug-release formulations in humans

In this example, 10 mcg of paclitaxel released over 10 days (D3) following DES implantation appeared to have little effect on NIH production, whereas the same dosage of the drug released over a 30-day (D5) period led to a profound reduction in NIH, with a more than halving (57% reduction) of the rate of LLL. Interestingly, 30 mcg of the same drug released over a 10-day period (D4) was also less effective. Corresponding tables and graphs of the drug release kinetics are shown. The design of the Conor stent is also illustrated (lower right image).
Adapted and reproduced with permission from Serruys et al [127].

	D1	D2	D3	D4	D5	D6
Dose (ug/17-mm stent)	10	10	10	30	10	30
Duration of elution (days)	5	10	10	10	30	30
Direction of elution	Abluminal and luminal (bidirectional)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal (mural)
Key	10/5b	10/10b	10/10/m	30/10b	10/30/m	30/30/m



of the release of the drug. The PISCES trial [127] was the first human study to demonstrate this principle involving the use of the Conor stent and six different polymer-drug release formulations. The main finding of the trial was that the duration of the drug release had a far greater impact on the inhibition of NIH than the dose of the drug delivered (» Figure 12).

The polymer-free biolimus A9-eluting stent, with 2 differing doses of biolimus, has been investigated in animal models [128] and the first-in-human BIOFREEDOM study [129]. Initial studies in animals indicated that the lower (112 µg/per 14 mm of stent length) and higher dose (225 µg/per 14 mm of stent length) biolimus A9-eluting stents have equivalent effects on the NIH response and both have a superior late reduction in NIH as compared to SES at 180 days [128]. In the subsequent BIOFREEDOM study [129] in humans, powered to test for non-inferiority, statistical equivalency was achieved in all 3 groups with an in-stent late lumen loss reported as 0.17 mm ("standard-dose biolimus" group - 15.6 µg/per mm of stent length), 0.22 mm ("low-dose biolimus" group - 7.8 µg/per mm of stent length) and 0.35 mm for the Taxus stent with no differences in MACE or reported cases of stent thrombosis in all 3 groups.

It would therefore appear that a certain threshold of drug needs to be delivered to the vessel wall over a sustained, prolonged period of time, during the process of endothelialisation of the DES, in order to "dampen" down the inflammatory response and limit NIH formation. This is supported by molecular biology studies which have suggested that genes responsible for the proliferative response potentially remain active for a period of up to 21 days after vessel injury [130]. Achieving the fine balance between the drug type, dosage and delivery over the appropriate time are therefore crucial factors in DES design.

In addition, an early peak in drug release may theoretically be of importance to inhibit the early inflammatory reaction of the vessel wall caused by the traumatic vessel wall injury following stent implantation. The early suppression of injury-induced inflammation may result in an antithrombotic effect, which may explain the decreased risk of acute stent thrombosis observed in a recent study comparing the newer-

generation everolimus-eluting stent with a bare metal stent for primary PCI [131].

Type of DES? Type of drug?

Differences relating to first-generation DES are discussed in the Late restenosis section of *Arterial factors*. Data from the SCAAR registry, involving >35,000 patients implanted with four different types of DES (ZES, SES, Taxus® Express® [Boston Scientific] and Liberté® [Boston Scientific]) in real-world practice at 2-year follow-up, showed that the rates of restenosis with DES implantation were significantly higher in diabetics and that important differences existed in the efficacy of differing brands of DES to reduce restenosis [21]. In particular, the restenosis rates with Endeavor® (Medtronic, Inc., Minneapolis, MN, USA) were twice as high in diabetics as compared to other DES types. Higher restenosis rates were also evident in diabetics with Endeavor (RR: 1.77, 95% CI: 1.29 to 2.43) and SES (RR: 1.25, 95% CI: 1.04 to 1.51) when compared to non-diabetics. Five-year unpublished follow-up data from the SCAAR registry continued to demonstrate differences in the efficacy of the first and second-generation DES in reducing rates of stenosis, with a trend for better outcomes seen after nearly 2 years' use of the everolimus-eluting stent.

The EES releases 80% of the drug within 30 days and nearly all the drug within 4 months. In the Spirit I, II, and III trials, a LLL of 0.10, 0.16, and 0.33 mm and TVR rates of 3.8%, 3.4%, and 4.6% were observed at 6, 12, and 24 months, respectively [43]. Conversely, the Endeavor reported a LLL of 0.60 mm and 0.67 mm and TVR of 6.3% and 4.5%, respectively, in the Endeavor III and IV trials at 12 months. The Endeavor, however, elutes 95% of its drug very rapidly (within 14 days): this is highly likely to be the main reason for the poorer results seen.

The next-generation Endeavor® Resolute stent (Medtronic, Inc.), consisting of the same cobalt chromium metallic platform (Driver BMS; Medtronic, Inc.) and the same drug (zotarolimus) as the Endeavor stent, but incorporating the BioLinx™ polymer - an enhanced triple polymer combining a hydrophobic coating covering the stent, a hydrophilic, more biocompatible polymer on the abluminal surface with a third polymer binding the previous two polymers – allowed for substantially longer polymer drug release kinetics (180 days), compared to 14 days with the Endeavor stent. The Endeavor Resolute stent reported an in-stent LLL of 0.12, 0.22, and 0.27 mm at 4, 9, and 13 months, respectively, with angiographic equivalency (LLL 0.19 mm) in terms of meeting the criteria for non-inferiority being met when compared with EES. Equivalency in the 12-month primary endpoint of target lesion failure (a composite of cardiac death, target vessel MI, and clinically driven target lesion revascularisation [8.2% versus 8.3%]) and a slight increase in the rate of definite stent thrombosis (1.2% versus 0.3%, p=0.01) were also seen [132].

Type of drug

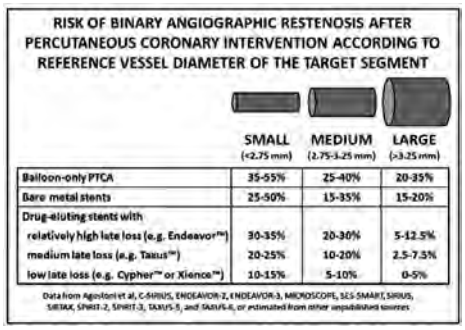
Based on the vast experimental and clinical evidence associating inflammation with restenosis as previously discussed, multiple immunosuppressive and antiproliferative drugs – such as dexamethasone, actinomycin D, cytochalasin D, 17-beta-estradiol, mycophenolic acid, and angiopeptin – have been investigated for their effect in inhibiting the pathway of NIH [133,134]. As an example, methylprednisolone, although shown to be promising in a porcine model [135], demonstrated a restenosis (>50% diameter stenosis at follow-up) rate of 13.3% and a LLL of 0.45 mm at follow-up in the STRIDE (Study of antirestenosis with BiodivYsio dexamethasone-eluting stent) European Study [136]. The very short release profile of the drug – almost completely eluted in the first 24 hours after deployment – no doubt had a strong influence on the clinical effect of the drug.

The drugs that have been demonstrated to have superior performance in a consistent and reproducible fashion both in preclinical investigations and in clinical trials are sirolimus (rapamycin) and paclitaxel in first-generation stents, and the limus family of drugs (which includes sirolimus) in second-generation DES [133,134]. Although polymer release kinetics are crucial to the antiproliferative effects of these drugs as previously described, because of the differing and potentially more potent mechanisms of action of the limus family of drugs compared to paclitaxel, the limus family of drugs are thought to deliver a more sustained antiproliferative NIH effect [133,134]. Furthermore, in the randomised PAINT trial, Lemos et al. [137] conducted a head-to-head comparison of 2 DES with the same metallic stent platform and biodegradable-polymer carrier but releasing either sirolimus or paclitaxel, and a BMS of the same metallic platform. Nine-month in-stent late loss was significantly more favourable towards sirolimus (paclitaxel: 0.54-0.44 mm, sirolimus: 0.32-0.43 mm, vs. BMS: 0.90-0.45 mm, respectively, p< 0.01) in the 274 patients studied.

New-generation DES, such as the everolimus-eluting stent (XIENCE; Abbott Vascular) has shown superiority compared to the Taxus PES and shown itself to be a powerful independent predictor of 2-year freedom from ischaemia-driven target lesion revascularisation (hazard ratio: 0.59 [95% CI: 0.47–0.74], p=0.0001), ischaemia-driven target vessel revascularisation (0.70 [0.58,0.84]; p=0.0002), myocardial infarction (hazard ratio: 0.54 [95% CI: 0.41–0.71]; p=0.0001) and MACE (hazard ratio: 0.64 [0.54, 0.77]; p<0.0001) [138]. Furthermore, the biolimus-eluting stent with a biodegrad-

FIGURE 13

The modelling of the impact of different late losses on follow-up binary angiographic restenosis after PCI in coronary segments with small (<2.75 mm), medium (2.75–3.25 mm), and large (>3.25 mm) reference vessel diameter. Reproduced (Figure and Figure legend) with permission from Biondi-Zoccai et al [146].



able polymer has demonstrated non-inferiority to the SES (Cypher) at up to 4 years follow-up [139,140]. It is likely that a combination of favourable polymer release kinetics and the limus-based drug are reasons for the more advantageous clinical effects seen. Conversely, the Endeavor DES, eluting the limus-based zotarolimus drug, led to unfavourable clinical outcomes due to the very short polymer release kinetics (14 days) as previously discussed.

Stent gap, non-uniform strut distribution and drug deposition

Takebayashi et al [141] classically described the number and distribution of DES struts, as identified by IVUS, as being independent significant risk factors (fewer struts and non-uniform stent strut distribution) for NIH formation and the subsequent risk of restenosis. Non-uniform DES strut distribution has been suggested as being attributable to features such as stent design (e.g., open versus closed cell), stent gap, vessel curvature, coronary bifurcations, ostial lesions, stent underexpansion or overexpansion, polymer peeling, and stent fracture.

Small vessels and strut thickness

Small coronary artery disease is a recognised challenging subset within the field of coronary artery intervention with significant and unacceptable risks of restenosis seen with both POBA and BMS [142-145]. A meta-analysis [146] of the use of DES in small vessel disease demonstrated that both late loss and binary restenosis were largely dependent on the type of DES implanted (» Figure 13).

Mechanisms suggested to explain the poorer outcomes associated with small vessels include: (1) a high degree of vessel stretch and injury, (2) a smaller post-procedural lumen area, and (3) a higher metal density [147]. The overstretch theory is, however, controversial, with evidence suggesting a possible adverse effect with increased NIH [119,120], no significant effect [148], or even potential benefit [142,148]. The latter beneficial effects have been proposed to be related to a higher balloon-to-artery ratio, the so-called bigger is better paradigm (see Implantation factors), leading to appropriate apposition of the stent to the vessel wall.

Thicker stent struts have been linked to an increased risk of restenosis with BMS [149] and small vessels [147,150,151]. The underlying rationale is that a thinner stent strut would have less of a "footprint" on the vessel wall with a consequential reduced inflammatory response. With DES, however, a complex relationship exists between the strut material and characteristics, stent design, polymer type, and drug release kinetics. Both Cypher and XIENCE appear to have the lowest risk of binary restenosis in small vessels, despite a large disparity in stent strut thicknesses (approximately 150 µm versus 90 µm); moreover, Endeavor had the worst outcomes despite its strut thickness being approximately 10 microns more than the XIENCE V® [146]. A fairer comparison perhaps would be between the Taxus Liberté and Express as both contain identical metallic platform materials, polymer coatings and drug concentrations (1 µg/mm^2 of paclitaxel), except that the Taxus Liberté contains thinner struts, more flexible cell geometry, and uniform cell distribution. In the SCAAR registry, the Taxus Express was shown to have a mild but significantly higher adjusted risk of restenosis compared to Taxus Liberté (RR: 1.32, 95% CI: 1.10-1.60).21

"On" and "off" label use of DES

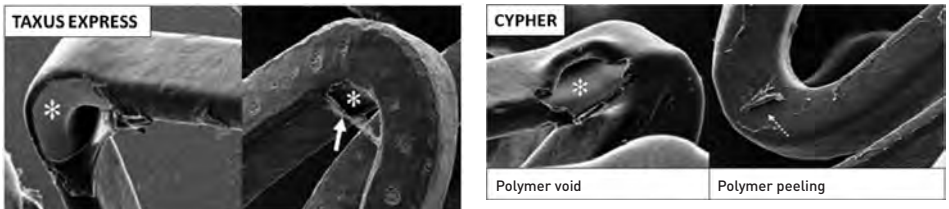
The Strategic Transcatheter Evaluation of New Therapies (STENT) Group is the largest, multicentre, prospective registry involving >15,000 patients to have evaluated the late outcomes associated with DES implantation in the United States [152]. This compared on-label (short de novo lesions in coronary arteries measuring >2.5 mm and <3.5 mm for SES or <3.75 mm PES) and off-label (ostial, left main stem, chronic total occlusion, saphenous vein graft, small or large vessels/multivessel, STEMI, ISR lesions) indications for DES implantation. A near doubling in the TVR rate was seen in the off-label group at 9 months (5.7% versus 3.2%, p<0.0001) and 2 years (11.8% versus 6.5%, p<0.0001) [153].

Data from the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX)

FIGURE 14

Polymer defects in first-generation DES

Polymer void and bridging on a Taxus Express stent and polymer void and peeling on a Cypher DES. Adapted and reproduced with permission from Otsuka et al [159].



study, reflecting a population of patients with highly complex off-label use of DES in 3-vessel or left main stem disease, have reported even higher rates of TVR at 1, 2, 3 and 4 years at 11.6%, 17.4%, 19.7% and 23%, respectively [154]. Furthermore, recent evidence has suggested that one of the main determinants of future clinical events, including revascularisation, is the clinical risk profile of the patient. High EuroSCORE patients from the SYNTAX trial - in particular in the 3VD population - have been associated with more adverse clinical outcomes [155,156]. Registries have also suggested these observations in patients with left main disease [157,158]. Further study is required to validate these findings.

Polymer disruption, peeling and cracking

Polymer disruption, peeling and cracking have been demonstrated to occur in bench studies involving both first [159] (» Figure 14) and second (» Figure 15) generation DES, [160,161] using light or scanning electron microscopy.

Although there is no direct evidence to suggest that the integrity of the polymer coating is a direct cause of restenosis, there are sufficient theoretical concerns to warrant concern through non-uniform local drug distribution or the disrupted polymer potentially acting as a nidus for an ongoing inflammatory response with the subsequent risk of restenosis [27-29,54].

Other concerns with regard to the potential for polymer disruption involve the percutaneous coronary intervention procedure itself. Wiemer et al. [162,163] demonstrated that, in DES that had failed to be delivered to the intended implantation site in tortuous calcified lesions, significant damage and cracking of the polymer had occurred to varying extents with multiple types of second-generation DES. Scanning electron microscopy revealed many cases of deep damage to the polymer with exposure of the bare metal: in particular, the Endeavor RX stents showed up to 20% damage to the surface area (» Figure 16). With polymer-free DES, a large proportion of the surface area was shown to be without any layer of drug (» Figure 16).

Bifurcation stenting, especially if very complex, has been hypothesised as possibly leading to polymer disruption, peeling or even polymer void [159], with the consequent risk of non-uniform drug distribution and focal stenosis. In bench work utilising scanning electron microscopy of the polymer integrity of 5 different types of DES (Cypher, Cypher Select, Endeavor, Taxus Express, and Taxus Liberté) after undergoing kissing balloon post-dilatation, Guerin et al. [164] demonstrated significantly greater coating damage to the ostial struts, especially along the overstretched segments, with cracking of the polymer seen in all cases and even exposure of bare metal. Of note is that the Endeavor stent showed a subtotal destruction of its coating on the luminal surface in all segments, whereas the other DES demonstrated more focal localised abnormalities.

Stent fractures

Stent fracture related to DES implantation in coronary arteries was first reported in 2004 (» Figure 17) [165]. Subsequent retrospective and prospective registries have quoted restenosis rates ranging from 15% to 100% in patients identified as having stent fractures [166]. In the only randomised controlled trial reporting the incidence of stent fracture and outcomes after DES implantation and subsequent mandatory angiographic follow-up (LONG-DES-II study), a 14% incidence of restenosis was observed [167].

The pattern of restenosis associated with DES fractures appears to be focal, reflecting the local trauma sustained by the vessel at the fracture site once this has occurred. Due to the underlying mechanism of DES fracture (as explained below), restenosis tends to occur fairly late, and invariably after most if not all of the antiproliferative drug has been eluted.

FIGURE 15

Polymer defects seen in second-generation DES
Adapted and reproduced with permission from Basalus et al [160].

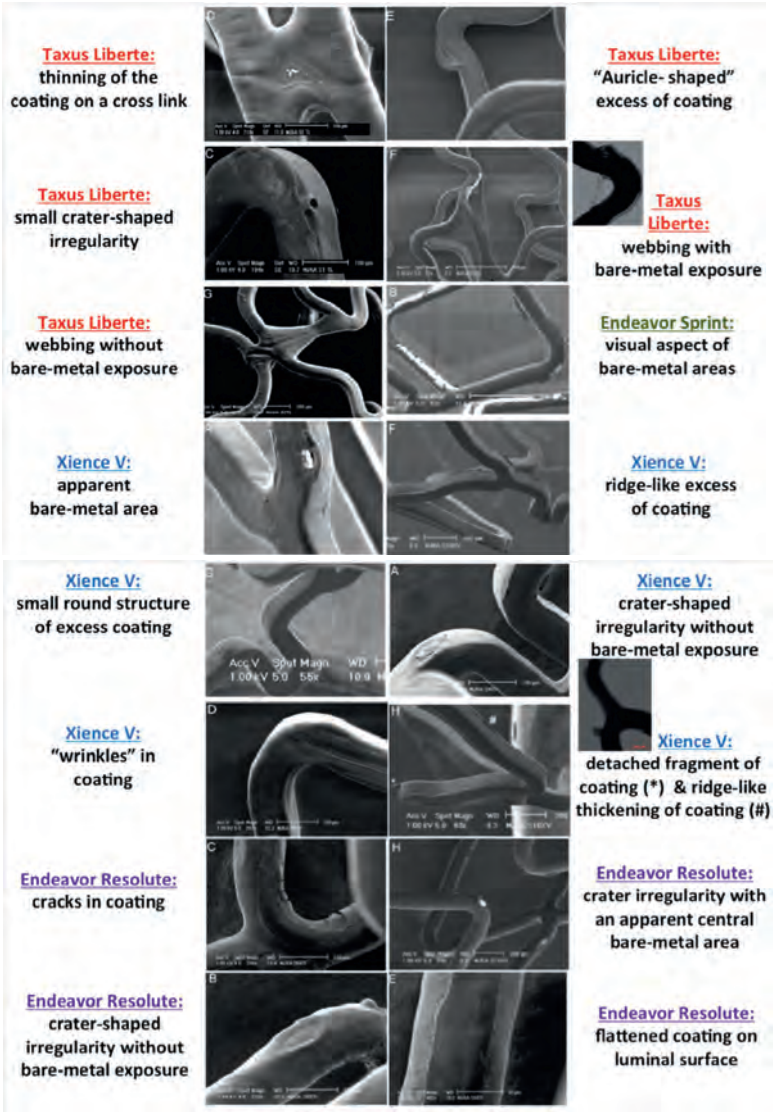
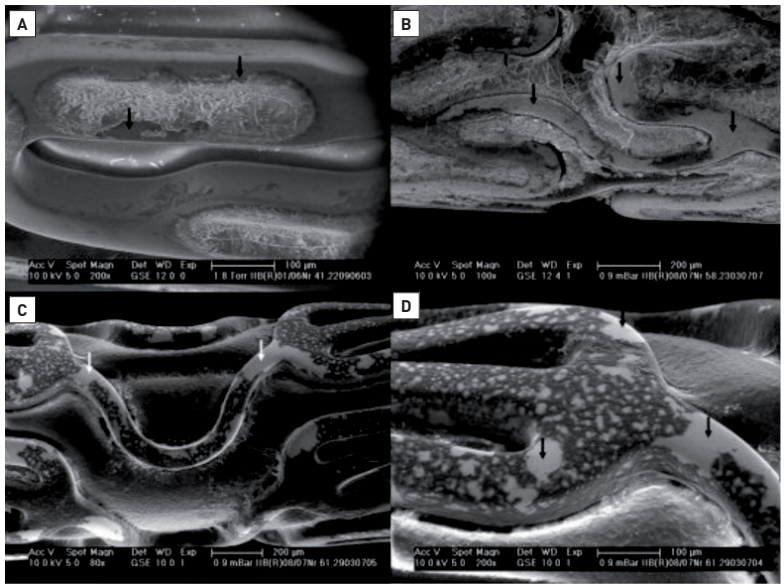


FIGURE 16

Polymer defects in second-generation DES that could not be delivered through calcified, tortuous vessels. Adapted and reproduced with permission from Wiemer et al [163].
A: unexpanded Janus Carbostent Flex (Sorin, Milan, Italy): small polymer irritations (black arrows) at the fringe (magnification x 200.
B: unexpanded Yukon Choice Stent (Translumina GmbH, Hechingen, Germany): very thin, irregular drug layer covering stent and balloon. A large area of the surface of the stent was found to be without drug coverage (black arrows) (magnification ? (x100)).
C: unexpanded Axxion (Biosensors International, Singapore): large continuous areas and spots without any drug coverage (white arrows) (magnification (x80).
D: unexpanded XIENCE V®: typical wrinkling and cracking of polymer with bare metal exposure at loop region (black arrows) after failed attempt to pass the DES through a calcified vessel (magnification x 150.



The subsequent healing response therefore occurs without any drug to suppress the NIH response, which in itself is exacerbated by further exposure of the vessel to the disrupted polymer. The aetiology of the DES fractures also appears to be relatively well understood and is related to two principal factors.

The first is the location of the implantation site of the DES. Mechanical fatigue of the metallic stent can occur due to excessive movement during cardiac contraction, especially at a "hinge point" where the potential for 2 opposing forces may occur at the same site [168]. In these situations, excessive movements can occur to the DES implanted in one part of a vessel during cardiac contraction, in particular in the right coronary artery or a saphenous vein graft, because of their greater propensity for angulation and tortuosity [166,168].

Secondly, the design of the DES itself has been strongly incriminated with causing DES fracture. A closed-cell design, such as occurs with SES, is less likely to be able to withstand the pressures related to excessive movements compared with the open-cell design of a PES. In a recent meta-analysis, [166] the incidence of stent fracture was reported to be less than 0.1% with the open-cell PES and approximately 2.3% with the closed-cell SES.

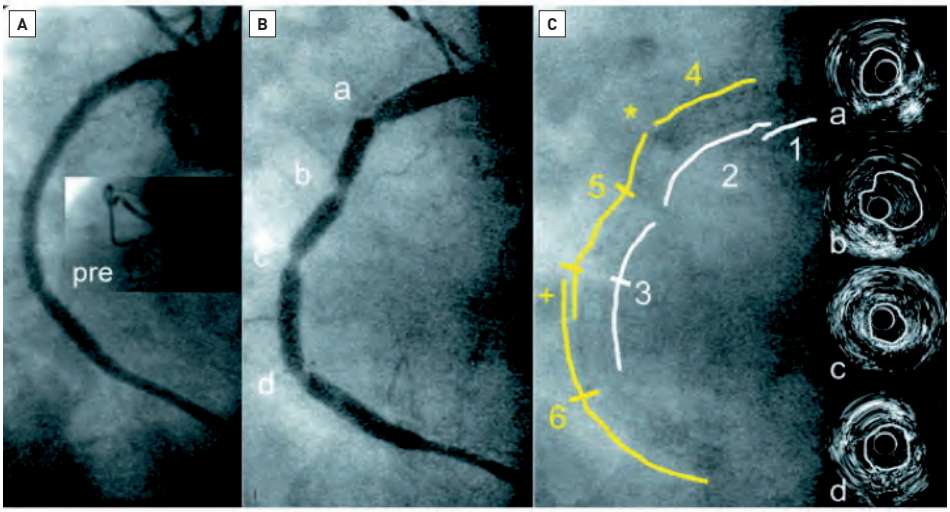
Long stents, overlapping stents, tight lesions that have been "vigorously post-dilated and expanded," [167] myocardial bridge sites, areas of significant curvature (due to the lack of conformability of certain DES, especially of closed-cell design) are all other factors which may predispose to DES fracture [165-173].

Newer-generation DES have consequently aimed to maintain the open-cell design and have thinner struts by using new metallic alloys. Although the radial strength has been preserved with next-generation DES - recent case reports have suggested that, with certain types of next-generation DES,

FIGURE 17

The first reported DES fracture in the literature made by our group in 2004

The initial RCA result **(A)** following implantation of 3 overlapping 3 mm Cypher DES (post-dilated with a 3.5 mm balloon). 5 months later the patient re-presented with unstable angina – 4 very focal lesions, giving the vessel a beaded appearance, were demonstrated on both coronary angiography **(B-C)** and IVUS C), indicative of DES fracture. Reproduced with permission from Sianos et al [165].



the longitudinal strength of the device may potentially be affected, increasing the likelihood for stent deformation (longitudinal elongation or compression) requiring post-dilation or further stent placement - episodes of late stent thrombosis have also been reported [174-176]. Higher incidences of restenosis have, at the time of writing, not yet been reported.

IMPLANTATION FACTORS

Incomplete stent expansion

A smaller post-procedural minimal lumen diameter (MLD) and a greater residual stenosis (» Figure 17) have been associated with long-term DES patency and clinical outcomes [177-187]. Evidence of stent underexpansion has been reported in 20-40% of cases when assessed by quantitative coronary angiography (QCA) and 38-70% of cases when assessed by IVUS [182-184]. However, what proportion of these cases with stent underexpansion are clinically relevant in causing restenosis remains unclear. Serial IVUS analyses from the SIRIUS trial [185] and other studies [186,187] investigating SES use, have demonstrated a cut-off of a post-procedural MSA of between 5.0-5.5 mm^2 as being the optimal area to reduce the likelihood of restenosis.

In an important meta-analysis, Casella et al [188] compared IVUS against angiographic-guided BMS implantation (n=2,972 patients) and demonstrated that, at 6 months follow-up, there was reduced TVR (OR 0.62; 95% CI: 0.49-0.78; p=0.00003), binary restenosis (OR 0.75; 95% CI: 0.60-0.94; p=0.01) and MACE (OR 0.79; 95% CI: 0.64-0.98; p=0.03) when an IVUS approach to BMS implantation was used. Since then, the only new published randomised controlled trials of IVUS versus angiographic-guided stent implantation were the AVID trial [189] for BMS and a small trial (Jakabcin et al [190]) for DES.

The AVID trial was published 10 years after the data collection and had mixed results, with no benefit in the incidence of 12-month TLR, a larger minimum stent area post BMS implantation and, on subgroup analysis, a lower 12-month TLR rate for vessels ≥2.5 mm or vessels with a high-grade pre-stent stenosis. With DES, Jakabcin et al failed to show any differences in the clinical endpoints of MACE (death, myocardial infarction and reintervention) at 18 months.

FOCUS BOX 5

- Polymer release kinetics – namely antiproliferative drug dose and time course of delivery – play a crucial role in the prevention of restenosis
- The genes responsible for the proliferative response potentially remain active for a period of up to 21 days after vessel injury – a critical time period for antiproliferative drug delivery from DES
- DES with shorter drug release kinetics, such as Endeavor (14 days), lead to greater restenosis compared to DES with longer drug release kinetics
- Newer-generation DES with thinner struts, longer drug release kinetics, more biocompatible polymers have led to more effective neointima inhibition
- Off-label use of DES, such as in ostial, left main stem, chronic total occlusion, saphenous vein graft, small or large vessels/multivessel, STEMI, ISR lesions, are associated with higher restenosis and revascularisation rates
- Polymer disruption, peeling and cracking, either on the DES at baseline or induced by delivery or by interventional procedure, have been demonstrated with first and second-generation DES. As to whether this is implicated in restenosis is theoretical
- Stent fractures are more likely to occur with the closed-cell design of first-generation DES and in sites where there is greater angulation or tortuosity (i.e., hinge points). They tend to occur late, when there is little or no antiproliferative drug to cover the vessel injury

Furthermore, the initial results of the AVIO (Angiographic Versus IVUS Optimisation) randomised, multicentre trial assessing IVUS-guided DES implantation were presented in 2010 [191,192]. In 142 patients with complex lesions implanted with IVUS-guided DES, no clinical benefit was demonstrated compared to controls, with comparable clinical outcomes in the combined endpoint of MI, target lesion revascularisation (TLR), TVR or cardiac death at 30 days and 9 months (85.9% vs. 83.1%, p=0.47). The primary endpoint of a higher MLD was seen in the IVUS-guided DES implantation group (2.70 mm vs. 2.51 mm, p=0.0002). As only 39% of patients had QCA at 9 months, no comments could be made as to whether this approach would potentially lead to a reduction in restenosis rates. Until large-scale trials unequivocally demonstrate the clinical efficacy of an IVUS-guided DES implantation approach, IVUS will remain to be used at the operator's discretion.

The most plausible and the strongest theory to explain the underlying mechanism relating stent underexpansion to restenosis is the so-called "bigger-is-better" paradigm [193]. Effectively, if the minimum stent area (MSA) is smaller at baseline, then the expected NIH formation post DES implantation would be more likely to be of significance in leading to a flow-limiting lesion. Conversely, if the MSA was larger, then the growth of the same amount of NIH would be clinically less relevant in causing binary restenosis [193]. Other suggestions of DES underexpansion as a cause of ISR have been related to possible asymmetrical stent expansion, which may affect the pattern of neointimal growth through possible uneven drug delivery [194,195]. Numerous factors, including "off-label" indications for DES implantation, as previously described, are involved in increasing the risk of suboptimal stent deployment (» Table 5).

TABLE 5

Factors associated with an increased risk of suboptimal stent deployment [228]

LIST OF CONDITIONS ASSOCIATED WITH AN INCREASED RISK OF SUBOPTIMAL STENT DEPLOYMENT
Low-pressure stent deployment (<12 atm)
Lesions with heavy calcification
Lesions with large plaque burden (severe stenosis)
Lesions with a mismatch of proximal and distal reference size
Ostial lesions
Bifurcation lesions treated with stenting of side branch
Long lesions requiring multiple stents
Small vessel treatment
Treatment of diffuse in-stent restenosis

Geographical miss/barotrauma to unstented segments

Geographical miss (» Figure 18), as the name suggests, is essentially a failure to cover appropriately an injured vessel or atherosclerotic plaque. This may be a consequence of lesion predilatation, balloon-associated vessel barotrauma and the subsequent failure to cover the entire injured site with a DES, incomplete coverage of the diseased segment of the vessel with significant plaque remaining at the stent margins, or failure adequately to overlap DES in long segments of disease.

Geographical miss has more accurately been described as longitudinal geographical miss (LGM: injured or diseased stenotic segment not fully covered by DES) or axial geographical miss (AGM: balloon-artery size ratio <0.9 or >1.3 mismatch) (» Figure 19) [196]. Geographical miss, associated with the implantation of SES, was investigated in the STLLR study [196]. As a whole, geographical miss was observed in nearly two thirds of the study group (66.5%), with almost half the patients experiencing LGM (47.6%), over one third AGM (35.2%), and 16.5% a combination of the two. At 1-year follow-up, there was more than a 2-fold increase in TVR (5.1% vs. 2.5%; p=0.025) and a 3-fold increase in MI (2.4% vs. 0.8%; p=0.04) in patients with geographical miss. Subgroup analyses indicated that these findings were almost exclusively related to LGM (6.1% vs. 2.6%; p=0.001), with two thirds of cases being second-

FIGURE 18

The potential benefit of IVUS-guided stent implantation

Comparison of angiographic and IVUS findings before and after high-pressure stent post-dilatation. Reproduced with permission from Romagnoli et al. [228]

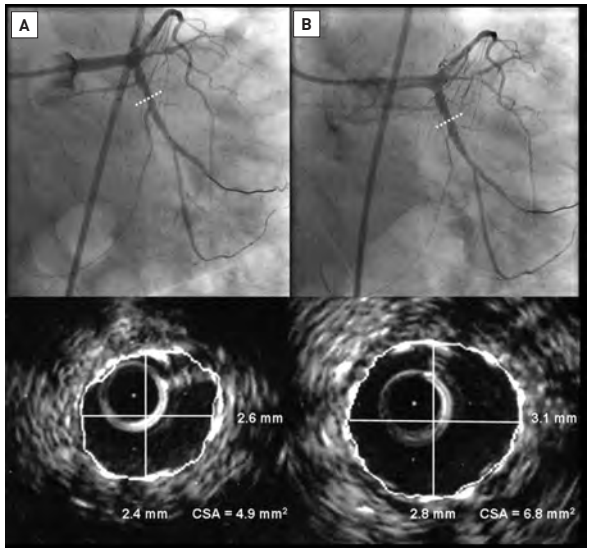
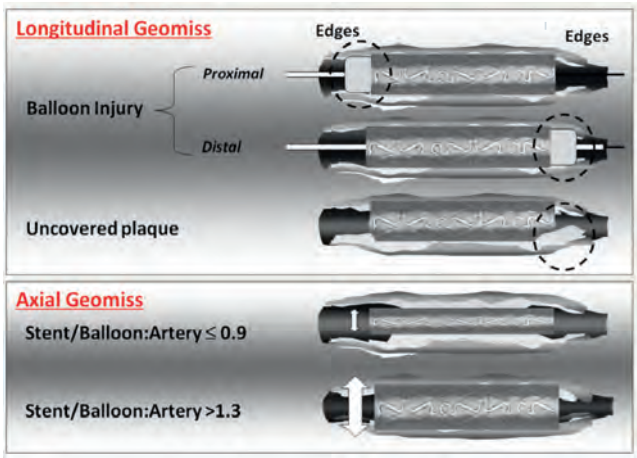


FIGURE 19

Geographical miss

Illustration of the mechanism of longitudinal (LGM) and axial geographical miss (AGM). Reproduced and adapted with permission from Costa et al [196].



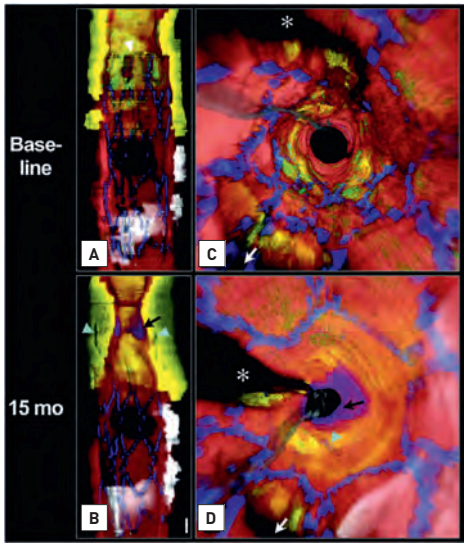
ary to balloon injury outside the stent margins, and AGM not seeming to be an important factor (4.2% vs. 4.3%; p non-significant). This latter finding has been corroborated, where it was shown that the balloon-to-artery ratio [148] or the occurrence of edge dissections (potentially associated with AGM) [197] did not have a significant impact on the risk of restenosis: this does perhaps argue against the practice of IVUS-guided DES implantation. The occurrence of edge dissections has, however, been linked to an increased periprocedural and 1-month MACE rate, driven primarily by an elevated risk of stent thrombosis and subsequent TVR [198].

More recently, a substudy of the STLLR study demonstrated that the clinical effects of balloon injury secondary to LGM were more pronounced in diabetics [199]. More than a four-fold increase (8%) in the need for target lesion revascularisation in diabetics, and almost a two-fold increase in non-diabetics (3.8%), in the presence of LGM were reported compared to no LGM being present.

FIGURE 20

Late drug-eluting stent (DES) failure

This report illustrates a case of incomplete stent coverage of a necrotic-core plaque mass, despite adequate coverage of the angiographic stenosis. Incomplete coverage of the lipid-core lesion with the DES at the index procedure **(A, C)** appeared to be associated with plaque progression leading to stent failure due to angiographic edge restenosis at 15 months **(B, D)**. Corresponding 2D OCT images (not illustrated) demonstrated the mechanism of restenosis to be progression of the necrotic core rather than neointimal hyperplasia. Red colour indicates artery wall; green, macrophages; yellow, lipid core; blue, stent; white, calcium; purple, thrombus; grey, guidewire. White arrow denotes side branch in **(C)** and **(D)**. *Guidewire shadow. Reproduced with permission from Waxman et al [201].



The vascular response at the stent edges has been evaluated with first-generation DES. It appears to be dependent on the implanted device and the periprocedural-induced vascular trauma, as a consequence of the geographical miss phenomenon, as described. [196] Within the IVUS substudies of the E-SIRIUS and SIRIUS trials, both AGM and LGM were shown to be potentially reduced when periprocedural implantation parameters such as conservative pre-dilatation, less forceful stent implantation (~16 atm) and selective post-dilatation with balloons shorter than the stent were undertaken [200].

The landing zone of the implanted device may be a potential mechanism for restenosis. Failure to cover fully a stenotic lipid-core lesion due to LGM as described has potentially been shown to increase the likelihood of DES failure due to plaque progression at the DES edge and subsequent edge restenosis (» Figure 20) [17,170,196,201,202]. Further studies are required to assess if the use of intracoronary imaging to ensure full lesion/plaque coverage is undertaken and to assess whether this leads to improved clinical outcomes.

Deployment of a DES in a clot-laden arterial segment

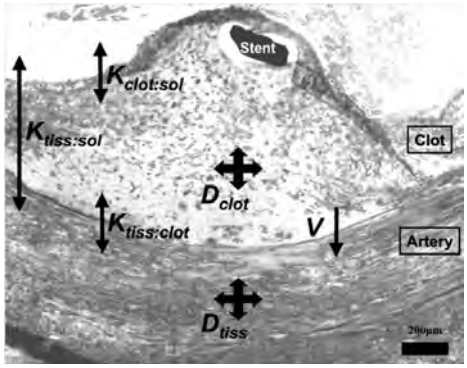
Deployment of a DES in a clot-laden arterial segment has been shown in an *ex vivo* model to lead to significant variability in arterial drug distribution [203] which may potentially affect clinical outcomes (» Figure 21). Essentially in this study it was shown that thrombus between the stent strut and vessel wall lead to a reduction in drug penetration into the vessel wall by a factor of up to 10-fold. Despite these theoretical concerns, multiple studies [204-212] and a meta-analysis of 13 trials (n=7,244) [213] have shown the significant short-term benefits of DES over BMS. Specifically in the meta-analysis by Piscione et al, [213] a reduction of TVR (5.11% versus 11.19%, p<0.00001) and recurrent MI (3.03% versus 3.70%, p=0.02) in patients with STEMI were demonstrated up to 1 year. The widespread use of glycoprotein-IIb/IIIa inhibitors and aspiration thrombectomy may be the reasons why these concerns have not materialised in clinical trials in the short term.

Concerns over the long-term safety of DES in STEMI do persist, however, because of the potential risk of late-acquired stent malapposition and consequent LST [214,215]. The concerns about reduced absorption of the drug from DES should be borne in mind in a thrombus-laden vessel, especially when there has been inadequate resolution of thrombus and DES implantation is to be considered.

FIGURE 21

Deployment of a DES in a clot-laden arterial segment

This can potentially lead to variability in arterial drug distribution in *ex vivo* models, potentially affecting clinical outcomes. The concepts of drug diffusivities in clot (Dclot) and tissue (Dtiss), drug capacity of clot relative to solution (Kclot:sol), drug capacity of arterial tissue relative to clot (Ktiss:clot), drug capacity of arterial tissue relative to solution (Ktiss:sol) and drug convective velocities (V), as illustrated, demonstrate the complexity of stenting in acute myocardial infarction. Reproduced with permission from Hwang et al [203].



FOCUS BOX 6

- Implantation factors are the most controllable factors for potentially reducing restenosis
- A smaller post-procedural minimal lumen diameter (MLD) and a greater residual stenosis have been strongly associated with long-term DES patency and clinical outcomes
- IVUS-guided BMS implantation has been associated with a reduced TVR and binary restenosis in classical meta-analyses
- To date, no randomised controlled trial has demonstrated the clinical superiority of IVUS-guided DES implantation despite being associated with a post-procedural higher MLD
- Longitudinal geographical miss has been associated with greater TVR and MI, an effect that may be pronounced in diabetics
- Reductions in TVR and MI have been associated with DES implanted after STEMI at up to 1 year, despite theoretical concerns that thrombus may interfere with local drug absorption. Concerns over the long-term safety of DES in STEMI do persist

PERSONAL PERSPECTIVE – PATRICK W. SERRUYS

Despite the low incidence of DES restenosis, the burden of ISR in absolute numbers will probably continue to grow with the increasing uptake of second-generation DES in conventional percutaneous coronary intervention practice. Moreover, it is probable that these cases will select themselves as more resistant cases which may make treatment subsequently more challenging. Large-scale clinical trials and registries are required to translate these restenotic mechanisms best into either enhanced DES design or further effective treatment options. For example, the pooled data of the randomised controlled trials investigating EES comprise almost 15,000 patients and, apart from mortality, would potentially be of sufficient power to detect rare events such as stent thrombosis.

Although the treatment of ISR is beyond the scope of this review, an understanding of the mechanisms involved in DES restenosis and the controllable and non-controllable factors can give the practising interventional cardiologist further useful clinical information to reduce DES restenosis in his/her own practice. Apart from biological factors, there are potentially controllable factors within arterial and *stent factors*. However, it should be acknowledged that in the treatment of ISR the evidence for using a DES with a different drug remains unproven [44]. Ultimately, the implantation factors are the most important controllable factors from the perspective of the interventional cardiologist.

REFERENCES

1. Thornton MA, Gruentzig AR, Hollman J, King SB, 3rd, Douglas JS. Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. *Circulation.* 1984;69:721-7.
2. Holmes DR, Jr., Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Gruentzig AR, Kelsey SF, Detre KM, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol.* 1984;53:77C-81C.
3. Henricus J Duckers EGN, Patrick W Serruys. Essentials of Restenosis For the Interventional Cardiologist: Humana Press; 2007.
4. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, Kent KM, Griffin J, Leon MB. Patterns and Mechanisms of In-Stent Restenosis: A Serial Intravascular Ultrasound Study. *Circulation.* 1996;94:1247-1254.
5. Ruygrok PN, Webster MW, Ardill JJ, Chan CC, Mak KH, Meredith IT, Stewart JT, Ormiston JA, Price S. Vessel caliber and restenosis: a prospective clinical and angiographic study of NIR stent deployment in small and large coronary arteries in the same patient. *Catheter Cardiovasc Interv.* 2003;59:165-71.
6. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-23.
7. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, Cohen DJ, Kuntz RE. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol.* 2002;40(12):2082-9.
8. Serruys PW, Kay IP. I like the candy, I hate the wrapper: the (32)P radioactive stent. *Circulation.* 2000;101:3-7.
9. Albiero R, Nishida T, Adamian M, Amato A, Vaghetti M, Corvaja N, Di Mario C, Colombo A. Edge restenosis after implantation of high activity (32)P radioactive beta-emitting stents. *Circulation.* 2000;101:2454-7.
10. van Der Giessen WJ, Regar E, Harteveld MS, Coen VL, Bhagwandien R, Au A, Levendag PC, Ligthart J, Serruys PW, den Boer A, Verdouw PD, Boersma E, Hu T, van Beusekom HM. "Edge Effect" of (32)p radioactive stents is caused by the combination of chronic stent injury and radioactive dose falloff. *Circulation.* 2001;104:2236-41.
11. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC, Jr., Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2006;113:e85-151.
12. Rensing BJ, Hermans WR, Deckers JW, de Feyter PJ, Tijssen JG, Serruys PW. Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution: a quantitative angiographic study in 1,445 successfully dilated lesions. *J Am Coll Cardiol.* 1992;19:939-45.
13. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. *Circulation.* 2005;111:3435-42.
14. **Byrne RA, Eberle S, Kastrati A, Dibra A, Ndrepepa G, Iijima R, Mehilli J, Schomig A. Distribution of angiographic measures of restenosis after drug-eluting stent implantation. *Heart.* 2009;95:1572-8.**
    The distribution of late lumen loss after first generation DES implantation - associating it with bimodal neointimal response.
15. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119:480-6.
16. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation.* 1999;100:1872-8.
17. Corbett SJ, Cosgrave J, Melzi G, Babic R, Biondi-Zoccai GG, Godino C, Morici N, Airoldi F, Michev

I, Montorfano M, Sangiorgi GM, Bonizzoni E, Colombo A. Patterns of restenosis after drug-eluting stent implantation: Insights from a contemporary and comparative analysis of sirolimus- and paclitaxel-eluting stents. *Eur Heart J*. 2006;27:2330-7.

18. Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, McFadden E, Sianos G, Smits PC, Hofma SH, de Feyter PJ, van Domburg RT, Serruys PW. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation*. 2004;109:1366-70.
19. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TKK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ. Unrestricted Utilization of Sirolimus-Eluting Stents Compared With Conventional Bare Stent Implantation in the "Real World": The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry. *Circulation*. 2004;109:190-195.
20. Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, Dirschinger J, Schomig A. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation*. 2006;113:2293-300.
21. **Frobert O, Lagerqvist B, Carlsson J, Lindback J, Stenestrand U, James SK. Differences in restenosis rate with different drug-eluting stents in patients with and without diabetes mellitus: a report from the SCAAR (Swedish Angiography and Angioplasty Registry). *J Am Coll Cardiol*. 2009;53:1660-7.**

   The different restenosis rates with different types of DES.
22. Farb A, Kolodgie FD, Hwang JY, Burke AP, Tefera K, Weber DK, Wight TN, Virmani R. Extracellular matrix changes in stented human coronary arteries. *Circulation*. 2004;110:940-7.
23. Welt FG, Rogers C. Inflammation and restenosis in the stent era. *Arterioscler Thromb Vasc Biol*. 2002;22:1769-76.
24. van Beusekom HM, Saia F, Zindler JD, Lemos PA, Swager-Ten Hoor SL, van Leeuwen MA, de Feijter PJ, Serruys PW, van der Giessen WJ. Drug-eluting stents show delayed healing: paclitaxel more pronounced than sirolimus. *Eur Heart J*. 2007;28:974-9.
25. Chieffo A, Foglieni C, Nodari RL, Briguori C, Sangiorgi G, Latib A, Montorfano M, Airoldi F, Michev I, Carlino M, Colombo A, Maseri A. Histopathology of clinical coronary restenosis in drug-eluting versus bare metal stents. *Am J Cardiol*. 2009;104:1660-7.
26. **Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.**

   One of the first reports of delayed arterial healing associated with first generation (Cypher and Taxus) DES.
27. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation*. 2005;112:270-8.
28. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol*. 2007;27:1500-10.
29. Finn AV, Nakazawa G, Kolodgie FD, Virmani R. Temporal course of neointimal formation after drug-eluting stent placement: is our understanding of restenosis changing? *JACC Cardiovasc Interv*. 2009;2(4):300-2.
30. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation*. 2003;108:1701-6.
31. Steinberg DH, Gaglia MA, Jr., Pinto Slottow TL, Roy P, Bonello L, De Labriolle A, Lemesle G, Torguson R, Kineshige K, Xue Z, Suddath WO, Kent KM, Satler LF, Pichard AD, Lindsay J, Waksman R. Outcome differences with the use of drug-eluting stents for the treatment of in-stent restenosis of bare-metal stents versus drug-eluting stents. *Am J Cardiol*. 2009;103:491-5.
32. Bainey KR, Norris CM, Graham MM, Ghali WA, Knudtson ML, Welsh RC. Clinical in-stent restenosis with bare metal stents: is it truly a benign phenomenon? *Int J Cardiol*. 2008;128(3):378-82.
33. Walters DL, Harding SA, Walsh CR, Wong P, Pomerantsev E, Jang IK. Acute coronary syndrome is a common clinical presentation of in-stent restenosis. *Am J Cardiol*. 2002;89:491-4.
34. Park CB, Hong MK, Kim YH, Park DW, Han KH, Lee CW, Kang DH, Song JK, Kim JJ, Park SW, Park SJ. Comparison of angiographic patterns of in-stent restenosis between sirolimus- and paclitaxel-eluting stent. *Int J Cardiol*. 2007;120:387-90.

35. Drozd J, Wojcik J, Malek R, Korona B, Zapolski T, Wysokinski A. Acute coronary syndrome - a frequent clinical manifestation of bare metal in-stent restenosis. *Kardiol Pol* .2010;68:637-45.
36. Rathore S, Kinoshita Y, Terashima M, Katoh O, Matsuo H, Tanaka N, Kimura M, Tsuchikane E, Nasu K, Ehara M, Asakura K, Asakura Y, Suzuki T. A comparison of clinical presentations, angiographic patterns and outcomes of in-stent restenosis between bare metal stents and drug eluting stents. *EuroIntervention*. 2010;5:841-6.
37. Bonello L, De Labriolle A, Lemesle G, Roy P, Steinberg DH, Slottow TL, Xue Z, Torguson R, Kaneshige K, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Comparison of outcomes of drug-eluting stents versus bare-metal stents in nonostial proximal left anterior descending coronary arteries. *Am J Cardiol*. 2009;103:496-500.
38. Steinberg DH, Pinto Slottow TL, Buch AN, Javaid A, Roy PK, Garg S, Okabe T, Torguson R, Smith KA, Xue Z, Suddath WO, Kent KM, Satler LF, Pichard AD, Lindsay J, Waksman R. Impact of in-stent restenosis on death and myocardial infarction. *Am J Cardiol*. 2007;100:1109-13.
39. Bossi I, Klersy C, Black AJ, Cortina R, Choussat R, Cassagneau B, Jordan C, Laborde JC, Laurent JP, Bernies M, Fajadet J, Marco J. In-stent restenosis: long-term outcome and predictors of subsequent target lesion revascularization after repeat balloon angioplasty. *J Am Coll Cardiol*. 2000;35:1569-76.
40. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J*. 2006;151:1260-4.
41. Nayak AK, Kawamura A, Nesto RW, Davis G, Jarbeau J, Pyne CT, Gossman DE, Piemonte TC, Riskalla N, Chauhan MS. Myocardial infarction as a presentation of clinical in-stent restenosis. Circ J 2006;70:1026-9.
42. Garg S, Serruys PW. Coronary stents: looking forward. *J Am Coll Cardiol*. 2010;56:S43-78.
43. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;56:S1-42.
44. Alfonso F. Treatment of drug-eluting stent restenosis the new pilgrimage: quo vadis? *J Am Coll Cardiol*. 2010;55:2717-20.
45. Richardson A, Kaye SB. Drug resistance in ovarian cancer: the emerging importance of gene transcription and spatio-temporal regulation of resistance. *Drug Resist Updat*. 2005;8:311-21.
46. Huang S, Houghton PJ. Mechanisms of resistance to rapamycins. *Drug Resist Updat*. 2001;4:378-91.
47. Hausleiter J, Kastrati A, Mehilli J, Vogeser M, Zohlnhofer D, Schuhlen H, Goos C, Pache J, Dotzer F, Pogatsa-Murray G, Dirschinger J, Heemann U, Schomig A. Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation*. 2004;110:790-5.
48. Teirstein PS. Drug-eluting stent restenosis: an uncommon yet pervasive problem. *Circulation*. 2010;122:5-7.
49. Ribichini F, Tomai F, De Luca G, Boccuzzi G, Presbitero P, Pesarini G, Ferrero V, Ghini AS, Abukaresh R, Aurigemma C, De Luca L, Zavalloni D, Soregaroli D, Marino P, Garbo R, Zanolla L, Vassanelli C. Immunosuppressive therapy with oral prednisone to prevent restenosis after PCI. A multicenter randomized trial. *The American journal of medicine*. 2011;124:434-43.
50. Ribichini F, Tomai F, Ferrero V, Versaci F, Boccuzzi G, Proietti I, Prati F, Crea F, Vassanelli C. Immunosuppressive oral prednisone after percutaneous interventions in patients with multi-vessel coronary artery disease. The IMPRESS-2/MVD study. *EuroIntervention*. 2005;1:173-80.
51. Ribichini F, Ferrero V, Rognoni A, Marino P, Brunelleschi S, Vassanelli C. Percutaneous treatment of coronary bifurcations: lesion preparation before provisional bare metal stenting and subsequent immunosuppression with oral prednisone. The IMPRESS-Y study. *Journal of interventional cardiology*. 2007;20:114-21.
52. Versaci F, Gaspardone A, Tomai F, Ribichini F, Russo P, Proietti I, Ghini AS, Ferrero V, Chiariello L, Gioffre PA, Romeo F, Crea F. Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). *JACC*. 2002;40:1935-42.
53. Ferrero V, Tomai F, Versaci F, Feola M, Proietti I, Rognoni A, Ghini AS, Gaspardone A, Vacca G, De Luca L, Vassanelli C, Ribichini F. Long-term results of immunosuppressive oral prednisone after coronary angioplasty in non-diabetic patients with elevated C-reactive protein levels. *EuroIntervention* : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2009;5:250-4.
54. Nakazawa G, Finn AV, Ladich E, Ribichini F, Coleman L, Kolodgie FD, Virmani R. Drug-eluting

stent safety: findings from preclinical studies. *Expert Rev Cardiovasc Ther.* 2008;6:1379-91.

55. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Juni P, Virmani R, Windecker S. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation.* 2009;120:391-9.
56. Koster R, Vieluf D, Kiehn M, Sommerauer M, Kahler J, Baldus S, Meinertz T, Hamm CW. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet.* 2000;356:1895-7.
57. Keane FM, Morris SD, Smith HR, Rycroft RJ. Allergy in coronary in-stent restenosis. *Lancet.* 2001;357:1205-6; author reply 1206-7.
58. Ha T, Lalla S. Allergy in coronary in-stent restenosis. Lancet 2001;357(9263):1206; author reply 1206-7.
59. Mimouni D, Trattner A, David M. Allergy in coronary in-stent restenosis. *Lancet.* 2001;357:1206-7; author reply 1206-7.
60. Norgaz T, Hobikoglu G, Serdar ZA, Aksu H, Alper AT, Ozer O, Narin A. Is there a link between nickel allergy and coronary stent restenosis? *Tohoku J Exp Med.* 2005;206:243-6.
61. Hillen U, Haude M, Erbel R, Goos M. Evaluation of metal allergies in patients with coronary stents. *Contact Dermatitis.* 2002;47:353-6.
62. Saito T, Hokimoto S, Oshima S, Noda K, Kojyo Y, Matsunaga K. Metal allergic reaction in chronic refractory in-stent restenosis. *Cardiovasc Revasc Med.* 2009;10:17-22.
63. Iijima R, Ikari Y, Amiya E, Tanimoto S, Nakazawa G, Kyono H, Hatori M, Miyazawa A, Nakayama T, Aoki J, Nakajima H, Hara K. The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol.* 2005;104:319-25.
64. Pache J, Dibra A, Schaut C, Schuhlen H, Dirschinger J, Mehilli J, Kastrati A, Schomig A. Sustained increased risk of adverse cardiac events over 5 years after implantation of gold-coated coronary stents. *Catheterization and cardiovascular interventions.* 2006;68:690-5.
65. Ekqvist S, Svedman C, Moller H, Kehler M, Pripp CM, Bjork J, Gruvberger B, Holmstrom E, Gustavsson CG, Bruze M. High frequency of contact allergy to gold in patients with endovascular coronary stents. *The British journal of dermatology.* 2007;157:730-8.
66. Kastrati A, Schomig A, Dirschinger J, Mehilli J, von Welser N, Pache J, Schuhlen H, Schilling T, Schmitt C, Neumann FJ. Increased risk of restenosis after placement of gold-coated stents: results of a randomized trial comparing gold-coated with uncoated steel stents in patients with coronary artery disease. *Circulation.* 2000;101:2478-83.
67. Svedman C, Moller H, Gustavsson CG, Bruze M. Coronary restenosis and contact allergy to stent material. *The Journal of invasive cardiology.* 2011;23:3 p following E94.
68. Svedman C, Ekqvist S, Moller H, Bjork J, Pripp CM, Gruvberger B, Holmstrom E, Gustavsson CG, Bruze M. A correlation found between contact allergy to stent material and restenosis of the coronary arteries. *Contact Dermatitis.* 2009;60:158-64.
69. Nakazawa G, Tanabe K, Aoki J, Onuma Y, Higashikuni Y, Yamamoto H, Ohtsuki S, Yachi S, Yagishita A, Nakajima H, Hara K. Sirolimus-eluting stents suppress neointimal formation irrespective of metallic allergy. *Circ J.* 2008;72:893-6.
70. Niccoli G, Montone RA, Ferrante G, Crea F. The evolving role of inflammatory biomarkers in risk assessment after stent implantation. *JACC.* 2010;56:1783-93.
71. Park DW, Lee CW, Yun SC, Kim YH, Hong MK, Kim JJ, Park SW, Park SJ. Prognostic impact of preprocedural C reactive protein levels on 6-month angiographic and 1-year clinical outcomes after drug-eluting stent implantation. *Heart.* 2007;93:1087-92.
72. Katsaros KM, Kastl SP, Zorn G, Maurer G, Wojta J, Huber K, Christ G, Speidl WS. Increased restenosis rate after implantation of drug-eluting stents in patients with elevated serum activity of matrix metalloproteinase-2 and -9. *JACC Cardiovasc Interv.* 2010;3:90-7.
73. Bendeck MP, Zempo N, Clowes AW, Galardy RE, Reidy MA. Smooth muscle cell migration and matrix metalloproteinase expression after arterial injury in the rat. *Circ Res.* 1994;75:539-45.
74. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. *Circ Res.* 2002;90:251-62.
75. Southgate KM, Fisher M, Banning AP, Thurston VJ, Baker AH, Fabunmi RP, Groves PH, Davies M, Newby AC. Upregulation of basement membrane-degrading metalloproteinase secretion after balloon injury of pig carotid arteries. *Circ Res.* 1996;79:1177-87.
76. Katsaros KM, Speidl WS, Kastl SP, Zorn G, Huber K, Maurer G, Glogar D, Wojta J, Christ G. Plasminogen

activator inhibitor-1 predicts coronary in-stent restenosis of drug-eluting stents. *Journal of thrombosis and haemostasis : JTH*. 2008;6:508-13.

77. Speidl WS, Katsaros KM, Kastl SP, Zorn G, Huber K, Maurer G, Wojta J, Christ G. Coronary late lumen loss of drug eluting stents is associated with increased serum levels of the complement components C3a and C5a. *Atherosclerosis*. 2010;208:285-9.

78. Monraats PS, Pires NM, Agema WR, Zwinderman AH, Schepers A, de Maat MP, Doevendans PA, de Winter RJ, Tio RA, Waltenberger J, Frants RR, Quax PH, van Vlijmen BJ, Atsma DE, van der Laarse A, van der Wall EE, Jukema JW. Genetic inflammatory factors predict restenosis after percutaneous coronary interventions. *Circulation*. 2005;112:2417-25.

Study associating polymorphisms in genes considered to be involved in the inflammatory reaction after vessel injury, and shown to be associated with repeat revascularisation after PCI.

79. Vogiatzi K, Apostolakis S, Voudris V, Thomopoulou S, Kochiadakis GE, Spandidos DA. Interleukin 8 gene polymorphisms and susceptibility to restenosis after percutaneous coronary intervention. *J Thromb Thrombolysis*. 2010;29:134-40.

80. Kastrati A, Koch W, Berger PB, Mehilli J, Stephenson K, Neumann FJ, von Beckerath N, Bottiger C, Duff GW, Schomig A. Protective role against restenosis from an interleukin-1 receptor antagonist gene polymorphism in patients treated with coronary stenting. *J Am Coll Cardiol*. 2000;36:2168-73.

81. de Maat MP, Jukema JW, Ye S, Zwinderman AH, Moghaddam PH, Beekman M, Kastelein JJ, van Boven AJ, Bruschke AV, Humphries SE, Kluft C, Henney AM. Effect of the stromelysin-1 promoter on efficacy of pravastatin in coronary atherosclerosis and restenosis. *Am J Cardiol*. 1999;83:852-6.

82. Kitsios G, Zintzaras E. ACE (I/D) polymorphism and response to treatment in coronary artery disease: a comprehensive database and meta-analysis involving study quality evaluation. BMC medical genetics 2009;10:50.

83. Shaaban AM, Duerinckx AJ. Wall Shear Stress and Early Atherosclerosis: *A Review. Am. J. Roentgenol*. 2000;174:1657-1665.

84. Wentzel JJ, Gijsen FJ, Schuurbiers JC, van der Steen AF, Serruys PW. The influence of shear stress on in-stent restenosis and thrombosis. *EuroIntervention*. 2008;4 Suppl C:C27-32.

85. Wentzel JJ, Gijsen FJ, Stergiopulos N, Serruys PW, Slager CJ, Krams R. Shear stress, vascular remodeling and neointimal formation. *J Biomech*. 2003;36:681-8.

86. Suzuki N, Nanda H, Angiolillo DJ, Bezerra H, Sabate M, Jimenez-Quevedo P, Alfonso F, Macaya C, Bass TA, Ilegbusi OJ, Costa MA. Assessment of potential relationship between wall shear stress and arterial wall response after bare metal stent and sirolimus-eluting stent implantation in patients with diabetes mellitus. *Int J Cardiovasc Imaging*. 2008;24:357-64.

87. Bassiouny HS, Song RH, Hong XF, Singh A, Kocharyan H, Glagov S. Flow regulation of 72-kD collagenase IV (MMP-2) after experimental arterial injury. *Circulation*. 1998;98:157-63.

88. Bassiouny HS, Song RH, Kocharyan H, Kins E, Glagov S. Low flow enhances platelet activation after acute experimental arterial injury. *J Vasc Surg*. 1998;27:910-8.

89. Gijsen FJ, Oortman RM, Wentzel JJ, Schuurbiers JC, Tanabe K, Degertekin M, Ligthart JM, Thury A, de Feyter PJ, Serruys PW, Slager CJ. Usefulness of shear stress pattern in predicting neointima distribution in sirolimus-eluting stents in coronary arteries. *JACC*. 2003;92:1325-8.

90. Sterpetti AV, Cucina A, D'Angelo LS, Cardillo B, Cavallaro A. Shear stress modulates the proliferation rate, protein synthesis, and mitogenic activity of arterial smooth muscle cells. *Surgery*. 1993;113:691-9.

91. Carlier SG, van Damme LCA, Blommerde CP, Wentzel JJ, van Langehove G, Verheye S, Kockx MM, Knaapen MWM, Cheng C, Gijsen F, Duncker DJ, Stergiopulos N, Slager CJ, Serruys PW, Krams R. Augmentation of Wall Shear Stress Inhibits Neointimal Hyperplasia After Stent Implantation: Inhibition Through Reduction of Inflammation? *Circulation*. 2003;107:2741-2746.

92. Kim YH, Park DW, Suh IW, Jang JS, Hwang ES, Jeong YH, Lee SW, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. Long-term outcome of simultaneous kissing stenting technique with sirolimus-eluting stent for large bifurcation coronary lesions. *Catheter Cardiovasc Interv* .2007;70:840-6.

93. Morton AC, Siotia A, Arnold ND, Korgul P, Bowles J, Heppenstall J, Gunn J. Simultaneous kissing stent technique to treat left main stem bifurcation disease. *Catheter Cardiovasc Interv*. 2007;69:209-15.

94. Stinis CT, Hu SP, Price MJ, Teirstein PS. Three-year outcome of drug-eluting stent implantation for coro-

nary artery bifurcation lesions. *Catheter Cardiovasc Interv.* 2010;75:309-14.

95. Papafaklis MI, Bourantas CV, Theodorakis PE, Katsouras CS, Naka KK, Fotiadis DI, Michalis LK. The Effect of Shear Stress on Neointimal Response Following Sirolimus- and Paclitaxel-Eluting Stent Implantation Compared With Bare-Metal Stents in Humans. *J Am Coll Cardiol Intv.* 2010;3:1181-1189.
The role of shear stress and how its clinical effects can be modulated with certain DES.

96. Oikawa Y YJ, Costa M, Matsuno S, Akabane M, Funada R, Inaba T, Nakagawa Y, Nakamura M, Nagashima K, Kirigaya H, Ogasawara K, Sawada H, Aizawa T. Intravascular ultrasound, angioscopic and histopathological characterisation of heterogeneous patterns of restenosis after sirolimus-eluting stent implantation: insights into potential "thromborestenosis" phenomenon. *EuroInterv.* 2010;6:380-387.

97. Rittersma SZH, van der Wal AC, Koch KT, Piek JJ, Henriques JPS, Mulder KJ, Ploegmakers JPHM, Meesterman M, de Winter RJ. Plaque Instability Frequently Occurs Days or Weeks Before Occlusive Coronary Thrombosis: A Pathological Thrombectomy Study in Primary Percutaneous Coronary Intervention. *Circulation.* 2005;111:1160-1165.

98. Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* .1988;112:1018-31.

99. Okura H, Morino Y, Oshima A, Hayase M, Ward MR, Popma JJ, Kuntz RE, Bonneau HN, Yock PG, Fitzgerald PJ. Preintervention arterial remodeling affects clinical outcome following stenting: an intravascular ultrasound study. *J Am Coll Cardiol.* 2001;37:1031-5.

100. Nakamura M, Yock PG, Bonneau HN, Kitamura K, Aizawa T, Tamai H, Fitzgerald PJ, Honda Y. Impact of peri-stent remodeling on restenosis: a volumetric intravascular ultrasound study. *Circulation.* 2001;103:2130-2.

101. Farb A, Sangiorgi G, Carter AJ, Walley VM, Edwards WD, Schwartz RS, Virmani R. Pathology of acute and chronic coronary stenting in humans. *Circulation.* 1999;99:44-52.

102. Carter AJ, Aggarwal M, Kopia GA, Tio F, Tsao PS, Kolata R, Yeung AC, Llanos G, Dooley J, Falotico R. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. *Cardiovasc Res.* 2004;63:617-24.

103. Raber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, Cook S, Moschovitis A, Vogel R, Kalesan B, Seiler C, Eberli F, Luscher TF, Meier B, Juni P, Windecker S. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation.* 2011;123:2819-28, 6 p following 2828.
The association of late restenosis with the implantation of certain DES

104. Wilson GJ, Nakazawa G, Schwartz RS, Huibregtse B, Poff B, Herbst TJ, Baim DS, Virmani R. Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting stents in porcine coronary arteries. *Circulation.* 2009;120:141-9, 1-2.

105. Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol.* 2011;57:390-8.

106. Naito M, Stirk CM, Smith EB, Thompson WD. Smooth muscle cell outgrowth stimulated by fibrin degradation products. The potential role of fibrin fragment E in restenosis and atherogenesis. *Thromb Res.* 2000;98:165-74.

107. Liistro F, Stankovic G, Di Mario C, Takagi T, Chieffo A, Moshiri S, Montorfano M, Carlino M, Briguori C, Pagnotta P, Albiero R, Corvaja N, Colombo A. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. *Circulation.* 2002;105:1883-6.

108. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol.* 2011;57:1314-22.
The pathogenesis underlying neoatherosclerosis in bare and drug eluting stents - an essential read.

109. Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, Mizuno K. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol.* 2009;55:26-32.

110. Habara M, Terashima M, Nasu K, Kaneda H, Inoue K, Ito T, Kamikawa S, Kurita T, Tanaka N, Kimura M, Kinoshita Y, Tsuchikane E, Matsuo H, Ueno K,

Katoh O, Suzuki T. Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study. *Circ Cardiovasc Interv.* 2010;4:232-8.

111. Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation.* 2011;123:2954-63.
112. Kimura T, Yokoi H, Nakagawa Y, Tamura T, Kaburagi S, Sawada Y, Sato Y, Hamasaki N, Nosaka H, et al. Three-year follow-up after implantation of metallic coronary-artery stents. *N Engl J Med.* 1996;334:561-6.
113. Asakura M, Ueda Y, Nanto S, Hirayama A, Adachi T, Kitakaze M, Hori M, Kodama K. Remodeling of in-stent neointima, which became thinner and transparent over 3 years: serial angiographic and angioscopic follow-up. *Circulation.* 1998;97:2003-6.
114. Kimura T, Abe K, Shizuta S, Odashiro K, Yoshida Y, Sakai K, Kaitani K, Inoue K, Nakagawa Y, Yokoi H, Iwabuchi M, Hamasaki N, Nosaka H, Nobuyoshi M. Long-term clinical and angiographic follow-up after coronary stent placement in native coronary arteries. *Circulation.* 2002;105:2986-91.
115. Byrne RA, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schomig A, Kastrati A. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv.* 2009;2:291-9.
116. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR, Jr., Ellis SG, Topol EJ. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation.* 1996;94(7):1690-7.
117. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation.* 2007;115:2435-41.
118. Smits PC, Kedhi E, Royaards KJ, Joesoef KS, Wassing J, Rademaker-Havinga TA, McFadden E. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). *JACC.* 2011;58:11-8.
119. Stone GW, Rizvi A, Sudhir K, Newman W, Applegate RJ, Cannon LA, Maddux JT, Cutlip DE, Simonton CA, Sood P, Kereiakes DJ. Randomized comparison of everolimus- and paclitaxel-eluting stents. 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. *JACC.* 2011;58:19-25.
120. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, Wilson PS, Skorija K, Cheng Q, Xu X, Gold HK, Kolodgie FD, Virmani R. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol.* 2008;52:333-42.
121. Togni M, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, Meier B, Hess OM. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. *J Am Coll Cardiol.* 2005;46:231-6.
122. Togni M, Raber L, Cocchia R, Wenaweser P, Cook S, Windecker S, Meier B, Hess OM. Local vascular dysfunction after coronary paclitaxel-eluting stent implantation. *Int J Cardiol.* 2007; 21;120:212-20.
123. Hofma SH, van der Giessen WJ, van Dalen BM, Lemos PA, McFadden EP, Sianos G, Ligthart JM, van Essen D, de Feyter PJ, Serruys PW. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur Heart J.* 2006;27:166-70.
124. Hamilos MI, Ostojic M, Beleslin B, Sagic D, Mangovski L, Stojkovic S, Nedeljkovic M, Orlic D, Milosavljevic B, Topic D, Karanovic N, Wijns W. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J Am Coll Cardiol.* 2008;51:2123-9.
125. Hamilos M, Sarma J, Ostojic M, Cuisset T, Sarno G, Melikian N, Ntalianis A, Muller O, Barbato E, Beleslin B, Sagic D, De Bruyne B, Bartunek J, Wijns W. Interference of drug-eluting stents with endothelium-dependent coronary vasomotion: evidence for device-specific responses. *Circ Cardiovasc Interv.* 2008;1:193-200.
126. Fujii K, Kawasaki D, Oka K, Akahori H, Fukunaga M, Sawada H, Masutani M, Lee-Kawabata M, Tsujino T, Ohyanagi M, Masuyama T. Endothelium-dependent coronary vasomotor response and neointimal coverage of zotarolimus-eluting stents 3 months after implantation. *Heart.* 2011;97:977-82.
127. **Serruys PW, Sianos G, Abizaid A, Aoki J, den Heijer P, Bonnier H, Smits P, McClean D, Verheye S, Belardi J, Condado J, Pieper M, Gambone L, Bressers M, Symons J, Sousa E, Litvack F. The effect of variable**

dose and release kinetics on neointimal hyperplasia using a novel paclitaxel-eluting stent platform: the Paclitaxel In-Stent Controlled Elution Study (PISCES). *J Am Coll Cardiol.* 2005;46:253-60.

The first human study to demonstrate the principle of polymer release kinetics with six different polymer-drug release formulations. The main finding of the trial was that the duration of the anti-proliferative drug release had a far greater impact on the neointimal inhibition than the dose of the drug delivered.

128. Tada N, Virmani R, Grant G, Bartlett L, Black A, Clavijo C, Christians U, Betts R, Savage D, Su S-H, Shulze J, Kar S. Polymer-Free Biolimus A9-Coated Stent Demonstrates More Sustained Intimal Inhibition, Improved Healing, and Reduced Inflammation Compared With a Polymer-Coated Sirolimus-Eluting Cypher Stent in a Porcine Model. *Circ Cardiovasc Interv.* 2010;3:174-183.
129. Grube E. 12-Month angiographic follow-up of the novel non-polymeric Biolimus A9-coated stent for the treatment of de novo coronary lesions: results from the prospective, multicenter, randomized BIOFREEDOM Clinical Trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21 to 25, 2010; Washington DC.
130. Tanner FC, Yang ZY, Duckers E, Gordon D, Nabel GJ, Nabel EG. Expression of cyclin-dependent kinase inhibitors in vascular disease. *Circ Res.* 1998;82:396-403.
131. Sabate M. A randomised comparison between everolimus-eluting stents and cobalt-chromium bare-metal stents in ST-elevation myocardial infarction. Presented at European Society of Cardiology Congress, August 30 , 2011; Paris, France 2011.
132. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, KelbÃ?k H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. N*ew England Journal of Medicine.* 2010;363:136-146.
133. Papafaklis MI, Chatzizisis YS, Naka KK, Giannoglou GD, Michalis LK. Drug-eluting stent restenosis: Effect of drug type, release kinetics, hemodynamics and coating strategy. *Pharmacol Ther*. 2011 Dec 22. 2012;134:43-53.
134. Giordano A, Romano A. Inhibition of human in-stent restenosis: a molecular view. *Current opinion in pharmacology.* 2011;11:372-7.
135. de Scheerder I, Wang K, Wilczek K, van Dorpe J, Verbeken E, Desmet W, Schacht E, Piessens J. Local methylprednisolone inhibition of foreign body response to coated intracoronary stents. *Coronary artery disease.* 1996;7:161-6.
136. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. *Circulation*. 2005;111:2257-73.
137. **Lemos PA, Moulin B, Perin MA, Oliveira LA, Arruda JA, Lima VC, Lima AA, Caramori PR, Medeiros CR, Barbosa MR, Brito FS, Jr., Ribeiro EE, Martinez EE. Randomized evaluation of two drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. *Catheterization and cardiovascular interventions.* 2009;74:665-73.**

Head to head comparison of paclitaxel vs. sirolimus anti-proliferative drugs in 2 otherwise identical metallic stent and polymer platforms, demonstrating the superiority of sirolimus over paclitaxel in neointima suppression.

138. Kereiakes DJ, Smits PC, Kedhi E, Parise H, Fahy M, Serruys PW, Stone GW. Predictors of death or myocardial infarction, ischaemic-driven revascularisation, and major adverse cardiovascular events following everolimus-eluting or paclitaxel-eluting stent deployment: pooled analysis from the SPIRIT II, III, IV and COMPARE trials. *EuroIntervention.* 2011;7:74-83.
139. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163-73.
140. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Juni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet*. 2011;378:1940-8.

141. Takebayashi H, Mintz GS, Carlier SG, Kobayashi Y, Fujii K, Yasuda T, Costa RA, Moussa I, Dangas GD, Mehran R, Lansky AJ, Kreps E, Collins MB, Colombo A, Stone GW, Leon MB, Moses JW. Nonuniform strut distribution correlates with more neointimal hyperplasia after sirolimus-eluting stent implantation. *Circulation.* 2004;110:3430-4.

142. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation.* 1998;98:1875-80.

143. Kasaoka S, Tobis JM, Akiyama T, Reimers B, Di Mario C, Wong ND, Colombo A. Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol.* 1998;32:1630-5.

144. Akiyama T, Moussa I, Reimers B, Ferraro M, Kobayashi Y, Blengino S, Di Francesco L, Finci L, Di Mario C, Colombo A. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. *J Am Coll Cardiol.* 1998;32:1610-8.

145. Agostoni P, Biondi-Zoccai GG, Gasparini GL, Anselmi M, Morando G, Turri M, Abbate A, McFadden EP, Vassanelli C, Zardini P, Colombo A, Serruys PW. Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. *Eur Heart J.* 2005;26:881-9.

146. Biondi-Zoccai G, Moretti C, Abbate A, Sheiban I. Percutaneous coronary intervention for small vessel coronary artery disease. *Cardiovasc Revasc Med.* 2010;11:189-98.

Meta-analyses on small vessel disease demonstrating the disparity of clinical outcomes with differing DES, due to the complex interaction with metallic stent platform, polymer type, polymer release kinetics and type of anti-proliferative drug.

147. Briguori C, Sarais C, Pagnotta P, Liistro F, Montorfano M, Chieffo A, Sgura F, Corvaja N, Albiero R, Stankovic G, Toutoutzas C, Bonizzoni E, Di Mario C, Colombo A. In-stent restenosis in small coronary arteries: impact of strut thickness. *J Am Coll Cardiol.* 2002;40:403-9.

148. Eshtehardi P, Cook S, Wandel S, Raber L, Wenaweser P, Togni M, Vogel R, Garachemani A, Eberli FR, Luscher TF, Juni P, Hess OM, Meier B, Windecker S. Impact of arterial injury on neointimal hyperplasia after implantation of drug-eluting stents in coronary arteries: an intravascular ultrasound study. *EuroIntervention.* 2010;6:467-74.

149. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, Fleckenstein M, Pfafferott C, Seyfarth M, Schomig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation.* 2001;103:2816-21.

150. Raisuke I, Yuji I, Akiyoshi M, Hiroyoshi N, Kazuhiro H. Predictors of restenosis after implantation of 2.5 mm stents in small coronary arteries. *Circ J.* 2004;68:236-40.

151. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Muller M, Dirschinger J, Schomig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J Am Coll Cardiol.* 2003;41:1283-8.

152. Brodie BR, Stuckey T, Downey W, Humphrey A, Bradshaw B, Metzger C, Hermiller J, Krainin F, Juk S, Cheek B, Duffy P, Smith H, Edmunds J, Varanasi J, Simonton CA, STENT Group. Outcomes and Complications With Off-Label Use of Drug-Eluting Stents: Results From the STENT (Strategic Transcatheter Evaluation of New Therapies) Group. *J Am Coll Cardiol Intv.* 2008;1:405-414.

153. Brodie BR, Stuckey T, Downey W, Humphrey A, Bradshaw B, Metzger C, Hermiller J, Krainin F, Juk S, Cheek B, Duffy P, Smith H, Edmunds J, Varanasi J, Simonton CA. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. *JACC Cardiovasc Interv.* 2008;1:405-14.

154. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *European Heart Journal.* 2011;32:2125-34.

155. Serruys PW, Farooq V, Vrancx P, Brugaletta S, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Ståhle E, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. The SYNTAX Trial at 3 Years: a Global Risk approach to identify patients with 3-vessel and/or left main stem disease who could safely and efficaciously be treated with percutaneous coronary inter-

vention. Part 1: the randomised population. Presented at: TCT, San Francisco, USA, 8 Nov 2011.

156. Farooq V, Serruys PW, Vrancx P, Brugaletta S, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Ståhle E, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. The SYNTAX trial at 3 years: a Global Risk approach to identify patients with 3-vessel and/or left main stem disease who could safely and efficaciously be treated with percutaneous coronary intervention. Part 2: The 'All-Comers' population. Presented at: TCT, San Francisco, USA, 8 Nov 2011.
157. Capodanno D, Caggegi A, Miano M, Cincotta G, Dipasqua F, Giacchi G, Capranzano P, Ussia G, Di Salvo ME, La Manna A, Tamburino C. Global Risk Classification and Clinical SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) Score in Patients Undergoing Percutaneous or Surgical Left Main Revascularization. *J Am Coll Cardiol Intv.* 2011;4:287-297.
158. Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, Sanfilippo A, Capranzano P, Tamburino C. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *American heart journal.* 2010;159:103-9.
159. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. *J Invasive Cardiol.* 2007;19:71-6.
160. Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. *EuroIntervention.* 2009;5:157-65.
161. Basalus MW, Tandjung K, van Westen T, Sen H, van der Jagt PK, Grijpma DW, van Apeldoorn AA, von Birgelen C. Scanning electron microscopic assessment of coating irregularities and their precursors in Unexpanded durable polymer-based drug-eluting stents. *Catheter Cardiovasc Interv.* 2011 Jul 29. 2012 1;79:644-53.
162. Wiemer M, Butz T, Mahmood K, Horstkotte D. Major polymer damage of drug-eluting stents. *Circ Cardiovasc Interv.* 2008;1:154.
163. Wiemer M, Butz T, Schmidt W, Schmitz KP, Horstkotte D, Langer C. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: from nearly undamaged to major damaged polymers. *Catheter Cardiovasc Interv.* 2010;75:905-11.
164. Guerin P, Pilet P, Finet G, Goueffic Y, N'Guyen JM, Crochet D, Tijou I, Pacaud P, Loirand G. Drug-eluting stents in bifurcations: bench study of strut deformation and coating lesions. *Circ Cardiovasc Interv.* 2010;3:120-6.
165. Sianos G, Hofma S, Ligthart JM, Saia F, Hoye A, Lemos PA, Serruys PW. Stent fracture and restenosis in the drug-eluting stent era. *Catheter Cardiovasc Interv.* 2004;61:111-6.
166. Canan T, Lee MS. Drug-eluting stent fracture: incidence, contributing factors, and clinical implications. *Catheter Cardiovasc Interv.* 2010;75:237-45.
167. Kim HS, Kim YH, Lee SW, Park DW, Lee CW, Hong MK, Park SW, Ko JK, Park JH, Lee JH, Choi SW, Seong IW, Cho YH, Lee NH, Kim JH, Chun KJ, Park SJ. Incidence and predictors of drug-eluting stent fractures in long coronary disease. *Int J Cardiol.* 2009;133:354-8.
168. Aoki J, Nakazawa G, Tanabe K, Hoye A, Yamamoto H, Nakayama T, Onuma Y, Higashikuni Y, Otsuki S, Yagishita A, Yachi S, Nakajima H, Hara K. Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv.* 2007;69:380-6.
169. Yamada KP, Koizumi T, Yamaguchi H, Kaneda H, Bonneau HN, Honda Y, Fitzgerald PJ. Serial angiographic and intravascular ultrasound analysis of late stent strut fracture of sirolimus-eluting stents in native coronary arteries. *Int J Cardiol.* 2008;130:255-9.
170. Lemos PA, Saia F, Ligthart JMR, Arampatzis CA, Sianos G, Tanabe K, Hoye A, Degertekin M, Daemen J, McFadden E, Hofma S, Smits PC, de Feyter P, van der Giessen WJ, van Domburg RT, Serruys PW. Coronary Restenosis After Sirolimus-Eluting Stent Implantation: Morphological Description and Mechanistic Analysis From a Consecutive Series of Cases. *Circulation.* 2003;108:257-260.
171. Umeda H, Gochi T, Iwase M, Izawa H, Shimizu T, Ishiki R, Inagaki H, Toyama J, Yokota M, Murohara T. Frequency, predictors and outcome of stent fracture after sirolimus-eluting stent implantation. *Int J Cardiol.* 2009;133:321-6.
172. Okumura M, Ozaki Y, Ishii J, Kan S, Naruse H, Matsui S, Ishikawa M, Hattori K, Gochi T, Nakano T, Yamada A, Kato S, Motoyama S, Sarai M, Takagi Y, Ismail TF, Nomura M, Hishida H. Restenosis and stent

fracture following sirolimus-eluting stent (SES) implantation. *Circ J*. 2007;71:1669-77.

173. Lee SH, Park JS, Shin DG, Kim YJ, Hong GR, Kim W, Shim BS. Frequency of stent fracture as a cause of coronary restenosis after sirolimus-eluting stent implantation. *Am J Cardiol*. 2007;100:627-30.
174. Hanratty CG, Walsh SJ. Longitudinal compression: a "new" complication with modern coronary stent platforms - time to think beyond deliverability? *EuroIntervention*. 2011;7:872-7.
175. Mortier P, De Beule M. Stent design back in the picture: an engineering perspective on longitudinal stent compression. *EuroIntervention*. 2011;7:773, 775.
176. Williams PD, Mamas MA, Morgan KP, El-Omar M, Clarke B, Bainbridge A, Fath-Ordoubadi F, Fraser DG. Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms. *EuroIntervention*. 2011 Nov 4.
177. Castagna MT, Mintz GS, Leiboff BO, Ahmed JM, Mehran R, Satler LF, Kent KM, Pichard AD, Weissman NJ. The contribution of "mechanical" problems to in-stent restenosis: An intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. *Am Heart J*. 2001;142:970-4.
178. Bertrand OF, De Larochelliere R, Joyal M, Bonan R, Mongrain R, Tardif JC. Incidence of stent underdeployment as a cause of in-stent restenosis in long stents. *Int J Cardiovasc Imaging*. 2004;20:279-84.
179. Fujii K, Mintz GS, Kobayashi Y, Carlier SG, Takebayashi H, Yasuda T, Moussa I, Dangas G, Mehran R, Lansky AJ, Reyes A, Kreps E, Collins M, Colombo A, Stone GW, Teirstein PS, Leon MB, Moses JW. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. *Circulation*. 2004;109:1085-8.
180. Escolar E, Mintz GS, Canos D, Cheneau E, Pichard AD, Satler LF, Kent KM, Waksman R, Weissman NJ. Serial intravascular ultrasound comparison of the extent and distribution of intimal hyperplasia six months after stent implantation for de novo versus in-stent restenosis lesions. *Am J Cardiol*. 2005;96:897-900.
181. Doi H, Maehara A, Mintz GS, Yu A, Wang H, Mandinov L, Popma JJ, Ellis SG, Grube E, Dawkins KD, Weissman NJ, Turco MA, Ormiston JA, Stone GW. Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv*. 2009;2:1269-75.
182. de Ribamar Costa J, Jr., Mintz GS, Carlier SG, Fujii K, Sano K, Kimura M, Tanaka K, Costa RA, Lui J, Na Y, Castellanos C, Biro S, Moussa I, Stone GW, Moses JW, Leon MB. Intravascular ultrasound assessment of drug-eluting stent expansion. *Am Heart J*. 2007;153:297-303.
183. Yoon SC, Laskey WK, Assadourian A, Kelly D, Gellman J, Herzog W, Stafford JL. Assessment of contemporary stent deployment using intravascular ultrasound. *Catheter Cardiovasc Interv*. 2002;57:150-4.
184. Hanekamp CE, Koolen JJ, Pijls NH, Michels HR, Bonnier HJ. Comparison of quantitative coronary angiography, intravascular ultrasound, and coronary pressure measurement to assess optimum stent deployment. *Circulation*. 1999;99:1015-21.
185. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y, Kuntz RE, Fitzgerald PJ. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J Am Coll Cardiol*. 2004;43:1959-63.
186. Takebayashi H, Kobayashi Y, Mintz GS, Carlier SG, Fujii K, Yasuda T, Moussa I, Mehran R, Dangas GD, Collins MB, Kreps E, Lansky AJ, Stone GW, Leon MB, Moses JW. Intravascular ultrasound assessment of lesions with target vessel failure after sirolimus-eluting stent implantation. *Am J Cardiol*. 2005;95:498-502.
187. Hong MK, Mintz GS, Lee CW, Park DW, Choi BR, Park KH, Kim YH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J*. 2006;27:1305-10.
188. Casella G, Klauss V, Ottani F, Siebert U, Sangiorgio P, Bracchetti D. Impact of intravascular ultrasound-guided stenting on long-term clinical outcome: a meta-analysis of available studies comparing intravascular ultrasound-guided and angiographically guided stenting. *Catheter Cardiovasc Interv*. 2003;59:314-21.
189. Russo RJ, Silva PD, Teirstein PS, Attubato MJ, Davidson CJ, DeFranco AC, Fitzgerald PJ, Goldberg SL, Hermiller JB, Leon MB, Ling FS, Lucisano JE, Schatz RA, Wong SC, Weissman NJ, Zientek DM. A randomized controlled trial of angiography versus intravascular ultrasound-directed bare-metal coronary stent placement (the AVID Trial). *Circ Cardiovasc Interv*. 2009;2:113-23.

190. Jakabcin J, Spacek R, Bystron M, Kvasnak M, Jager J, Veselka J, Kala P, Cervinka P. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance. Randomized control trial. HOME DES IVUS. *Catheter Cardiovasc Interv.* 2010;75:578-83.

191. Rogacka R, Latib A, Colombo A. IVUS-Guided Stent Implantation to Improve Outcome: A Promise Waiting to be Fulfilled. *Curr Cardiol Rev.* 2009;5:78-86.

192. Colombo A. AVIO: a prospective randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions. Presented at: Transcatheter Cardiovascular Therapeutics; September 21 to 25, 2010; Washington, DC.

193. Honda Y, Fitzgerald PJ. Stent expansion as a mechanical parameter to predict late stent patency: back to the basics. *JACC Cardiovasc Interv.* 2009;2:1276-8.

194. Hwang C-W, Wu D, Edelman ER. Physiological Transport Forces Govern Drug Distribution for Stent-Based Delivery. *Circulation*. 2001;104:600-605.

195. Lambert T, Dev V, Rechavia E, Forrester J, Litvack F, Eigler N. Localized arterial wall drug delivery from a polymer-coated removable metallic stent. Kinetics, distribution, and bioactivity of forskolin. *Circulation*. 1994;90:1003-1011.

196. Costa MA, Angiolillo DJ, Tannenbaum M, Driesman M, Chu A, Patterson J, Kuehl W, Battaglia J, Dabbons S, Shamoon F, Flieshman B, Niederman A, Bass TA. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol.* 2008;101:1704-11.
One of the first reported associations of geographical miss with restensois.

197. Liu X, Tsujita K, Maehara A, Mintz GS, Weisz G, Dangas GD, Lansky AJ, Kreps EM, Rabbani LE, Collins M, Stone GW, Moses JW, Mehran R, Leon MB. Intravascular ultrasound assessment of the incidence and predictors of edge dissections after drug-eluting stent implantation. *JACC Cardiovasc Interv.* 2009;2:997-1004.

198. Biondi-Zoccai GG, Agostoni P, Sangiorgi GM, Airoldi F, Cosgrave J, Chieffo A, Barbagallo R, Tamburino C, Vittori G, Falchetti E, Margheri M, Briguori C, Remigi E, Iakovou I, Colombo A. Incidence, predictors, and outcomes of coronary dissections left untreated after drug-eluting stent implantation. *Eur Heart J*. 2006;27:540-6.

199. Tahara S, Bezerra HG, Kyono H, Carrigan T, Mehanna E, Wang W, Costa MA. Impact of acute gain on clinical outcomes of patients treated with sirolimus-eluting stent. - A sub-analysis study from the STLLR trial. *Circulation journal*. 2011;75:2113-9.

200. Hoffmann R, Guagliumi G, Musumeci G, Reimers B, Petronio AS, Disco C, Amoroso G, Moses JW, Fitzgerald PJ, Schofer J, Leon MB, Breithardt G. Vascular response to sirolimus-eluting stents delivered with a nonaggressive implantation technique: comparison of intravascular ultrasound results from the multicenter, randomized E-SIRIUS, and SIRIUS trials. *Catheter Cardiovasc Interv.* 2005;66:499-506.

201. Waxman S, Freilich MI, Suter MJ, Shishkov M, Bilazarian S, Virmani R, Bouma BE, Tearney GJ. A case of lipid core plaque progression and rupture at the edge of a coronary stent: elucidating the mechanisms of drug-eluting stent failure. *Circ Cardiovasc Interv.* 2010;3:193-6.

202. Sarno G, Garg S, Gomez-Lara J, Garcia Garcia HM, Ligthart J, Bruining N, Onuma Y, Witberg K, van Geuns RJ, de Boer S, Wykrzykowska J, Schultz C, Duckers HJ, Regar E, de Jaegere P, de Feyter P, van Es GA, Boersma E, van der Giessen W, Serruys PW. Intravascular ultrasound radiofrequency analysis after optimal coronary stenting with initial quantitative coronary angiography guidance: an ATHEROREMO substudy. EuroIntervention : *journal of EuroPCR* in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2011;6:977-84.

203. Hwang CW, Levin AD, Jonas M, Li PH, Edelman ER. Thrombosis modulates arterial drug distribution for drug-eluting stents. *Circulation*. 2005;111:1619-26.

204. Spaulding C, Henry P, Teiger E, Beatt K, Bramucci E, Carrie D, Slama MS, Merkely B, Erglis A, Margheri M, Varenne O, Cebrian A, Stoll HP, Snead DB, Bode C. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med*. 2006;355:1093-104.

205. Valgimigli M, Percoco G, Malagutti P, Campo G, Ferrari F, Barbieri D, Cicchitelli G, McFadden EP, Merlini F, Ansani L, Guardigli G, Bettini A, Parrinello G, Boersma E, Ferrari R. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA*. 2005;293:2109-17.

206. Valgimigli M, Campo G, Percoco G, Bolognese L, Vassanelli C, Colangelo S, de Cesare N, Rodriguez AE, Ferrario M, Moreno R, Piva T, Sheiban I, Pasquetto G, Prati F, Nazzaro MS, Parrinello G, Ferrari R. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA*. 2008;299:1788-99.

207. Laarman GJ, Suttorp MJ, Dirksen MT, van Heerebeek L, Kiemeneij F, Slagboom T, van der Wieken LR, Tijssen JG, Rensing BJ, Patterson M. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med*. 2006;355:1105-13.

208. Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Mockel M, Ochala A, Kellock A, Parise H, Mehran R. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med*. 2009;360:1946-59.

209. Menichelli M, Parma A, Pucci E, Fiorilli R, De Felice F, Nazzaro M, Giulivi A, Alborino D, Azzellino A, Violini R. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol*. 2007;49:1924-30.

210. Diaz de la Llera LS, Ballesteros S, Nevado J, Fernandez M, Villa M, Sanchez A, Retegui G, Garcia D, Martinez A. Sirolimus-eluting stents compared with standard stents in the treatment of patients with primary angioplasty. *Am Heart J*. 2007;154:164 e1-6.

211. van der Hoeven BL, Liem SS, Jukema JW, Suraphakdee N, Putter H, Dijkstra J, Atsma DE, Bootsma M, Zeppenfeld K, Oemrawsingh PV, van der Wall EE, Schalij MJ. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol*. 2008;51:618-26.

212. Kelbaek H, Thuesen L, Helqvist S, Clemmensen P, Klovgaard L, Kaltoft A, Andersen B, Thuesen H, Engstrom T, Botker HE, Saunamaki K, Krusell LR, Jorgensen E, Hansen HH, Christiansen EH, Ravkilde J, Kober L, Kofoed KF, Terkelsen CJ, Lassen JF. Drug-eluting versus bare metal stents in patients with st-segment-elevation myocardial infarction: eight-month follow-up in the Drug Elution and Distal Protection in Acute Myocardial Infarction (DEDICATION) trial. *Circulation*. 2008;118:1155-62.

213. Piscione F, Piccolo R, Cassese S, Galasso G, De Rosa R, D'Andrea C, Chiariello M. Effect of drug-eluting stents in patients with acute ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: a meta-analysis of randomised trials and an adjusted indirect comparison. *EuroIntervention*. 2010;5:853-60.

214. Hassan AK, Bergheanu SC, Stijnen T, van der Hoeven BL, Snoep JD, Plevier JW, Schalij MJ, Wouter Jukema J. Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. *European Heart Journal*. 2010;31:1172-80.

215. Alfonso F, Cruz A, Garcia J. Late stent malapposition: innocent phenomenon or major risk marker? European *Heart Journal* 2010;31:260; author reply 260-1.

216. Aoki J, Colombo A, Dudek D, Banning AP, Drzewiecki J, Zmudka K, Schiele F, Russell ME, Koglin J, Serruys PW. Peristent remodeling and neointimal suppression 2 years after polymer-based, paclitaxel-eluting stent implantation: insights from serial intravascular ultrasound analysis in the TAXUS II study. *Circulation*. 2005;112:3876-83.

217. Aoki J, Abizaid AC, Serruys PW, Ong AT, Boersma E, Sousa JE, Bruining N. Evaluation of four-year coronary artery response after sirolimus-eluting stent implantation using serial quantitative intravascular ultrasound and computer-assisted grayscale value analysis for plaque composition in event-free patients. *J Am Coll Cardiol*. 2005;46:1670-6.

218. Collet CA, Costa JR, Abizaid A, Chamie D, Staico R, Costa R, Siquera D, Obregon J, Feres F, Sousa A, Sousa JE. Assessing the temporal course of neointimal hyperplasia formation after different generations of drug-eluting stents. *JACC Cardiovasc Interv*. 2011;4:1067-74.

219. Raber L, Serruys PW. Late vascular response following drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2011;4:1075-8.

220. Park KW, Kim CH, Lee HY, Kang HJ, Koo BK, Oh BH, Park YB, Kim HS. Does "late catch-up" exist in drug-eluting stents: insights from a serial quantitative coronary angiography analysis of sirolimus versus paclitaxel-eluting stents. *Am Heart J*. 2010;159:446-453 e3.

221. Park DW, Hong MK, Mintz GS, Lee CW, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Weissman NJ, Park SW, Park SJ. Two-year follow-up of the quantitative angiographic and volumetric

intravascular ultrasound analysis after nonpolymeric paclitaxel-eluting stent implantation: late "catch-up" phenomenon from ASPECT Study. *J Am Coll Cardiol.* 2006;48:2432-9.

222. Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW, Sousa AG. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation.* 2005;111:2326-9.
223. Morice MC, Serruys PW, Barragan P, Bode C, Van Es GA, Stoll HP, Snead D, Mauri L, Cutlip DE, Sousa E. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. *J Am Coll Cardiol.* 2007;50:1299-304.
224. Weisz G, Leon MB, Holmes DR, Jr., Kereiakes DJ, Popma JJ, Teirstein PS, Cohen SA, Wang H, Cutlip DE, Moses JW. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) Trial. *J Am Coll Cardiol.* 2009;53:1488-97.
225. Silber S, Colombo A, Banning AP, Hauptmann K, Drzewiecki J, Grube E, Dudek D, Baim DS. Final 5-year results of the TAXUS II trial: a randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for de novo coronary artery lesions. *Circulation.* 2009;120:1498-504.
226. Mauri L, Massaro JM, Jiang S, Meredith I, Wijns W, Fajadet J, Kandzari DE, Leon MB, Cutlip DE, Thompson KP. Long-term clinical outcomes with zotarolimus-eluting versus bare-metal coronary stents. *JACC Cardiovasc Interv.* 2010;3:1240-9.
227. Caixeta A, Lansky AJ, Serruys PW, Hermiller JB, Ruygrok P, Onuma Y, Gordon P, Yaqub M, Miquel-Hebert K, Veldhof S, Sood P, Su X, Jonnavithula L, Sudhir K, Stone GW. Clinical follow-up 3 years after everolimus- and paclitaxel-eluting stents: a pooled analysis from the SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) and SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. *JACC Cardiovasc Interv.* 2010;3:1220-8.
228. Romagnoli E, Sangiorgi GM, Cosgrave J, Guillet E, Colombo A. Drug-Eluting Stenting: The Case for Post-Dilation. *J Am Coll Cardiol Intv.* 2008;1:22-31.
229. Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, van der Giessen W, Regar E. Optical coherence tomography patterns of stent restenosis. *Am Heart J.* 2009;158:284-93.
230. Spanos V, Stankovic G, Tobis J, Colombo A. The challenge of in-stent restenosis: insights from intravascular ultrasound. *Eur Heart J.* 2003;24:138-50.
231. Raber L, Serruys PW. Late vascular response following drug-eluting stent implantation. *JACC. Cardiovascular interventions.* 2011;4:1075-8.
232. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *Journal of the American College of Cardiology.* 2011;57:1314-22.

UNIVERSAL PCR CLASSIFICATION

Theme	Coronary interventions
Clinical presentation	ACS
	STEMI
	stable
Specific technique treatment	bare metal stent
	drug-eluting stent
	drug-eluting balloon
Complication	miscellaneous

PART VI

Understanding the impact of cardiac enzyme release on clinical outcomes

Chapter 6.1

Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting

Vranckx P, Farooq V, Garg S, Van Es GA, Silber S, Windecker S, Stone GW, Serruys PW

Heart. 2012;98(19):1424-30 (Impact Factor: 5.014)

Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting

Pascal Vranckx,[1,2] Vasim Farooq,[3] Scot Garg,[3] Gerrit-Anne Van Es,[2] Sigmund Silber,[4] Stephan Windecker,[5] Gregg W Stone,[6] Patrick W Serruys[3]

See Editorial, p 1397.

► Additional materials are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2012-302267).

[1]Department of Cardiac Intensive Care and Interventional Cardiology, Hartcentrum Hasselt, Hasselt, Belgium
[2]Cardialysis, Clinical Research Management and Core Laboratories, Rotterdam, The Netherlands
[3]Department of Interventional Cardiology, Thoraxcenter, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands
[4]Department of Cardiology, Kardiologische Praxis und Praxisklinik, Munich, Germany
[5]Department of Interventional Cardiology, Bern University Hospital, Bern, Switzerland
[6]Columbia University Medical Center, New-York Presbyterian Hospital and the Cardiovascular Research Foundation, New York, New York, USA

Correspondence to
Professor Patrick W Serruys, Ba583a, Thoraxcenter, Erasmus MC,'s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands; p.w.j.c.serruys@erasmusmc.nl

Accepted 19 June 2012
Published Online First 21 July 2012

ABSTRACT

Objective To assess the differential implications of cardiac biomarker type on peri-procedural myocardial infarction (PMI) reporting.

Setting The Resolute 'All-Comers' stent trial.

Interventions Blood samples for creatine kinase (CK), CK-myoband (CK-MB) mass or cardiac troponin (cTn) (optional) were collected before and at 6, 12 and 18 h after the assigned percutaneous coronary intervention or at discharge. PMIs were adjudicated using either the 2007 universal definition of MI (type-4a) or the extended historical definition of MI.

Patients 2121/2292 patients (92.5%) had an analysable dataset for either biomarker. 890/2121 patients (42%) presented with an acute coronary syndrome (ACS). 267/890 patients (30%) were within 24 h of an ST-segment elevation MI.

Main outcome measures Type-4a MI was diagnosed in 208/2121 patients (9.8%) when cTn was used (CK-MB mass if cTn not available), and in 93/2121 of patients (4.4%) when CK-MB mass was used (cTn if CK-MB mass not available). With the extended historical CK-based definition of MI, PMI was diagnosed in 65/2121 patients (3.1%). Adjudication of type-4a MI in patients with an ACS was problematic with $<10\%$ of the potential type-4a MI being confirmed as an event, as compared with approximately 95% in stable patients undergoing elective PCI. Type-4a MI was not associated with the subsequent hazard for cardiac mortality ($p=0.6$).

Conclusions The percentage of adjudicated PMI events is driven by the MI-definition criteria and biomarker type. Type-4a MI may not be a reliable component of the primary composite end point in coronary stent investigations which recruit patients with ACS.

Trial registration number http://www.ClinicalTrials.gov; Unique identifier: NCT00617084.

INTRODUCTION

In coronary stent investigations the reported incidence of peri-procedural myocardial infarction (PMI) may vary according to the metrics (ie, the definition of MI used for adjudication and the preferred cardiac biomarker) and the clinical presentation of the patient at the time of the index percutaneous coronary intervention (PCI).[1–4] The clinical and therapeutic implications of PMI remain the subject of continuing debate.[1–3]

Contemporary all-comers coronary stent trials reflect routine PCI practice.[5–9] These studies provide a unique opportunity to compare clinical outcomes among patients presenting with and without acute coronary syndromes (ACS). In the Resolute 'All-Comers' (Resolute-AC) trial we implemented two different sets of criteria to define PMI, and sampled three different cardiac biomarkers to detect myocardial injury—namely, creatine kinase (CK), CK-MB isoenzyme (mass) and cardiac-specific troponin (cTn).[5 6]

The purpose of this prespecified subanalysis of the Resolute-AC trial is to improve the understanding of the differential implications of cardiac biomarker type on PMI reporting and the associated death of patients.

METHODS

Study design

The design, detailed methods and end point definitions of the Resolute-AC trial (ClinicalTrials.gov number: NCT00617084) have been detailed in a previous publication.[5] In brief the Resolute-AC is a prospective, multicentre, drug-eluting stent (DES)-versus-DES trial. Between 30 April 2008 and 28 October 2008 17 institutions enrolled a total of 2292 patients with symptomatic coronary artery disease on an all-comers basis, including patients with stable angina, silent angina and ACS. The main outcome measure for this analysis was cardiac death at 2 years.

All outcome measures in Resolute-AC, including MI, were adjudicated by three members of an independent clinical end points committee (CEC) blinded to treatment assignment before locking the database. The institutional review boards of all participating institutions reviewed and approved the protocol of the Resolute-AC trial. All enrolled patients gave written informed consent.

Definitions of MI

MI was defined according to the 2007 universal definition, using as the preferred biomarker either cTn (CK-MB mass when cTn was not available) or CK-MB (cTn when CK-MB mass was not available; Academic Research Consortium (ARC) recommendation), and the extended, historical (WHO) CK-based definition.[10–12]

For the 2007 universal definition of MI, the joint European Society of Cardiology, American College

of Cardiology, American Heart Association and World Heart Foundation task force recently classified cardiac biomarker levels above ×3 the 99th centile of the upper reference limit (URL), as indicative of PMI following PCI. Furthermore, the replacement of CK-MB mass with cTn was recommended for the diagnosis of a PMI in all cases. Although the 2007 universal definition of MI was endorsed by the ARC, after long and intense discussions the ARC recommended that CK-MB mass should remain the preferred biomarker for the diagnosis of PMI.[10 11]

The historical (WHO) definition of MI was used to adjudicate PMI in previous (Medtronic) stent trials in elective patients with simple lesions. The historical definition was adapted ('extended') to better accommodate 'all-comers' populations by considering patients presenting with ACS.[12 13] A hierarchical approach was used for the adjudication of PMI based upon cardiac biomarker availability when an analysable cardiac biomarker dataset was missing (CK-MB mass when CK was not available, cTn when CK and CK-MB mass were not available) (online supplementary table 1). In order to be adjudicated as a trial end point, PMI had to be new, and therefore distinguishable (ie, new clinical signs or symptoms, angiographic flow-limiting complications) from the index clinical event. Dependent on the clinical situation at the time of the index procedure, PMI could be adjudicated considering either (new) symptoms suggestive of ischaemia/infarction (>20 min), ECG changes, appropriate cardiac biomarker data or pathological evidence of MI, or a mixture of these factors.

Ascertainment of peri-procedural myocardial infarction

Blood samples for cardiac biomarkers—CK and CK-MB mass—were issued according to protocol (cTn was optional) within 6 h before the index-PCI procedure, and at 6, 12 and 18 h after the assigned study procedure or at hospital discharge, whichever came first. Additional samples up to 48 h after the index-PCI procedure were also considered in this analysis. An analysable cardiac biomarker set consisted of a baseline value, and at least one other measurement of the same biomarker in the 48 h period after the index-PCI procedure.

Cardiac biomarkers were analysed at local site laboratories, yielding a mixture of biomarker tests and upper limits of normal (supplementary table 2, supplementary appendix). The limitations of the analytical performance of commercial assays for biomarkers were considered. A coefficient of variation at the MI decision limit (99th centile of a healthy reference population) was expected at <10% for CK-MB mass and cTn assays used during this trial.[14–17]

Current analysis

For the purpose of this analysis the Resolute-AC study population was assessed as a cohort. All patients with a reference biomarker available before the index-PCI (baseline), and one or more corresponding samples in the same biomarker family (CPK, CK-MB, cTn) within 48 h after the index-PCI, were suitable for analysis. Seven (7.1) per cent of patients (163/2290) were excluded from the analysis, because either no baseline (n=81, 3.5%) or no samples within 48 h after the index-PCI (n=82, 3.5%) were taken. Six patients had no baseline and no post-PCI biomarker of the same family. Two patients in the study underwent coronary bypass graft surgery within 48 h of the index-PCI procedure and were excluded from this analysis.

A comparison of the rates of PMI using the 2007 universal definition, measuring either cTn (joint task force recommendation) or CK-MB mass (ARC recommendation) as the preferred biomarker, with the extended historical definition, in the adjudication of PMI was undertaken. Subgroup analyses were performed for patients with (n=890, 42.0%) or without ACS (n=1231, 58.0%). Patients in this analysis were categorised as having ACS at the time of the index-PCI procedure if they had either a biomarker above the URL before the index-PCI procedure and/or clinical signs and/or symptoms (>20 min) consistent with continuing myocardial ischaemia as declared by the investigator. The analysis was repeated in the cohort of patients who had both an analysable cTn and CK-MB dataset (935, n=44.1%).

We assessed the 2-year cardiac mortality in patients with or without PMI according to either the 2007 universal definition of MI using either cTn or CK-MB as preferred biomarker (as outlined earlier) or the extended historical definition of MI.

Statistics

All statistical analyses were exploratory. The counts of PMI are summarised and tabulated according to frequency. Differences in outcomes between patients with and without PMI are compared by Fisher's exact test or χ^2 testing. For univariate analyses, cumulative event rates of cardiac mortality for the different types of PMI at up to 2 years were estimated with Kaplan—Meier analyses and Cox proportional HRs with 95% CIs. Multivariable analyses evaluating the association between PMI and mortality were performed by Cox proportional hazards regression. Multivariable models considered the following baseline covariates: age, sex and diabetes mellitus. Statistical analyses were performed with the use of SAS software, version 9.2 by a dedicated independent statistician. A two-sided p value <0.05 was considered to indicate statistical significance.

RESULTS

Two thousand one hundred and twenty-one of 2290 (92.5%) patients from the Resolute-AC were suitable for analysis. Baseline demographics and clinical characteristics are listed in supplementary table 3. Over one-fifth of patients (n=452, 21.3%) presented with an acute MI within 24 h of symptom onset, including 267 patients (59.1%) with an ST elevation MI. The mean SYNTAX Score was 14.7±9.2.

Availability of biomarkers of myocardial necrosis before and within 48 h after the index-PCI

Figure 1A depicts the number of patients with available cardiac biomarker of myocardial injury (BMI) sample values at baseline and one or more sample values within 48 h ('analysable cardiac biomarker dataset', n=2121). The Venn diagrams illustrate the availability of one BMI (CK or CK-MB mass or cTn), two BMI (CK and CK-MB mass or CK and cTn or CK-MB mass and cTn) or all three BMI (CK and CK-MB mass and cTn). Although cTn sampling was an optional investigation in the Resolute-AC trial, an analysable dataset for cTn was available in 55.3% (1173/2121) patients. In addition 44.1% (935/2121) patients had an analysable dataset for both cTn and CK-MB.

Figure 1B depicts all analysable cardiac biomarker sample values datasets (n=2121) in all patients in the analysis, stable patients and patients presenting with ACS with at least one cardiac biomarker sample value above the designated threshold for defining a PMI. Notably, 19.0% (178/935) (figure 1A) of patients with an analysable biomarker dataset available for both cTn and CK-MB mass had a peak cTn >3 times 99th centile URL, but a peak CK-MB ≤3 times 99th centile URL. Figure 1C is limited to patients with an ACS at the time of the index-PCI (n=890). Figure 1D is limited to stable patients having an elective PCI (n=1231).

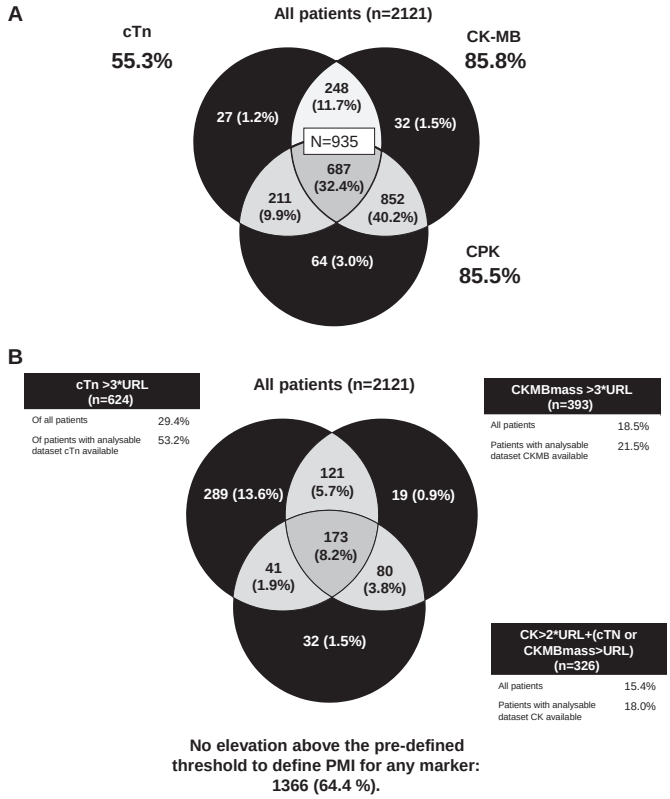


Figure 1 (A) Patients with an analysable cardiac biomarker sets with both a pre- (baseline) and one or more post-PCI biomarker sample value(s) of the same family. (B–D) Patients, either with or without ongoing MI, with a baseline cardiac biomarker sample value (either for cTn, CK-MB mass, CK) and an increase in the corresponding 6–48 h post-PCI biomarker sample value above the predefined threshold to qualify as a suspect PMI, before final PMI-event adjudication by the clinical end points committee (figure 2B). For patients presenting with an acute coronary syndrome a 20% increase in cardiac biomarker sample value was taken into account (see also figure 1, flowchart). Patients with suspected ongoing MI (figure 2C) at the time of the index-PCI and stable patients undergoing elective PCI (figure 2D) are represented separately. CK-MB, creatine kinase-myoband; CPK, creatine kinase; cTn, cardiac troponin; PMI, peri-procedural myocardial infarction; URL, upper reference limit upper reference limit.

Diagnosis of PMI based on selection of cardiac biomarkers

Elevated biomarkers of myocardial necrosis before and within 48 h after the index-PCI

The number of stable patients undergoing elective PCI with cardiac biomarker elevations above the designated threshold required to define PMI was four times higher when measuring cTn than when measuring CK (161 vs 46 patients), and double when measuring CK-MB mass rather than CK (68 vs 46 patients). Conversely, the number of patients with an ACS at the time of the index-PCI with cardiac biomarker elevations above the designated threshold required to define PMI was only 1.5 times higher when measuring cTn compared with CK (47 vs 19 patients) (table 1).

PMI adjudicated by the CEC

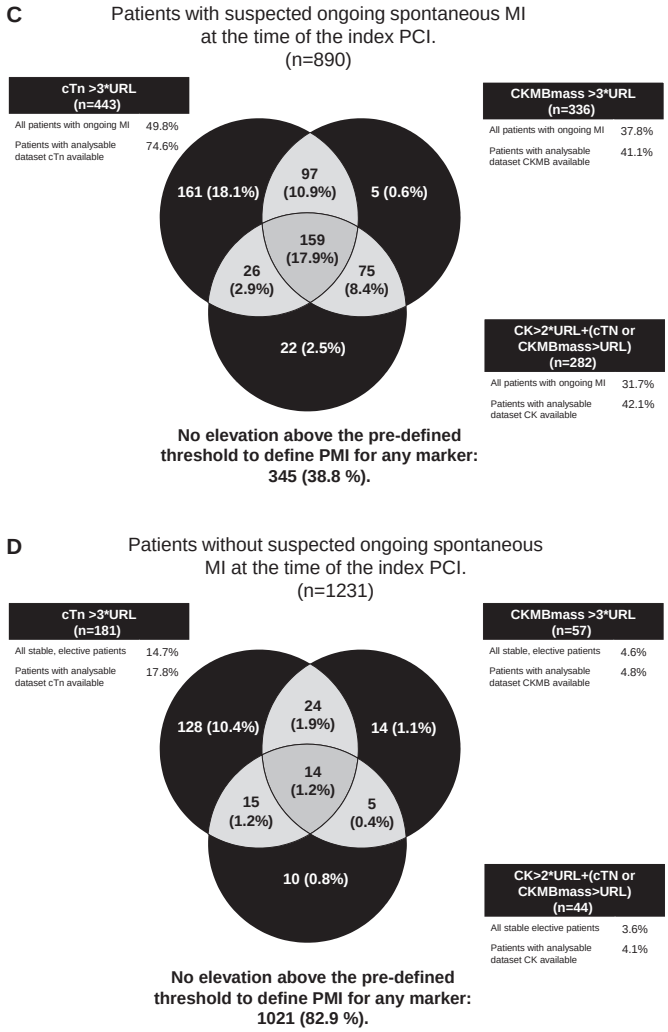
For the 2007 universal definition of MI, type-4a MI was adjudicated by the CEC in 208/2121 patients (9.8%) when cTn was used (CK-MB mass if cTn not available), and in 93/2121 of patients (4.4%) when CK-MB mass was used (cTn if CK-MB mass not available, ARC recommendation). With the extended historical CK-based definition of MI, PMI was adjudicated in 65/2121 patients (3.1%).

The percentage of the adjudicated PMI over the suspected events based on cardiac biomarker elevations ('event-to-trigger percentages') was predominantly driven by the clinical presentation at the time of the index-PCI, with this percentage being nearly 10-fold higher for stable patients undergoing elective PCI than for patients presenting with an ACS. Adjudication of type-4a MI in patients with a suspected ongoing MI was problematic with <10% of the potential type-4a MI being confirmed as an event by the CEC, as opposed to approximately 95% in stable patients undergoing elective PCI.

PMI in patients with an analysable dataset for both CK-MB mass and cTn

The trends outlined above are similar for the patient subpopulation with analysable cardiac biomarker datasets for both CK-MB and cTn (supplementary table 4). In the subset of patients, in whom an analysable dataset for both cTn and CK-MB mass was available (n=935), myocardial injury—as defined by a cardiac biomarker sample value >99th centile URL—was

Figure 1 Continued



detected in 54.0% (505/935) measuring cTn and in 49.7% (465/935) measuring CK-MB mass. Type-4a MI was diagnosed in 11.0% (103/935) patients and 5.2% (49/935) patients, respectively.

Associated 2-year cardiac mortality

During the 2-year follow-up 54 patients in Resolute-AC died owing to cardiac causes, 51 of them are in the 2121 cohort. PMI versus no PMI adjudicated by the extended historical definition of MI was associated with 2-year crude cardiac mortality (HR=3.5; 95% CI 1.4 to 8.9; p=0.007), but not type-4a when cTn was used (HR=1.2; 95% CI 0.5 to 2.9; p=0.65) or when CK-MB (HR=1.4; 95% CI 0.4 to 4.4; p=0.61) was used to adjudicate MI (table 2, figure 2). After adjustment for baseline covariates, PMI by the extended historical definition of MI, analysed as dichotomous variable, remained a significant correlate of 2-year mortality (HR=3.7, 95% CI 1.4 to 9.2, p=0.0065).

DISCUSSION

The Resolute-AC study design provided a unique opportunity to study the implications of the use of different biomarkers for the detection of myocardial injury in patients undergoing PCI, and

Table 1 Peri-procedural myocardial infarction (PMI) adjudication upon cardiac biomarkers guided either by the 2007 universal (troponin based)-myocardial infarction (MI) definition or the WHO (creatine kinase (CK)-based)-MI definition in counts and percentages (all patients; N=2121)

	2007 Universal-MI definition		WHO-MI definition extended for AC trials
	Primary marker cTn, (CK-MB mass if cTn unavailable)*	(ARC recommendation) Primary marker CK-MB mass, (cTn if CK-MB mass unavailable)*	Primary CK (with confirming cTn or CK-MB), (CK-MB mass if CK unavailable, cTn if CK and CK-MB mass unavailable)*
Stable angina (N=1231)			
Adjudicated PMI/trigger† to PMI	161/190 (84.7)	68/75 (90.7)	46/52 (88.5)
Investigator reported	73/84 (86.9)	35/35 (100.0)	30/31 (96.8)
ACS (N=890)			
Adjudicated PMI/trigger† to PMI	47/519 (9.1)	25/366 (6.8)	19/354 (5.4)
Investigator reported	12/20 (60.0)	7/12 (58.3)	6/10 (60.0)

*In 1533/2121 (72%), 1975/2121 (93%) and 1983/2121 (93.4%) cases the preferred biomarker, respectively cardiac specific troponin (cTn), creatine kinase (CK) and CK-myoband (MB), was available for analysis.
†Trigger is defined as a suspected PMI based upon cardiac biomarker sample value elevation and/or clinical signs or symptoms consistent with myocardial ischaemia.
ACS, acute coronary syndrome; ARC, Academic Research Consortium.

the adjudication of unreported PMI among patients presenting with or without an ACS at the time of the index procedure. The main conclusions of this analysis are:

1. PMI constituted the majority of all MIs in the Resolute-AC PCI trial. However, the PMI event count varied considerably according to the choice of cardiac biomarker and/or the criteria used for adjudication. Comparing the 2007 universal definition of MI and the extended historical (WHO) CK-based definition of MI, using cTn resulted in a tripling of the rate of PMI. Applying the 2007 universal definition of MI with cTn resulted in a doubling of the rate of PMI compared with CK-MB mass.
2. The PMI 'event-to-trigger' percentage was dependent on the clinical presentation at the time of the index-PCI procedure, rising from <9% in patients presenting with ACS at the time of the index-PCI procedure, to >80% in patients undergoing elective PCI for stable symptomatic coronary artery disease regardless of which biomarker one uses.
3. The frequency of undetected MI with the 2007 universal definition of MI was approximately five times higher than the extended historical (WHO) CK-based definition of MI, mainly reflecting the greater sensitivity of cTn to detect myocardial injury (with subsequent investigator under-reporting).
4. More than 50% of adjudicated PMI events in patients undergoing elective PCI for stable symptomatic coronary artery disease were unreported and only detected through analysis of serial cardiac biomarker sample values.
5. In Resolute-AC, type-4a MI with the actual proposed biomarker thresholds and regardless of the biomarker used, was not associated with subsequent cardiac mortality at 2 years.

This analysis represents the largest prospective comparison of the three most commonly used serum biomarkers for detection of PMI. These findings are likely to be representative of contemporary PCI practice, as patient-, lesion- and procedure-related risk factors are all previously established predictors of PMI,[3] and the baseline and angiographic characteristics of Resolute-AC have been reported to be consistent with other recently reported 'real-world' coronary stent investigations.[5–8 18] The stable patient subset undergoing elective PCI to treat stable coronary lesions matched those recruited in historical stent trials.

The diagnosis of acute, evolving or recent MI requires, in the absence of pathological confirmation, a typical rise and/or fall of biomarkers of myocardial necrosis in conjunction with clinical evidence of myocardial ischaemia.[10] A PMI is defined by a typical new cardiac biomarker elevation above a predefined threshold occurring during the immediate peri-procedural period (<48 h), and an established causality to the index study procedure. This causality may or may not be declared by the investigator (eg, coronary artery dissections, distal plaque embolisation). With ACS the PMI must be identified as a new event, clearly distinct from the index clinical event in the same predefined peri-procedural period of 48 h. In the Resolute-AC trial, most suspected PMIs were reported by the investigators at clinical sites. Yet not all cardiac biomarker elevations above the predefined threshold ('triggers') will identify new events.

The adjudication of PMI in an 'All-Comers' trial resembling everyday PCI practice may be characterised by a signal-to-noise problem. For this analysis we disentangled two specific clinical situations—patients with or without an ACS at the time of the index-PCI. The adjudication of type-4a MI, implementing the 2007 universal definition of MI, in patients with acute presentations (ie, ACS) at the time of the index-PCI is problematic, and exacerbated when measuring a sensitive biomarker such as cTn.[19] Unless there is a clear indication that the cardiac biomarker sample values were falling after the index event and then rising again (above the predefined thresholds) after the index-PCI procedure, there would be insufficient biomarker data

Table 2 Two-year cardiac mortality according to the occurrence of procedure-related MI (different definitions) or not

Primary biomarker	KM estimate, PMI* (%)	KM estimate, no PMI* (%)	Log rank, p value	HR and 95% CI†
cTn	2.90	2.43	0.649	1.2 (0.5 to 2.9)
CK-MB	3.25	2.44	0.606	1.4 (0.4 to 4.4)
CK	7.74	2.31	0.007	3.5 (1.4 to 8.9)

*Percentage failure based on Kaplan–Meier (KM) estimates.
†Cox Model, assuming proportional Hazards.
CK-MB, creatine kinase-myoband; cTn, cardiac troponin; KM, Kaplan–Meier; PMI peri-procedural myocardial infarction.

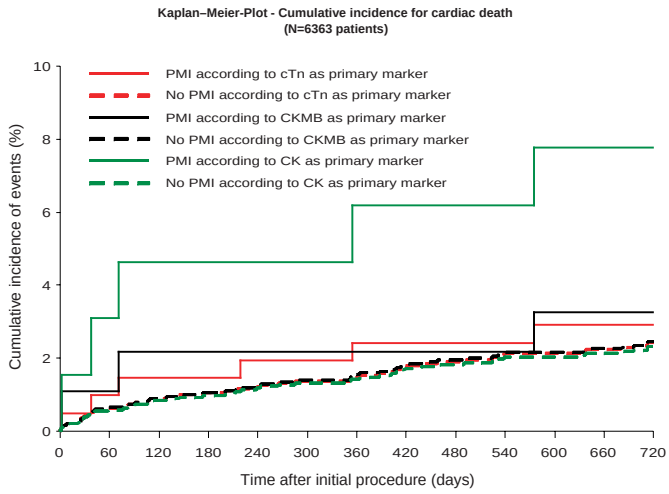


Figure 2 Cumulative cardiac mortality according to PMI up to 2-years. Shown are the Kaplan—Meier curves for cardiac mortality after the occurrence of PMI according to either the extended historical definition of MI (green) and the 2007 universal definition of MI measuring cTn (CK-MB if cTn is not available) (red) or CK-MB (cTn if CK-MB is not available, Academic Research Consortium recommendation) (blue). CK-MB, creatine kinase-myoband; cTn, cardiac troponin; PMI, peri-procedural myocardial infarction.

to adjudicate a PMI.[19 20] The critical challenge for the members of the CEC is to distinguish whether a new MI was induced by the index-PCI procedure (ie, additional component of an already injured myocardial region, new procedural flow-limiting complications), or if the cardiac biomarker release was still the tail end of the continuing initial myocardial insult.[1 19]

In Resolute-AC, while the event-to-(biomarker) trigger ratio was as low as 5% for the 2007 universal definition of MI, these events proved to be numerically important and contributed to half of the unreported PMIs (based on serial cardiac biomarker sample value analyses only) (table 1). It should be emphasised that including clinical information from the investigator, such as evidence of new myocardial ischaemia and coronary artery flow-limiting complications, resulted in a 10 times higher event-to-trigger percentage, and may improve the signal-to-noise ratio (table 1). Conversely, in stable patients undergoing uncomplicated contemporary elective PCI, >50% of PMIs were detected upon review of serial cardiac biomarker sample values alone, with >80% of all suspected type-4a MI adjudicated as an event. On the basis of the traditional concept of PMI described here, considering a high 'trigger' and 'trigger-to-event ratio' in stable patients undergoing elective PCI, the missing biomarker data may affect outcome reporting and should be considered while interpreting trial results.

The extent of myocardial injury following PCI, as detected by release of CK and/or CK-MB mass, has been correlated with late clinical outcomes in several studies.[21–27] Despite these findings, the threshold level of cTn associated with a prognostic significance remains elusive.[1 10] This analysis adds to the evidence that type-4a MIs, as a class in real-world patients with the current set biomarker thresholds, are not of significant prognostic importance after PCI using contemporary management strategies. Cardiac biomarker elevation following PCI should therefore always be interpreted in relation to the clinical presentation at the time of the index procedure.

The lack of association between a CK-MB mass elevation more than three times the diagnostic level based on the 2007 universal definition of MI, and 1-year mortality among patients with moderate to high risk ACS undergoing PCI, was also reported in the ACUITY trial.[23] Conversely, in the EVENT (Evaluation of drug eluting stents and ischaemic events) registry, consisting of almost 5000 patients undergoing elective PCI, the same degree of cardiac enzyme elevation independently predicted 1-year mortality. In addition, the EVENT investigators reported similar hazards for negative clinical outcomes related to cTn, but only when 20 times the upper limit of normal was used as decision limit.[24] Patients in the subanalysis in the EVENT registry were, however, not separated on the detection of a baseline cTn level ≥99th centile of the URL.

In patients with ACS it is undisputed that an increased cTn (baseline) is a marker of patients at increased risk.[27] Furthermore, it appears that almost all the prognostic information is contained in the baseline cardiac enzyme value, and that this may be a reflection of the underlying coronary atherosclerotic burden and/or plaque instability. At what level, if any, additional cTn elevation following PCI contributes to the hazard for 1-year negative outcomes remains unanswered.

This issue(s) and the stark variations in reported rates of PMI call into question the inclusion of PMI as a component of the primary composite end points of contemporary coronary device trials, particularly when recruiting patients presenting with ACS.

Limitations

This study has several limitations. First, in 2008 cTn was not yet widely implemented as cardiac biomarker to detect myocardial injury, thereby according to protocol cTn sampling was optional in Resolute-AC. Despite this limitation, up to 54% of patients had an analysable cTn dataset and the major conclusions of the study were unchanged when a subset of patients with both cTn and CK-MB were sampled (supplementary table 3). While recent advances in assay technology have led to more sensitive and precise cTn assays, the issues raised in this manuscript towards trial conduct and data interpretation remain, and may even be accentuated.[28]

Our results did not include the direct metrics (eg, MRI) of the extent of myocardial injury. The findings of the study do, however, suggest that most MIs were small or moderate. We cannot exclude the possibility of a slight variation in the results if a central core laboratory had undertaken the analyses of the cardiac biomarkers.[29] The 99th centile of the reference medical decision cut-off point for the cTn assays was determined in each local laboratory by internal studies with the specific assay that is used in clinical practice. The previous limitations do, however, cause no concern in interpreting the major conclusions of this analysis.

CONCLUSIONS

As currently defined, type-4a MI following PCI is not a valid outcome measure in contemporary outcome trials. Meaningful thresholds for individual cardiac biomarkers should be identified based on large outcome trials. Adjudication of PMI in patients with an ACS at the time of the index-PCI remains problematic.

Acknowledgements We thank Yvonne Teunissen and Peter Paul Kint for their support towards the completion of this analysis. Tessa A M Rademaker-Havinga was responsible for the preparation of the dataset and statistical programming and analysis. We thank all staff of the participating hospitals for their care of the study patients.

Contributors PV, PWS: Study concept and design, data analysis and interpretation, manuscript writing. VF, SG, G-AvE, GWS: Critical revision of the intellectual content of the manuscript and final approval of the version to be published. SS: Data collection. Critical revision of the intellectual content of the manuscript and final approval of the version to be published. SW: Study concept and design, data collection. Critical revision of the intellectual content of the manuscript and final approval of the version to be published.

Funding Funding for Resolute-AC and its analysis was provided by grants from Medtronic Cardiovascular, Santa Rosa, California, USA.

Competing interests GWS reports consulting fees from Abbott Vascular, Boston Scientific and Medtronic; SW reports grants support through his institution from Abbott Vascular, Boston Scientific, Biosensors, Cordis and Medtronic. No other potential conflict of interest relevant to this article was reported.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the institutional review board of participating sites.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement I am unable to share data beyond the ones used in this analysis owing to data sharing agreements in place with the sponsor and Cardialysis. Data are stored in a central database (Med Net Solutions INC, Minnetonka, USA) and maintained by a contract research organisation (Cardialysis BV, Rotterdam, The Netherlands).

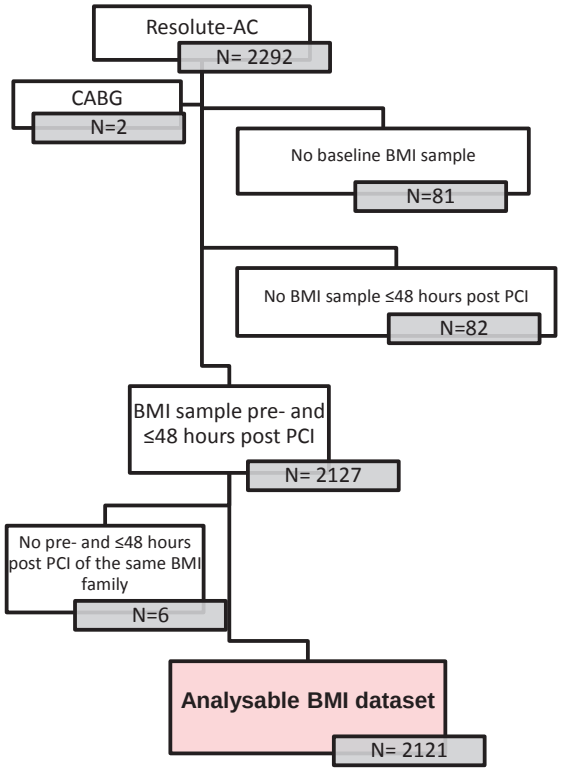
REFERENCES

1. **Prasad A,** Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med* 2011;**364**:453—64.
2. **Cuculi F,** Lim CC, Banning AP. Periprocedural myocardial injury during elective percutaneous coronary intervention: is it important and how can it be prevented? *Heart* 2010;**96**:736—40.
3. **Herrmann J.** Peri-procedural myocardial injury: 2005 update. *Eur Heart J* 2005;**26**:2493—519.
4. **Morrow DA,** Cannon CP, Jesse RL, *et al*. National Academy of clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation* 2007;**115**:e356—75.
5. **Serruys PW,** Silber S, Garg S, *et al*. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;**363**:123—35.
6. **Silber S,** Windecker S, Vranckx P, *et al*; RESOLUTE All Comers Investigators. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. *Lancet* 2011;**377**:1241—7.
7. **Kedhi E,** Joesoef KS, McFadden E, *et al*. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 2010;**375**:201—9.
8. **Windecker S,** Serruys PW, Wandel S, *et al*. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;**372**:1163—73.
9. **de Boer SP,** Lenzen MJ, Oemrawsingh RM, *et al*. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011;**32**:2161—7.
10. **Thygesen K,** Alpert JS, White HD, *et al*; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007;**28**:2525—38.
11. **Cutlip DE,** Windecker S, Mehran R, *et al*. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344—51.
12. **Vranckx P,** Cutlip DE, Mehran R, *et al*. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. *EuroIntervention* 2010;**5**:871—4.
13. **Mauri L,** Hsieh W, Massaro JM, *et al*. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;**356**:1020—9.
14. **Agewall S,** Giannitsis E, Jernberg T, *et al*. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J* 2011;**32**:404—11.
15. **Westgard J,** Klee G. Quality management. In: Burtis CA, Ashwood ER, Bruns DE, eds. *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*. 4th edn. St Louis, MO: Elsevier Saunders, 2006:498—9.
16. **Panteghini M,** Apple FS, Christenson RH, *et al*. Use of biochemical markers in acute coronary syndromes. IFCC Scientific Division, Committee on Standardization of Markers of Cardiac Damage. International Federation of Clinical Chemistry. *Clin Chem Lab Med* 1999;**37**:687—93.
17. **Panteghini M,** Gerhardt W, Apple FS, *et al*. Quality specifications for cardiac troponin assays. *Clin Chem Lab Med* 2001;**39**:175—9.
18. **Stefanini GG,** Serruys PW, Silber S, *et al*. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). *J Am Coll Cardiol* 2011;**57**:2221—32.
19. **Jaffe AS,** Apple FS, Lindahl B, *et al*. Why all the struggle about CK-MB and PCI? *Eur Heart J* 2012;**33**:1046—8.
20. **Babu GG,** Walker JM, Yellon DM, *et al*. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. *Eur Heart J* 2011;**32**:396—403.
21. **Akkerhuis KM,** Alexander JH, Tardiff BE, *et al*. Minor myocardial damage and prognosis: are spontaneous and percutaneous coronary intervention-related events different? *Circulation* 2002;**105**:554—6.
22. **Stone GW,** Mehran R, Dangas G, *et al*. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation* 2001;**104**:642—7.
23. **Prasad A,** Gersh BJ, Bertrand ME, *et al*. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial *J Am Coll Cardiol* 2009;**54**:477—86.
24. **Novack V,** Pencina M, Cohen DJ, *et al*. Troponin criteria for myocardial infarction after percutaneous coronary intervention. *Arch Intern Med* 2012;**172**:502—8.
25. **Kini AS,** Lee P, Marmur JD, *et al*. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. *Am J Cardiol* 2004;**93**:18—23.
26. **Natarajan MK,** Kreatsoulas C, Velianou JL, *et al*. Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol* 2004;**93**:750—3.
27. **Scirica BM,** Morrow DA. Troponins in acute coronary syndromes. *Prog Cardiovasc Dis* 2004;**47**:177—88.
28. **Twerenbold R,** Jaffe A, Reichlin T, *et al*. High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J* 2012;**33**:579—86.
29. **Apple FS,** Jesse RL, Newby LK, *et al*. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical issues for biochemical markers of acute coronary syndromes. *Circulation* 2007;**115**:e352—5.

SUPPLEMENTARY APPENDIX:

SUPPLEMENTAL FIGURE 1: PATIENTS INCLUDED IN THIS ANALYSIS.

Patient flow diagram showing patients from the total Resolute-AC study cohort and reasons for exclusion from this analysis. BMI indicates biomarker of myocardial injury, CABG indicates coronary artery bypass grafting, MI indicates myocardial infarction,


Resolute-AC
N= 2292
CABG
N=2
No baseline BMI sample
N=81
No BMI sample ≤48 hours post PCI
N=82
BMI sample pre- and ≤48 hours post PCI
N= 2127
No pre- and ≤48 hours post PCI of the same BMI family
N=6
Analysable BMI dataset
N= 2121

SUPPLEMENTAL TABLE 1: CRITERIA FOR PERI-PROCEDURAL MYOCARDIAL INFARCTION FOLLOWING PERCUTANEOUS CORONARY INTERVENTION.

	2007 UNIVERSAL DEFINITION OF MI	EXTENDED HISTORICAL DEFINITION OF MI
STABLE PATIENTS UNDERGOING AN ELECTIVE PCI		
	cTn ($CKMB_{mass}$,ARC recommendation) >3*URL	New pathologic q waves in ≥ 2 contiguous ECG leads and - Any $CKMB_{mass}$ > 1*URL or - In the absence of $CKMB_{mass}$: cTn >1*URL **or** - In the absence of $CKMB_{mass}$ and cTn: CK>1*URL **or** - In the absence of $CKMB_{mass}$, cTn and CK: CEC decision upon clinical scenario Appropriate cardiac enzyme data: - CK ≥2*URL confirmed by: ▪ $CKMB_{mass}$ **or** ▪ In the absence of $CKMB_{mass}$: cTn >1*URL **or** ▪ In the absence of $CKMB_{mass}$, cTn : CEC decision upon clinical scenario **OR** - In the absence of CK: $CKMB_{mass}$ >3*URL **OR** - In the absence of CK and $CKMB_{mass}$: cTn >3*URL
SIGNS AND/OR SYMPTOMS CONSISTENT WITH MYOCARDIAL ISCHEMIA OR ELEVATED CARDIAC BIOMARKERS OF MYOCARDIAL INJURY		
BIOMARKERS OF MYOCARDIAL INJURY HAVE NOT YET PEAKED	If biomarkers increasing or peak not reached, then insufficient data to diagnose MI-extension/new myocardial infarction.	Recurrent signs and/or symptoms >20minutes consistent with myocardial infarction And Appropriate cardiac enzyme data: - A rise of CK within 24hours of the index event >2*URL (confirmed by either $CKMB_{mass}$ or cTn>1*URL) and ≥50% above the previous level **or** - In the absence of CK: a post PCI rise of $CKMB_{mass}$ within 24 hours of the index event >3*URL and and ≥50% above the previous level **or** - In the absence of CK and $CKMB_{mass}$: a post PCI rise in cTn within 24 hours of the index event <3*URL and and ≥50% above the previous level.
BIOMARKERS OF MYOCARDIAL INJURY HAVE PEAKED, BUT DID NOT YET RETURNED <1*URL	Stable or decreasing cTn ($CKMB_{mass}$,ARC recommendation) values on 2 consecutive samples **AND** 20% increase 3h – 6h after second sample.	Appropriate cardiac enzyme data: - A rise of CK within 24hours of the index event >2*URL (confirmed by either $CKMB_{mass}$ or cTn>1*URL) and ≥50% above the previous level **or** - In the absence of CK: a post PCI rise of $CKMB_{mass}$ within 24 hours of the index event >3*URL and and ≥50% above the previous level **or** - In the absence of CK and $CKMB_{mass}$: a post PCI rise in cTn within 24 hours of the index event <3*URL and and ≥50% above

		the previous level.

PCI denotes percutaneous coronary intervention, cTn denotes cardiac specific troponin, URL denotes the upper reference of normal, CEC denotes clinical event committee, ARC denotes academic research consortium.

SUPPLEMENTAL TABLE 2 : Resolute All-comers , cardiac troponin immune assays used

Site	cTn isoform	99th percentile of a normal reference population ng/ml (URL = upper reference limit).*
10100	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
10200	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
10300	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
10301	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
10500	I Beckman Access	**0.04**
11000	I Bayer Centaur	**0.16**
11001	I Bayer Centaur	**0.16**
12000	I Bayer Centaur	**0.16**
12001	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
12002	I Dade-Behring Dimension RxL	**0.03**
12003	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
13000	I Beckman Access	**0.04**
14001	I Diagnostic Products Corporation, Immulite 2000	**0.2**
15000	I Beckman Access	**0.04**
15900	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
40600	cTn T, Roche Diagnostics, Elecsys 2010 platform, fourth generation	**0.01**
41000	**none**	

Which cTn isoform (troponin T or I) were used was determined by local practice at each study site. The 99th percentile of a reference decision-limit (medical decision cutoff) for cTn assays was determined for each local laboratory as per guidelines. [25]

SUPPLEMENTARY TABLE 3. BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS (PER PATIENT)

Patient Characteristics	Total	Ongoing MI	No Ongoing MI
n	2121	890	1231
Age [yrs]	64.3±10.8	62.9±11.6	65.3±10.1
Male	76.6% (1625/2121)	78.2% (696/890)	75.5% (929/1231)
Diabetes Mellitus	23.3% (494/2121)	21.3% (190/890)	24.7% (304/1231)
Hypertension	71.9% (1524/2121)	63.8% (568/890)	77.7% (956/1231)
Current smoker	26.4% (559/2121)	36.1% (321/890)	19.3% (238/1231)
Hyperlipidemia	65.9% (1398/2121)	54.8% (488/890)	73.9% (910/1231)
Prior MI	29.9% (621/2075)	25.5% (224/877)	33.1% (397/1198)
Prior PCI	32.2% (684/2121)	21.5% (191/890)	40.0% (493/1231)
Prior CABG	9.6% (204/2121)	6.2% (55/890)	12.1% (149/1231)
Revascularization for Angina or MI	88.1% (1869/2121)	95.5% (850/890)	82.8% (1019/1231)
Stable Angina	35.1% (744/2121)	10.6% (94/890)	52.8% (650/1231)
Unstable Angina	19.2% (408/2121)	4.4% (39/890)	30.0% (369/1231)
MI (pre-procedure <72 hours)	33.8% (717/2121)	80.6% (717/890)	0.0% (0/1231)
Acute MI (within 24 hours)	21.3% (452/2121)	50.8% (452/890)	0.0% (0/1231)
ST elevation (STEMI)	12.6% (267/2121)	30.0% (267/890)	0.0% (0/1231)
Non ST elevation (NSTEMI)	8.7% (185/2121)	20.8% (185/890)	0.0% (0/1231)
Left Ventricular Ejection Fraction Mean ± SD	55.8±11.7	54.2±11.6	56.8±11.7
Multi vessel	25.4% (538/2121)	28.0% (249/890)	23.5% (289/1231)
Small Vessel (<=2.75 mm)	67.3% (1210/1798)	66.4% (452/681)	67.9% (758/1117)
Number of lesions treated			
One	64.7% (1371/2119)	63.1% (562/890)	65.8% (809/1229)
Two	26.5% (561/2119)	26.2% (233/890)	26.7% (328/1229)
Three	6.5% (137/2119)	8.0% (71/890)	5.4% (66/1229)
>= Four	2.4% (50/2119)	2.7% (24/890)	2.1% (26/1229)
Long Lesion (>18mm)	19.9% (358/1798)	22.9% (156/681)	18.1% (202/1117)
Number of lesions treated Mean ± SD	1.5±0.7	1.5±0.8	1.4±0.7
Off label	66.2% (1404/2121)	86.2% (767/890)	51.7% (637/1231)
Mean SYNTAX SCORE Mean ± SD			
n	1888	828	1060
Mean ± SD	14.7±9.2	16.0±9.3	13.7±8.9
(Min, Max)	(0 - 55)	(0 - 55)	(0 - 49)

SUPPLEMENTAL TABLE 4: PATIENTS WITH ANALYSABLE CARDIAC BIOMARKER DATA SET FOR CARDIAC SPECIFIC TROPONIN (CTN)AND CRETANINE KINASE-MYOBAND (CKMB) (PRE AND POST PROCEDURE CTN AND CK-MB AVAILABLE, N=935).

	2007 Universal-MI- definition						WHO-MI-definition extended for AC-trials		
	Primary marker cTn, (CK-MB mass if cTn unavailable)			(ARC- recommendation) Primary marker CK-MB mass, (cTn if CK-MB mass unavailable)			Primary CK (with confirming trop or CKMB), (CK-MB mass if CK unavailable, cTn if CK and CK-MB mass unavailable)		
STABLE ANGINA (N=487)									
Adjudicated PMI/trigger** to PMI	69/	73	(94.5)	34/	36	(94.4)	23/	26	(88.5)
Investigator reported	41/	42	(97.6)	23/	23	(100)	13/	14	(92.9)
ACS (N=448)									
Adjudicated PMI/trigger** to PMI	34/	293	(11.6)	16/	180	(8.8)	10/	177	(5.6)
Investigator reported	8/	12	(66.7)	5/	8	(62.5)	3/	5	(60.0)

**Trigger is defined as a suspected PMI based upon cardiac biomarker sample elevation and/or clinical signs or symptoms consistent with myocardial ischaemia

Chapter 6.2

Incidence, Correlates, and Significance of Abnormal Cardiac Enzyme Rises in Patients Treated With Surgical or Percutaneous Based Revascularisation: A Substudy from the Synergy Between PCI with TAXUS Express and Cardiac Surgery (SYNTAX) Trial

Farooq V, Serruys PW, Vranckx P, Girasis C, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, Bourantas CV, de Vries, T, Van Es GA, Dawkins KD, Mohr FW, James S, Ståhle E

Int J Cardiol. 2013;168(6):5287-92 (Impact Factor: 5.509)

Incidence, correlates, and significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous based revascularisation☆,☆☆
A substudy from the Synergy between Percutaneous Coronary Interventions with Taxus and Cardiac Surgery (SYNTAX) Trial

Vasim Farooq [a], Patrick W Serruys [a,*], Pascal Vranckx [a,l], Christos V Bourantas [a], Chrysafios Girasis [a], David R Holmes [b], Arie Pieter Kappetein [c], Michael Mack [d], Ted Feldman [e], Marie Claude Morice [f], Antonio Colombo [g], Marie-angèle Morel [h], Ton de Vries [h], Keith D Dawkins [i], Friedrich W Mohr [j], Stefan James [k], Elisabeth Ståhle [k]

[a] Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands
[b] The Mayo Clinic, Rochester, MN, USA
[c] Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands
[d] Medical City Dallas Hospital, Dallas, TX, USA
[e] Evanston Hospital, Evanston, IL, USA
[f] Institut Jacques Cartier, Massy, France
[g] San Raffaele Scientific Institute, Milano, Italy
[h] Cardialysis BV, Rotterdam, The Netherlands
[i] Boston Scientific Corporation, Natick, MA, USA
[j] Herzzentrum, Leipzig, Germany
[k] University Hospital Uppsala, Uppsala, Sweden
[l] Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessaziekenhuis, Hasselt, Belgium

ARTICLE INFO

Article history:
Received 10 May 2013
Received in revised form 12 July 2013
Accepted 3 August 2013
Available online 14 August 2013

Keywords:
SYNTAX
Biomarkers
CABG
PCI
Mortality

ABSTRACT

Aims: The aim of the present investigation was to determine the long-term prognostic association of post-procedural cardiac enzyme elevation within the randomised Synergy between Percutaneous Coronary Intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) Trial.

Methods: 1800 patients with unprotected left main or de novo three-vessel coronary artery disease were randomised to undergo coronary artery bypass graft (CABG) surgery or PCI. Per protocol patients underwent post-procedural blood sampling with creatine kinase (CK), and the cardiac specific MB iso-enzyme (CK-MB) only if the preceding CK ratio was $\geq 2\times$ the upper limit of normal (ULN). An independent chemistry laboratory evaluated all collected blood samples.

Results: Post-procedural CK sampling was available in 1629 of 1800 patients (90.5%). As per protocol, CK-MB analyses were undertaken in 474 of 491 patients (96.5%) in the CABG arm, and 53 of 61 patients (86.9%) in the PCI arm. Within the CABG arm, despite the limitations of incomplete data, a post-procedural CK-MB ratio $<3/\geq 3$ ULN separated 4-year mortality into low- and high-risk groups (2.3% vs. 9.5%, $p = 0.03$). Additionally, in the CABG arm, a post-procedural CK-MB ratio ≥ 3 ULN was associated with an increased frequency of a high SYNTAX Score (≥ 33) tertile (high [≥ 33] SYNTAX Score: 39.5%, intermediate [23–32] SYNTAX Score 31.0%, low [≤ 22] SYNTAX Score 29.5%, $p = 0.02$). Within the PCI arm, a post-procedural CK ratio of <2 or ≥ 2 ULN separated 4-year mortality into low- and high-risk groups (10.8% vs. 23.3%, $p = 0.001$). Notably, there was an early (within 6 months) and late (after 2 years) peak in mortality in patients with a post-PCI CK ratio of ≥ 2 ULN. Lack of pre-procedural thienopyridine, carotid artery disease, type 1 diabetes, and presence of coronary bifurcations were independent correlates of a CK ratio ≥ 2 ULN post-PCI.

Conclusion: Cardiac enzyme elevations post-CABG or post-PCI are associated with an adverse long-term mortality; the causes of which are multifactorial.

☆ Funding: The SYNTAX Trial was funded by the Boston Scientific Corporation.
☆☆ Author disclosures: KD Dawkins is all full-time employee in Boston Scientific and holds stock in Boston Scientific. M Mack has served on the Speaker's Bureau of Boston Scientific, Cordis and Medtronic. T Feldman reported serving on the Speaker's Bureau of Boston Scientific, receiving grant support from Abbott, Atritech, BSC, Edwards, and Evalve, and consulting for Abbott, Coherex, Intervalve, Square One, and WL Gore. M Morice reported that her institution received a research grant from Boston Scientific. The other authors report no conflicts of interest.

* Corresponding author at: Interventional Cardiology Department Erasmus MC, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands. Tel.: +31 10 7035260; fax: +31 10 4369154.
E-mail address: p.w.j.c.serruys@erasmusmc.nl (P.W. Serruys).

0167-5273/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2013.08.013

1. Introduction

Cardiac enzyme elevation post-coronary artery bypass graft (CABG) or post-percutaneous coronary intervention (PCI) has been demonstrated to have a detrimental impact on mortality post-revascularisation [1–4]. The aims of the present investigation were to determine the incidence, correlates and prognostic significance of post-procedural cardiac biomarker release following surgical or percutaneous revascularisation in the SYNTAX Trial [5–8].

2. Methods

The SYNTAX Trial is a randomised, prospective, multicentre trial that incorporated an 'all-comers' design, and consisted of prespecified left main (isolated or associated with 1, 2 or 3 vessel disease [3VD]) and de novo 3VD cohorts [5–8]. Patients were randomised on a 1:1 basis by the Heart Team consensus to undergo either CABG or PCI with Taxus Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Mass) (n = 1800). Patients considered unsuitable for randomisation were nested in registries for CABG- or PCI-ineligible patients. Exclusions were only limited to patients with prior coronary revascularisation, the requirement of concomitant cardiac surgery, or on-going acute MI. The calculation of the SYNTAX Score (http://www.syntaxscore.com) [9–13] was carried out by the Heart Team prior to randomisation, and corroborated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands), blinded to the treatment assignment.

2.1. Cardiac enzymes

Per protocol randomised patients from the SYNTAX Trial were scheduled to undergo blood sampling with creatine kinase (CK) pre- and post-revascularisation, and the cardiac specific MB iso-enzyme (CK-MB) only if the CK ratio ≥2× the upper limit of normal (ULN) [7,14]. If the CK ratio <2 ULN, CK-MB assessment was not mandated. Revascularisation with CABG or PCI was only permitted if the pre-procedural cardiac enzymes were <2 ULN. All samples were evaluated locally and by an independent central chemistry laboratory (Covance Inc., Geneva, Switzerland, and Indianapolis, Ind). Data from the central chemistry laboratory was available in the SYNTAX Trial database; local data was not collected in the SYNTAX Trial database.

For patients discharged >24 h post-procedure, three sets of CK (and CK-MB if CK ratio ≥2 ULN) were mandated, at 6 and 12 h post-procedure, and as close to discharge as possible. For patients discharged less than 24 h post-procedure, two sets of CK (and CK-MB if CK ratio ≥2 ULN) were required, at 6 h post-procedure, and as close to discharge as possible. In cases of chest pain, with or without ECG changes, additional serial cardiac enzymes were required to be sampled immediately, and at 6 and 12 h (and CK-MB if CK ratio ≥2 ULN). For all CK and CK-MB analyses, the peak (12-hour) post-procedural sample was used for the analyses — where this was not available, either the 6 hour or discharge sample was used, whichever was greater. Cardiac enzyme levels were categorised and differences in four-year mortality determined.

Predictors of post-PCI CK release were determined, since there was over 90% complete data [15]. Predictors of CK or CK-MB release post-CABG, and CK-MB release post-PCI, were not determined due to skeletal muscle damage post-CABG confounding the CK analyses in the CABG arm, and incomplete data for CK-MB sampling in the CABG and PCI arms due to the study protocol mandating CK-MB sampling only if the CK ratio >2 ULN.

2.2. Statistical analysis

Categorical variables are presented as counts/percentages, and compared with the Chi-square test. Continuous data are presented as medians and interquartile ranges (IQR), and compared using the Mann–Whitney rank sum test. Different thresholds of cardiac enzyme ratios were investigated to determine the best discrimination between groups. Comparisons of four-year clinical outcomes (Kaplan–Meier curves) were performed with the log-rank test between cardiac enzyme groups in the CABG and PCI arms. Relationships of post-PCI cardiac enzyme elevation to covariates (CK ratio ≥2 ULN for PCI), utilising previously published baseline and peri-procedural related characteristics [6], were investigated with univariate logistic regression models. Two models were constructed, the first model incorporating the SYNTAX Score, and the second model components of the SYNTAX Score, to determine individual anatomical factors associated with cardiac enzyme release. Correlates identified in univariable analyses were introduced into a multivariable model using the forced enter method, with variable entry criteria of 0.05 and no exit criteria. A 2-sided p-value <0.05 was considered significant. All analyses were conducted using SPSS 19.0 (SPSS Inc., Chicago IL).

3. Results

Within the randomised SYNTAX population (n = 1800), baseline demographics and clinical characteristics for the treatment arms were well balanced and have been described previously [6]. A flow chart illustrates the availability of post-procedural cardiac enzyme levels (per protocol) within the randomised SYNTAX population (Fig. 1).

3.1. Incidence and distribution of post-procedural CK/CK-MB release

Post-procedural CK sampling was available in 1629 out of 1800 patients (91%) (Fig. 1); CK-MB analyses were undertaken in 474 of 491 patients (97%) in the CABG arm, and 54 of 61 patients (89%) in the PCI arm.

The distribution of the post-procedural CK and CK-MB ratios is illustrated (Fig. 2). The median CK ratio in the CABG arm was significantly greater compared to the PCI arm (CABG: 2.5 ULN, IQR 1.6–4.1; PCI: 0.5 ULN, IQR 0.4–0.9; p < 0.001). The median CK-MB ratio in the PCI arm

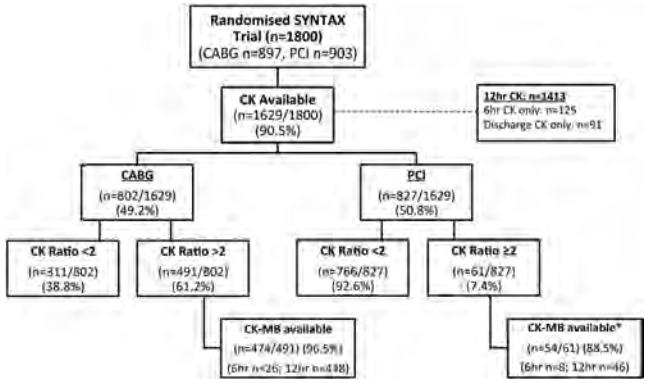


Fig. 1. Flow chart of the post-procedural cardiac biomarker availability in the randomised SYNTAX Trial (n = 1800). Percentages in parentheses indicate the proportion of the entire randomised SYNTAX population (n = 1800). *1 patient included with CK-MB level with no prior CK level assessment. Abbreviations: CABG coronary artery bypass surgery, PCI percutaneous coronary intervention, CK creatine kinase, CK-MB creatine kinase-MB fraction, hr hour.

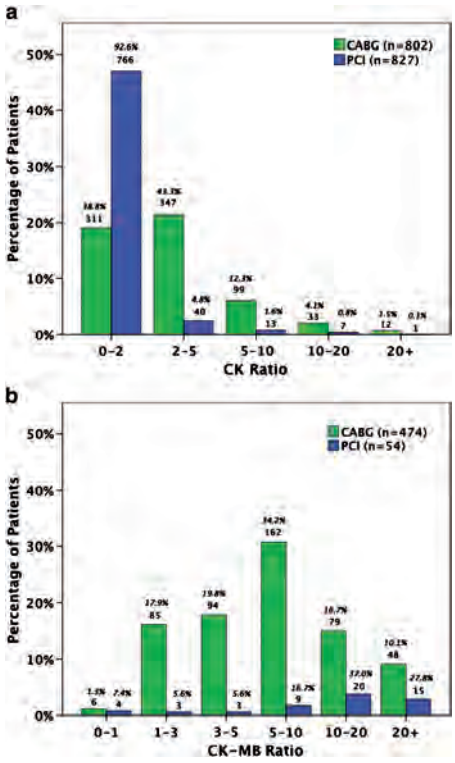


Fig. 2. Distribution of post-procedural CK ratios (n = 1629) (a) and post-procedural CK-MB ratios (n = 528) (b) in the CABG and PCI cohorts of the randomised SYNTAX Trial.

was significantly greater compared to the CABG arm (CABG: 6.2 ULN, IQR 3.6–10.4; PCI: 12.6 ULN, IQR 6.8–28.1; p < 0.001).

3.2. Clinical outcomes based upon post-procedural cardiac enzyme release

3.2.1. Post-procedural CK-ratio

Within the CABG arm, a post-procedural CK ratio separated by <2 and ≥2 ULN demonstrated no significant differences in all-cause death at four-years (Fig. 3). Within the PCI arm, a post-procedural CK ratio separated by <2 and ≥2 ULN, divided patients into low- and high-risk groups for all-cause death at 30 days (0.9% [7/765] vs. 10.0% [6/60], p < 0.001), 6 months (2.2% [17/762] vs. 13.3% [8/60], log rank p < 0.001) and 4 years (10.8% [81/750] vs. 23.3% [14/60], log rank p = 0.001) (Fig. 3). Notably in the PCI arm, an early (within 6 months) and late (after 2 years) peak in mortality was evident following a post-procedural CK ratio ≥2 ULN.

3.2.2. Post-procedural CK-MB ratio

Since post-procedural CK-MB sampling in the CABG and PCI arms was limited to patients with a prior CK ratio ≥2 ULN, as directed by the study protocol [7], clinical outcomes based on post-procedural CK-MB analyses should be interpreted with caution, due to the incomplete data.

Within the CABG arm, a post-procedural CK-MB ratio <3 and ≥3 ULN separated 4-year mortality into low- and high-risk groups (CK-MB ratio <3 ULN: 2.3% [2/87]; post-procedural CK-MB ratio group ≥3 ULN 9.5% [34/359], log rank p = 0.03) (Fig. 4a). Post-procedural CK-MB ratios at higher thresholds (<5 and ≥5 ULN, <10 and ≥10 ULN) did not separate 4-year mortality into low and high-risk groups.

Within the PCI arm, there was limited power for analyses due to a low occurrence of a post-procedural CK ratio ≥2 ULN, and subsequent per-protocol CK-MB analyses (n = 54/61 [3.0% of the study population]). Nevertheless, significantly greater mortality was evident in the high compared to the low post-procedural CK-MB ratio group (separated by the median CK-MB ratio of 12.6 ULN) at 4 years (7.4% [2/27] vs. 38.5% [10/26], log rank p = 0.006) (Fig. 4b).

3.3. Predictors of post-procedural cardiac enzyme release

3.3.1. CABG arm

A post-procedural CK-MB ratio ≥3 ULN was associated with a significantly increased frequency of a high SYNTAX Score tertile (≥33)

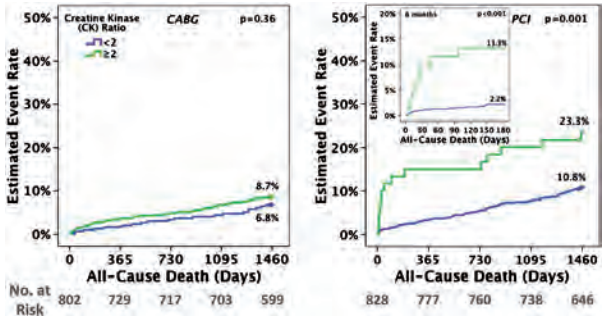


Fig. 3. Four-year mortality stratified to post-procedural CK <2 ULN and post-procedural CK ≥2 ULN in patients undergoing CABG (n = 802) (left) or PCI (n = 827) (right) based revascularisation. Inset right image are findings for six-month (180 days) mortality.

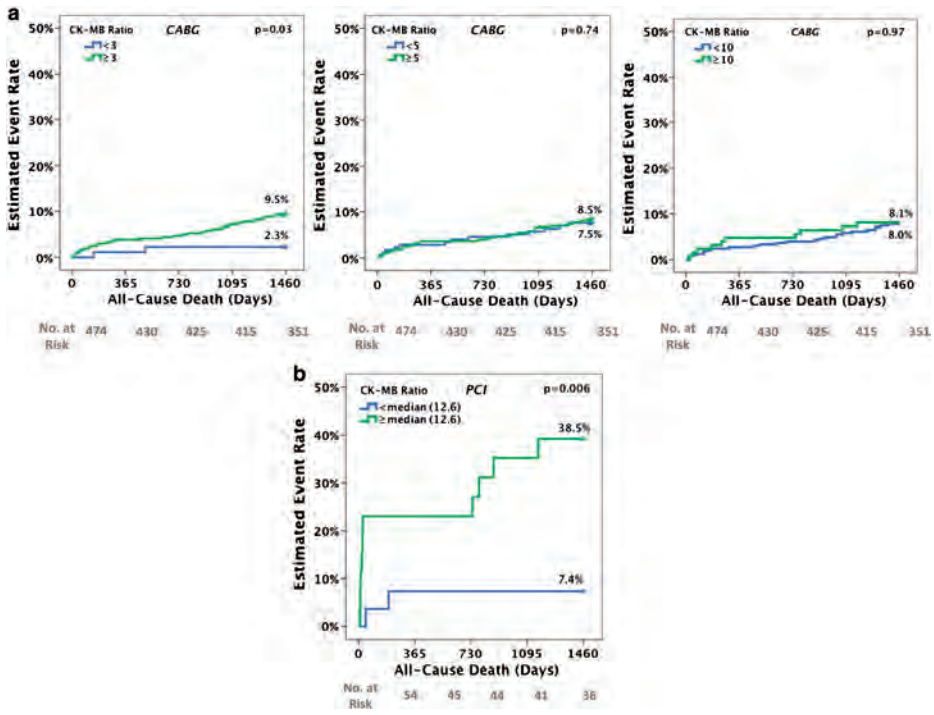


Fig. 4. Four-year mortality stratified to categories of post-procedural CK-MB ratio in the CABG (a) and PCI (b) arms. Within the CABG arm (n = 474), 4-year mortality separated by a post-procedural CK-MB ratio </≥3, </≥5, and </≥10 ULN are illustrated. Within the PCI arm (n = 54), due to limitations of power, 4-year mortality data is shown separated by a post-procedural CK-MB ratio </≥ median (12.60, IQR 6.8–28.1) ULN.

compared to intermediate and low SYNTAX Score tertiles (<33) (p = 0.02) (Fig. 5). Due to incomplete data in post-procedural CK-MB sampling within the CABG arm, determination as to whether a high SYNTAX Score tertile was an independent correlate of cardiac enzyme release post-CABG could not be determined.

3.3.2. PCI arm

Within the PCI arm, since >90% had post-procedural CK sampling performed (n = 827/903, 91.7%), independent correlates of cardiac enzyme release (CK ratio ≥2 ULN) could be determined (Table 1). Lack of pre-procedural thienopyridine was the strongest independent correlate of a post-procedural CK ratio ≥2 ULN post-PCI (HR 8.49, CI 2.95–24.43, p < 0.001), followed by carotid artery disease (HR 2.14, CI 21.00–4.60, p = 0.052), type I diabetes (HR 3.38, CI 0.86–13.25, p = 0.081) and SYNTAX Score per 10 points increase (HR 1.25, CI 1.00–1.57, p = 0.052). Within the SYNTAX Score, the presence of a coronary bifurcation was an independent correlate of enzyme release (HR 2.17, CI 1.17–4.05, p = 0.015), and the presence of diffuse coronary disease or small peripheral vessels appeared protective (HR 0.43, CI 0.19–0.95, p = 0.036).

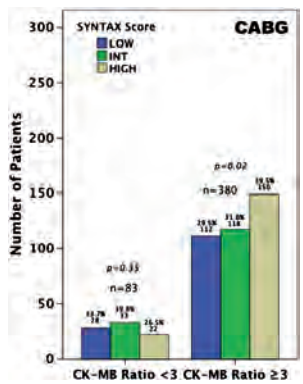


Fig. 5. Distribution of tertiles of the SYNTAX Score (low ≤22, intermediate 23–32, high ≥33) within the randomised SYNTAX population, stratified by low and high post-procedural CK-MB ratios (CK-MB ratio <3 and ≥3 ULN) in the CABG arm (n = 463).

4. Discussion

The main findings of this study are that: 1) cardiac enzyme elevation post-CABG or post-PCI (CK and subsequent CK-MB sampling)

Table 1
Univariate (selected variables shown) and independent correlates of post-procedural cardiac enzyme release (CK ratio ≥2 ULN) following PCI based revascularisation. Model 1 incorporates the SYNTAX Score. Model 2 incorporates components of the SYNTAX Score.

PCI	Odds ratio	95% C.I.	p-Value
Univariate correlates of post-PCI CK ratio ≥2			
SYNTAX Score per increase in 10 points	1.22	0.98, 1.52	0.072
Any coronary bifurcation	2.21	1.20, 4.07	0.011
Any heavy calcification	1.34	0.79, 2.26	0.28
Any aorto-ostial disease	1.28	0.64, 2.52	0.49
Any angiographically visible thrombus	1.20	0.27, 5.22	0.81
Any total occlusion	0.87	0.46, 1.65	0.68
Left main coronary artery disease	0.85	0.50, 1.47	0.57
Any severe tortuosity	0.84	0.49, 1.44	0.52
Diffuse disease or small peripheral vessels	0.49	0.23, 1.06	0.069
Lack of pre-procedural thienopyridine[a]	7.35	2.62, 20.62	<0.001
Type 1 diabetes	3.49	0.95, 12.86	0.060
Carotid artery disease	1.96	0.92, 4.17	0.079
Stent length >100 mm	1.37	0.78, 2.40	0.27
Peripheral vascular disease	1.25	0.55, 2.84	0.60
Poor left ventricular ejection fraction	1.24	0.16, 9.84	0.84
Moderate left ventricular ejection fraction	1.17	0.61, 2.27	0.63
Age per increase in 10 years	1.08	0.82, 1.41	0.60
Incomplete revascularisation	1.06	0.63, 1.79	0.82
Total stent length (mm)	1.00	1.00, 1.01	0.50
Type II diabetes	0.97	0.53, 1.74	0.91
Good left ventricular ejection fraction	0.91	0.49, 1.68	0.75
Model 1 — SYNTAX Score	Odds ratio	95% C.I.	p-Value
Independent correlates of post-PCI CK ratio ≥2			
Lack of pre-procedural thienopyridine[a]	8.49	2.95, 24.43	<0.001
Carotid artery disease	2.14	1.00, 4.60	0.052
Type 1 diabetes	3.38	0.86, 13.25	0.081
SYNTAX Score per increase in 10 points	1.25	1.00, 1.57	0.052
Model 2 — components of the SYNTAX Score	Odds ratio	95% C.I.	p-Value
Independent correlates of post-PCI CK ratio ≥2			
Lack of pre-procedural thienopyridine[a]	8.35	2.84, 24.57	<0.001
Type 1 diabetes	3.63	0.91, 14.52	0.068
Carotid artery disease	2.35	1.09, 5.08	0.030
Any coronary bifurcation	2.17	1.17, 4.05	0.015
Diffuse disease or small peripheral vessels	0.43	0.19, 0.95	0.036

[a] Clopidogrel or ticlopidine.

had a detrimental impact on long-term mortality in the SYNTAX Trial; 2) that in the CABG arm, despite limitations of the data, a post-procedural CK-MB ratio <3/≥3 ULN separated 4-year mortality into low- and high-risk groups, and that a post-procedural CK-MB ratio ≥3 ULN appeared to be associated with a significantly increased frequency of a high SYNTAX Score tertile (≥33); 3) a post-procedural CK-ratio ≥2 ULN post-PCI was associated with an early (within 6 months) and late (after 2 years) peak in mortality; and 4) a lack of pre-procedural thienopyridine, carotid artery disease, type 1 diabetes, and presence of coronary bifurcations were independent correlates of a CK ratio ≥2 ULN post-PCI.

4.1. CABG arm

The requirement of a CK ratio ≥2 ULN to allow for CK-MB ratio analyses in the present study was not supported by the clinical findings in the CABG arm, namely that no differences in mortality were seen between post-CABG CK ratios <2 or ≥2 ULN. This is likely to be secondary to the fact that skeletal muscle damage, particularly when undertaking a sternotomy, leads to post-operative rises in CK levels [16]. At the time of the design of the SYNTAX Trial in 2004, it was concluded that it was a reasonable strategy to determine the CK-MB only if the CK ratio was ≥2 ULN [7,14]. In hindsight this practice underpowered the subsequent analyses on the CK-MB ratios. Despite these limitations, a post-CABG CK-MB ratio of <3 or ≥3 ULN was still able to discriminate low and high risk groups for mortality at up to four years.

Furthermore, these results are consistent with the findings from Costa et al. who first associated minor cardiac enzyme elevation post-CABG with early mortality in the randomised Arterial Revascularization Therapies Study (ARTS) [4]. Subsequently, Domanski et al. confirmed these findings in a large meta-analysis of seven trials (n = 18,908) [2]. Notably in this meta-analysis, the doubling of one-year mortality was associated with a post-operative CK-MB ratio of 4.4 ULN, consistent with the findings in the present study, where a substantial increase in mortality occurred in patients with a post-CABG CK-MB ratio between 3 and 5 ULN (Fig. 4a).

As to the potential mechanism linking mortality (>1 year) with minor elevations of CK-MB in CABG patients, this is more complex and has not yet been clearly defined [2]. Due to the incomplete data collected on CK-MB analyses, as mandated by the study protocol, multivariate analyses to determine independent correlates of post-operative cardiac enzyme release could not be performed. Notably, the presence of a post-operative CK-MB ratio ≥3 ULN was associated with a significant increase in the frequency of a high SYNTAX Score tertile (Fig. 5). It is therefore possible that the CK-MB ratio ≥3 ULN may be confounding, and potentially related to more complex baseline coronary disease, and consequent leakage of cardiac enzymes during administration of cardioplegia solution during CABG [17]. This hypothesis is supported by historical data associating more extensive baseline preoperative coronary disease to longer-term (>10 years) mortality [18,19].

4.2. PCI arm

Historically, a post-PCI elevated CK ratio (≥2 ULN) has been associated with adverse long-term mortality [16,20,21]. As all patients within the present study underwent PCI only if the pre-procedural CK-ratio was ≤2 ULN, the elevation of the CK-ratio after PCI is highly likely to be related to the presence of significant peri-procedural myocardial necrosis; the only caveat perhaps being a groin haematoma as a complication of a femoral approach to PCI.

Furthermore, given the magnitude of cardiac enzyme release in patients with a CK ratio ≥2 ULN post-PCI (median CK-MB ratio: 12.6 ULN [IQR 6.6–28.1]), and that progressive rises in post-PCI CK-MB ratios are clearly linked to an increase in mortality [1,22,23], it is not inconceivable that a doubling of 4-year mortality was seen in patients with a CK ratio ≥2 ULN. Notably, an early (within 6 months) and late peak (>2 years) in mortality was evident in patients with a post-PCI CK ratio ≥2 ULN (Fig. 3). These findings may be related to the clinical consequences of an acute MI in the short term, and complications related to heart failure or arrhythmias in the long term.

In so far as preventing cardiac enzyme elevation post-PCI, the 2 potentially reversible independent correlates of cardiac enzyme elevation included lack of pre-procedural thienopyridine, and the presence of a coronary bifurcation (Table 1). The coronary bifurcation (compared to non-coronary bifurcations) has historically been associated with poorer outcomes following PCI [24–27]. As compared to the one-stent approach for the treatment of the coronary bifurcations, the two-stent approach utilising first generation DES has been shown to be less favourable, with a recommendation of a one-stent (provisional) strategy wherever possible [28–30].

5. Study limitations

The present study represents a post hoc analysis of the SYNTAX Trial and the results should be considered as hypothesis generating. The main limitation of this study was the incomplete data on CK-MB ratios due to the protocol defined reliance on a mandatory CK-ratio performed beforehand [7]. It has previously been reported that 10–20% of patients with elevated CK-MB measurements have a normal total CK [31]. We therefore cannot exclude the possibility of selection bias in patients investigated with elevated CK-MB. It is however unlikely that the myocardial injury was of a sizable magnitude, as it would have been identified

by the total CK assessment. In addition, there was lack of troponin data since the SYNTAX Trial was commenced prior to the Academic Research Consortium publication of standardised definitions and clinical outcomes [32]. Site reported data on cardiac enzymes was not collected. The incomplete data on CK-MB sampling precluded multivariate analyses for cardiac enzyme release and long-term mortality. Multivariable correlates of long-term mortality, without inclusion of cardiac enzymes, have however recently been reported [33].

6. Conclusion

Cardiac enzyme elevation post-CABG or post-PCI is associated with an adverse long-term mortality; the causes of which are multifactorial.

Acknowledgements

The authors express their gratitude to all of the study centres and participants whose work made this study possible. Thanks are provided to Peggy Pereda and Jian Huang of Boston Scientific Corporation for their invaluable support in accessing the study database.

References

[1] Vranckx P, Farooq V, Garg S, et al. Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting. Heart 2012;98:1424–30.
[2] Domanski MJ, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA 2011;305:585–91.
[3] Brener SJ, Lytle BW, Schneider JP, Ellis SG, Topol EJ. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. J Am Coll Cardiol 2002;40:1961–7.
[4] Costa MA, Carere RG, Lichtenstein SV, et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). Circulation 2001;104:2689–93.
[5] Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation 2010;121:2645–53.
[6] Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
[7] Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151:1194–204.
[8] Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
[9] SYNTAX score calculator. http://www.syntaxscore.com , SYNTAX Working-Group; 2009 [Launched 19th May 2009].
[10] Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50–6.
[11] Sianos G, Morel MA, A.P.K., et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention; 2005 219–27.
[12] Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;97:1902–13.
[13] Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. Heart 2013. http://dx.doi.org/10.1136/heartjnl-2012-302482.
[14] Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 1994;90:583–612.
[15] Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367:1355–60.
[16] Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998;31:241–51.
[17] Guru V, Omura J, Alghamdi AA, Weisel R, Fremes SE. Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials. Circulation 2006;114: I331–8.
[18] Myers WO, Blackstone EH, Davis K, Foster ED, Kaiser GC. CASS Registry long term surgical survival, Coronary Artery Surgery Study. J Am Coll Cardiol 1999;33:488–98.
[19] van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. Eur Heart J 2009;30:453–8.
[20] Kong TQ, Davidson CJ, Meyers SN, Tauke JT, Parker MA, Bonow RO. Prognostic implication of creatine kinase elevation following elective coronary artery interventions. JAMA 1997;277:461–6.
[21] Abdelmeguid AE, Ellis SG, Sapp SK, Whitlow PL, Topol EJ. Defining the appropriate threshold of creatine kinase elevation after percutaneous coronary interventions. Am Heart J 1996;131:1097–105.
[22] Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. J Am Coll Cardiol 2003;42:1406–11.
[23] Jang JS, Jin HY, Seo JS, et al. Prognostic value of creatine kinase-myocardial band isoenzyme elevation following percutaneous coronary intervention: a meta-analysis. Catheter Cardiovasc Interv 2013;81(6):959–67.
[24] Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation 2004;109: 1244–9.
[25] Ge L, Iakovou I, Cosgrave J, et al. Treatment of bifurcation lesions with two stents: one year angiographic and clinical follow up of crush versus T stenting. Heart 2006;92: 371–6.
[26] Latib A, Colombo A, Sangiorgi GM. Bifurcation stenting: current strategies and new devices. Heart 2009;95:495–504.
[27] Colombo A, Al-Lamee R. Bifurcation lesions: an inside view. Circ Cardiovasc Interv 2010;3:94–6.
[28] Hildick-Smith D, Lassen JF, Albiero R, et al. Consensus from the 5th European Bifurcation Club meeting. EuroIntervention 2010;6:34–8.
[29] Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. Circulation 2010;121:1235–43.
[30] Diletti R, Garcia-Garcia HM, Bourantas CV, et al. Clinical outcomes after zotarolimus and everolimus drug eluting stent implantation in coronary artery bifurcation lesions: insights from the RESOLUTE All Comers Trial. Heart 2013;99(17):1267–74.
[31] Dillon MC, Calbreath DF, Dixon AM, et al. Diagnostic problem in acute myocardial infarction: CK-MB in the absence of abnormally elevated total creatine kinase levels. Arch Intern Med 1982;142:33–8.
[32] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
[33] Farooq V, Serruys PW, Bourantas C, et al. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial. Eur Heart J 2012;33:3105–13.

PART VII

Understanding predictors of mortality in the SYNTAX Trial

Chapter 7

Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial

Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Ståhle E

Eur Heart J. 2012;33(24):3105-13 (Impact Factor: 14.097)

Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial

Vasim Farooq[1], Patrick W. Serruys[1]*, Christos Bourantas[1], Pascal Vranckx[1], Roberto Diletti[1], Hector M. Garcia Garcia[1], David R. Holmes[2], Arie-Pieter Kappetein[3], Michael Mack[4], Ted Feldman[5], Marie Claude Morice[6], Antonio Colombo[7], Marie-angèle Morel[8], Ton de Vries[8], Gerrit Anne van Es[8], Ewout W. Steyerberg[9], Keith D. Dawkins[10], Friedrich W. Mohr[11], Stefan James[12], and Elisabeth Ståhle[12]

[1]Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, s-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands; [2]The Mayo Clinic, Rochester, MN, USA; [3]Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands; [4]Medical City Dallas Hospital, Dallas, TX, USA; [5]Evanston Hospital, Evanston, IL, USA; [6]Institut Jacques Cartier, Massy, France; [7]San Raffaele Scientific Institute, Milano, Italy; [8]Cardialysis BV, Rotterdam, The Netherlands; [9]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [10]Boston Scientific Corporation, Natick, MA, USA; [11]Herzzentrum, Leipzig, Germany; and [12]University Hospital Uppsala, Uppsala, Sweden

Received 29 April 2012; revised 21 August 2012; accepted 3 October 2012; online publish-ahead-of-print 26 October 2012

Aims The aim of this investigation was to determine the incidence and multivariable correlates of long-term (4-year) mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention (PCI) with TAXUS Express and Cardiac Surgery (SYNTAX) trial.

Methods and results A total of 1800 patients were randomized to undergo coronary artery bypass graft (CABG) surgery ($n = 897$) or PCI ($n = 903$). Prospectively collected baseline and peri- and post-procedural data were used to determine independent correlates of 4-year all-cause death in the CABG and the PCI arms (Cox proportional hazards model). Four-year mortality rates in the CABG and the PCI arms were 9.0% [74 deaths (12 in-hospital)] and 11.8% [104 deaths (16 in-hospital)], respectively (log-rank P-value $= 0.063$). Censored data comprised 78 patients (8.7%) in the CABG arm, and 24 patients (2.7%) in the PCI arm (log-rank P-value < 0.001). Within the CABG arm, the strongest independent correlates of 4-year mortality were lack of discharge aspirin [hazard ratio (HR) 3.56; 95% CI: 2.04, 6.21; $P < 0.001$], peripheral vascular disease (PVD) (HR: 2.65; 95% CI: 1.49, 4.72; $P = 0.001$), chronic obstructive pulmonary disease, age, and serum creatinine. Within the PCI arm, the strongest independent correlate of 4-year mortality was lack of post-procedural anti-platelet therapy (HR: 152.16; 95% CI: 53.57, 432.22; $P < 0.001$), with 10 reported early (within 45 days) in-hospital deaths secondary to multifactorial causes precluding administration of anti-platelet therapy. Other independent correlates of mortality in the PCI arm included amiodarone therapy on discharge, pre-procedural poor left ventricular ejection fraction, a 'history of gastrointestinal bleeding or peptic ulcer disease', PVD (HR: 2.13; 95% CI: 1.26, 3.60; $P = 0.005$), age, female gender (HR: 1.60; 95% CI: 1.01, 2.56; $P = 0.048$), and the SYNTAX score (Per increase in 10 points: HR: 1.25; 95% CI: 1.06, 1.47; $P = 0.007$).

* Corresponding author. Tel: +31 10 7035260, Fax: +31 10 4369154, Email: p.w.j.c.serruys@erasmusmc.nl

Conclusion Independent correlates of 4-year mortality in the SYNTAX trial were multifactorial. Lack of discharge aspirin and lack of post-procedural anti-platelet therapy were the strongest independent correlates of mortality in the CABG and the PCI arms, respectively. Peripheral vascular disease is a common independent correlate of 4-year mortality and may be a marker of the severity of baseline coronary disease and risk of future native coronary disease (and extra-cardiac disease) progression.

Keywords SYNTAX score • Death • SYNTAX trial • Multivariable correlates • Gender

Introduction

The SYNTAX trial has established a framework in which patients with unprotected left main or 3-vessel coronary artery disease are managed by the consensus of the Heart Team, in which the cardiac surgeon and interventional cardiologist determine the optimal revascularization modality for patients.[1–6] The results from the primary endpoint of the SYNTAX trial at 4 years have recently been reported,[7,8] with follow-up through to 5 years planned. The aim of this study was to analyse the incidence and multivariable correlates of all-cause death at 4 years following surgical or percutaneous revascularization in the randomized SYNTAX trial.

Methods

The SYNTAX trial is a randomized, prospective, multicentre trial that incorporates an 'All-Comers' design and in this study, consisted of pre-specified left main [isolated or associated with 1, 2, or 3 vessel disease (3VD)] and 3VD arms.[1,3,5] Patients were randomized on a 1:1 basis by the Heart Team consensus to undergo either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) with TAXUS Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, MA, USA) ($n = 1800$). Patients considered unsuitable for randomization were entered in nested registries for CABG- or PCI-ineligible patients. Exclusions were limited only to patients with prior coronary revascularization, the requirement of concomitant cardiac surgery, or on-going acute MI. An independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands), blinded to the treatment assignment, calculated the SYNTAX score (http://www.syntaxscore.com).[3,4,6,9]

Pre-procedurally, the study protocol mandated in the CABG arm aspirin (>70 mg per day) at least 12 h pre-CABG, and in the PCI arm aspirin (>70 mg per day) at least 12 h pre-PCI and clopidogrel (300 + mg 24 h pre-PCI) or ticlopidine (2 × 250 mg daily 48 h pre-PCI). Post-procedurally, aspirin (>70 mg/day) was mandated in the CABG and the PCI arms, and clopidogrel (75 mg) or ticlopidine (2 × 250 mg) for at least 6 months in the PCI arm. Within the CABG and the PCI arms, it was recommended that optimal medical treatment be continued long-term according to the ACC/AHA guidelines.[10–12]

Baseline and peri- and post-procedural data and blood samples were prospectively collected by the individual participating centres. Post-procedural and discharge medications encompassed specific medications (or lack of) immediately after revascularization (CABG or PCI) and at hospital discharge, respectively. Pre- and post-revascularization per protocol blood sampling with creatine kinase (CK) were undertaken, with the cardiac-specific MB iso-enzyme (CK-MB) measured only if the CK ratio ≥2× upper limit of normal (ULN).[5] Revascularization with CABG or PCI was permitted only if the cardiac enzymes were <2× ULN. All the samples were evaluated by an independent central chemistry laboratory (Covance, Inc., Geneva, Switzerland, and Indianapolis, IN, USA).

Statistical analysis

In this article, continuous variables are presented as means ± standard deviation (SD). Categorical variables are presented as counts or percentages. Comparisons of 4-year clinical all-cause death (Kaplan–Meier estimates) were performed with the log-rank test. Similar analyses were conducted for censored patients using the time to censored event for all-cause death. Relationships of 4-year all-cause to covariates, utilizing previously published baseline and peri- and post-procedural characteristics,[3] were investigated with univariate Cox regression models. The correlates of worse prognosis identified in univariable analyses were then introduced into a multivariable model using the forced enter method, with a variable entry criterion of 0.05; all the variables were retained in the final model irrespective of statistical significance. The proportionality of hazards (PH) assumption was checked using the global PH test based on Schoenfeld residuals.[13] There was no departure from the PH assumption in the CABG [$\chi^2 = 10.29$, degrees of freedom (df) = 10, $P = 0.42$] and the PCI arms ($\chi^2 = 13.96$, df = 10, $P = 0.17$). Intercorrelation between variables was undertaken with the Pearson correlation coefficient where appropriate. A two-sided P-value of <0.05 was considered significant for all tests. All analyses were conducted using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA) and STATA 11.0 (Stata Corp., College Station, TX, USA).

Results

Within the randomized SYNTAX trial ($n = 1800$), baseline demographics, and clinical characteristics for the CABG ($n = 897$) and the PCI ($n = 903$) arms were well balanced and have previously been described.[3] At 4 years, clinical data were available in 819 of 897 patients in the CABG arm, and 879 of 903 patients in the PCI arm. Censored data comprised 78 patients (8.7%) in the CABG arm, and 24 patients (2.7%) in the PCI arm (log-rank P-value < 0.001). The most common reason for censoring was the withdrawal of consent after randomization [61 patients (CABG $n = 50$, PCI $n = 11$)], with the remainder of patients primarily lost to follow-up.

Four-year mortality was 9.0% (74 all-cause deaths) in the CABG arm and 11.8% (104 all-cause Deaths) in the PCI arm (log-rank P-value = 0.063). Univariate and independent correlates of cumulative 4-year mortality in the CABG and the PCI arms are shown in *Tables 1–4*.

Table 1 **Univariate (selected variables shown) correlates of 4-year mortality in the entire coronary artery bypass graft population of the randomized SYNTAX trial (n = 897)**

CABG (n = 897) univariate correlates of 4-year mortality	Incidence of mortality: no./total (%)	Hazard ratio (95% CI)	P-value
Categorical variables (%)			
Lack of discharge aspirin	27/96 (28.1)	5.03 (3.11–8.14)	<0.001
Peripheral vascular disease	21/87 (24.1)	3.72 (2.24–6.16)	<0.001
Pre-procedural poor LVEF	5/18 (27.8)	3.65 (1.47–9.05)	0.005
Chronic obstructive pulmonary disease	17/77 (22.1)	3.20 (1.86–5.50)	<0.001
History of GI bleeding or peptic ulcer disease	8/37 (21.6)	2.87 (1.38–5.98)	0.005
Amiodarone therapy on discharge	16/105 (15.2)	2.01 (1.16–3.51)	0.014
Hypertension	63/625 (10.1)	1.97 (1.01–3.84)	0.046
Lack of pre-procedural aspirin	56/535 (10.5)	1.91 (1.10–3.33)	0.023
Metabolic syndrome	33/292 (11.3)	1.57 (0.94–2.63)	0.084
Left main coronary artery disease	37/324 (11.4)	1.55 (0.98–2.45)	0.059
Diabetes	27/230 (11.7)	1.53 (0.95–2.46)	0.078
On pump CABG	63/687 (9.2)	1.45 (0.66–3.16)	0.36
Anterograde administration of cardioplegia	61/668 (9.1)	1.33 (0.66–2.67)	0.43
Crystalloid cardioplegia	27/263 (10.3)	1.29 (0.79–2.08)	0.31
Incomplete revascularization	31/306 (10.1)	1.28 (0.80–2.04)	0.3
Male	61/653 (9.3)	1.19 (0.66–2.17)	0.56
Current Smoker	16/172 (9.3)	1.07 (0.62–1.87)	0.81
High SYNTAX score tertile	25/294 (8.5)	0.90 (0.56–1.46)	0.67
Blood cardioplegia	34/405 (8.4)	0.91 (0.57–1.45)	0.69
Retrograde administration of cardioplegia	6/116 (5.2)	0.54 (0.23–1.24)	0.15
Continuous variables[a]			
Age per increase in 10 years	71 ± 8	2.16 (1.64–2.86)	<0.001
Serum creatinine (mg/dL)	1.32 ± 1.17	1.52 (1.27–1.82)	<0.001
SYNTAX score per increase in 10 points	30 ± 13	1.10 (0.91–1.34)	0.34
Cross-clamp time (minutes)	54 ± 23	1.00 (0.99–1.01)	0.89
BMI	27 ± 5	0.97 (0.92–1.02)	0.25
Post-CABG peak CK–MB ratio[b]	17.63 ± 39.8	1.02 (1.01–1.03)	0.002

GI, gastrointestinal; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft surgery; CK-MB, creatine kinase myoglobin; BMI, body mass index.
[a]Continuous variables are presented as mean ± SD in patients who died within four years (age and SYNTAX score are presented as actual values).
[b]The CK–MB ratio was not inserted in the multivariable model because of incomplete data as per the SYNTAX trial protocol (available in 474 of 897 patients—26.3% of study population).

Randomized coronary artery bypass graft arm

Within the randomized CABG arm, incomplete revascularization and on-pump CABG were not shown to be univariate correlates of 4-year mortality (*Table 1*). Lack of pre-procedural aspirin was not an independent correlate of mortality (*Table 2*). Lack of discharge aspirin was the strongest independent correlate of 4-year mortality [hazard ratio (HR) 3.56; 95% CI: 2.04, 6.21; $P < 0.001$]. Only a weak correlation was apparent between lack of pre-procedural aspirin and lack of discharge aspirin (Pearson correlation 0.14, $P < 0.001$). Twenty-seven out of 96 CABG-treated patients (28.1%) not discharged on aspirin died within 4 years (0 in-hospital deaths). Notably, 15 of the 27 deaths were cardiac ($n = 13$) or vascular ($n = 2$) related and 12 deaths non-cardiac related. A 'history of gastrointestinal (GI) bleeding or peptic ulcer disease' demonstrated a trend towards significance of being an independent correlate of 4-year mortality ($P = 0.085$). A 'history of GI bleeding or peptic ulcer disease' had no correlation with a lack of discharge aspirin therapy (Pearson correlation 0.03, $P = 0.36$).

Pre-procedural poor left ventricular ejection fraction (LVEF) was not an independent correlate of 4-year mortality. Amiodarone therapy on discharge demonstrated a trend towards being a significant independent correlate of 4-year mortality ($P = 0.070$). No correlation of pre-procedural poor LVEF and amiodarone therapy on discharge was evident (Pearson correlation 0.01, $P = 0.76$).

Other key independent correlates of 4-year mortality in the randomized CABG arm included peripheral vascular disease (PVD) (HR: 2.65; 95% CI: 1.49, 4.72; $P = 0.001$)—with 21 of 87 patients (24.1%) dying within 4-years (five in-hospital deaths), chronic obstructive pulmonary disease (HR: 2.44; 95% CI: 1.30, 4.60; $P = 0.006$), age, and renal function (*Table 2*).

Table 2 **Independent correlates of 4-year mortality in the entire coronary artery bypass graft population of the randomized SYNTAX trial ($n = 897$)**

CABG ($n = 897$) independent correlates of 4-year mortality (*variables with a P-value >0.05 italicized*)	Hazard ratio	95% CI	*P*-value
Lack of discharge aspirin	3.56	2.04–6.21	<0.001
Peripheral vascular disease	2.65	1.49–4.72	0.001
Chronic obstructive pulmonary disease	2.44	1.30–4.60	0.006
History of GI bleeding or peptic ulcer disease	2.14	0.90–5.07	*0.085*
Age per increase in 10 years	1.95	1.41–2.69	<0.001
Pre-procedural poor LVEF	1.86	0.65–5.33	*0.25*
Amiodarone therapy on discharge	1.79	0.95–3.35	*0.07*
Serum creatinine (mg/dL)	1.47	1.17–1.84	0.001
Hypertension	1.28	0.62–2.67	*0.51*
Lack of pre-procedural aspirin	1.18	0.64–2.19	*0.59*

CABG, coronary artery bypass graft surgery; GI, gastrointestinal; LVEF, left ventricular ejection fraction.

Randomized percutaneous coronary intervention arm

Within the randomized PCI arm, total number of stents, total stent length, and stent length >100 mm were not shown to be correlates of 4-year mortality (*Table 3*). The strongest independent correlate of mortality was lack of post-procedural anti-platelet therapy (HR: 152.16, 95% CI: 53.57, 432.22, $P < 0.001$) (*Table 4*). Further analyses indicated that 11 PCI-treated patients had a lack of post-procedural anti-platelet therapy (neither aspirin nor thienopyridine) with 10 reported early in-hospital deaths (<45 days) and the 11th patient's clinical outcome censored. All 10 deaths were cardiac related and of multifactorial causes which precluded anti-platelet administration. Two deaths were related to GI bleeding, one death secondary to retroperitoneal bleeding resulting from procedure-related femoral vascular access, three deaths secondary to coronary perforation (two cases requiring surgical intervention), and three further cases necessitating CABG after PCI-related complications following stent implantation (two cases secondary to post-procedural acute stent thrombosis and one case for extraction of ruptured balloon catheter after stent implantation), with withdrawal of treatment in one case due to poor prognosis. Detailed patient narratives of these 10 deaths are available in the Supplementary material online, Appendix.

Being discharged on one anti-platelet agent alone was not an independent correlate of mortality ($n = 39$, one patient event censored), with no in-hospital deaths reported. There was no correlation between a 'history of GI bleeding or peptic ulcer disease' and a lack of post-procedural anti-platelet therapy (Pearson correlation −0.02, $P = 0.51$) or patients taking one anti-platelet agent at discharge (Pearson correlation 0.04, $P = 0.28$).

Amiodarone therapy on discharge [5 of 12 patients dying within 4 years (1 death in-hospital)] (HR: 4.49, 95% CI: 1.36, 14.83, $P = 0.014$) and pre-procedural poor left LVEF were independent correlates of 4-year mortality. Both variables showed minor correlation (Pearson correlation 0.3, $P < 0.001$).

Other independent correlates of 4-year mortality included a 'history of GI bleeding or peptic ulcer disease,' PVD [22 of 80 patients (27.5%) dying within 4 years (4 in-hospital deaths)] (HR = 2.13, 95% CI: 1.26, 3.60, $P = 0.005$), age and female gender [38 of 207 patients (18.4%) dying within 4 years (8 in-hospital deaths)] (HR: 1.60; 95% CI: 1.01, 2.56; $P = 0.048$). Female gender had a weak negative correlation with the SYNTAX score (Pearson correlation coefficient: −0.09, $P = 0.007$) and a weak positive correlation with age (Pearson correlation coefficient 0.18, $P < 0.001$).

The SYNTAX score was an independent correlate of 4-year mortality in the PCI arm. For every 10-point-increase in the SYNTAX score, this associated with a 1.25 times greater risk of 4-year mortality in the PCI-treated patients.

Discussion

The following are the main findings of this study: (i) within the CABG arm, the lack of discharge aspirin therapy was the strongest independent correlate of 4-year mortality; (ii) within the PCI arm, clinical factors were more strongly associated with 4-year all-cause death compared with anatomical factors (namely the SYNTAX score); in addition procedural related factors, such as stent number or length, were not correlates of 4-year mortality; (iii) female gender was an independent correlate of 4-year mortality in the PCI arm; (iv) PVD was a common independent correlate of 4-year mortality in the CABG and the PCI arms—the presence of which may be a marker of native coronary disease severity and the risk of future coronary disease progression; and (v) the possibility of the outcomes of the SYNTAX trial having been affected by the significant differences in censored patient numbers between the CABG and the PCI arms cannot be excluded.

Table 3 **Univariate (selected variables shown) correlates of 4-year mortality in the entire percutaneous coronary intervention population of the randomized SYNTAX trial (n = 903)**

PCI (n = 903) univariate correlates of 4-year mortality	Incidence of mortality: no./total (%)	Hazard ratio (95% CI)	P-value
Categorical variables (%)			
No post-procedural anti-platelet therapy[a,b]	10/10 (100)[b]	173.76 (71.24–423.78)	<0.001
Pre-procedural poor LVEF	6/12 (50)	5.37 (2.35–12.26)	<0.001
Amiodarone therapy on discharge	5/12 (41.7)	4.85 (1.97–11.91)	0.001
Peripheral vascular disease	22/80 (27.5)	3.05 (1.91–4.89)	<0.001
History of GI bleeding or peptic ulcer disease	9/37 (24.3)	2.42 (1.22–4.79)	0.011
Female gender	38/207 (18.4)	1.95 (1.31–2.91)	0.001
Lack of pre-procedural thienopyridine[c]	4/20 (20)	1.78 (0.66–4.85)	0.26
Diabetes	41/247 (16.6)	1.76 (1.19–2.61)	0.005
Hypertension	83/642 (12.9)	1.52 (0.93–2.48)	0.092
Metabolic syndrome	47/327 (14.4)	1.51 (0.99–2.32)	0.057
Incomplete angiographic revascularization	53/381 (13.9)	1.41 (0.96–2.08)	0.081
Single (aspirin or thienopyridine[c]) on discharge	6/39 (15.4)	1.34 (0.59–3.06)	0.49
Current smoking	23/161 (14.3)	1.29 (0.81–2.05)	0.28
Stent length >100 mm	35/287 (12.2%)	1.09 (0.72–1.65)	0.67
Any total occlusion	26/209 (12.4%)	1.05 (0.68–1.64)	0.82
Left main coronary disease	40/349 (11.5)	0.94 (0.64–1.40)	0.77
Continuous variables[d]			
Age per increase in 10 years	70 ± 8	1.81 (1.45–2.26)	<0.001
SYNTAX score per increase in 10 points	32 ± 12	1.33 (1.14–1.54)	<0.001
Serum creatinine (mg/dL)	1.13 ± 0.43	1.29 (1.05–1.60)	0.018
Post-PCI peak CK ratio[e]	1.61 ± 3.18	1.21 (1.13–1.29)	<0.001
Total number of stents	5 ± 2	1.06 (0.97–1.15)	0.19
Total stent length (mm)	90 ± 46	1.00 (1.00–1.01)	0.45
BMI	28 ± 6	1.00 (0.96–1.04)	0.92
Post-PCI peak CK–MB ratio[e]	36.6 ± 21.6	1.05 (1.02–1.07)	<0.001

PCI, percutaneous coronary intervention; GI, gastrointestinal; LVEF, left ventricular ejection fraction; CK, creatine kinase; CK-MB, creatine kinase myoglobin, BMI, body mass index.
[a]Aspirin nor thienopyridine.
[b]All deaths occurred in-hospital and within 45 days.
[c]Clopidogrel or ticlopidine.
[d]Continuous variables are presented as mean ± SD in patients who died within four years (age and SYNTAX score are presented as actual values).
[e]The CK ratio (available in 766 of 903 patients—84.8% of the study population) and the CK–MB ratio (available in 54 of 903 patients—3% of study population) were not inserted in the multivariable model because of incomplete data as per the SYNTAX trial protocol.

Mechanism of late (4-year) mortality in coronary artery bypass graft and percutaneous coronary intervention patients

Within the CABG and the PCI arms, PVD was an independent correlate of 4-year Death. The presence and the severity of extracardiac disease, defined by parameters such as carotid intima media thickness (CIMT) and ankle brachial pressure index, have previously been associated with more extensive baseline coronary artery disease.[14–21] For example, Ikeda *et al.*[15] recently associated the severity of the SYNTAX score with the CIMT. More complex baseline coronary artery disease has in turn been associated with adverse long-term prognosis as reported in the Coronary Artery Surgery Study[21] and Rotterdam[18] registries. Within these registries, more extensive baseline preoperative coronary disease was associated with long-term mortality (>10 years), which were further linked to a higher prevalence and severity of other clinical risk factors. Notably, within the Bypass Angioplasty Revascularization Investigation trial, native coronary disease progression, and not failed revascularization, was the predominant determinant of jeopardized myocardium and recurrence of angina at 5-year follow-up in CABG- or PCI-treated patients.[22]

Lack of discharge anti-platelet therapy in the coronary artery bypass graft arm

The findings of lack of discharge aspirin after CABG to be an independent correlate of 4-year mortality are contrasted by previous studies that have potentially related aspirin therapy on the day of surgery to a reduction in in-hospital or at most 30-day mortality.[23] Historically, aspirin therapy on the day of surgery has been

Table 4 **Independent correlates of 4-year mortality in the entire percutaneous coronary intervention population of the randomized SYNTAX trial ($n = 903$)**

PCI ($n = 903$) independent correlates of 4-year mortality (*variables with a P- value >0.05 italicized*)	Hazard ratio	95% CI	*P*-value
No post-procedural anti-platelet therapy[a]	152.16	53.57–432.22	<0.001
Amiodarone therapy on discharge	4.49	1.36–14.83	0.014
Pre-procedural poor LVEF	3.31	1.03–10.64	0.045
History of GI bleeding or peptic ulcer disease	2.93	1.41–6.12	0.004
Peripheral vascular disease	2.13	1.26–3.60	0.005
Age per increase in 10 years	1.62	1.26–2.09	<0.001
Female gender	1.6	1.01–2.56	0.048
Serum creatinine	1.28	0.95–1.72	*0.11*
Diabetes	1.28	0.83–2.00	*0.27*
SYNTAX score per increase in 10 points	1.25	1.06–1.47	0.007

PCI, percutaneous coronary intervention; CI, confidence interval; GI, gastrointestinal; LVEF, left ventricular ejection fraction.
[a]Neither aspirin nor thienopyridine.

associated with a 50–70% reduction in early and late (up to 1-year) aorto-coronary vein-graft occlusion.[24–26] Graft patency at 1-year has, however, not translated into increased mortality. Moreover within the angiographic sub-study of SYNTAX trial,[27] despite over a quarter of the CABG patients (27.2%) found to have significantly diseased (≥50 to<100%) or obstructed (100%) bypass grafts at 15 months, this was not significantly associated with early major adverse cardiovascular and cerebrovascular events. Potential reasons for this latter phenomenon have been related to bypass grafts prematurely failing if anastomosed distal to functionally non-significant lesions, because of competitive flow, or the recurrence of anginal symptoms if bypass grafts to a functionally significant lesion failed.[27–30]

Why aspirin therapy in the present study was a strong independent correlate of 4-year mortality in the CABG arm is unclear. As previously discussed, patients with more complex coronary disease have been associated with the presence of extra-cardiac arteriopathy.[14–21] It may, therefore, be hypothesized that aspirin therapy was potentially protective against ischaemic complications arising from cardiac and systemic atherosclerotic disease (cerebral, renal, and GI), which may perhaps be more likely to occur in the study population.[14–21] This hypothesis is supported by the findings of most of the deaths in patients not on aspirin therapy at discharge in the CABG arm to be cardiac or vascular related (15 out of 27 deaths).

History of gastrointestinal bleeding or peptic ulcer disease

A history of GI bleeding or peptic ulcer disease was an independent correlate of 4-year mortality in the PCI arm ($P = 0.004$), with a trend towards significance in the CABG arm ($P = 0.085$). Aspirin alone, clopidogrel alone, and their combination have all been associated with an increased risk of GI bleeding.[31–33] Consequently, the association of a 'history of GI bleeding or peptic ulcer disease' with mortality is perhaps not unexpected, given the mandatory requirement of dual anti-platelet therapy after PCI to prevent stent thrombosis, and the potential long-term protective effect of aspirin therapy in CABG-treated patients as previously discussed. Notably, Iakovou *et al.*,[34] in a well-designed 'real-world' registry of first-generation DES (sirolimus- or paclitaxel-eluting stents) ($n = 2229$), demonstrated that the premature discontinuation of anti-platelet therapy is strongly associated with acute stent thrombosis at 9-months following DES implantation.

Within PCI patients, the use of concomitant proton pump inhibitors with clopidogrel therapy for gastro-protection has been controversial, because of a potential interaction with the anti-platelet effect of clopidogrel. Until now, no study has convincingly demonstrated any significant impact on adverse clinical outcomes, although this effect cannot be excluded in certain subgroups, such as poor metabolizers of clopidogrel.[35–38] Further studies are required to investigate the cost/risk–benefit ratio of selectively or routinely adopting prophylactic gastro-protective therapy in PCI (and possibly CABG)-treated patients.

Gender

Despite adjustments for risk factors, including age and the SYNTAX score, female gender was an independent correlate of 4-year mortality in the PCI arm of the SYNTAX trial, a finding at odds with other contemporary DES trials showing no gender effect.[39–43] The main difference being that females in the SYNTAX trial had more complex baseline coronary disease (and therefore potentially a greater atherosclerotic burden)—mean SYNTAX score of 26.5 ± 11.9—compared with $12.9 + 8.4$ in women from three pooled All-Comers randomized DES trials (SIRTAX, LEADERS, RESOLUTE).[39]

A recent sub-study of the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree)[44,45] has shown that there may be a potential 'gender effect' in the pathophysiology and composition of atherosclerotic plaque leading to acute coronary syndrome. Women (compared with men) were shown to have less extensive coronary artery

disease by angiographic and intravascular ultrasound assessments, less plaque rupture, less necrotic core and calcium, similar plaque burden, and smaller lumens. Conversely, the presence of thin-cap fibroatheroma was demonstrated to be a stronger marker of plaque vulnerability and risk of future clinical events in women compared with men. Importantly, despite these differences, clinical outcomes were reported to be comparable between the sexes in the PROSPECT trial, although most events occurred in angiographically inapparent lesions. Patients from the SYNTAX trial had substantially more complex coronary disease compared with the PROSPECT trial (which excluded patients with left main coronary artery disease and 3VD requiring PCI). Thus, the possibility of more unfavourable plaque composition in obstructive and non-obstructive lesions of females with advanced atherosclerotic disease being a possible explanation for the potential increased mortality in the SYNTAX trial cannot be dismissed.[14,45,46]

Study limitations

This study represents a *post hoc* analysis of the SYNTAX trial and the results should be considered hypothesis generating. Since the proportion of patients lost to follow-up varied between the two study arms (CABG arm: 8.7%, PCI arm: 2.7%, $P < 0.001$), this potential confounding factor should be considered when interpreting the results. Although multivariable adjustments were performed for significant confounders ($P < 0.05$), the possibility of other unmeasured confounders having affected the results cannot be excluded. Within the CABG arm as all correlates that were significantly associated with increased mortality on univariable analyses ($P < 0.05$) were included in the multivariable model, this may have resulted in over-fitting since there were 78 deaths. As the confidence intervals of these correlates were narrow, this would have limited this risk.[47] In the PCI population, there were enough events (104 deaths) to include all significant correlates. The lack of CK–MB ratios in all study patients precluded its assessment in the multivariable analyses.

Conclusion

Independent correlates of 4-year mortality in the SYNTAX trial were multifactorial. Lack of discharge aspirin (CABG arm) and female gender (PCI arm) are notable independent correlates of 4-year mortality that require confirmation in further studies. Peripheral vascular disease is a common independent correlate of 4-year mortality and may be a marker of the severity of baseline coronary disease and the risk of future native coronary disease (and extra-cardiac disease) progression.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The authors express their gratitude to all the study centres and participants whose work made this study possible. Thanks are due to Peggy Pereda and Jian Huang of Boston Scientific Corporation for their invaluable technical support in accessing the study database.

Funding

The SYNTAX trial was funded by Boston Scientific Corporation.

Conflict of interest: K.D.D., P.P., and J.H. are all full-time employees in Boston Scientific. K.D.D. holds stock in Boston Scientific. M.M. has served on the Speaker's Bureau of Cordis and Medtronic and reports no financial disclosures. T.F. reported research grants and consulting from Abbott Vascular, Boston Scientific, and Edwards Lifesciences. M.M. reported that her institution received a research grant from Boston Scientific. The other authors report no conflicts of interest.

References

1. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011; **32**:2125–2134.
2. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) Trial. *Circulation* 2010;**121**: 2645–2653.
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**:961–972.
4. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50–56.
5. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006;**151**:1194–1204.
6. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;**1**:219–227.
7. Holmes DR, Vazales B, Cannon LA, Stahle E, Morice MC, Mack MJ, Feldman TE, Kappetein AP, Colombo A, Dawkins KD, Mohr FW, Serruys PW. TCT-228: Four-year Follow-up of the SYNTAX Trial: optimal revascularization strategy in patients with three-vessel disease and/or left main disease. *J Am Coll Cardiol* 2011;**58**:B61 doi:10.1016/j.jacc.2011.10.233.
8. Mohr FW, Suttorp M, van Boven WJ, Morice MC, Mack MJ, Feldman TE, Kappetein AP, Colombo A, Holmes DR, Stahle E, Dawkins KD, Serruys PW. TCT-27: four-year follow-up of the SYNTAX Trial: optimal revascularization strategy in patients with three-vessel disease. *J Am Coll Cardiol* 2011;**58**:B8 doi: 10.1016/j.jacc.2011.10.031.
9. SYNTAX score calculator: http://www.syntaxscore.com. SYNTAX workinggroup. Launched 19th May 2009.
10. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004;**110**:1168–1176.
11. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA, Antman EM, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA 2004 guideline update for coronary artery

bypass graft surgery: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *J Am Coll Cardiol* 2004;**44**:e213–e310.
12. Smith SC Jr, Dove JT, Jacobs AK, Ward Kennedy J, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines): a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 2001;**37**:2239.
13. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;**69**:239–241.
14. Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR Jr, Kappetein AP, Mack MJ, Feldman T, Morice MC, Stahle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: The SYNTAX Trial at 3 Years. *JACC: Cardiovasc Intervent* 2012;**5**:606–617.
15. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. *Eur Heart J* 2012; **33**:113–119.
16. Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, Lloyd-Jones DM. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol* 2011;**57**:1838–1845.
17. Steinvil A, Sadeh B, Arbel Y, Justo D, Belei A, Borenstein N, Banai S, Halkin A. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. *J Am Coll Cardiol* 2011;**57**:779–783.
18. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. *Eur Heart J* 2009;**30**:453–458.
19. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197–208.
20. Otah KE, Madan A, Otah E, Badero O, Clark LT, Salifu MO. Usefulness of an abnormal ankle-brachial index to predict presence of coronary artery disease in African-Americans. *Am J Cardiol* 2004;**93**:481–483.
21. Myers WO, Blackstone EH, Davis K, Foster ED, Kaiser GC. CASS Registry long term surgical survival. Coronary Artery Surgery Study. *J Am Coll Cardiol* 1999; **33**:488–498.
22. Alderman EL, Kip KE, Whitlow PL, Bashore T, Fortin D, Bourassa MG, Lesperance J, Schwartz L, Stadius M. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 2004;**44**: 766–774.
23. Mangano DT. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002;**347**:1309–1317.
24. Chesebro JH, Fuster V, Pugo FJ. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2003;**348**:1057–1059; author reply 1057–9.
25. Chesebro JH, Fuster V, Elveback LR, Clements IP, Smith HC, Holmes DR Jr, Bardsley WT, Pluth JR, Wallace RB, Puga FJ, Orszulak TA, Piehler JM, Danielson GK, Schaff HV, Frye RL. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. *N Engl J Med* 1984;**310**:209–214.
26. Chesebro JH, Clements IP, Fuster V, Elveback LR, Smith HC, Bardsley WT, Frye RL, Holmes DR Jr, Vlietstra RE, Pluth JR, Wallace RB, Puga FJ, Orszulak TA, Piehler JM, Schaff HV, Danielson GK. A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. *N Engl J Med* 1982; **307**:73–78.
27. Morice MC, Feldman TE, Mack MJ, Stahle E, Holmes DR, Colombo A, Morel MA, van den Brand M, Serruys PW, Mohr F, Carrie D, Fournial G, James S, Leadley K, Dawkins KD, Kappetein AP. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with TAXUS express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). *EuroIntervention* 2011;**7**:670–679.
28. Nakajima H, Kobayashi J, Toda K, Fujita T, Shimahara Y, Kasahara Y, Kitamura S. A 10-year angiographic follow-up of competitive flow in sequential and composite arterial grafts. *Eur J Cardiothorac Surg* 2011;**40**:399–404.
29. Glineur D, D'Hoore W, El Khoury G, Sondji S, Kalscheuer G, Funken JC, Rubay J, Poncelet A, Astarci P, Verhelst R, Noirhomme P, Hanet C. Angiographic predictors of 6-month patency of bypass grafts implanted to the right coronary artery a prospective randomized comparison of gastroepiploic artery and saphenous vein grafts. *J Am Coll Cardiol* 2008;**51**:120–125.
30. Botman CJ, Schonberger J, Koolen S, Penn O, Botman H, Dib N, Eeckhout E, Pijls N. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg* 2007;**83**: 2093–2097.
31. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Simes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010; **31**:2501–2555.
32. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, Furberg CD, Johnson DA, Kahi CJ, Laine L, Mahaffey KW, Quigley EM, Scheiman J, Sperling LS, Tomaselli GF. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2010;**56**:2051–2066.
33. Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, Johnson DA, Mahaffey KW, Quigley EM, Harrington RA, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Hlatky MA, Kaul S, Lindner JR, Moliterno DJ, Mukherjee D, Schofield RS, Rosenson RS, Stein JH, Weitz HH, Wesley DJ. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2008;**52**:1502–1517.
34. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**: 2126–2130.
35. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, Mahaffey KW, Angiolillo DJ, Husted S, Cannon CP, James SK, Kilhamn J, Steg PG, Harrington RA, Wallentin L. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes Trial. *Circulation* 2012;**125**:978–986.
36. Pham JP, Ueno M, Tello-Montoliu A, Ferreiro JL, Tomasello SD, Dharmashankar K, Kodali M, Seecheran N, Capodanno D, Desai B, Bass TA, Angiolillo DJ. Impact of gastric acid-suppressing therapies on platelet reactivity in patients with coronary artery disease treated with clopidogrel: results of a pharmacodynamic study. *J Am Coll Cardiol* 2011;**58**:1396–1398.
37. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, Shook TL, Lapuerta P, Goldsmith MA, Laine L, Scirica BM, Murphy SA, Cannon CP. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; **363**:1909–1917.
38. O'Donoghue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, Michelson AD, Hautvast RW, Ver Lee PN, Close SL, Shen L, Mega JL, Sabatine MS, Wiviott SD. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;**374**:989–997.
39. Stefanini GG, Kalesan B, Pilgrim T, Raber L, Onuma Y, Silber S, Serruys PW, Meier B, Juni P, Windecker S. Impact of sex on clinical and angiographic outcomes among patients undergoing revascularization with drug-eluting stents. *JACC: Cardiovasc Intervent* 2012;**5**:301–310.
40. Kornowski R, Vaknin-Assa H, Assali A, Lev EI, Porter A, Battler A, Bental T. A comparative analysis of major clinical outcomes with drug-eluting stents versus

bare metal stents in male versus female patients. *EuroIntervention* 2012;**7**: 1051–1059.
41. Kovacic JC, Mehran R, Karajgikar R, Baber U, Suleman J, Kim MC, Krishnan P, Dangas G, Sharma SK, Kini A. Female gender and mortality after percutaneous coronary intervention: results from a large registry. *Catheter Cardiovasc Interv* 2012;**80**:514–21.
42. Solinas E, Nikolsky E, Lansky AJ, Kirtane AJ, Morice MC, Popma JJ, Schofer J, Schampaert E, Pucelikova T, Aoki J, Fahy M, Dangas GD, Moses JW, Cutlip DE, Leon MB, Mehran R. Gender-specific outcomes after sirolimus-eluting stent implantation. *J Am Coll Cardiol* 2007;**50**:2111–2116.
43. Lansky AJ. Outcomes of percutaneous and surgical revascularization in women. *Prog Cardiovasc Dis* 2004;**46**:305–319.
44. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;**364**:226–235.
45. Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, De Bruyne B, Farhat N, Niess G, Jankovic I, Lazar D, Xu K, Fahy M, Serruys PW, Stone GW. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *JACC: Cardiovasc Imaging* 2012;**5**: S62–S72.
46. WRITING GROUP MEMBERS, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VrL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. 2010 update. *Circulation* 2010;**121**:e46–e215.
47. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995;**48**:1503–1510.

Incidence and Multivariable Correlates of Long-Term (up to 4-Year) Mortality in Patients Treated with Surgical or Percutaneous Revascularisation in the Synergy Between PCI with TAXUS Express and Cardiac Surgery Trial

Supplementary Appendix

Contents

1. Supplementary Methods

Continuous data are presented as medians and interquartile range (IQR) and were compared with the Mann-Whitney rank sum test. Categorical variables were compared with the chi-square test.

2. Supplementary Tables

Table 1

Comparison of anatomical and clinical variables between patients with and without discharge antiplatelet therapy in the CABG arm (n=897).

CABG	No Antiplatelet Therapy on Discharge (n=100)	Antiplatelet Therapy on Discharge (n=770)	p-value
Categorical Variables			
Peripheral vascular disease	13/100 (13%)	78/770 (10.1%)	0.38
Pre-procedural poor LVEF	6/100 (6.0%)	14/770 (1.8%)	0.009
COPD	15/100 (15.0%)	66/770 (8.6%)	0.037
History of GI bleeding peptic ulcer disease	7/99 (7.1%)	31/764 (4.1%)	0.17
Amiodarone therapy on discharge	9/99 (9.1%)	102/770 (13.2%)	0.24
Hypertension	83/99 (83.8%)	581/765 (75.9%)	0.080
Lack of pre-procedural aspirin	83/99 (83.8%)	482/770 (62.6%)	<0.001
Metabolic syndrome	43/73 (58.9%)	270/616 (43.8%)	0.014
Left main coronary artery disease	30/100 (30.0%)	313/769 (40.7%)	0.039
Diabetes	33/100 (33.0%)	208/770 (27.0%)	0.21
On pump CABG	89/99 (89.0%)	635/753 (82.5%)	0.25
Anterograde administration of cardioplegia	84/99 (84.8%)	618/754 (82.0%)	0.48
Crystalloid cardioplegia	33/99 (33.0%)	244/753 (31.7%)	0.72
Incomplete revascularisation	39/99 (39.4%)	280/770 (36.4%)	0.56
Male	73/100 (73.0%)	618/770 (80.3%)	0.091
Current Smoker	22/97 (22.7%)	168/768 (21.9%)	0.86
High SYNTAX Score tertile	33/99 (33.3%)	275/766 (35.9%)	0.62
Blood cardioplegia	45/99 (45.0%)	382/753 (49.6%)	0.45
Retrograde administration of cardioplegia	14/99 (14.1%)	109/754 (14.5%)	0.93
Continuous Variables* **			
Age per increase in 10 years	69 (IQR 60-75)	66 (IQR 58-72)	0.26
Creatinine (mg/dL)	1.00 (IQR 0.90-1.20)	1.00 (IQR 0.85-1.10)	0.93
SYNTAX Score per increase in 10 points	27 (IQR 20-36)	28 (IQR 21-37)	0.95
Cross-clamp time (minutes)	52 (IQR 37-64)	51 (IQR 38-67)	0.077
BMI	28 (IQR 26-31)	27 (IQR 25-30)	0.91
Post CABG peak CK-MB ratio	7.6 (IQR 4.4-11.9)	6.0 (IQR 3.5-10.3)	0.001

***Continuous variables are presented as mean±SD in patients who died within 4-years (age and SYNTAX Score are presented as actual values).

Abbreviations: GI gastrointestinal; COPD chronic obstructive pulmonary disease; IQR interquartile range; LVEF left ventricular ejection fraction; CABG coronary artery bypass graft surgery; CK-MB creatine kinase myoglobin, BMI body mass index.

Table 2

Comparison of anatomical and clinical variables between patients with and without post-procedural antiplatelet therapy in the PCI arm (n=903).

PCI	No Post-Procedural Antiplatelet Therapy* (n=11)	Antiplatelet Therapy on Discharge†* (n=885)	p-value
Categorical Variables			
Pre-procedural poor LVEF	0/11 (0%)	12/885 (1.4%)	0.70
Amiodarone therapy on discharge	0/11 (0%)	13/885 (1.5%)	0.69
Peripheral vascular disease	2/11 (18.2%)	80/885 (9.0%)	0.30
History of GI bleeding or peptic ulcer disease	0/10 (0%)	37/881 (4.2%)	0.51
Female gender	6/11 (54.5%)	204/885 (23.1%)	0.014
Lack of pre-procedural thienopyridine**	2/11 (18.2%)	26/885 (2.9%)	0.004
Diabetes	6/11 (54.5%)	248/885 (28.0%)	0.052
Hypertension	9/11 (81.8%)	649/878 (73.9%)	0.55
Metabolic syndrome	6/9 (66.7%)	331/722 (45.8%)	0.21
Incomplete revascularisation	7/11 (63.6%)	381/885 (43.1%)	0.17
Current smoking	3/11 (27.3%)	163/885 (18.4%)	0.45
Stent length greater than 100 mm	5/8 (62.5%)	286/869 (32.9%)	0.077
Any total occlusion	2/11 (18.2%)	212/879 (24.1%)	0.65
Left main coronary disease	4/11 (36.4%)	348/885 (39.3%)	0.84
Continuous Variables* **			
Age per increase in 10 years	73 (IQR 70-75)	66 (IQR 59-73)	0.012
SYNTAX Score per increase in 10 points	32 (IQR 17-39)	27 (IQR 20-35)	0.38
Serum creatinine (mg/dL)	1.00 (IQR 0.90-1.60)	1.00 (IQR 0.80-1.10)	0.46
Post PCI peak CK ratio	2.8 (IQR 0.5-4.9)	0.54 (IQR 0.35-0.91)	0.014
Total number of stents	7 (IQR 4-8)	4 (IQR 3-6)	0.12
Total stent length (mm)	136 (IQR 64-148)	80 (IQR 52-112)	0.13
BMI	25 (IQR 24-26)	27 (IQR 25-31)	0.10
Post PCI peak CK-MB ratio	24.8 (IQR 14.3-32.8)	12.5 (IQR 6.2-20.3)	0.21

*Aspirin or thienopyridine
**Clopidogrel or ticlopidine
***Continuous variables are presented as medians±IQR in patients who died within 4-years (age and SYNTAX Score are presented as actual values).

Abbreviations: PCI percutaneous coronary intervention; GI gastrointestinal; IQR interquartile range; LVEF left ventricular ejection fraction; CK creatine kinase; CK-MB creatine kinase myoglobin, BMI body mass index.

3. Patient Narratives

Table 3

Known patient related events, as detailed in the patient narratives, preceding death in the 10 of the 11 patients not taking any anti-platelet therapy at the time of death.

Age/ Gender	SYNTAX Score	Known Events Preceding Death (Autopsy Details Provided Where Available)
79/F	13 (LM + 2VD)	Anaemia and thrombocytopenia (unknown cause), on warfarin long term (recurrent DVT/PE). Transfused 2 units packed red cells and platelets pre-procedure. 5 days post procedure melaena and anaemia. 9 days post index PCI, sudden cardiac arrest/death. No autopsy performed.
73/F	15 (3VD)	24 hours post index PCI, a significant fall in haemoglobin necessitating 3 unit blood transfusion. Upper GI endoscopy demonstrated 'duodenitis.' 9 days post index procedure, developed sudden anterior infarct/cardiac arrest. Autopsy: *"Taxus Express stents were deployed in the LM-LAD and LM-LCx bifurcations, so both stents extended to the proximal segment of these vessels (LAD and LCx). The stent thrombosis occurred in each of these stents."*
74/M	64 (LM + 3VD)	Rapidly progressive hypotension and cardiac arrest during index PCI procedure with bleeding from right femoral puncture site. Patient was anticoagulated with coumadin preadmission and received abciximab. Computed tomography imaging of abdomen confirmed retroperitoneal bleeding as cause of haemorrhagic shock. Developed disseminated intravascular coagulopathy, multiorgan failure and expired 3 days post index procedure.
67/F	17 (3VD)	Attempted RCA PCI - coronary dissection with inferior ST elevation (no stents implanted). Emergency CABG: SVG TO RCA and LCx OM branches. Cardiogenic shock post-procedure: patient expired within 6 hours. Autopsy: *"acute myocardial infarction of the wall of the left ventricle…haemopericardium developed, this was the direct cause of death."*
81/F	31 (3VD)	Peri-procedural small distal perforation conservatively treated: *"small area of intramyocardial dye 'staining' probably due to a small distal perforation induced by the hydrophilic guidewire."* 6 hours post PCI developed sudden hypotension secondary to cardiac tamponade leading to death. Autopsy: cause of death haemopericardium, *"...the examination of the 3 coronary vessels documented the presence of normally positioned and patent stents…"*
72/F	39 (3VD)	Left main, mid LAD stent implantation. Coronary perforation in LAD. Cardiac tamponade necessitating pericardiocentesis and cardiac surgery – bleeding site identified in right anterior wall next to proximal LAD. SVG to LAD, LCx and PDA. Developed systemic inflammatory response syndrome, *"multi-organ failure with disseminated intravascular coagulation…massive liver failure, increasing lactic acidosis…"* 13 days post index procedure patient expired.
71/M	38 (LM + 3VD)	PCI to trifurcation lesion of left main (crush technique) and mid LAD. PCI to RCA 4 days later as staged procedure. Acute stent thrombosis 1 day post staged procedure – catheterisation revealed thrombotic occlusion of common trunk. *"Using PTCA, partial rehabilitation of the anterior descending artery was obtained. Recanalization of the intermediate ramus and circumflex was not obtained."* Underwent emergency CABG: LIMA LAD, SVG D1 and OM (no RCA graft documented). Seven days post CABG, *"suddenly…the blood pressure decreased…subsequently experienced refractory hypotension…patient expired."* No autopsy performed.
56/F	32 (3VD)	Acute stent thrombosis/LAD abrupt closure 1 hour post 3VD PCI necessitating emergency PCI. Over the following 5 days developed respiratory sepsis, congestive heart failure and cardiogenic shock. New severe mitral regurgitation and worsening left ventricular function necessitating surgical mitral valve repair (no documented grafts) and biventricular assist device. Persistent ventricular failure and profound acidosis. Treatment withdrawn due to poor prognosis. Patient expired 17 days post index procedure.
75/M	65 (LM + 3VD)	Patient became haemodynamically and electrically unstable during the procedure. Peri-procedural death despite placement of stent in the left main stem. No autopsy performed.
76/M	33 (3VD)	Balloon catheter rupture during PCI to LCx (only 1 stent deployed) with retainment of material. Underwent emergency CABG for extraction of ruptured balloon catheter and SVG to PDA, LAD and OM. Patient developed cardiogenic shock a few hours post CABG requiring inotropic support. Patient expired 9 days post index procedure.

Abbreviations: 2VD 2 vessel disease; 3VD 3 vessel disease; CABG coronary artery bypass graft; DVT deep vein thrombosis; GI gastrointestinal; LCx left circumflex; LAD left anterior descending; LIMA left internal mammary artery graft; LM left main; OM obtuse marginal; PCI percutaneous coronary intervention; PE pulmonary embolism; PTCA percutaneous transluminal coronary angioplasty; RCA right coronary artery; SVG saphenous vein graft

PART VIII

Risk stratification and decision-making

Chapter 8.1

A Global Risk approach to identify patients with left main or 3 vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years

Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia Garcia HM, Holmes DR Jr, Kappetein AP, Mack MJ, Feldman T, Morice MC, Ståhle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW
JACC Cardiovasc Interv. 2012;5(6):606-17 (Impact Factor: 6.552)

CME

A Global Risk Approach to Identify Patients With Left Main or 3-Vessel Disease Who Could Safely and Efficaciously Be Treated With Percutaneous Coronary Intervention

The SYNTAX Trial at 3 Years

Patrick W. Serruys, MD, PhD,* Vasim Farooq, MBChB,* Pascal Vranckx, MD,* Chrysafios Girasis, MD,* Salvatore Brugaletta, MD,* Hector M. Garcia-Garcia, MD,* David R. Holmes, Jr, MD,† Arie-Pieter Kappetein, MD, PhD,‡ Michael J. Mack, MD,§ Ted Feldman, MD,‖ Marie-Claude Morice, MD,¶ Elisabeth Ståhle, MD,# Stefan James, MD,# Antonio Colombo, MD,** Peggy Pereda, MS,†† Jian Huang, MD, MS,†† Marie-Angèle Morel, BSc,‡‡ Gerrit-Anne Van Es, PhD,‡‡ Keith D. Dawkins, MD,†† Friedrich W. Mohr, MD,§§ Ewout W. Steyerberg, PhD‖‖

Rotterdam, the Netherlands; Rochester, Minnesota; Dallas, Texas; Evanston, Illinois; Massy, France; Uppsala, Sweden; Milan, Italy; Natick, Massachusetts; and Leipzig, Germany

JACC: CARDIOVASCULAR INTERVENTIONS CME

This article has been selected as this issue's CME activity, available online at http://interventions.onlinejacc.org/ by selecting the CME tab on the top navigation bar.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME Certificate

To obtain credit for this CME activity, you must:

1. Be an ACC member or *JACC: Cardiovascular Interventions* subscriber.
2. Carefully read the CME-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME credit.
4. Complete a brief evaluation.
5. Claim your CME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME Objective for This Article: To understand the potential role of anatomical and clinical factors in the Heart Team consensus in determining the optimal revascularization modality in patients with complex coronary artery disease.

CME Editor Disclosure: *JACC: Cardiovascular Interventions* CME Editor Habib Samady, MB, ChB, FACC, has research grants from the Wallace H. Coulter Foundation, Volcano Corp., St. Jude Medical, Forrest Pharmaceuticals Inc., and Pfizer Inc.

Author Disclosure: The SYNTAX study was funded by Boston Scientific. Dr. Mack has served on the Speaker's Bureau of Boston Scientific, Cordis, and Medtronic. Dr. Feldman serves on the Speaker's Bureau of Boston Scientific; receives grant support from Abbott, Atritech, Boston Scientific, Edwards, and Evalve; and consults for Abbott, Coherex, Intervalve, Square One, and W.L. Gore. Dr. Morice reports that her institution received a research grant from Boston Scientific. Dr. Dawkins, Ms. Pereda, and Dr. Huang are all full-time employees of Boston Scientific. Dr. Dawkins holds stock in Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval:

Issue Date: June 2012
Expiration Date: May 31, 2013

A Global Risk Approach to Identify Patients With Left Main or 3-Vessel Disease Who Could Safely and Efficaciously Be Treated With Percutaneous Coronary Intervention

The SYNTAX Trial at 3 Years

Objectives The aim of this study was to assess the additional value of the Global Risk—a combination of the SYNTAX Score (SXscore) and additive EuroSCORE—in the identification of a low-risk population, who could safely and efficaciously be treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI).

Background PCI is increasingly acceptable in appropriately selected patients with left main stem or 3-vessel coronary artery disease.

Methods Within the SYNTAX Trial (Synergy between PCI with TAXUS and Cardiac Surgery Trial), all-cause death and major adverse cardiac and cerebrovascular events (MACCE) were analyzed at 36 months in low (GRC_{LOW}) to high Global Risk groups, with Kaplan-Meier, log-rank, and Cox regression analyses.

Results Within the randomized left main stem population (n = 701), comparisons between GRC_{LOW} groups demonstrated a significantly lower mortality with PCI compared with CABG (CABG: 7.5%, PCI: 1.2%, hazard ratio [HR]: 0.16, 95% confidence interval [CI]: 0.03 to 0.70, p = 0.0054) and a trend toward reduced MACCE (CABG: 23.1%, PCI: 15.8%, HR: 0.64, 95% CI: 0.39 to 1.07, p = 0.088). Similar analyses within the randomized 3-vessel disease population (n = 1,088) demonstrated no statistically significant differences in mortality (CABG: 5.2%, PCI: 5.8%, HR: 1.14, 95% CI: 0.57 to 2.30, p = 0.71) or MACCE (CABG: 19.0%, PCI: 24.7%, HR: 1.35, 95% CI: 0.95 to 1.92, p = 0.10). Risk-model performance and reclassification analyses demonstrated that the EuroSCORE—with the added incremental benefit of the SXscore to form the Global Risk—enhanced the risk stratification of all PCI patients.

Conclusions In comparison with the SXscore, the Global Risk, with a simple treatment algorithm, substantially enhances the identification of low-risk patients who could safely and efficaciously be treated with CABG or PCI. (J Am Coll Cardiol Intv 2012;5:606–17) © 2012 by the American College of Cardiology Foundation

The SYNTAX score (SXscore) (1–4) has established itself as an important tool in the SYNTAX trial (The Synergy between PCI with TAXUS and Cardiac Surgery Trial) pioneered Heart Team approach, in which the cardiac surgeon and interventional cardiologist determined the optimal revascularization modality for patients with untreated left main stem (LMS) or 3-vessel (3VD) coronary artery disease (1,5–7). The SXscore has since been validated in the LMS percutaneous coronary intervention (PCI) population at short- and long-term follow-up (8–11); the 3VD PCI population at short-term (1-year) follow-up (12,13); and "All-Comers" patients undergoing PCI in contemporary stent trials at 1-year follow-up (14,15). In addition, both the current U.S. and European Guidelines on myocardial revascularization (16–18) advocate the use of the SXscore to determine the optimal revascularization modality in patients with unprotected left main or complex coronary disease, without the explicit use of clinical vari-

From the *Department of Interventional Cardiology, Erasmus University, Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; †The Mayo Clinic, Rochester, Minnesota; ‡Department of Cardiothoracic Surgery, Erasmus University, Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; §Medical City Dallas Hospital, Dallas, Texas; ‖Evanston Hospital, Evanston, Illinois; ¶Institut Jacques Cartier, Massy, France; #University Hospital Uppsala, Uppsala, Sweden; **San Raffaele Scientific Institute, Milan, Italy; ††Boston Scientific Corporation, Natick, Massachusetts; ‡‡Cardialysis BV, Rotterdam, the Netherlands; §§Herzzentrum, Leipzig, Germany; and the ‖‖Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands. The SYNTAX study was funded by Boston Scientific. Dr. Mack has served on the Speaker's Bureau of Boston Scientific, Cordis, and Medtronic. Dr. Feldman serves on the Speaker's Bureau of Boston Scientific; receives grant support from Abbott, Atritech, Boston Scientific, Edwards, and Evalve; and consults for Abbott, Coherex, Intervalve, Square One, and W.L. Gore. Dr. Morice reports that her institution received a research grant from Boston Scientific. Dr. Dawkins, Ms. Pereda, and Dr. Huang are all full-time employees of Boston Scientific. Dr. Dawkins holds stock in Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Stephen G. Ellis, MD, served as Guest Editor for this paper. Drs. Serruys and Farooq contributed equally to this paper.

Manuscript received February 7, 2012; revised manuscript received March 16, 2012, accepted March 22, 2012.

ables. Furthermore, the U.S. guidelines now gives surgical revascularization for unprotected left main coronary disease a Class 1B recommendation (16,17), compared with a Class 1A recommendation in previous guidelines (19).

Because the SXscore relies on the scoring of the coronary anatomy in isolation to objectively select the appropriate revascularization strategy for the individual patient, criticism has emerged, due to potentially important prognostic information being missing secondary to the absence of clinical factors (20,21). The EuroSCORE (22,23), a cardiac surgery-based clinical risk score, has been shown to have a reliable impact on prognosis and to be an independent predictor of major adverse cardiac events and mortality in surgical and percutaneously treated patients in the SYNTAX trial, thus confirming findings from previous studies (24–28).

Attempts have previously been made to combine the SXscore and additive EuroSCORE to form the Global Risk classification (29,30) and have been shown to potentially improve the risk stratification of patients undergoing surgical or percutaneous LMS intervention, compared with the SXscore alone. The Global Risk categorical approach reported in the present study, adapted from the previously reported Global Risk classification (29,30), uses the historically accepted cutoff levels for tertiles of the additive EuroSCORE (22,23)—of which a high EuroSCORE tertile has previously been shown to be an independent predictor of adverse outcomes after PCI (24,26–28)—and the now broadly accepted tertiles of the SXscore (Fig. 1) (1–4). Therefore the goal of the Global Risk is to improve in the identification of low-risk groups with LMS or 3VD, compared with the SXscore, who would achieve comparable surgical and percutaneous outcomes in terms of efficacy and safety at 3 years.

Abbreviations and Acronyms

3VD = 3-vessel disease
BMS = bare-metal stent(s)
CABG = coronary artery bypass graft surgery
CI = confidence interval
GRC_{LOW} = Low Global Risk
GRC_{INT} = Intermediate Global Risk
GRC_{HIGH} = High Global Risk
HR = hazard ratio
LMS = left main stem
MACCE = major adverse cardiac and cerebrovascular event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SXscore = SYNTAX Score

Methods

The SYNTAX trial is a randomized, prospective, multicenter trial that incorporated an "All-Comers" design and consisted of pre-specified LMS (isolated or associated with 1-, 2-, or 3-vessel disease) and 3VD cohorts (1,6,7). Patients were randomized on a 1:1 basis to undergo either coronary artery bypass graft surgery (CABG) or PCI or placed in nested registries when considered unsuitable for randomization by the Heart Team (CABG nested registry for PCI-ineligible patients and PCI nested registry for CABG-ineligible patients). Exclusions were only limited to patients with prior coronary revascularization, the requirement of concomitant cardiac surgery, or ongoing acute myocardial infarction (MI). Recent MI with resolution of cardiac enzymes (<2× upper limit of normal) and unstable angina (no elevation in biomarkers) were not exclusion criteria.

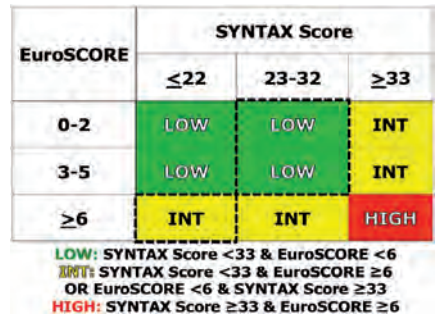


Figure 1. The Proposed Global Risk

The Global Risk demonstrating recategorization of established tertiles of risk for the SYNTAX Score and additive EuroSCORE to form low (GRC_{LOW}), intermediate (GRC_{INT}), and high (GRC_{HIGH}) Global Risk groups. **Highlighted (dashed) boxes** indicate patients moved (reclassified) into or out of the low SYNTAX Score group to form the low Global Risk group (GRC_{LOW}). Adapted from Capodanno et al. (29,30).

The PCI techniques between the randomized and nested registry populations were similar except that TAXUS Express (Boston Scientific Corporation, Natick, Massachusetts) paclitaxel-eluting stents were only permitted in the randomized population. Within the PCI nested registry the implantation of any type of drug-eluting stent or bare-metal stent (BMS) was permitted, although the use of TAXUS paclitaxel-eluting stents was encouraged. Of the 589 stents implanted within the PCI nested registry, 57% were TAXUS Express or Liberté (Boston Scientific Corporation), 19% were another drug-eluting stent, and 24% were BMS; 4 PCI nested registry patients did not receive a stent. Conversely CABG techniques between the randomized and nested registry were broadly similar, except that double left and right internal mammary artery grafts were more frequently performed in the randomized (27.6%) CABG population, compared with the CABG nested registry (16.1%).

The Global Risk was calculated by combining the SXscore (2–4)—calculated by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands)—and the additive EuroSCORE, as assessed by the Heart Team before randomization (22,23). The additive EuroSCORE was used to form the Global Risk, because this was shown

Table 1. Comparison of Anatomical Factors (SXscore) and Clinical Risk Scores for the CABG and PCI Populations

	CABG				PCI				
Anatomical/Clinical Risk Score	Randomized (n = 897)	Nested Registry (n = 644)	All-Comers (n = 1,541)	p Value†	Randomized (n = 899)	Nested Registry (n = 195)	All-Comers (n = 1,094)	p Value†	p Value*
SXscore	29.1 ± 11.4	37.8 ± 13.3	32.7 ± 12.9	<0.001	28.4 ± 11.5	31.3 ± 12.5	28.9 ± 11.7	0.002	<0.001
Total Parsonnet score	8.4 ± 6.8	9.0 ± 7.1	8.7 ± 6.9	0.15	8.5 ± 7.0	14.4 ± 9.5	9.6 ± 7.8	<0.001	0.001
Additive EuroSCORE	3.8 ± 2.69	3.9 ± 2.7	3.8 ± 2.7	0.47	3.8 ± 2.6	5.8 ± 3.1	4.1 ± 2.8	<0.001	0.008
Logistic EuroSCORE, %	3.9 ± 4.4	4.0 ± 4.4	3.9 ± 4.4	0.46	3.8 ± 4.5	7.7 ± 8.9	4.5 ± 5.8	<0.001	0.009

Mean score ± 1 SD. *p value represents comparisons between the All-Comers (randomized and nested registry) coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) populations. †p value represents comparisons between the randomized and nested registry populations for the CABG and PCI populations.
SXscore = SYNTAX Score.

to be more predictive of clinical outcomes in the PCI population compared with the logistic EuroSCORE, findings consistent with a previous study (29). Patients were subsequently categorized into 3 classes of Global Risk, on the basis of predefined anatomical and clinical-risk categories (low, intermediate, and high) for the SXscore (2–4) and additive EuroSCORE, respectively (22,23) (Fig. 1).

Statistical methods. Comparisons of all-cause death and major adverse cardiac and cerebrovascular events (MACCE) (a composite of all-cause death, MI, stroke, and all-cause revascularization) (1,7) were performed (Kaplan-Meier curves) with the log-rank test and Cox proportional hazard ratios between the low Global Risk (GRC_{LOW}) groups for CABG and PCI. This prognostic model-based approach to identify a low subgroup of patients defined by prognostic factors is in contrast to the traditional approach to subgroup analysis (31–33). A logistic regression model that incorporated the SXscore and EuroSCORE as covariates was used to give each score proper relative weighting to each other within the Global Risk. This analysis allowed for the assessment of the predictive ability of the Global Risk: 1) the Hosmer–Lemeshow test for calibration—the assessment of the correctness of the prediction by the risk model, with poor fit indicated by a significant p value (<0.05); 2) receiver operator curves for discrimination (C-statistic)—the ability of the risk model to appropriately assign the correct risk prediction in patients who have the outcome, ranging from 0.50 (no discrimination) to 1.0 (perfect discrimination); 3) the Brier score—an overall risk model performance measure capturing both discrimination and calibration aspects of the risk model, ranging from 0 to 1, with a lower value (closer to 0) suggestive of a more predictive risk model (34–36). Comparisons were made with other risk models, namely, the SXscore (2,4); age, creatinine, and ejection fraction/modified age, creatinine, and ejection fraction scores (37,38); the Clinical SXscore (39,40); and the additive/logistic EuroSCOREs (22,23)—a brief description of which is enclosed in the Online Appendix.

Analyses on those groups that were reclassified according to the Global Risk compared with the SXscore alone were undertaken, following the principles of Net Reclassification Improvement (38,41) (Fig. 1). These reclassification analyses were to test whether the low Global Risk group (GRC_{LOW}) appropriately risk-stratified patients, compared with a low SXscore. Higher anatomical risk patients (i.e., intermediate SXscores with low-intermediate EuroSCOREs) would be appropriately reclassified as lower-risk (GRC_{LOW}) if they had comparable (or more favorable) PCI outcomes, compared with CABG. Conversely lower anatomical risk patients with a high clinical comorbidity (i.e., low SXscore with a high EuroSCORE) would only be appropriately reclassified to a higher risk group (GRC_{INT}) if they had more favorable surgical outcomes, compared with PCI. Further detailed methodology, including illustrative figures describing the reclassification concepts, is included in the Online Appendix. A 2-sided p value <0.05 was considered significant for all tests. All analyses were conducted with SAS System Software (version 8.0 or higher, SAS Institute, Cary, North Carolina) and SPSS (version 17.0, SPSS, Inc., Chicago, Illinois).

Results

All randomized patients underwent planned follow-up. Within the nested registries, all PCI patients underwent planned follow-up, and 649 of the 1,077 CABG patients were randomly allocated for follow-up, on the basis of the original study protocol (1,7). Complete data, including clinical outcomes relating to the Global Risk, were available in 1,789 of 1,800 randomized patients (PCI, n = 899; CABG, n = 890), and 2,610 of 3,075 "All-Comers" patients (PCI, n = 1,088; CABG, n = 1,522) at 3-year follow-up.

Within the randomized SYNTAX population baseline demographic data and clinical characteristics for the treatment arms have previously been described and were well-balanced (1). Within the "All-Comers" population more complex coronary anatomy was present in the CABG population (mean SXscore ± 1 SD: CABG: 32.7 ± 12.9, PCI: 28.9 ± 11.7, p < 0.001) (Table 1). Conversely, significantly more comorbidity was present in the "All-

Comers" PCI population, as evidenced by significantly greater Parsonnet (42) and EuroSCOREs (Table 1).

Clinical outcomes with PCI. Within the randomized and "All-Comers" LMS (Fig. 2) and 3VD (Fig. 3) PCI populations, a low Global Risk group (GRC_{LOW}) could be differentiated from the higher risk groups ($GRC_{INT-HIGH}$) for All-Cause death and MACCE. Furthermore, within the LMS PCI population, the Global Risk demonstrated a clear incremental increase in predictive ability (C-statistics and overall risk model performance measures), compared with either the SXscore or the EuroSCORE in isolation (Fig. 4). Within the randomized and "All-Comers" 3VD PCI population, the additive EuroSCORE had a superior predictive ability for all-cause death and MACCE compared with the SXscore alone, with little or no additional improvements in the predictive ability of the Global Risk compared with the additive EuroSCORE (Fig. 4).

Clinical outcomes with CABG. At 36 months the Global Risk could differentiate between the $GRC_{INT-HIGH}$ groups only for all-cause death and MACCE in the randomized and "All-Comers" CABG populations (Figs. 2 and 3). The Global Risk added little or no improvement to the predictive ability, compared with the additive EuroSCORE used in isolation (Fig. 4).

Comparison of CABG and PCI: low-risk LMS population. Within the GRC_{LOW} group of the randomized LMS population (n = 701), CABG resulted in significantly higher 3-year mortality compared with PCI (CABG: 7.5%, PCI: 1.2%, HR: 0.16, 95% CI: 0.03 to 0.70, p = 0.0054), with a trend toward a lower incidence of MACCE (CABG: 23.1%, PCI: 15.8%, HR: 0.64, 95% CI: 0.39 to 1.07, p = 0.088) and stroke (CABG: 3.5%, PCI: 0.6%, HR: 0.17, 95% CI: 0.02 to 1.46, p = 0.067). No statistically significant differences in MI or all-cause revascularization were found.

Within the GRC_{LOW} group of the "All-Comers" LMS population (n = 1,079), no statistically significant differences in mortality (CABG: 5.3%, PCI: 2.7%, HR: 0.51, 95% CI: 0.18 to 1.44, p = 0.19) or MACCE (CABG: 18.0%, PCI: 18.5%, HR: 1.02, 95% CI: 0.65 to 1.60, p = 0.94) were observed. A significantly greater incidence of stroke was evident with CABG (CABG: 4.0%, PCI: 0.6%, HR: 0.13, 95% CI: 0.02 to 1.05, p = 0.025), and a significantly greater frequency of MI was evident with PCI (CABG: 0.9%, PCI: 3.9%, HR: 4.30, 95% CI: 0.89 to 20.70, p = 0.047). No statistically significant differences in all-cause revascularization were seen (CABG: 10.7%, PCI: 14.8%, HR: 1.40, 95% CI: 0.81 to 2.42, p = 0.23).

Comparison of CABG and PCI: low-risk 3VD population. Within the GRC_{LOW} group of the randomized 3VD population (n = 1,088), no statistically significant differences in 3-year mortality (CABG: 5.2%, PCI: 5.8%, HR: 1.14, 95% CI: 0.57 to 2.30, p = 0.71) or MACCE (CABG: 19.0%, PCI: 24.7%, HR: 1.35, 95% CI: 0.95 to 1.92, p = 0.10) were observed. Percutaneous coronary intervention was associated with a significantly increased risk of all-cause revascularization (CABG: 10.5%, PCI: 18.5%, HR: 1.88, 95% CI: 1.19 to 2.96, p = 0.0055). No statistically significant differences in the risk of stroke were seen (CABG: 2.9%, PCI: 1.3%, HR: 0.45, 95% CI: 0.13 to 1.49, p = 0.18).

Within the "All-Comers" 3VD population (n = 1,531) no statistically significant differences in mortality were observed (CABG: 5.1%, PCI: 5.9%, HR: 1.16, 95% CI: 0.62 to 2.17, p = 0.65). A significantly higher incidence of MACCE was evident with PCI (CABG: 17.9%, PCI: 24.4%, HR: 1.42, 95% CI: 1.03 to 1.96, p = 0.031) secondary to predominantly greater all-cause revascularization (CABG: 9.1%, PCI: 18.5%, HR: 2.20, 95% CI: 1.44 to 3.35, p = 0.0002). No statistically significant differences in the incidences of stroke were seen (CABG: 3.2%, PCI: 1.5%, HR: 0.46, 95% CI: 0.16 to 1.30, p = 0.13).

Analyses of reclassified patients. Within the LMS population, patients (i.e., patients with an intermediate SXscore and low-moderate EuroSCOREs) were appropriately reclassified to the GRC_{LOW} group (Fig. 1). More favorable outcomes were seen with PCI, compared with CABG (randomized population: 3-year all-cause death: CABG 10.8%, PCI 1.3%; 3-year MACCE: CABG 24.4%, PCI 15.6%). Conversely, patients reclassified to a higher-risk (GRC_{INT}) group (i.e., patients with a low SXscore and a high EuroSCORE) had more favorable surgical outcomes in the larger "All-Comers" population (Fig. 1), predominantly secondary to reduced MACCE with CABG (3-year MACCE: CABG 20.4%, PCI 27.0%).

Within the 3VD population more favorable surgical outcomes were evident in patients reclassified to the GRC_{LOW} group. Further analyses indicated that a GRC_{LOW} with an intermediate SXscore would remain better-managed by CABG, and a GRC_{LOW} with a low SXscore would have comparable surgical and PCI outcomes. More favorable surgical outcomes were evident in patients (i.e., with a low SXscore and a high EuroSCORE) reclassified to the higher-risk (GRC_{INT}) group (randomized population: 3-year death: CABG 9.6%, PCI 21.3%; 3-year MACCE: CABG 22.5%, PCI 39.1%). Further detailed results of the reclassification analyses are included in the Online Appendix.

Comparison of the Global Risk with other risk models. The Global Risk was superior in predictive performance compared with other combined anatomical/clinical scores (derived from the SXscore) and their components. This included the Clinical SXscore (39) (Fig. 4).

Discussion

The main findings of this study are: 1) clinical variables (EuroSCORE) per se are more predictive of clinical outcomes (all-cause death and MACCE), compared with anatomical variables (SXscore) in the PCI population; 2) within the LMS PCI population the Global Risk demonstrated a clear incre-

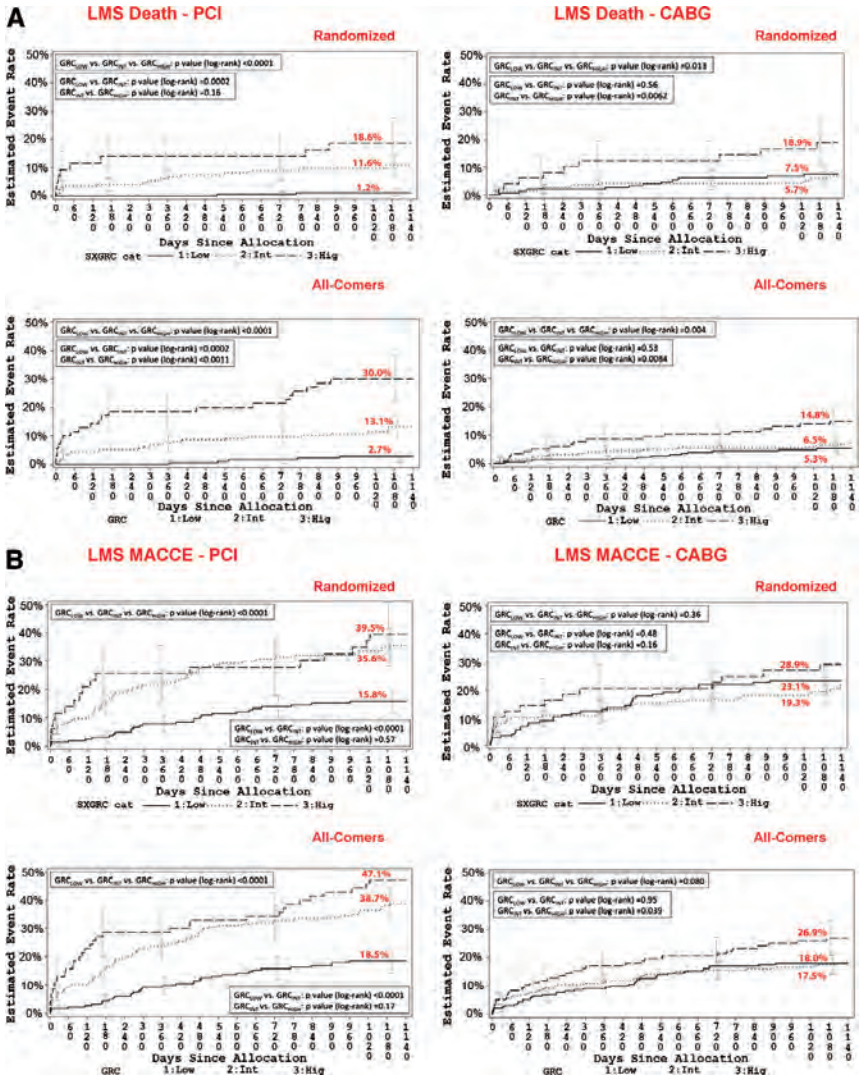


Figure 2. Comparisons of Clinical Outcomes by Categories of Global Risk in the SYNTAX LMS Population

Kaplan-Meier curves for cumulative rate of death **(A)** and MACCE **(B)** at 3-year follow-up stratified according to the Global Risk group; event rate ± 1.5 SE. CABG = coronary arty bypass grafting; GRCLOW = Low Global Risk; GRCINT = Intermediate Global Risk; GRCHIGH = High Global Risk; LMS = left main stem; MACCE = major adverse cardiac and cerebrovascular event(s); PCI = percutaneous coronary intervention.

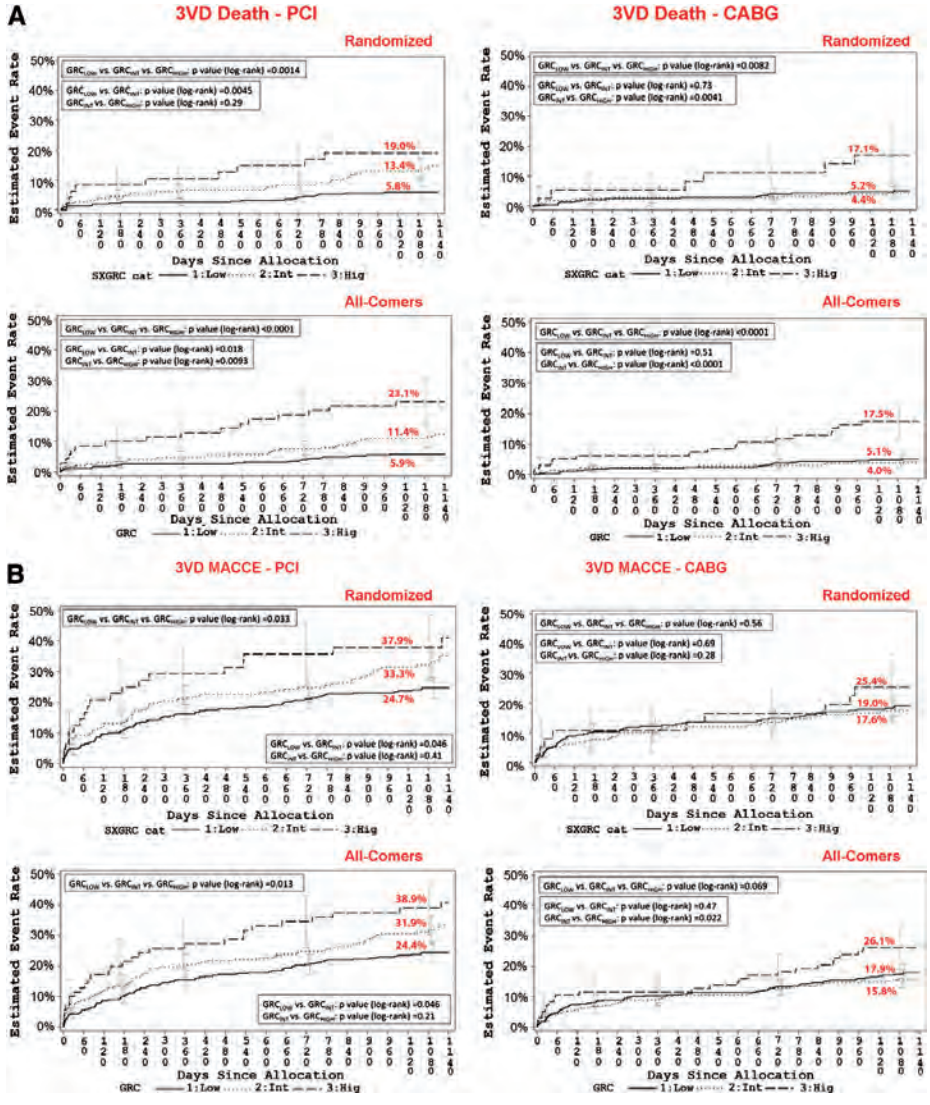


Figure 3. Comparisons of Clinical Outcomes by Categories of Global Risk in the SYNTAX 3VD Population

Kaplan-Meier curves for cumulative rate of death **(A)** and MACCE **(B)**, at 3-year follow-up stratified according to the Global Risk group; event rate ± 1.5 SE. 3VD = 3-vessel disease; other abbreviations as in Figure 2.

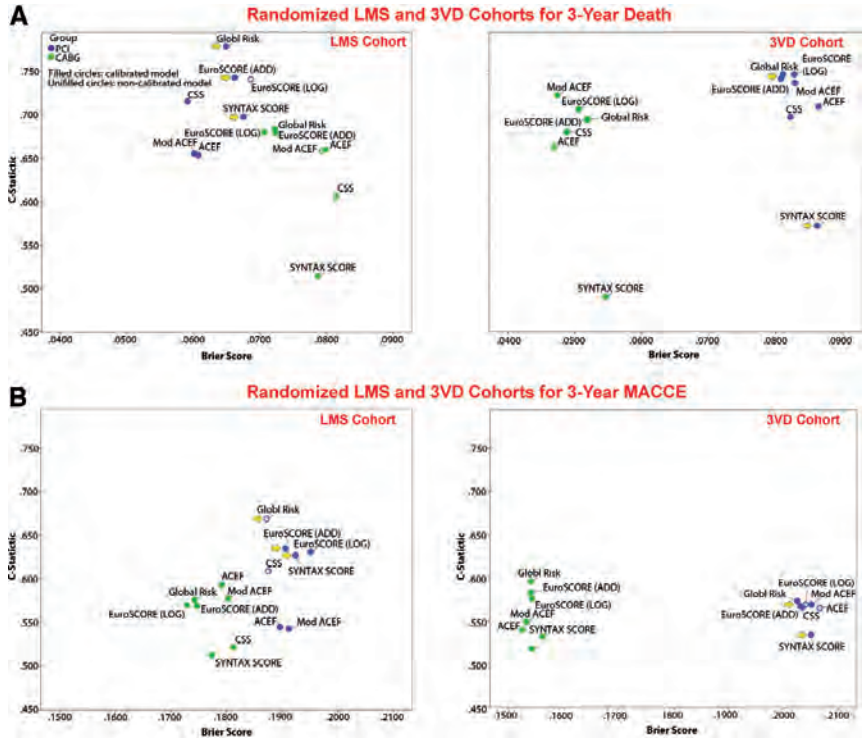


Figure 4. Comparison of Different Risk Models for the Randomized LMS and 3VD Populations for Death and MACCE at 3 Years

Comparison of different risk models for the randomized LMS and 3VD populations for death **(A)** and MACCE **(B)** at 3 years, with calibration (Hosmer–Lemeshow test), discrimination (C-statistic, y axes), and overall model performance measures (Brier score, x axes) (36). **Yellow arrows** in the LMS cohort demonstrate the incremental benefit, in terms of predictive ability, of the Global Risk compared with the additive EuroSCORE and SYNTAX Score as evidenced by a greater C-statistic and lower Brier score. **Yellow arrows** in the 3VD cohort demonstrate the incremental benefit of the additive EuroSCORE compared with the SYNTAX Score with little/no improvement of the predictive ability of the Global Risk compared with the additive EuroSCORE, as evidenced by comparable C-statistics and Brier scores. Note how even minor differences in the Brier score reflect overall improvements in the model performance and the different scales for the Brier scores for death and MACCE reflecting the findings that the risk models are superior in predicting death. ACEF = age, creatinine, and ejection fraction (score); CSS = clinical SYNTAX score; other abbreviations as in Figures 2 and 3.

mental benefit in its predictive ability, compared with the SXscore or EuroSCORE used in isolation; 3) within the 3VD PCI population, the Global Risk improved the risk stratification of patients, compared with the SXscore alone, by demonstrating that low SXscore patients with a high EuroSCORE to attain a mortality benefit in undergoing CABG compared to PCI; and 4) that the Global Risk substantially enhanced the identification of a low-risk population who could safely and efficaciously be treated with CABG or PCI at 3 years.

The application of the Global Risk to the SYNTAX population was complicated by the differing prognostic and morbidity outcomes between the LMS and 3VD populations. However, a low-risk population was identified with outcomes comparable to CABG and PCI at 3 years in terms of efficacy and safety, namely a GRC_{LOW} group in the LMS population and a GRC_{LOW} group with a low SXscore in the 3VD population. Ultimately reclassification analyses proved vital in ensuring the optimal revascularization modality in specific groups of patients. For example, high-EuroSCORE

patients with a low SXscore were shown to confer a clear mortality benefit from undergoing CABG in the 3VD population, and intermediate-SXscore patients with low-moderate EuroSCOREs were shown to confer a potential survival advantage in undergoing PCI in the LMS population. On the basis of these findings a treatment algorithm is proposed to simplify these concepts, which admittedly will require further validation in other unselected registries (Fig. 5).

The main strengths of the Global Risk are that the additive EuroSCORE is a simple bedside calculation and that the Global Risk can be applied across the entire spectrum of surgical and percutaneously treated patients. Within the "All-Comers" SYNTAX population the adoption of this treatment algorithm (Fig. 5) would potentially identify a smaller population of patients, compared with using the SXscore alone, who would have similar outcomes to CABG and PCI at 3 years in terms of efficacy and safety—namely, 39% of the LMS population (compared with 51% with low-moderate SXscores) and 21% of the 3VD population (compared with 26% with a low SXscore).

By identifying a low Global Risk (GRC_{LOW}) group within the randomized LMS population, a significant mortality benefit and trend toward a reduction in MACCE was evident for PCI at 3 years. This was not apparent in the "All-Comers" population. Several factors might explain this disparity in results. First, the "All-Comers" PCI population had significantly greater comorbidity (Table 1)—factors well known to be associated with in-hospital and long-term adverse outcomes after PCI (24,26–28). Second, a low EuroSCORE could not exclude nonadjustable characteristics, such as the judgment of the treating clinician in declining a patient for CABG and thus undergoing PCI instead, such as patients with a short-term survival—as were recruited within the "All-Comers" SYNTAX trial. Third, the CABG nested registry might potentially have been diluted with a proportion of lower-anatomical-risk patients who might have been suitable for PCI, because the concept of the clinical outcomes on the basis of tertiles of the SXscore were unknown at the time of the SYNTAX trial. Fourth, is the use of BMS in the nested PCI registries: although specific data pertaining to the indications for use of BMS were not collected, it is probable that a sizeable proportion of these patients might have had comorbidities that precluded the use of prolonged dual antiplatelet therapy. The adoption of the "All-Comers" approach is nonetheless more likely to mirror contemporary clinical practice and is perceived by many as the recommended approach (18,43).

Adverse clinical comorbidity: CABG or PCI? In both the LMS and 3VD populations the surgical benefit in the higher comorbidity patients (i.e., with a low SXscore and high EuroSCORE) was more pronounced, compared with PCI. In particular a substantial mortality benefit favoring CABG was evident in low-SXscore patients with a high EuroSCORE in the 3VD population. Although it has been previously demonstrated that a high EuroSCORE is a potential predictor of adverse outcomes after PCI (24,26–28), conventional clinical practice has suggested that high-comorbidity patients might be more suitable for PCI compared with CABG. In contrast to this accepted clinical practice, it seems that it is precisely these types of patients who would potentially stand to gain more from CABG on prognostic and morbidity grounds. These findings are probably related to PCI treating the individual lesion, whereas CABG would potentially protect the entire treated vessel from future cardiac events for the lifespan of the graft.

There is nevertheless a recognition that a certain threshold of operative risk would have to be acceptable for the cardiac surgeon and patient, and the latter of who may adamantly refuse a surgical approach due to the anticipated prohibitive risk of the proposed surgical intervention. It should, however,

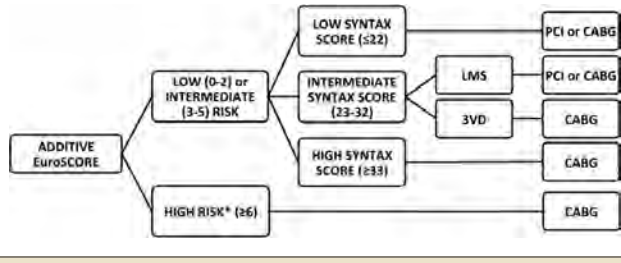


Figure 5. Proposed Treatment Algorithm for the Management of LMS and 3VD Incorporating Clinical and Anatomical Variables

Proposed treatment algorithm for the management of LMS and 3VD incorporating clinical (additive EuroSCORE) and anatomical (SYNTAX Score) variables. Although not explicitly stated PCI might be the preferred revascularization modality in low-risk patients subject to the Heart Team discussion. *If an acceptable threshold of operative risk is exceeded for the patient and cardiac surgeon, consideration of PCI should be considered—appropriate discussion concerning risk stratification should be undertaken. Abbreviations as in Figures 2 and 3.

be recognized that PCI may potentially be more hazardous for the patient with regard to long-term outcomes, compared with CABG. A greater understanding of this phenomenon may potentially reduce the threshold value for which surgical revascularization is declined during the Heart Team discussion.

Anatomical and clinical variables in the LMS PCI population. Before the introduction of the SXscore, heterogeneity of the LMS anatomical description and its impact on clinical outcomes were previously recognized by the use of classical terminology describing isolated LMS or LMS + 1-, 2-, or 3-vessel disease. The SXscore was an attempt to eliminate the historical and arbitrarily defined subdivisions of the coronary tree into LMS and 3VD and to create a common anatomical denominator (2,3). It now seems that the LMS outcomes are largely a reflection of the presence of distal LMS bifurcation disease, clinical comorbidity, and importantly, the increasing prevalence of 3VD and its association with clinical comorbidities (as discussed in the following) and anatomical complexities, such as multiple bifurcations and the presence of total occlusions leading to higher SXscores.

Anatomical and clinical variables in the 3VD PCI population. Within the 3VD PCI population the SXscore added very little incremental benefit to the additive EuroSCORE in predicting death and MACCE (Fig. 4). It might be hypothesized that the severity of 3VD (as evidenced by a higher SXscore) might be representative of patients with a more adverse risk profile who have evidence of systemic atherosclerosis and therefore are at greater longer-term cardiovascular and cerebrovascular risk. Consequently these patients might potentially benefit from CABG on prognostic and morbidity grounds due to the bypass grafts protecting the coronary vessel as discussed. This might also be an explanation for the comparability in long-term stroke outcomes between CABG and PCI for the 3VD SYNTAX population (6).

This hypothesis is supported by the significant and direct relationship of the 10-year predicted Framingham risk scores with the prevalence and magnitude of coronary artery calcium scores (44). Furthermore, the ankle-brachial pressure index (45–49) and common carotid intima-media thickness (50–53), both markers of peripheral vascular disease, have been correlated with the severity of coronary artery disease and clinical events.

Implications of the Global Risk for future trials. Given the heterogeneity of the outcomes between LMS and 3VD, the strategy for the future is to construct separate trials for the LMS and 3VD populations that should incorporate anatomical and clinical variables. Left main stem disease is currently subject to the ongoing EXCEL (Evaluation of Xience Prime or Xience V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, recruiting patients on anatomical entry criteria only—namely low-moderate SXscores—and does not directly take into account clinical variables except within the Heart Team discussion.

Within the 3VD population perhaps a more targeted identification of patients by other markers of atherosclerotic burden, such as ankle-brachial pressure index and common carotid intima-media thickness as discussed, in conjunction with the SXscore or Global Risk might prove beneficial. Another recently described approach is the "Functional SYNTAX Score"—utilizing the functional assessment of coronary lesions—and has potentially been shown to improve the identification of low and higher risk patients (54). In addition, the potential noninvasive calculation of the Functional SYNTAX Score, with computational fluid dynamics applied to coronary computed tomography angiography, has shown significant promise (55,56).

Summary of the potential clinical implications of the Global Risk. The practical clinical application of the Global Risk is summarized in a treatment algorithm in Figure 5. Although validation of the Global Risk concept is required, the practicalities are that not only high-anatomical-risk patients but also patients with significant comorbidity are best served by undergoing surgical revascularization, because they seem to be one of the patient groups that stand to potentially gain more from surgical revascularization on prognostic and morbidity grounds, particularly if they have 3VD. Clearly a threshold of operative risk for surgical revascularization should not be exceeded; therefore these issues are vital in the Heart Team discussion in selecting the most appropriate revascularization modality.

Study limitations. This study represents a post hoc analysis of the original SYNTAX Trial, and the predictive models were developed retrospectively at 3-year follow-up. The further analyses undertaken in the LMS and 3VD cohorts (1,7) should be considered as hypothesis-generating. Furthermore, the focus of this study was on low Global risk (GRC_{LOW}) groups, because CABG is the standard of care in the management of patients in the higher-Global Risk groups (1,5,6). Comparisons between the higher-Global Risk groups are nevertheless provided in the Online Appendix. In addition there was limited statistical power for the comparison between CABG and PCI for events such as stroke and MI and analyses of reclassified patients. Consequently external validation of the proposed Global Risk is required in unselected registries, with numbers greater than the SYNTAX "All-Comers" population. The "All-Comers" concept of the SYNTAX trial, although more representative of contemporary clinical practice compared with the randomized approach (18,43), has been reported to potentially not result in the inclusion of consecutive patients, predominantly due to the inability to gain appropriate informed consent and refusal to participate (57).

It is not possible to judge and account for the decisions made by the Heart Team in selecting a patient for randomization. However, this approach is representative of contemporary practice. It should also be acknowledged that, although the SYNTAX Trial was based on contemporary revascularization practice at the time, improvements in technology in both CABG and PCI might yield differences in clinical outcomes in future trials. Noninvasive or invasive carotid imaging to screen

for the presence of significant carotid disease was undertaken by the clinical consensus of the Heart Team to calculate the EuroSCORE. The possibility of a small minority of patients with clinically silent carotid disease cannot be excluded. The cardiac-related comorbidities within the EuroSCORE are more likely to reflect outcomes after PCI, whereas extracardiac factors (e.g., the presence of chronic obstructive pulmonary disease and poor neurological status) are unlikely to reflect outcomes (24–28)—this point should be borne in mind when interpreting the Global Risk. Furthermore, the use of the EuroSCORE with a continuous approach might have affected the results of the analysis. However, the categorical approach was adopted from the outset to allow application of the same risk model in CABG and PCI patients, given that a high SXscore tertile has consistently been shown to be an independent predictor of adverse outcomes after PCI (24,26–28). The newly developed EuroSCORE II (58) cannot be applied to the concept of the Global Risk, because this information was not collected during the original SYNTAX trial.

Conclusions

In comparison with the SXscore, the Global Risk—with a simplified treatment algorithm—substantially enhances the identification of low-risk patients who could safely and efficaciously be treated with CABG or PCI.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Department of Interventional Cardiology, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE, Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
2. Sianos G, Morel MA, APK, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
3. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the syntax study. EuroIntervention 2009;5:50–6.
4. SYNTAX score calculator: SYNTAX working-group. Available at: http://www.syntaxscore.com. Accessed April 1, 2012.
5. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the synergy between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) trial. Circulation 2010;121:2645–53.
6. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
7. Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151:1194–204.
8. Park DW, Kim YH, Yun SC, et al. Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. J Am Coll Cardiol 2011;57:2152–9.
9. Chakravarty T, Buch MH, Naik H, et al. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. Am J Cardiol 2011;107:360–6.
10. Capodanno D, Capranzano P, Di Salvo ME, et al. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. J Am Coll Cardiol Intv 2009;2:731–8.
11. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts outcome of surgery for left main disease. Ann Thorac Surg 2009;87:1097–104, discussion 1104–5.
12. Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of the syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. Catheter Cardiovasc Interventions 2009;73:612–7.
13. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the SYNTAX score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–81.
14. Garg S, Sarno G, Girasis C, et al. A patient-level pooled analysis assessing the impact of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. J Am Coll Cardiol Intv 2011;4:645–53.
15. Palmerini T, Genereux P, Caixeta A, et al. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. J Am Coll Cardiol 2011;57:2389–97.
16. Levine GN, Bates ER, Blankenship JC, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the society for cardiovascular angiography and interventions. J Am Coll Cardiol 2011;2011:e44–122.
17. Hillis LD, Smith PK, Anderson JL, et al. ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, society of cardiovascular anesthesiologists, and society of thoracic surgeons. J Am Coll Cardiol 2011;2011:e123–210.
18. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic surgery (EACTS). Eur Heart J 2010;31:2501–55.
19. Kushner FG, Hand M, Smith SC Jr., et al. Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update): and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;2009:2205–41.
20. Applegate RJ. Toward better stratification of patients with left main disease: value of clinical and angiographic-derived risk scores. J Am Coll Cardiol Intv 2011;4:298–9.
21. Serruys PW. Integrating lessons from recent clinical trials into practice: beyond the SYNTAX score. Presented at: Transcatheter Therapeutics. Asia Pacific, April 29, 2010; Seoul, South Korea.
22. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.
23. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
24. Rodés-Cabau J, Deblois J, Bertrand OF, et al. Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. Circulation 2008;118:2374–81.
25. Min SY, Park DW, Yun SC, et al. Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left

main coronary disease: analysis from the MAIN-COMPARE study. Circ Cardiovasc Interventions 2010;3:127–33.
26. Kim YH, Ahn JM, Park DW, et al. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. Am J Cardiol 2006;98:1567–70.
27. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. Heart 2009;95: 43–8.
28. Kim Y-H, Park D-W, Kim W-J, et al. Validation of SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. J Am Coll Cardiol Intv 2010;3:612–23.
29. Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. Am Heart J 2010;159:103–9.
30. Capodanno D, Caggegi A, Miano M, et al. Global risk classification and clinical SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) score in patients undergoing percutaneous or surgical left main revascularization. J Am Coll Cardiol Intv 2011;4:287–97.
31. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064–9.
32. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–94.
33. Steyerberg EW, Homs MY, Stokvis A, Essink-Bot ML, Siersema PD, for the SIREC Study Group. Stent placement or brachytherapy for palliation of dysphagia from esophageal cancer: a prognostic model to guide treatment selection. Gastrointest Endosc 2005;62:333–40.
34. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606.
35. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115:928–35.
36. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010; 21:128–38.
37. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009;119:3053–61.
38. Ranucci M, Castelvecchio S, Surgical and Clinical Outcome Research (SCORE) group. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. EuroIntervention 2010;6:549–53.
39. Garg S, Sarno G, Garcia-Garcia HM, et al. A new tool for the risk stratification of patients with complex coronary artery disease: the clinical SYNTAX score. Circ Cardiovasc Interventions 2010;3:317–26.
40. Wykrzykowska JJ, Garg S, Onuma Y, et al. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the "All-Comers" LEADERS trial. Circ Cardiovasc Interventions 2011;4:47–56.
41. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Statist Med 2008;27:157–72, discussion 207–12.
42. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79:I3–12.
43. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331–41.
44. Okwuosa TM, Greenland P, Ning H, et al. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. J Am Coll Cardiol 2011;57:1838–45.
45. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197–208.
46. Otah KE, Madan A, Otah E, Badero O, Clark LT, Salifu MO. Usefulness of an abnormal ankle-brachial index to predict presence of coronary artery disease in African-Americans. Am J Cardiol 2004;93:481–3.
47. Sukhija R, Aronow WS, Yalamanchili K, Peterson SJ, Frishman WH, Babu S. Association of ankle-brachial index with severity of angiographic coronary artery disease in patients with peripheral arterial disease and coronary artery disease. Cardiology 2005;103:158–60.
48. Igarashi Y, Chikamori T, Tomiyama H, et al. Diagnostic value of simultaneous brachial and ankle blood pressure measurements for the extent and severity of coronary artery disease as assessed by myocardial perfusion imaging. Circ J 2005;69:237–42.
49. Papamichael CM, Lekakis JP, Stamatelopoulos KS, et al. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. Am J Cardiol 2000;86:615–8.
50. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998;128:262–9.
51. Adams MR, Nakagomi A, Keech A, et al. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. Circulation 1995;92:2127–34.
52. Steinvil A, Sadeh B, Arbel Y, et al. Prevalence and predictors of concomitant carotid and coronary artery atherosclerotic disease. J Am Coll Cardiol 2011;57:779–83.
53. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. Eur Heart J 2012;33:113–9.
54. Nam CW, Mangiacapra F, Entjes R, et al. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. J Am Coll Cardiol 2011;58:1211–8.
55. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989–97.
56. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;97:1902–13.
57. de Boer SP, Lenzen MJ, Oemrawsingh RM, et al. Evaluating the "all-comers" design: a comparison of participants in two "all-comers" PCI trials with non-participants. Eur Heart J 2011;32:2161–7.
58. EuroSCORE, II. Available at: http://www.euroscore.org/calc.html. Presented at the 25th EACTS Annual Meeting, 3rd October 2011, Lisbon, Portugal. Accessed April 1, 2012.

Key Words: 3-vessel disease ■ Global Risk ■ left main disease ■ SYNTAX Score.

APPENDIX

For supplementary figures, tables, text, and references, please see the online version of this article.

To participate in this CME activity by taking the quiz and claiming your CME credit certificate, please go to **http://interventions.onlinejacc.org/** and select the CME tab on the top navigation bar.

The SYNTAX Trial at 3 Years:

A Global Risk Approach to Identify Patients With 3-Vessel and/or Left Main Stem Disease Who Could Safely and Efficaciously Be Treated With Percutaneous Coronary Intervention

Supplementary Appendix

Contents

overall model performances (Brier score) in the Global Randomised SYNTAX Population.

Tables 1-3: Comparisons (CABG and PCI) of low Global Risk Groups (GRC_{LOW}) in the Global, LMS and 3VD Randomised SYNTAX Populations.

c. Outcomes for the Global Risk for the endpoint Death/MI/Stroke in the Randomised SYNTAX population

Figure 7: Kaplan Meier curves for cumulative rates of Death/MI/Stroke in the Randomised LMS population

Figure 8: Kaplan Meier curves for cumulative rates of Death/MI/Stroke in the Randomised LMS population

IV. Additional Comparative Analyses for the GRC_{INT} and GRC_{HIGH} groups in the Randomised SYNTAX Populations

Tables 4-6: Comparisons (CABG and PCI) for the intermediate Global Risk Groups (GRC_{INT})

Tables 7-9: Comparisons (CABG and PCI) for the high Global Risk Groups (GRC_{HIGH})

V. Reclassification Analyses for Randomised SYNTAX Population

Tables 10-11: Reclassification Analyses

VI. Additional Analyses for the 'All-Comers' SYNTAX Population

Figure 9: Kaplan Meier curves for cumulative rates of Death and MACCE in the Global 'All-Comers' SYNTAX Population.

Figures 10-11: Comparison of different risk models for Death and MACCE, utilising calibration (Hosmer-Lemeshow), discrimination (c-

statistic) and overall model performances (Brier score) in the Global 'All-Comers' SYNTAX Population.

Tables 12-14: Comparisons (CABG and PCI) of low Global Risk Groups (GRC_{LOW}) in the Global, LMS and 3VD 'All-Comers' SYNTAX Populations.

VII. Reclassification Analyses for "All-Comers' SYNTAX Population

Tables 15-16: Reclassification Analyses

VIII. Additional Material:

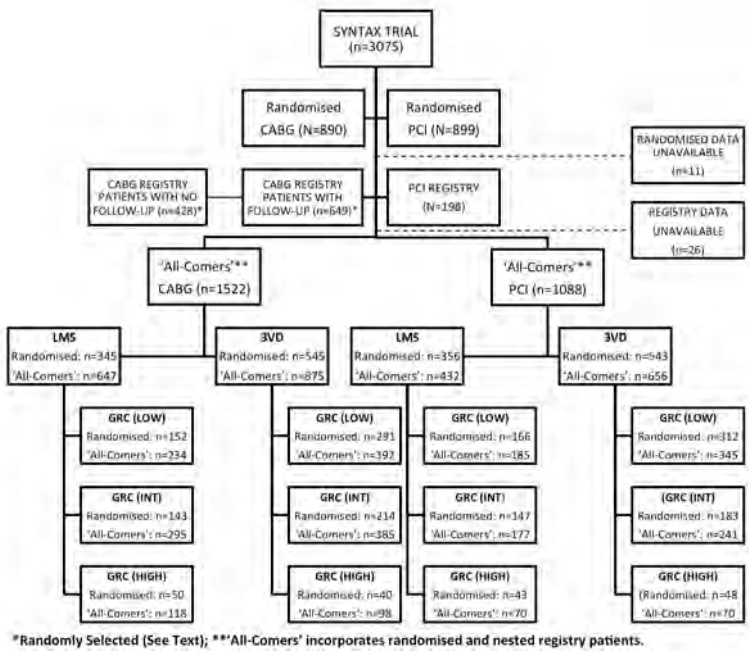
Figure 12: Vessel Distribution in the LMS Population According to SYNTAX Score Tertiles.

IX. Additional References

I. Flow chart of patients from the SYNTAX trial demonstrating availability of data .

Based on the original study protocol (1,29) 649 of the 1077 CABG nested registry patients were randomly allocated for follow up; data from 37 patients were unavailable (11 patients at baseline and a further 26 patients at follow up).

Figure 1. Flow chart.



II. Supplementary Methods

a) Definitions of Risk Scores

SYNTAX Score (1-4)

The SYNTAX Score Algorithm. (http://www.syntaxscore.com)

The following algorithm is applied to each individual coronary lesion that has a diameter stenosis greater than 50% and located in a vessel that is larger than 1.5 mm in diameter – the individual lesion scores are added together to give the final SYNTAX score.

The Syntax Score Algorithm
1. Arterial dominance 2. Arterial segments involved per lesion
Lesion characteristics 3. Total occlusion i. Number of segments involved ii. Age of the total occlusion (>3 months) iii. Blunt stump iv. Bridging collaterals v. First segment beyond the occlusion visible by antegrade or retrograde filling vi. Side branch involvement 4. Trifurcation i. Number of segments diseased 5. Bifurcation i. Medina type ii. Angulation between the distal main vessel and the side branch <70° 6. Aorto-ostial lesion 7. Severe tortuosity 8. Length >20 mm 9. Heavy calcification 10. Thrombus 11. Diffuse disease/small vessels i. Number of segments with diffuse disease/small vessels

ACEF Score (5-7)

The ACEF score is calculated using the formula:

ACEF= [Age/Ejection fraction (%)] + [1 (if creatinine >2mg/dl)].

The left ventricular ejection fraction (LVEF) is the value recorded prior to the index PCI procedure, and in the event of multiple available values, the lowest recorded figure. The serum creatinine value is the value recorded prior to the index PCI.

Clinical SYNTAX score (8)

The Clinical SYNTAX Score is calculated using the formula: Clinical SYNTAX Score = [SXscore] x [modified ACEF score]. The modified ACEF score is calculated using the formula: age/ejection fraction+1 point for every 10ml/min reduction in creatinine clearance below 60ml/min/1.73m^2 (up to a maximum of 6 points). The LVEF is the value recorded prior to the index PCI and in the event of multiple available values the lowest recorded figure. Creatinine clearance is calculated using the Cockcroft-Gault equation using the patient's age, weight, and serum creatinine values recorded prior to the index PCI. (9)

Additive EuroSCORE (10)

The additive EuroSCORE is calculated by summation of the individual scores from 17 different clinical variables.

Additive EuroSCORE		
Patient Factors		
Age	Per 5 years or part thereof over the age of 60 years	1
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for respiratory disease	1
Peripheral arteriopathy	Claudication/carotid stenosis >50%/Previous or planned intervention on the abdominal aorta, limb arteries, or carotids	2
Neurological dysfunction	Severely affected mobility or day-to-day function	2
Previous cardiac surgery	Previous opening of the pericardium	3
Serum creatinine	Pre-operatively >200 μmol/l	2

Active endocarditis	Antibiotic therapy at time of surgery	3
Critical pre-operative state	Pre-operative cardiac arrest, ventilation, renal failure, inotropic support, intra-aortic balloon pump use, ventricular arrhythmia	3
Cardiac factors		
Unstable angina	Rest pain requiring IV nitrates	2
Left ventricular function	Moderate (30%–50%)	1
	Poor (<30%)	3
Recent MI	Within 90 days	2
Pulmonary hypertension	Systolic pulmonary artery pressure >60 mm Hg	2
Operative factors		
Emergency Operation	Performed before the start of next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta		3
Post-infarct septal rupture		4

Logistic EuroSCORE (11)

The logistic EuroSCORE utilises the EuroSCORE logistic regression equation and uses the same risk factors as the additive EuroSCORE.

$$\text{predictedmortality} = \frac{e^{(\beta_0+\sum\beta_i X_i)}}{1+e^{(\beta_0+\sum\beta_i X_i)}}$$

b) Additional Reclassification Methodology

The SXscore and additive EuroSCORE consists of 3 categories of level of anatomical disease complexity (2-4) and clinical risk (10,11) respectively. By combining the two categorical based scores to form the Global Risk (GRC) 9 different risk groups were created. Based on the principle that comparable clinical outcomes, in patients with a low SXscore undergoing CABG or PCI, were evident at 3 years (1,12) it was hypothesised that patients without a high EuroSCORE and/or high SXscore would be a lower risk population (GRC_{LOW}) population, who would be equally amenable to CABG or PCI in terms of efficacy and safety.

The underlying principles of the reclassification analyses were therefore to ensure that – in the higher anatomical risk patients (i.e. *with intermediate SXscores and low-intermediate EuroSCORE*) reclassified as low Global Risk (GRC_{LOW}) – comparability (or more favourable PCI outcomes) in clinical outcomes between CABG and PCI would be maintained in this reclassified group. Conversely – in the lower anatomical risk patients with a high clinical comorbidity (i.e. *low SXscore with a high EuroSCORE*) reclassified as a higher Global Risk (GRC_{INT}) – more favourable surgical clinical outcomes would be evident in this reclassified group.

If reclassification analyses were not undertaken the main danger would be that higher (or lower risk) patients would be inappropriately reclassified to lower (or higher) risk groups. This may subsequently not be clinically apparent as the expected lower (or higher) clinical outcomes within the population the reclassified patients entered, would potentially dilute the clinical outcomes within the reclassified patients. Consequently, comparisons of clinical outcomes (between CABG and PCI) within the reclassified groups are required to ensure that the patients have been appropriately reclassified. Illustrative figures explaining these concepts are detailed below (**Figures 1-2**).

Figure 2: Comparability (or more favourable PCI outcomes) in Death and MACCE between CABG and PCI for the higher risk group (*intermediate SXscore and low-intermediate EuroSCOREs)* reclassified to a lower risk (GRC_{LOW}) group would be expected.

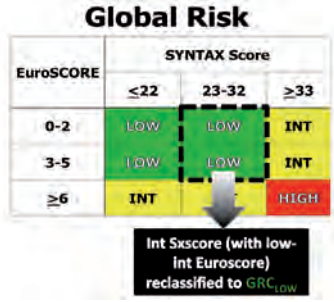
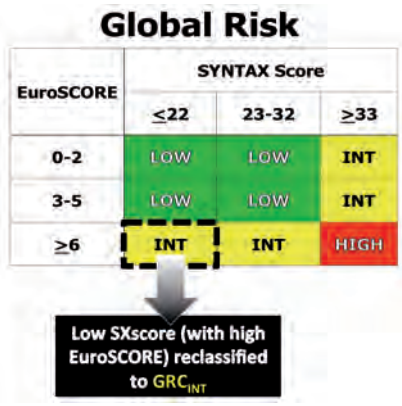


Figure 3: More favourable clinical outcomes (Death or MACCE) would be expected with CABG compared to PCI, for the lower risk group (*low SXscore and high EuroSCORE)* reclassified to a higher (GRC_{INT}) risk group. This is in keeping with previous findings of a high EuroSCORE to be an independent predictor of in-hospital mortality and MACCE after PCI. (13-16)



III Additional Analyses for the Randomised SYNTAX Population

a. Outcomes by tertiles of the SYNTAX Score

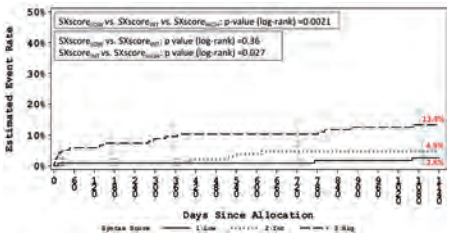
Figure 4

At 36-months within both the LMS and 3VD PCI cohorts, a low SXscore group could not be differentiated from the higher risk groups (low-intermediate SXscore) for Death and MACCE. Within the LMS PCI population a high SXscore group could only be differentiated from the lower SXscore groups (low to intermediate SXscore) for Death and MACCE.

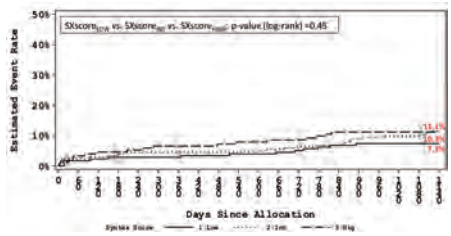
Title: Outcomes By Tertile of Risk of the SXscore in isolation within the Randomised LMS and 3VD PCI Population

Caption: Kaplan Meier curves for cumulative rate of Death (upper) and MACCE (lower) at 3-year follow-up, stratified to tertile of the SXscore, event rate ±1.5 SE.

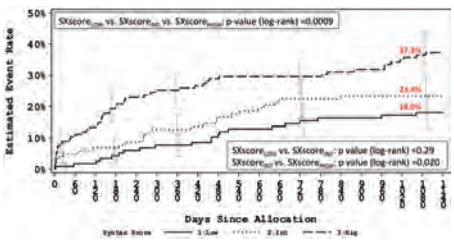
SXscore: LMS Death - PCI



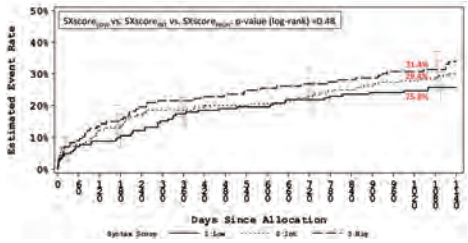
SXscore: 3VD Death- PCI



SXscore: LMS MACCE - PCI



SXscore: 3VD MACCE - PCI



b. Outcomes for the Global Risk for the endpoint of Death and MACCE in the randomised SYNTAX population

Figure 5: Kaplan Meier curves for cumulative rates of **Death** (upper), and **MACCE** (lower) in the Global Randomised SYNTAX population at 3-year follow-up stratified according to the group of Global Risk, event rate ±1.5 SE.

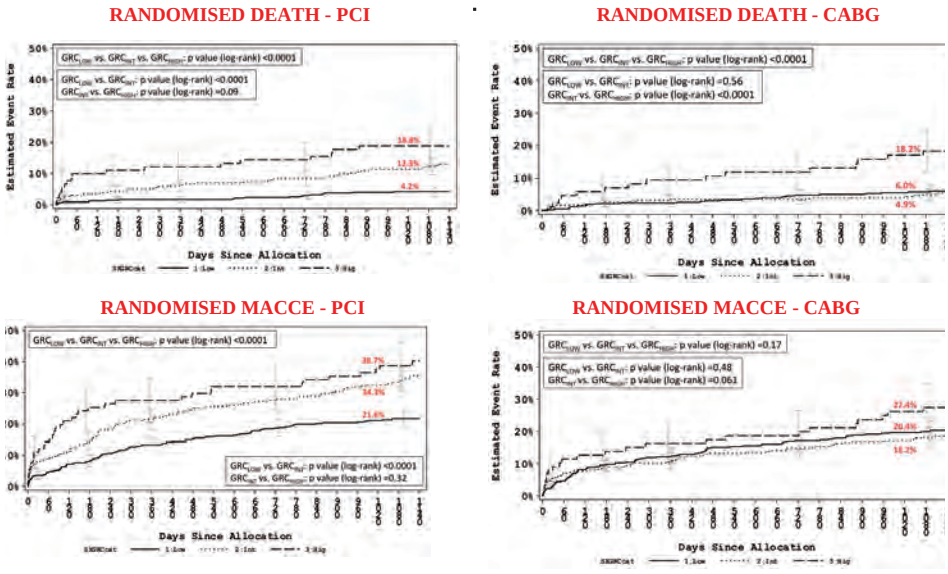
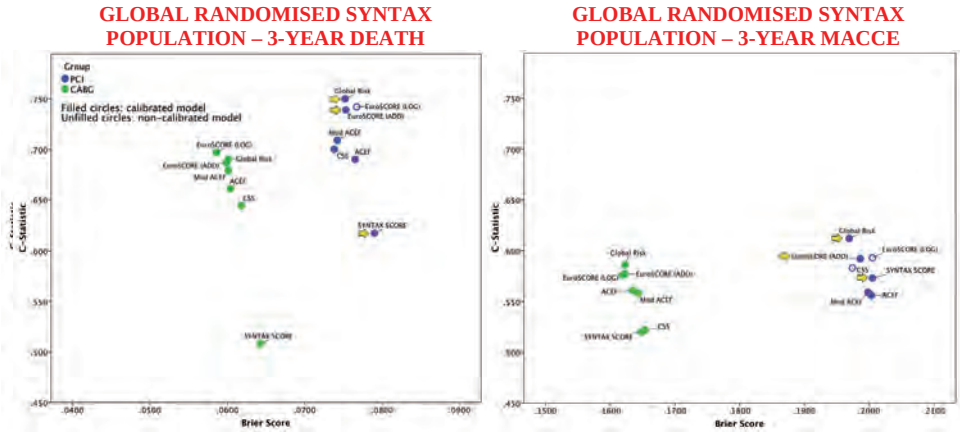


Figure 6: Comparison of different risk models for the Global Randomised SYNTAX population for Death (left) and MACCE (right), utilising calibration (Hosmer-Lemeshow), discrimination (c-statistic) and overall model performances (Brier score). (17)



Tables 1-3: Comparisons (CABG and PCI) of low Global Risk Groups (GRC_{LOW})

Table 1

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing low Global Risk groups (GRC_{LOW}) for the **Global Randomised PCI and Global Randomised CABG population** (N=921).

Event	CABG (N=443)	PCI (N=478)	Hazard Ratio [95% CI]	Difference	p-Value
3 Year					
Post-Allocation MACCE	20.4% (86)	21.6% (102)	1.06 [0.80, 1.41]	1.2%	0.69
Death/Stroke/MI, Any	11.2% (47)	8.5% (40)	0.74 [0.49, 1.14]	-2.7%	0.17
Death, Any	6.0% (25)	4.2% (20)	0.70 [0.39, 1.26]	-1.8%	0.24
Cerebrovascular Event (Stroke), Any	3.1% (13)	1.1% (5)	0.34 [0.12, 0.95]	-2.0%	0.031
MI, Any	3.1% (13)	4.9% (23)	1.58 [0.80, 3.12]	1.8%	0.18
Revascularisation, Any	12.0% (49)	16.5% (77)	1.43 [1.00, 2.04]	4.6%	0.050
PCI	11.3% (46)	14.2% (66)	1.30 [0.89, 1.89]	2.9%	0.17
CABG	1.2% (5)	3.7% (17)	3.04 [1.12, 8.23]	2.5%	0.02
Post-Procedure Stent Thrombosis/Graft Occlusion	3.9% (16)	3.9% (18)	0.99 [0.51, 1.95]	0.0%	0.99

Table 2

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{LOW} for the **Global Randomised LMS population** (N=318).

Event	CABG (N=152)	PCI (N=166)	Hazard Ratio [95% CI]	Difference	p-Value
3 Year					
Post-Allocation MACCE	23.1% (34)	15.8% (26)	0.64 [0.39, 1.07]	-7.3%	0.088
Death/Stroke/MI, Any	12.3% (18)	5.5% (9)	0.42 [0.19, 0.94]	-6.8%	0.029
Death, Any	7.5% (11)	1.2% (2)	0.16 [0.03, 0.70]	-6.3%	0.0054
Stroke, Any	3.5% (5)	0.6% (1)	0.17 [0.02, 1.46]	-2.9%	0.067
MI, Any	1.4% (2)	3.7% (6)	2.59 [0.52, 12.82]	2.3%	0.23
Revascularisation, Any	14.6% (21)	12.8% (21)	0.85 [0.46, 1.56]	-1.8%	0.60
PCI	13.3% (19)	10.9% (18)	0.81 [0.42, 1.54]	-2.3%	0.51
CABG	1.3% (2)	3.0% (5)	2.20 [0.43, 11.36]	1.7%	0.33
Post-Procedure Stent Thrombosis/Graft Occlusion	4.1% (6)	2.5% (4)	0.57 [0.16, 2.01]	-1.6%	0.37

Table 3

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{LOW} for **Global Randomised 3VD population** (N=603).

Event	CABG (N=291)	PCI (N=312)	Hazard Ratio [95% CI]	Difference	p-Value
3 Year					
Post-Allocation MACCE	19.0% (52)	24.7% (76)	1.35 [0.95, 1.92]	5.7%	0.10
Death/Stroke/MI, Any	10.6% (29)	10.0% (31)	0.95 [0.57, 1.58]	-0.5%	0.85
Death, Any	5.2% (14)	5.8% (18)	1.14 [0.57, 2.30]	0.7%	0.71
Stroke, Any	2.9% (8)	1.3% (4)	0.45 [0.13, 1.49]	-1.6%	0.18
MI, Any	4.0% (11)	5.6% (17)	1.40 [0.66, 2.99]	1.6%	0.38
Revascularisation, Any	10.5% (28)	18.5% (56)	1.88 [1.19, 2.96]	8.0%	0.0055
PCI	10.2% (27)	15.9% (48)	1.66 [1.04, 2.66]	5.7%	0.033
CABG	1.1% (3)	4.0% (12)	3.60 [1.02, 12.75]	2.9%	0.034
Post-Procedure Stent Thrombosis/Graft Occlusion	3.7% (10)	4.6% (14)	1.25 [0.56, 2.81]	0.9%	0.59

c. Outcomes for the Global Risk for the endpoint Death/MI/Stroke in the Randomised SYNTAX population

Figure 7: Kaplan Meier curves for cumulative rates of **Death/MI/Stroke** in the Randomised LMS SYNTAX population at 3-year follow-up stratified according to the group of Global Risk, event rate ±1.5 SE.

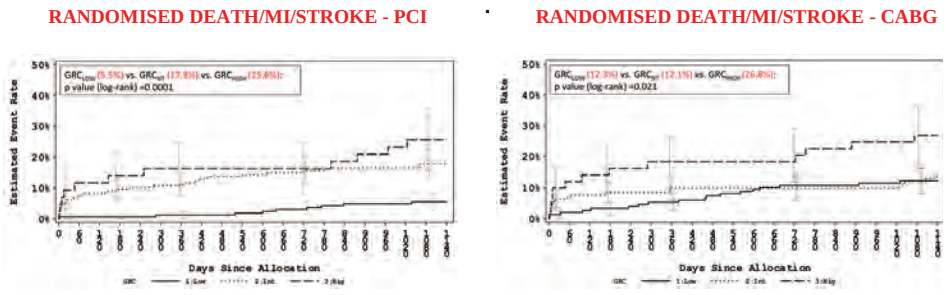
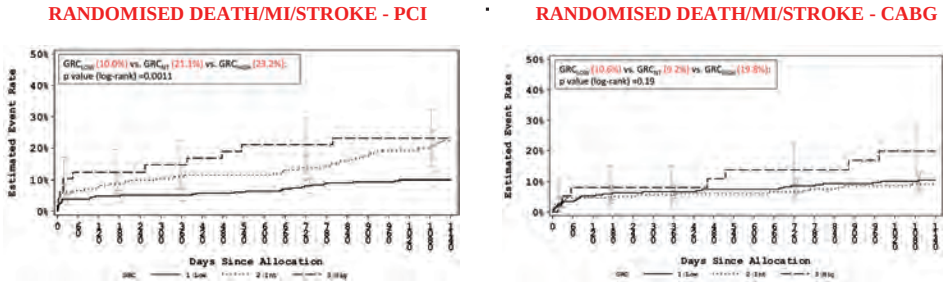


Figure 8: Kaplan Meier curves for cumulative rates of **Death/MI/Stroke** in the Randomised 3VD SYNTAX population at 3-year follow-up stratified according to the group of Global Risk, event rate ±1.5 SE.



IV. Additional Comparative Analyses (CABG and PCI) for the GRC_{INT} & GRC_{HIGH} groups in the Global, LMS & 3VD Randomised SYNTAX Populations

Tables 4-6: Comparisons (CABG & PCI) for the GRC_{INT} Groups

Table 4

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{INT} for the **Global Randomised PCI and Global Randomised CABG patients** (N=687)

Event	CABG (N=357)	TAXUS (N=330)	Hazard Ratio [95% CI]	Difference	Relative % Change	p-Value[1]
3 Year						
Post-Allocation MACCE	18.2% (63)	34.3% (112)	2.06 [1.51, 2.80]	16.1%	88.2%	<.0001
Death/Stroke/MI, Any	10.4% (36)	19.6% (64)	1.95 [1.30, 2.94]	9.2%	88.9%	0.0010
Death, Any	4.9% (17)	12.3% (40)	2.57 [1.46, 4.53]	7.4%	148.9%	0.0007
Cerebrovascular Event (Stroke), Any	2.7% (9)	3.0% (9)	1.09 [0.43, 2.75]	0.3%	11.7%	0.8515
MI, Any	4.3% (15)	9.6% (31)	2.26 [1.22, 4.19]	5.4%	125.7%	0.0076
Revascularization, Any	10.7% (36)	22.7% (72)	2.32 [1.56, 3.47]	12.1%	112.8%	<.0001
PCI	9.0% (30)	18.3% (58)	2.24 [1.44, 3.48]	9.3%	103.4%	0.0002
CABG	1.7% (6)	6.1% (19)	3.48 [1.39, 8.71]	4.4%	259.6%	0.0045
Post-Procedure Stent Thrombosis/Graft Occlusion	3.1% (10)	4.6% (15)	1.62 [0.73, 3.62]	1.6%	50.8%	0.2304

Table 5

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{INT} for the **Randomised LMS population** (N=290).

Event	CABG (N=143)	TAXUS (N=147)	Hazard Ratio [95% CI]	Difference	Relative % Change	p-Value[1]
3 Year						
Post-Allocation MACCE	19.3% (27)	35.6% (52)	2.00 [1.26, 3.19]	16.4%	84.9%	0.0028
Death/Stroke/MI, Any	12.1% (17)	17.8% (26)	1.49 [0.81, 2.75]	5.7%	46.8%	0.1959
Death, Any	5.7% (8)	11.0% (16)	1.96 [0.84, 4.59]	5.2%	91.2%	0.1123
Cerebrovascular Event (Stroke), Any	2.2% (3)	0.7% (1)	0.33 [0.03, 3.14]	-1.5%	-66.9%	0.3076
MI, Any	6.3% (9)	11.1% (16)	1.73 [0.76, 3.91]	4.7%	74.3%	0.1837
Revascularization, Any	11.7% (16)	27.4% (39)	2.57 [1.44, 4.60]	15.7%	133.8%	0.0010
PCI	8.9% (12)	21.0% (30)	2.65 [1.36, 5.18]	12.1%	135.4%	0.0030
CABG	2.8% (4)	9.4% (13)	3.22 [1.05, 9.86]	6.6%	232.6%	0.0307
Post-Procedure Stent Thrombosis/Graft Occlusion	4.5% (6)	6.9% (10)	1.63 [0.59, 4.49]	2.5%	55.4%	0.3394

Table 6

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{INT} for the **Randomised 3VD population** (N=397).

Event	CABG (N=214)	TAXUS (N=183)	Hazard Ratio [95% CI]	Difference	Relative % Change	p-Value[1]
3 Year						
Post-Allocation MACCE	17.6% (36)	33.3% (60)	2.08 [1.38, 3.15]	15.7%	89.3%	0.0004
Death/Stroke/MI, Any	9.2% (19)	21.1% (38)	2.39 [1.38, 4.14]	11.8%	127.8%	0.0014
Death, Any	4.4% (9)	13.4% (24)	3.14 [1.46, 6.75]	9.0%	203.9%	0.0020
Cerebrovascular Event (Stroke), Any	3.0% (6)	4.9% (8)	1.58 [0.55, 4.54]	1.9%	61.1%	0.3959
MI, Any	2.9% (6)	8.4% (15)	2.98 [1.16, 7.68]	5.6%	194.4%	0.0175
Revascularization, Any	10.0% (20)	18.9% (33)	2.06 [1.18, 3.59]	8.9%	89.1%	0.0092
PCI	9.1% (18)	16.2% (28)	1.92 [1.06, 3.47]	7.1%	77.8%	0.0280
CABG	0.9% (2)	3.4% (6)	3.54 [0.72, 17.56]	2.5%	260.3%	0.0980
Post-Procedure Stent Thrombosis/Graft Occlusion	2.1% (4)	2.8% (5)	1.46 [0.39, 5.43]	0.6%	29.9%	0.5716

Tables 7-9: Comparisons (CABG and PCI) for the GRC_{HIGH} Groups

Table 7

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{HIGH} for the **Global Randomised PCI and Global Randomised CABG patients** (N=181).

Event	CABG (N=90)	TAXUS (N=91)	Hazard Ratio [95% CI]	Difference	Relative % Change	p-Value[1]
3 Year						
Post-Allocation MACCE	27.4% (23)	38.7% (35)	1.56 [0.92, 2.63]	11.2%	40.9%	0.0973
Death/Stroke/MI, Any	23.8% (20)	24.3% (22)	1.05 [0.57, 1.92]	0.5%	2.1%	0.8796
Death, Any	18.2% (15)	18.8% (17)	1.09 [0.54, 2.18]	0.6%	3.1%	0.8095
Cerebrovascular Event (Stroke), Any	7.2% (6)	3.8% (3)	0.47 [0.12, 1.89]	-3.4%	-47.0%	0.2780
MI, Any	3.4% (3)	9.5% (8)	2.64 [0.70, 9.95]	6.1%	179.2%	0.1358
Revascularization, Any	3.9% (3)	25.5% (21)	7.35 [2.19, 24.63]	21.5%	548.4%	0.0001
PCI	3.9% (3)	22.1% (18)	6.19 [1.82, 21.01]	18.2%	463.7%	0.0008
CABG	0.0% (0)	3.6% (3)	NA [NA, NA]	3.6%	NA	0.0845
Post-Procedure Stent Thrombosis/Graft Occlusion	0.0% (0)	3.5% (3)	NA [NA, NA]	3.5%	NA	0.0895

Table 8

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{HIGH} for the **Randomised LMS population** (N=93).

Event	CABG (N=50)	TAXUS (N=43)	Hazard Ratio [95% CI]	Difference	Relative % Change	p-Value[1]
3 Year						
Post-Allocation MACCE	28.9% (14)	39.5% (17)	1.46 [0.72, 2.97]	10.6%	36.6%	0.2880
Death/Stroke/MI, Any	26.8% (13)	25.6% (11)	0.94 [0.42, 2.10]	-1.3%	-4.7%	0.8859
Death, Any	18.9% (9)	18.6% (8)	1.05 [0.41, 2.72]	-0.3%	-1.5%	0.9193
Cerebrovascular Event (Stroke), Any	10.6% (5)	5.4% (2)	0.45 [0.09, 2.34]	-5.2%	-49.2%	0.3315
MI, Any	6.0% (3)	5.7% (2)	0.77 [0.13, 4.61]	-0.3%	-4.8%	0.7773
Revascularization, Any	2.3% (1)	24.3% (9)	11.67 [1.48, 92.11]	22.1%	970.9%	0.0031
PCI	2.3% (1)	21.7% (8)	10.13 [1.27, 81.01]	19.4%	853.4%	0.0069
CABG	0.0% (0)	2.6% (1)	NA [NA, NA]	2.6%	NA	0.2712
Post-Procedure Stent Thrombosis/Graft Occlusion	0.0% (0)	0.0% (0)	NA [NA, NA]	0.0%	NA	Undef

Table 9

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{HIGH} for the **Randomised 3VD population** (N=88).

Event	CABG (N=40)	TAXUS (N=48)	Hazard Ratio [95% CI]	Difference	Relative % Change	p-Value[1]
3 Year						
Post-Allocation MACCE	25.4% (9)	37.9% (18)	1.71 [0.77, 3.80]	12.4%	49.0%	0.1850
Death/Stroke/MI, Any	19.8% (7)	23.2% (11)	1.28 [0.49, 3.29]	3.4%	17.0%	0.6146
Death, Any	17.1% (6)	19.0% (9)	1.16 [0.41, 3.26]	1.9%	11.3%	0.7772
Cerebrovascular Event (Stroke), Any	2.8% (1)	2.3% (1)	0.76 [0.05, 12.20]	-0.5%	-16.3%	0.8480
MI, Any	0.0% (0)	12.7% (6)	NA [NA, NA]	12.7%	NA	0.0253
Revascularization, Any	6.0% (2)	26.1% (12)	4.87 [1.09, 21.76]	20.1%	332.2%	0.0217
PCI	6.0% (2)	22.2% (10)	4.01 [0.88, 18.30]	16.2%	268.1%	0.0525
CABG	0.0% (0)	4.4% (2)	NA [NA, NA]	4.4%	NA	0.2090
Post-Procedure Stent Thrombosis/Graft Occlusion	0.0% (0)	6.3% (3)	NA [NA, NA]	6.3%	NA	0.1341

V. Reclassification Analyses for Randomised SYNTAX Population

Tables 10-11: Reclassification Analyses

Table 10

Reclassification analyses (intermediate SXscore and low-intermediate EuroSCORE reclassified to GRC_{LOW}) within the randomised SYNTAX Population: Kaplan-Meier event rates in reclassified PCI and CABG patients are shown.

Reclassified SYNTAX Population	Outcome	Event Rates/Total Reclassified CABG Patients	Event Rates/Total Reclassified PCI Patients
Randomised	3-Year MACCE	18.7% (39/222)	23.0% (55/242)
	3-Year death	6.4% (13/222)	5.4% (13/242)
Randomised LMS	3-Year MACCE	24.4% (16/68)	15.6% (12/77)
	3-Year Death	10.8% (7/68)	1.3% (1/77)
Randomised 3VD	3-Year MACCE	16.1% (23/154)	26.4% (43/165)
	3-Year Death	4.3% (6/154)	7.4% (12/165)

Table 11

Reclassification analyses (low SXscore and high EuroSCORE reclassified to GRC_{INT}) within the randomised SYNTAX Population: Kaplan-Meier event rates in the reclassified CABG and PCI patients are shown.

Reclassified SYNTAX Population	Outcome	Event Rates/Total Reclassified CABG Patients	Event Rates/Total Reclassified PCI Patients
Randomised	3-Year MACCE	24.8% (12/53)	32.1% (20/63)
	3-Year Death	10.1% (5/53)	14.5% (9/63)
Randomised LMS	3-Year MACCE	28.6% (5/19)	24.1% (7/29)
	3-Year Death	11.1% (2/19)	6.9% (2/29)
Randomised 3VD	3-Year MACCE	22.5% (7/34)	39.1% (13/34)
	3-Year Death	9.6% (3/34)	21.3% (7/34)

VI. Additional Analyses for the All-Comers (Entire Population and LMS/3VD Cohorts) SYNTAX Population

Figure 9: Kaplan Meier curves for cumulative rate of **Death** (upper), and **MACCE** (lower) in the Global 'All-Comers' SYNTAX population at 3-year follow-up stratified according to the group of Global Risk, event rate ±1.5 SE.

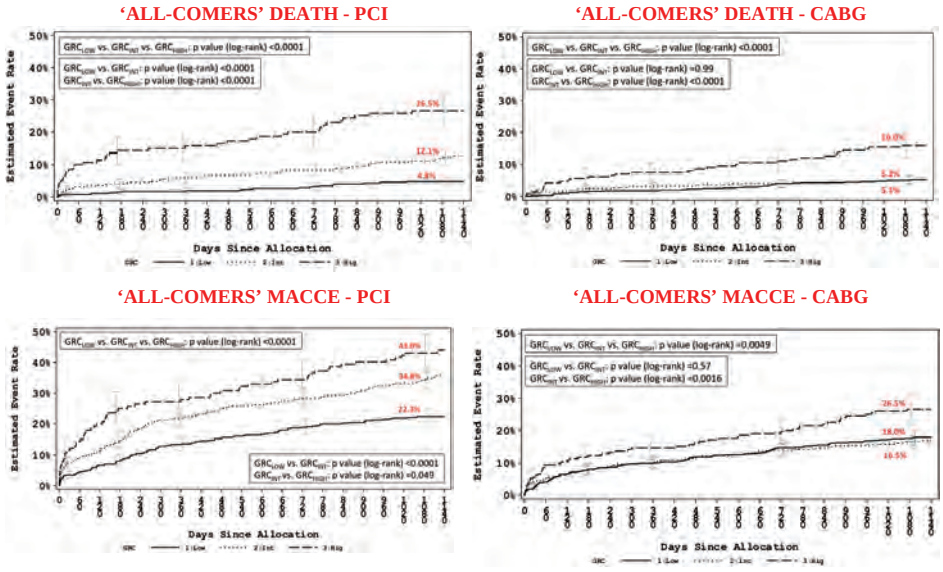


Figure 10

Comparison of different risk models for the Global 'All-Comers' SYNTAX population Death (left) and MACCE (right), utilising calibration (Hosmer-Lemeshow test), discrimination (c-statistic) and overall model performances (Brier score). *Renal function was not collected in all nested registry patients, consequently the ACEF based scores were excluded from the analysis below.*

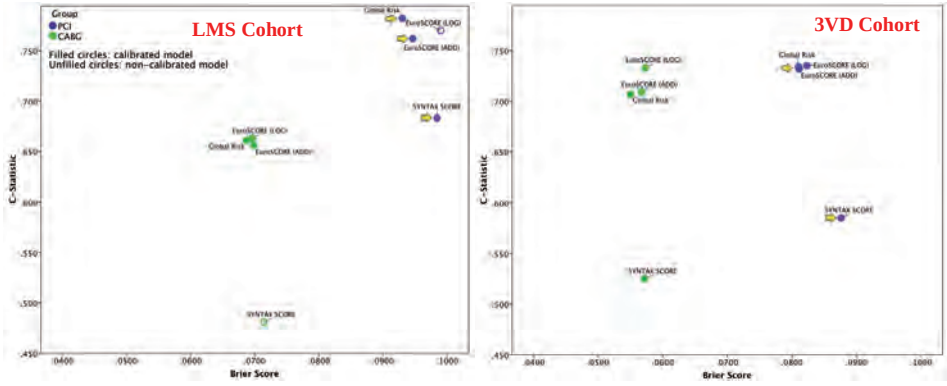
Figure 11

Comparison of different risk models for the 'All-Comers' LMS and 3VD populations for Death (upper) and MACCE (lower) at 3-Years. A smaller Brier score (x-axis) and larger c-statistic (y-axis) represents a better predictive ability of the risk model.(17) Yellow arrows represent the incremental predictive benefit of the GRC compared to the SXscore and additive EuroSCORE within the LMS PCI population, not evident within the 3VD PCI population with comparability of the GRC and additive EuroSCORE.

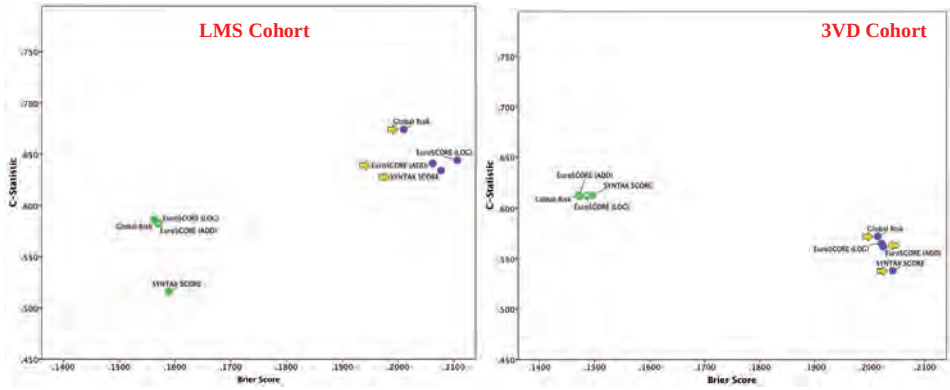
Striped circles represents calibrated additive EuroSCORE and non-calibrated logistic EuroSCORE in the LMS CABG (MACCE) population and calibrated additive EuroSCORE and non-calibrated GRC within the 3VD CABG (MACCE) population.

The renal function was not collected in all nested registry patients, consequently the ACEF based scores were excluded from the analysis below.

'ALL-COMERS' LMS and 3VD Cohorts: 3-Year Death



'ALL-COMERS' LMS and 3VD Cohorts: 3-Year MACCE



Tables 12-14: Comparisons (CABG and PCI) of low Global Risk Groups (GRC_{LOW})

Table 12

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, all low Global Risk groups (GRC_{LOW}) for **'All-Comers' CABG and 'All-Comers' PCI** patients (N=1156)

Event	CABG (N=626)	PCI (N=530)	Hazard Ratio [95% CI]	Difference	p-Value
3 Year					
Post-Allocation MACCE	18.0% (108)	22.3% (117)	1.28 [0.98, 1.66]	4.4%	0.067
Death/Stroke/MI, Any	10.3% (62)	8.8% (46)	0.84 [0.57, 1.23]	-1.5%	0.38
Death, Any	5.2% (31)	4.8% (25)	0.92 [0.54, 1.56]	-0.4%	0.76
Cerebrovascular Event (Stroke), Any	3.5% (21)	1.2% (6)	0.32 [0.13, 0.80]	-2.4%	0.01
MI, Any	2.8% (17)	4.8% (25)	1.70 [0.92, 3.15]	2.0%	0.088
Revascularisation, Any	9.7% (57)	17.2% (89)	1.87 [1.34, 2.61]	7.5%	0.0002
PCI	9.2% (54)	14.7% (76)	1.67 [1.18, 2.37]	5.5%	0.0035
CABG	0.8% (5)	3.7% (19)	4.41 [1.65, 11.82]	2.9%	0.0012
Post-Procedure Stent Thrombosis/Graft Occlusion	3.4% (20)	3.5% (18)	1.03 [0.55, 1.95]	0.1%	0.92

Table 13

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{LOW} groups for '**All-Comers' LMS CABG and 'All-Comers' LMS PCI** patients (N=419).

Event	CABG (N=234)	PCI (N=185)	Hazard Ratio [95% CI]	Difference	p-Value
3 Year					
Post-Allocation MACCE	18.0% (41)	18.5% (34)	1.02 [0.65, 1.60]	0.6%	0.94
Death/Stroke/MI, Any	9.6% (22)	6.6% (12)	0.65 [0.32, 1.32]	-3.1%	0.23
Death, Any	5.3% (12)	2.7% (5)	0.51 [0.18, 1.44]	-2.6%	0.19
Stroke, Any	4.0% (9)	0.6% (1)	0.13 [0.02, 1.05]	-3.5%	0.025
MI, Any	0.9% (2)	3.9% (7)	4.30 [0.89, 20.69]	3.0%	0.047
Revascularisation, Any	10.7% (24)	14.8% (27)	1.40 [0.81, 2.42]	4.1%	0.23
PCI	9.8% (22)	12.0% (22)	1.23 [0.68, 2.22]	2.2%	0.49
CABG	0.9% (2)	3.8% (7)	4.37 [0.91, 21.02]	3.0%	0.044
Post-Procedure Stent Thrombosis/Graft Occlusion	4.0% (9)	2.3% (4)	0.54 [0.17, 1.74]	-1.7%	0.29

Table 14

Principal effectiveness and safety results, summary of time-to-event analyses intent-to-treat, comparing GRC_{LOW} groups for '**All-Comers' 3VD PCI and 'All-Comers' 3VD CABG patients** (N=737).

Event	CABG (N=392)	PCI (N=345)	Hazard Ratio [95% CI]	Difference	p-Value
3 Year					
Post-Allocation MACCE	17.9% (67)	24.4% (83)	1.42 [1.03, 1.96]	6.4%	0.031
Death/Stroke/MI, Any	10.7% (40)	10.0% (34)	0.93 [0.59, 1.47]	-0.7%	0.76
Death, Any	5.1% (19)	5.9% (20)	1.16 [0.62, 2.17]	0.7%	0.65
Stroke, Any	3.2% (12)	1.5% (5)	0.46 [0.16, 1.30]	-1.7%	0.13
MI, Any	4.0% (15)	5.3% (18)	1.34 [0.67, 2.65]	1.3%	0.41
Revascularisation, Any	9.1% (33)	18.5% (62)	2.20 [1.44, 3.35]	9.5%	0.0002
PCI	8.8% (32)	16.2% (54)	1.96 [1.27, 3.04]	7.4%	0.0021
CABG	0.8% (3)	3.6% (12)	4.45 [1.26, 15.79]	2.8%	0.011
Post-Procedure Stent Thrombosis/Graft Occlusion	3.0% (11)	4.2% (14)	1.41 [0.64, 3.10]	1.2%	0.40

VII. Reclassification Analyses for 'All-Comers' SYNTAX Population

Tables 15-16: Reclassification Analyses

Table 15

Reclassification analyses (intermediate SXscore and low-intermediate EuroSCORE reclassified to GRC_{LOW}) within the 'All-Comers' SYNTAX Population: Kaplan-Meier event rates in reclassified PCI and CABG patients are shown.

Reclassified SYNTAX Population	Outcome	Event Rates/Total Reclassified CABG Patients	Event Rates/Total Reclassified PCI Patients
All-Comers	3-Year MACCE	16.7% (56/350)	23.3% (62/269)
	3-Year Death	4.8% (16/350)	6.0% (16/269)
All-Comers LMS	3-Year MACCE	18.8% (21/114)	19.0% (16/84)
	3-Year Death	6.3% (7/114)	3.6% (3/84)
All-Comers 3VD	3-Year MACCE	15.6% (35/236)	25.2% (46/185)
	3-Year Death	4.1% (9/236)	7.1% (13/185)

Table 16

Reclassification analyses (low SXscore and high EuroSCORE reclassified to GRC_{INT}) within the 'All-Comers' SYNTAX Population: Kaplan-Meier event rates in reclassified PCI and CABG patients are shown.

Reclassified SYNTAX Population	Outcome	Event Rates/Total Reclassified CABG Patients	Event Rates/Total Reclassified PCI Patients
All-Comers	3-Year MACCE	21.1% (13/66)	30.8% (25/82)
	3-Year Death	8.1% (5/66)	13.6% (11/82)
All-Comers LMS	3-Year MACCE	20.4% (5/26)	27.0% (10/37)
	3-Year Death	8.0% (2/26)	10.8% (4/37)
All-Comers 3VD	3-Year MACCE	21.4% (8/40)	33.9% (15/45)
	3-Year Death	8.2% (3/40)	15.9% (7/45)

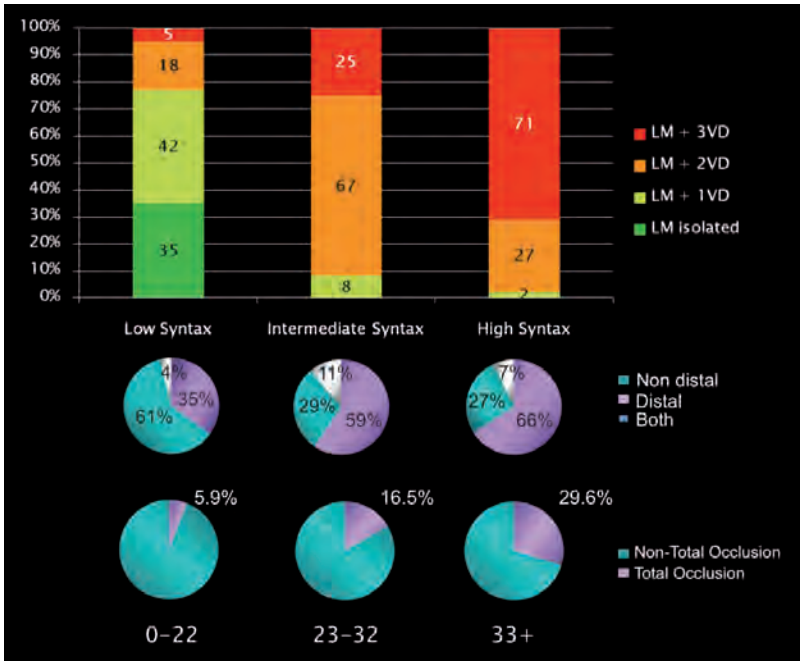
VIII. Additional Material:

Fig. 12 Vessel Distribution in the LMS Population According to SYNTAX Score Tertiles.

Upper graphs: proportion of LMS population with isolated LMS disease, or associated with one (1VD), two (2VD) or three vessel disease (3VD).

Middle graphs: proportion of LMS disease with non distal disease (non distal), distal bifurcation disease (distal) or both components (both).

Lower graphs: proportion of non-total occlusion and total-occlusion disease within the coronary tree (not within the LMS).



IX. Additional References

1. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
2. Sianos G, Morel MA, A.P. K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention, 2005 219-227.
3. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2009;5:50-6.
4. SYNTAX score calculator: http://www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.
5. Ranucci M, Castelvecchio S. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2010;6:549-53.
6. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009;119:3053-61.
7. Wykrzykowska JJ, Garg S, Onuma Y, et al. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. Circulation. Cardiovascular interventions 2011;4:47-56.
8. Garg S, Sarno G, Garcia-Garcia HM, et al. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. Circulation. Cardiovascular interventions 2010;3:317-26.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
10. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 1999;16:9-13.
11. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. European heart journal 2003;24:881-2.
12. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. European Heart Journal 2011.
13. Kim Y-H, Park D-W, Kim W-J, et al. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization. J Am Coll Cardiol Intv 2010;3:612-623.
14. Min SY, Park DW, Yun SC, et al. Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left main coronary disease: analysis from the MAIN-COMPARE study. Circulation. Cardiovascular interventions 2010;3:127-33.

15. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. Heart 2009;95:43-8.
16. Kim YH, Ahn JM, Park DW, et al. EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. The American journal of cardiology 2006;98:1567-70.
17. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology;21:128-38.

Chapter 8.2

Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX Score

Farooq V, Vergouwe Y, Räber L, Vranckx P, G.arcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW

Eur Heart J. 2012;33(24):3098-104 (Impact Factor: 14.097)

Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score

Vasim Farooq[1†], Yvonne Vergouwe[2†], Lorenz Räber[1], Pascal Vranckx[1], Hector Garcia-Garcia[1], Roberto Diletti[1], Arie Pieter Kappetein[3], Marie Angèle Morel[4], Ton de Vries[4], Michael Swart[4], Marco Valgimigli[5], Keith D. Dawkins[6], Stephan Windecker[7], Ewout W. Steyerberg[2], and Patrick W. Serruys[1*]

[1]Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands; [2]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [3]Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands; [4]Cardialysis BV, Rotterdam, The Netherlands; [5]Department of Interventional Cardiology, Cardiovascular Institute, University of Ferrara, Ferrara, Italy; [6]Boston Scientific Corporation, Natick, MA, USA; and [7]Cardiology Department, Bern University Hospital, Bern, Switzerland

Received 6 December 2011; revised 22 July 2012; accepted 9 August 2012; online publish-ahead-of-print 9 October 2012

See page 3008 for the editorial comment on this article (doi:10.1093/eurheartj/ehs346)

Background The SYNTAX score (SXscore), an anatomical-based scoring tool reflecting the complexity of coronary anatomy, has established itself as an important long-term prognostic factor in patients undergoing percutaneous coronary intervention (PCI). The incorporation of clinical factors may further augment the utility of the SXscore to longer-term risk stratify the individual patient for clinical outcomes.

Methods and results Patient-level merged data from >6000 patients in seven contemporary coronary stent trials was used to develop a logistic regression model—the Logistic Clinical SXscore—to predict 1-year risk for all-cause death and major adverse cardiac events (MACE). A core model (composed of the SXscore, age, creatinine clearance, and left ventricular ejection fraction) and an extended model [incorporating the core model and six additional (best performing) clinical variables] were developed and validated in a cross-validation procedure. The core model demonstrated a substantial improvement in predictive ability for 1-year all-cause death compared with the SXscore in isolation [area under the receiver operator curve (AUC): core model: 0.753, SXscore: 0.660]. A minor incremental benefit of the extended model was shown (AUC: 0.791). Consequently the core model alone was retained in the final the Logistic Clinical SXscore model. Validation plots confirmed the model predictions to be well calibrated. For 1-year MACE, the addition of clinical variables did not improve the predictive ability of the SXscore, secondary to the SXscore being the predominant determinant of all-cause revascularization.

Conclusion The Logistic Clinical SXscore substantially enhances the prediction of 1-year mortality after PCI compared with the SXscore, and allows for an accurate personalized assessment of patient risk.

Introduction

The SYNTAX score[1–4] (SXscore) has established itself as an important prognostic tool in risk stratifying patients in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) pioneered Heart Team approach, and has since been validated in patients undergoing percutaneous coronary intervention (PCI) at a short and longer-term follow-

† Both authors equally contributed to this research paper.

* Corresponding author. Tel: +31 10 7035260, Fax: +31 10 4369154, Email: p.w.j.c.serruys@erasmusmc.nl

up.[5–9] More recently the SXscore has been applied to contemporary 'All-Comers' coronary stent trials, and has consistently been shown to be an independent predictor of 1-year mortality and major adverse cardiac events (MACE).[10–12] In contrast, traditional risk scores for patients undergoing PCI principally allow for the estimation of procedural risk.[13–18]

The addition of clinical risk factors to the SXscore has been shown to potentially further augment its utility to objectively select the most appropriate revascularization strategy for patients planning to undergo surgical or percutaneous revascularization.[19–23] These approaches have involved the amalgamation of cardiac surgery-based summary risk scores to the SXscore to form the 'Global Risk' (SXscore and additive EuroSCORE)[23] and the 'clinical SXscore' (SXscore and the modified ACEF score).[19–22] As the individual clinical components of the cardiac surgery-based summary risk scores were not incorporated into the development of the combined risk models, and that these risk scores contained redundant information not relevant to the prediction of mortality after PCI—such as the chronic obstructive pulmonary disease and pulmonary hypertension in the EuroSCORE—this may have limited the predictive ability of the final risk models.[23] Furthermore, these approaches categorized patient risk without giving a more personalized risk assessment—with the Clinical SXscore[19–22] being able to identify a high-risk population only, and the Global Risk[23] a lower-risk population.

The aims of the present study are to combine the individual components of the Clinical SXscore—namely the continuous variables age, creatinine or creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), and the SXscore—to form the Logistic Clinical SYNTAX score (Logistic Clinical SXscore). The underlying hypothesis being that the addition of these 'Core' clinical variables would provide the majority of the improvement to the 1-year predictive ability of the SXscore compared with the addition of further clinical variables. The second aim of this study was to allow for a more personalized approach to risk stratification, compared with the categorical approaches of previous risk models.[19–23]

Methods

Patients

Patient-level data from seven contemporary coronary stent trials[3,24–29] incorporating 6508 patients with a calculated SXscore were pooled for the present study and have previously been described.[19] An additional trial was excluded from the original database ($n = 187$)[30] due to permission being unobtainable from the study sponsor, and a further 12 patients excluded due to missing values for death, leading to a total of 6309 patients in the present analysis. The endpoints for the prognostic analyses were 1-year all-cause death and MACE [a composite of all-cause death, myocardial infarction (MI) and all-cause revascularization].

Predictors and model development

During the development phase, two risk models were defined: (i) a core model that incorporated the SXscore and components of the ACEF and modified ACEF scores[31] (age, creatinine or CrCl and LVEF); (ii) an extended model that included the core model and the addition of best performing clinical variables that improved the performance of the core model. The CrCl was defined by the Cockcroft and Gault formula.[32] The left ventricular ejection fraction was defined as the percentage LVEF taken by transthoracic echocardiography or left ventriculography taken at the time of the diagnostic coronary angiogram.

As the Logistic Clinical SXscore was to be developed for predicting future longer-term (1-year) clinical outcomes, relatively weaker predictors (of borderline significance) were selected and retained in the extended model only if there was an appropriate increase in AUC when added to the core model in the multivariable logistic regression model, in line with work described by Harrell and others.[33,34]

Within all the coronary stent trials predictor values generally were >90% complete if the predictor was recorded. Multiple imputation of missing values in the trials with predictors recorded was undertaken using an advanced imputation strategy that takes the correlation between all potential predictors into account [method of chained equations (MICE algorithm in R software)].[35–37]

Statistical analysis

Logistic regression analyses were performed to examine individual and joint relations between the core model, other clinical characteristics (extended model), and the binary outcome of 1-year all-cause death and MACE. Interaction terms between predictors were examined with likelihood ratio tests, but none was of sufficient relevance to extend the models beyond the main effects for each predictor. All analyses were stratified by the coronary stent trial.

Determining how the variables should be modelled was a vital step in identifying which variables were most strongly related to 1-year clinical outcomes. For the continuous predictors, possible non-linearity with clinical outcomes was assessed with restricted cubic spline functions. These are flexible functions that can accommodate curves in the form of the association to assess the assumption that patient characteristics are linearly related to the log odds of the outcome event.[33,34] To allow for a direct comparison of the prognostic value of predictors recorded in different units or scales, the odds ratios (ORs) for continuous predictors were scaled to correspond to a change from the 25th to 75th percentile of the predictor distribution.[37] Pooled ORs were estimated over the imputed data set, and repeated using only the complete data, which gave similar results (unpublished data). Statistical analyses were performed with R software[37] and SPSS Version 17.0 (SPSS, Inc., Chicago IL, USA).

Validation

The predictive performance of the model was cross-validated by the omission of each of the coronary stent trials in turn, with the model fitted on the remaining pooled population, and the resulting fit tested on the omitted trial.[38–40] This methodology allowed for the estimation of the extent to which the predictive accuracy of the model (based on the entire sample) was affected by any differences between the seven coronary stent trials.[3,24–29] This form of cross-validation by trial was hence a stronger test of validity than if, for example, the study population had been divided at random into a development and validation cohort.[34,41,42]

The measure of predictive discrimination used to characterize the model performance in the original and the validation samples, was by the area under the receiver operating characteristic curve (AUC), and is equal to the *c*-statistic (the ability to distinguish a patient with and without a clinical outcome—and ranges from 0.50 (no better than flipping a coin) to 1.0 (model is 100% correct). Calibration—the agreement between observed and predicted risks—was assessed with the Hosmer–Lemeshow test and validation plots.[33,40]

Model presentation

The final model is presented in a score chart with the scores based on the original logistic regression coefficients and can be used to obtain approximate predictions for individual patients.[34,40] Scores were based on rounding of the regression coefficients. A constant was subtracted or added to rescale the scores in positive integers. The sum scores were related to the risks of 1-year mortality with logistic regression. The score chart can be used to obtain approximate predictions for individual patients.

Results

Development of the model

Within the analysed data set 175 all-cause deaths (2.8%) and 797 MACE (15.8%) were observed. The univariate associations of the SXscore and clinical variables to 1-year all-cause death and MACE are shown in *Table 1*. Creatinine clearance was demonstrated to be a stronger univariate predictor of 1-year all-cause death compared with serum creatinine and was therefore incorporated into the core model (CrCl, OR: 2.2; 95% CI: 1.8–2.8; creatinine, OR: 1.4; 95% CI: 1.2–1.6). Linear relationships were a good approximation for the SXscore, age, CrCl, and LVEF with 1-year mortality, except that constant risk was evident at higher values for the LVEF (≥50%) and CrCl (≥90 mL/min) (Supplementary material online, Appendix). The four factors (SXscore, age, CrCl, and LVEF) were entered into a multivariable logistic regression model (*Table 2*) and confirmed to be strong independent predictors of 1-year mortality, thus forming the core model.

Similar analyses were repeated with the core model and the best performing clinical variables (six clinical variables: presentation, body mass index (BMI), peripheral vascular disease, diabetes, previous MI, smoking) for 1-year mortality to form the extended model.

Table 1 Univariate associations between predictors of 1-year death and 1-year major adverse cardiac events in the pooled database of seven contemporary coronary stent trials

Characteristics	Coding	Death (n = 6309)		MACE (n = 5048)[a]	
		Number (%)	Univariate[b]	Number (%)	Univariate[b]
Core model					
SYNTAX score[c]	23 vs. 8	—	1.7 (1.6–1.8)	—	1.8 (1.7–1.8)
Age (years)[c]	72 vs. 56	—	2.9 (2.7–3.1)	—	1.2 (1.2–1.2)
CrCl[c]	67 vs. 109	—	2.2 (1.8–2.6)	—	1.2 (1.1–1.3)
Ejection fraction[d]	40 vs. 50	—	2.2 (1.8–2.8)	—	1.3 (1.1–1.5)
Extended model					
Presentation (%)					
Stable		72 (2.4)	1.0	386 (15.1)	1.0
UA		32 (2.5)	1.0 (0.7–1.6)	185 (15.2)	1.0 (0.8–1.2)
NSTEMI		25 (3.1)	1.8 (1.1–2.9)	102 (16.5)	1.1 (0.8–1.4)
STEMI		46 (3.6)	1.7 (1.1–2.9)	97 (14.9)	1.0 (0.8–1.3)
Female		58 (3.7)	1.5 (1.1–2.1)	215 (17.1)	1.2 (1.0–1.4)
BMI[c]	30 vs. 25	—	1.1 (1.0–1.1)	—	1.0 (1.0–1.1)
PVD		20 (6.9)	2.5 (1.5–4.1)	49 (20.6)	1.3 (0.9–1.8)
Diabetes (%)					
Non-insulin treated		32 (3.8)	1.8 (1.2–2.8)	146 (17.4)	1.3 (1.1–1.6)
Insulin treated		27 (6.8)	3.1 (2.0–4.8)	101 (25.4)	2.1 (1.6–2.6)
Hypertension (%)		134 (3.1)	1.5 (1.1–2.2)	579 (16.1)	1.2 (1.0–1.5)
Hyperlipidaemia (%)		95 (2.3)	0.6 (0.5–0.9)	523 (15.3)	1.0 (0.9–1.2)
Glycoprotein 2b3a use (%)		57 (3.3)	1.2 (0.8–1.9)	173 (16.3)	1.1 (0.9–1.4)
Previous smoking (%)		48 (2.3)	0.8 (0.6–1.2)	259 (13.9)	1.0 (0.8–1.2)
Current smoking (%)		37 (2.2)	0.8 (0.5–1.1)	178 (14.3)	0.9 (0.7–1.1)
Previous MI (%)		68 (3.9)	1.8 (1.3–2.4)	250 (16.8)	1.2 (1.0–1.4)
Previous PCI (%)		23 (1.9)	0.7 (0.4–1.1)	179 (16.9)	1.2 (0.9–1.4)
TIA or CVA (%)		10 (5.5)	1.5 (0.7–2.8)	33 (22.8)	1.4 (0.9–2.1)
Stent generation (%)	Newer generation	58 (2.1)	0.9 (0.5–1.6)	382 (14.1)	0.8 (0.6–1.1)

CrCl, creatinine clearance; Yrs, years; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; BMI, body mass index; PVD, peripheral vascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; CVA, cerebrovascular accident.
[a]n = 5048 without STRATEGY/MULTI-STRATEGY[24,28] and SIRTAX[26] trials secondary to all-cause revascularization not being recorded in the trials.
[b]Odds ratio (95% confidence interval).
[c]Odds ratios for continuous variables are given for the inter-quartile range.
[d]Odds ratio for a decrease in 10% for values below 50%.

Table 2 **Multivariable associations [odds ratio (95% CI)], between the individual components of the core model, for 1-year death and 1-year major adverse cardiac events in the pooled database of seven contemporary coronary stent trials**

Characteristics	Coding	Death (n = 6309)	MACE (n = 5048)[a]
Core model			
SYNTAX Score[b]	23 vs. 8	1.41 (1.15–1.73)	1.72 (1.54–1.91)
Age (years)[b]	72 vs. 56	2.06 (1.51–2.82)	1.06 (0.92–1.22)
CrCl (ml/min)[b]	67 vs. 109	1.53 (1.12–2.09)	1.11 (0.94–1.31)
LVEF (%)[c]	40 vs. 50	1.97 (1.61–2.41)	1.10 (0.93–1.30)

CrCl, creatinine clearance, LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.
[a]n = 5048 without STRATEGY/MULTI-STRATEGY[24,28] and SIRTAX[26] trials secondary to all-cause revascularization not being recorded in the trials.
[b]Odds ratios for continuous variables are given for the inter-quartile range (indicated in coding column).
[c]Odds ratio for a decrease in 10% for values <50%.

Table 3 **Performances of the Logistic Clinical SYNTAX score (core model) at cross-validation**

Study	Death		MACE	
	SYNTAX score	Core model	SYNTAX score	Core model
ARTS II[25]	0.69	0.75	0.69	0.70
LEADERS[27]	0.63	0.74	0.62	0.61
STRATEGY[24]/MULTI-STRATEGY[28]	0.62	0.84	—	—
RESOLUTE[29]	0.57	0.77	0.63	0.63
SIRTAX[26]	0.64	0.71	—	—
SYNTAX[3]	0.67	0.73	0.58	0.59
Overall[a]	0.660	0.753	0.605[b]	0.609[b]

The core model was developed by omitting each study in turn, with the model fitted on the remaining pooled population, and validated by testing the resulting fit on the omitted trial.[38–40] Values shown are c-statistics for testing the resulting fit on the omitted trial (cross-validation).
LEADERS, biolimus-eluting stent with biodegradable polymer vs. sirolimus-eluting stent with durable polymer for coronary revascularization trial;[27] MACE, major adverse cardiac events; RESOLUTE, RESOLUTE all-comers trial;[29] SIRTAX, the sirolimus-eluting vs. paclitaxel-eluting stents for coronary revascularization trial;[26] SYNTAX, Synergy between PCI with Taxus and cardiac surgery trial;[3] ARTS II, the arterial revascularization therapies study part II trial;[25] STRATEGY, the single high-dose bolus tirofiban and sirolimus-eluting stent vs. abciximab and bare metal stent in myocardial infarction trial;[24] MULTISTRATEGY, comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarctiontrial.[28]
[a]Pooled population (combining all trials).
[b]n = 5048 without STRATEGY/MULTI-STRATEGY and SIRTAX secondary to all-cause revascularization not being recorded in the trial.

Model performances

1-Year all-cause death (death)

The core model (SXscore, age, CrCl, and LVEF) demonstrated a significantly better predictive ability for 1-year all-cause death compared with the SXscore in isolation (*Table 3*). Within the pooled population (combining all trials), the AUC was substantially higher for the core model compared with the SXscore in isolation (core model: 0.753, SXscore 0.660). A minor incremental benefit of the extended model (AUC: 0.791) compared with the core model was evident. Consequently, the core model was retained in the final Logistic Clinical SXscore, and the extended model excluded. The Hosmer–Lemeshow test confirmed that there was no evidence of poor calibration for the core model in pooled analyses of the seven trials ($P = 0.55$). Validation plots of the core model indicated a good agreement between the observed and predicted risks in the three largest coronary stent trials ($n > 1000$) (*Figure 1*). Within the SYNTAX trial recalibration of the validation plots was necessary to prevent generalized underestimation of predicted risk, and involved resetting the intercept of the calibration slope to zero.

1-Year major adverse cardiac events

For the outcome of 1-year MACE, the core and extended models added little incremental increase in predictive ability compared with the SXscore in isolation (AUC core model: 0.609, AUC extended model: 0.618, SXscore: 0.605) (*Tables 2 and 3*). Further analyses indicated that all-cause revascularization least benefited from the addition of clinical variables compared with death or MI (Supplementary material online, Appendix). Since the Logistic Clinical SXscore conferred no major additional benefit to the SXscore in predicting MACE, further analyses for this endpoint are not reported.

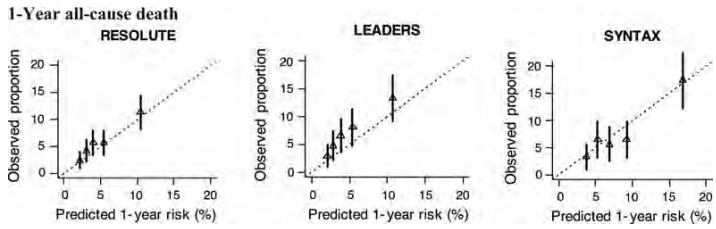


Figure 1 Validation plots at cross-validation for the three largest coronary stent trials ($n > 1000$). Plots are shown for the core model predicting 1-year all-cause death. The triangles indicate the observed frequencies by quintile of predicted probabilities with a 95% confidence interval. Good agreement was evident between observed and predicted risks, indicating that the core model did not over or under-estimate 1-year mortality (i.e. good calibration).

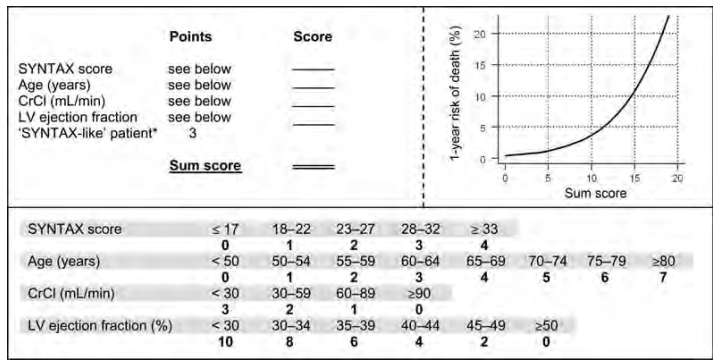


Figure 2 The Logistic Clinical SYNTAX score for the prediction of 1-year death. *SYNTAX-like patient defined as fulfilling the enrolment criteria for the SYNTAX All-Comers trial, i.e. left main stem (isolated or associated with one-, two-, or three-vessel disease) or three-vessel disease alone. CrCl, creatinine clearance, LV ejection fraction, left ventricular ejection fraction.

Score charts for 1-year all-cause death

A simple score chart for the bedside application of the final Logistic Clinical SXscore for predicting 1-year all-cause death after PCI is illustrated (*Figure 2*). An extra score is included for a "SYNTAX-like" patient, i.e. a patient presenting with left main disease (isolated or associated with 1, 2, or 3-vessel disease) or 3-vessel disease, due to the need to recalibrate risks to the SYNTAX trial patients as described previously. One-year mortality can be accurately estimated by the summation of scores. Similar charts for the extended model are enclosed in the Supplementary material online, Appendix.

Discussion

The main findings from this study are that: (i) the Logistic Clinical SXscore—consisting of four continuous variables (SXscore, age, CrCl, LVEF)—substantially enhances the risk stratification of PCI patients for the outcome of 1-year all-cause death compared with the SXscore in isolation; (ii) the Logistic Clinical SXscore was able to accurately distinguish patients with or without a clinical outcome (discrimination) and could accurately predict individual patient risk (calibration) without under or over-estimating risk; (iii) the addition of further clinical variables to the four key predictors of the Logistic Clinical SXscore (SXscore, age, CrCl, and LVEF) did not substantially increase its predictive ability; (iv) an individualized approach to the longer-term (1-year) risk stratification of patients after PCI was achievable utilizing the SXscore and (v) the SXscore in isolation was the predominant determinant of 1-year MACE with little additional predictive benefit of clinical variables, predominantly secondary to the SXscore being the main determinant of all-cause revascularization.

The logistic clinical SYNTAX score: predicting 1-year death

The findings of the Logistic Clinical SXscore, namely that a few strongly predictive clinical variables leading to the accurate prediction of 1-year all-cause death after PCI, are consistent with the concepts of the "law of parsimony" or "Occam's razor." Age, CrCl, and LVEF are objectively measured continuous clinical variables in line with the ACEF methodology, which has previously been shown to match or even surpass the EuroSCORE (consisting of 17 clinical variables) in predicting in-hospital mortality after elective coronary artery bypass graft surgery.[31,43,44] Explanations for this comparability have included that the clinical variables of the ACEF score were objectively defined and continuous.[31]

Notably the addition of a further six clinical variables to the Logistic Clinical SXscore to form the extended model lead to a minor incremental increase in its predictive ability. This is likely related to the inter correlation between the core model and the additional clinical variables. Clear correlations were evident (Pearson correlation coefficient 0.2 or greater, $P < 0.001$) for age and gender/hypertension; CrCl and gender/BMI; LVEF and MI; SXscore and prior PCI; BMI and diabetes mellitus. In addition the presence of diabetes has historically been associated with adverse outcomes after PCI.[45,46] It is however likely that patients with more severe diabetes were captured by the continuous variables in the Logistic Clinical SXscore, in particular a reduced CrCl. Both a reduced CrCl and proteinuria—a marker of diabetic nephropathy—have previously been shown to be significant determinants of adverse risk following PCI.[47–49] Furthermore diabetics without evidence of proteinuria have also previously been reported to have a similar survival compared with non-diabetics.[47]

SYNTAX score

The SXscore calculation has previously been reported to have moderate inter-observer variability when performed by interventional cardiologists,[4,50] which may be perceived as a limitation of the Logistic Clinical SXscore. Appropriate training of SXscore reporting has, however, been shown to substantially reduce inter-observer variability.[1,2,50] It has previously been suggested that the SXscore is a reflection of the underlying co-morbidity of the patient,[23] for which the present study provides further supportive evidence. This notion is also supported by the 10-year predicted Framingham risk scores being recently shown to have a significant and direct relationship with the prevalence and magnitude of coronary artery calcium scores.[51]

Comparisons with the clinical SYNTAX score

The Clinical SXscore, on which the Logistic Clinical SXscore is based, multiplied a variant of the surgical-based ACEF (age, creatinine, and ejection fraction) score (modified ACEF score) to the SXscore. In doing so the Clinical SXscore was shown to overestimate predicted risks (i.e. relatively poor calibration) despite modest increases in the discriminative ability of the Clinical SXscore being obtained.[20,23] The application of the Clinical SXscore to the present study (full data not shown) showed that it was able to identify a high-risk population only (mortality: 6.6% of the study population), compared with the intermediate- and low-risk groups (mortality: 2.3 and 1.1% of the study population, respectively) consistent with the previously reported literature.[19–23] Comparatively the Logistic Clinical SXscore within the present study was demonstrated to accurately predict risk across all risk groups (i.e. well calibrated) and importantly was able to provide an individualized risk assessment.

Comparisons with other risk models

The recently reported Functional SXscore (FSS)—a fractional flow reserve (FFR)-guided SYNTAX scoring methodology—has been shown to potentially improve the predictive accuracy of the SXscore.[52] Within this study, the more objective assessment of coronary stenoses compared with visual assessment (to form the FSS) lead to incremental increases in the predictive accuracies for the outcomes of 1-year MACE (AUC: SXscore, 0.630; FSS, 0.677), 1-year death or MI (AUC: SXscore, 0.621; FSS, 0.676) and 1-year all-cause revascularization (AUC: SXscore, 0.627; FSS, 0.657).[52] Notably, improvements in the predictive accuracy for 1-year death were not reported with the FSS. Comparatively the Logistic Clinical SXscore in the present study demonstrated a substantial increase in the prediction of 1-year death (AUC: SXscore, 0.660; core model, 0.753), and improvements in the prediction of 1-year death or MI (AUC: SXscore, 0.594; core model, 0.657, extended model 0.666—Supplementary material online, Appendix) without the need for invasive pressure-wire coronary assessment.

The longer-term (1-year) mortality predictions provided by the Logistic Clinical SXscore are the principle differences compared with other reported risk scores, namely the National Cardiovascular Data Registry[16] score, the Mayo Clinical Risk score,[13,15] the EuroHeart PCI score,[18] and the New York PCI risk score,[14] in that they report in-hospital Death[14,16,18] or in-hospital MACE,[50,51] or at the most 30-day mortality[16] after PCI. Other risk scores that longer-term risk stratify patients include the New Risk Stratification score (NERS).[53] As previously described with the Clinical SXscore, NERS categorized patients into levels of risk (high and low risk) without giving an individualized assessment of patient risk, which was achievable with the Logistic Clinical SXscore. Furthermore NERS is a more complicated score that consists of 17 clinical variables, 33 anatomical factors, and 4 procedural details, and was developed for patients with left main coronary artery disease undergoing PCI.[53]

Potential clinical application

Although the patient and clinician may wish to know the short-term risk of procedural complications associated with PCI, a longer-term perspective may also be beneficial. Not only would this appropriately inform the patient, but may also prove to be of benefit in determining whether surgical or percutaneous revascularization would be more appropriate as part of the Heart Team consensus. As recently reported, high co-morbidity patients may confer prognostic and morbidity benefits from undergoing surgical revascularization compared with PCI provided a certain threshold of operative risk is not exceeded.[23]

Limitations

Although the Logistic Clinical SXscore was derived from 'All-Comers' types patients in contemporary stent trials, each trial still retained certain inclusion and exclusion criteria.[11] These criteria were, however, minimal which should legitimize the application of the Logistic Clinical SXscore to contemporary clinical practice. The authors recognize that further external validation of the Logistic Clinical SXscore in 'real-world' 'unrestricted' registry populations is necessary when these registries reporting the SXscore become available. This would further strengthen the results of this study, although the present analyses were already undertaken in a pooled analysis of seven different contemporary stent trials and internally validated with a cross-validation procedure. Comparisons of the Logistic Clinical SXscore with the Global Risk[23] were not possible since the EuroSCORE was not collected in the seven contemporary stent trials.

Cardiogenic shock is a risk variable that has consistently been shown to be a powerful predictor of in-hospital mortality.[13–18] This important subset of patients, although not an exclusion criteria in the 'All-Comers' trials, by practice lead to the under-recruitment of these patient types predominantly due to the inability to gain appropriate informed consent or refusal to participate.[54] Consequently, the Logistic Clinical SXscore should at present not be applied to these patients where other risk scores would be better suited.[13–18]

Future directions

Potentially the integration of the Logistic Clinical SXscore into an online algorithm with the currently available SXscore[1] may serve to simultaneously allow for risk stratification of patients based on anatomical and clinical variables. In addition, the application of the Logistic Clinical SXscore in place of the SXscore to aid in determining the optimal revascularization modality in patients with complex coronary disease is a potential future application. The incorporation of the FSS as previously described,[52] to allow for a more objective assessment of the coronary anatomy, may enhance the predictive accuracy of the Logistic Clinical SXscore even further. Future direction with non-invasive imaging and FFR calculation[55]—utilizing computational fluid dynamics applied to coronary computed tomography angiography—may be feasible. The expansion of other risk variables to the Logistic Clinical SXscore such as the haemodynamic status as previously discussed may expand the use of this risk score to other patient types.

Conclusion

Compared with the SXscore in isolation, the Logistic Clinical SXscore substantially enhances the risk stratification of PCI patients for death at 1-year and allows for an accurate individualized assessment of patient risk. The use of the Logistic Clinical SXscore may also further aid in the Heart Team consensus in determining the optimal revascularization modality.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The authors express their gratitude to all of the study participants and the principal investigators of the trials whose work made this study possible. V.F. thanks the Dickinson Trust Travelling Scholarship, Manchester Royal Infirmary, Manchester, England, UK. Y.V. was supported by The Netherlands Organization for Scientific Research (917.11.383).

Funding

The SYNTAX Trial was funded by Boston Scientific Corporation.

Conflict of interest: M.V. reports research grants for lecturers and advisory boards: Iroko, Eli Lilly, Medtronic, and honoraria for lecturers and/or advisory boards: Cordis, Medtronic, Abbott, Eisai, Merck, AstraZeneca, Med Co, and Terumo. K.D.D. is a full-time employee of Boston Scientific and holds stock in Boston Scientific. S.W. received research grants from Abbott, Biosensors, Biotronik, Cordis, Boston Scientific, and Medtronic. The other authors report no conflicts of interest.

References

1. SYNTAX score calculator. http://www.syntaxscore.com. SYNTAX workinggroup. Launched 19th May 2009.
2. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *Euro Intervention* 2005;**1**:219–227.
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
4. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50–56.
5. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 2007;**99**:1072–1081.
6. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2009;**2**:731–738.
7. Kim Y-H, Park D-W, Kim W-J, Lee J-Y, Yun S-C, Kang S-J, Lee S-W, Lee CW, Park S-W, Park S-J. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. *J Am Coll Cardiol Interv* 2010;**3**:612–623.
8. Park DW, Kim YH, Yun SC, Song HG, Ahn JM, Oh JH, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol* 2011;**57**:2152–2159.
9. Chakravarty T, Buch MH, Naik H, White AJ, Doctor N, Schapira J, Mirocha JM, Fontana G, Forrester JS, Makkar R. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol* 2011;**107**:360–366.
10. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter

LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol* 2010;**56**:272–277.
11. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Raber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient-level pooled analysis assessing the impact of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score on 1-year clinical outcomes in 6508 patients enrolled in contemporary coronary stent trials. JACC. *Cardiovasc Interv* 2011;**4**: 645–653.
12. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. *J Am Coll Cardiol* 2011;**57**: 2389–2397.
13. Singh M, Rihal CS, Selzer F, Kip KE, Detre K, Holmes DR. Validation of Mayo Clinic risk adjustment model for in-hospital complications after percutaneous coronary interventions, using the National Heart, Lung, and Blood Institute dynamic registry. *J Am Coll Cardiol* 2003;**42**:1722–1728.
14. Wu C, Hannan EL, Walford G, Ambrose JA, Holmes DR Jr, King SB III, Clark LT, Katz S, Sharma S, Jones RH. A risk score to predict in-hospital mortality for percutaneous coronary interventions. *J Am Coll Cardiol* 2006;**47**:654–660.
15. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR Jr. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. *Mayo Clin Proc* 2007;**82**:701–708.
16. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV, Shaw RE, Roe MT, Ho KK, Klein LW, Krone RJ, Weintraub WS, Brindis RG, Rumsfeld JS, Spertus JA. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588 398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2010;**55**:1923–1932.
17. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart* 2011;**97**:1902–1913.
18. de Mulder M, Gitt A, van Domburg R, Hochadel M, Seabra-Gomes R, Serruys PW, Silber S, Weidinger F, Wijns W, Zeymer U, Hamm C, Boersma E. EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2011;**32**:1398–1408.
19. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 2010;**3**: 317–326.
20. Capodanno D, Caggegi A, Miano M, Cincotta G, Dipasqua F, Giacchi G, Capranzano P, Ussia G, Di Salvo ME, La Manna A, Tamburino C. Global risk classification and clinical SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score in patients undergoing percutaneous or surgical left main revascularization. *J Am Coll Cardiol Interv* 2011;**4**:287–297.
21. Girasis C, Garg S, Raber L, Sarno G, Morel MA, Garcia-Garcia HM, Luscher TF, Serruys PW, Windecker S. SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial. *Eur Heart J* 2011;**32**:3115–3127.
22. Wykrzykowska JJ, Garg S, Onuma Y, de Vries T, Goedhart D, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. *Circ Cardiovasc Interv* 2011;**4**:47–56.
23. Serruys PW, Farooq V, Vrancx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR, Jr., Kappetein AP, Mack MJ, Feldman T, Morice MC, Stahle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention. The SYNTAX trial at 3 years. *JACC Cardiovasc Interv* 2012;**5**:606–617.
24. Valgimigli M, Percoco G, Malagutti P, Campo G, Ferrari F, Barbieri D, Cicchitelli G, McFadden EP, Merlini F, Ansani L, Guardigli G, Bettini A, Parrinello G, Boersma E, Ferrari R. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA* 2005;**293**:2109–2117.
25. Serruys PW, Ong AT, Morice MC, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Donohoe D. Arterial revascularisation therapies study part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Euro Intervention* 2005;**1**:147–156.
26. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005;**353**:653–662.
27. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;**372**:1163–1173.
28. Valgimigli M, Campo G, Percoco G, Bolognese L, Vassanelli C, Colangelo S, de Cesare N, Rodriguez AE, Ferrario M, Moreno R, Piva T, Sheiban I, Pasquetto G, Prati F, Nazzaro MS, Parrinello G, Ferrari R. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTI-STRATEGY randomized trial. *JAMA* 2008;**299**:1788–1799.
29. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, KelbÃ!k H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;**363**:136–146.
30. Serruys PW, Garg S, Abizaid A, Ormiston J, Windecker S, Verheye S, Dubois C, Stewart J, Hauptmann KE, Schofer J, Stangl K, Witzenbichler B, Wiemer M, Barbato E, de Vries T, den Drijver AM, Otake H, Meredith L, Toyloy S, Fitzgerald P. A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study. *Euro Intervention*2010;**6**:195–205.
31. Ranucci M, Castelvecchio S. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. *Euro Intervention* 2010;**6**:549–553.
32. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
33. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis (Springer Series in Statistics)* New York: Springer-Verlag, Inc. 2001.
34. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating (Statistics for Biology and Health)*. New York: Springer Science+Business Media, LLC, 2009.
35. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991;**10**:585–598.
36. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002;**7**:147–177.
37. R Development Core Team. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna (Austria) 2006. Available: http://www.R-project.org/. Accessed 1 August 2011.
38. Efron B, Gong G. A leisurely look at the bootstrap, the jackknife, and cross-validation. *Am Statistician* 1983;**37**:36–48.
39. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41 021 patients. GUSTO-I Investigators. *Circulation* 1995;**91**:1659–1668.
40. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;**21**:128–138.
41. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med* 1999;**130**:515–524.
42. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000;**19**:453–473.
43. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 2009;**119**:3053–3061.
44. Ranucci M, Castelvecchio S, Conte M, Megliola G, Speziale G, Fiore F, Guarracino F, Scolletta S, Escobar RM, Falco M, Bignami E, Landoni G. The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29 659 patients undergoing elective cardiac surgery. *J Thorac Cardiovasc Surg* 2011;**142**:581–586.
45. Weber FD, Schneider H, Wiemer M, Pfannebecker T, Tebbe U, Hamm CW, Senges J, Schneider S, Nienaber CA. Sirolimus eluting stent (Cypher) in patients with diabetes mellitus: results from the German Cypher Stent Registry. *Clin Res Cardiol* 2008;**97**:105–109.
46. Mack MJ, Banning AP, Serruys PW, Morice MC, Taeymans Y, Van Nooten G, Possati G, Crea F, Hood KL, Leadley K, Dawkins KD, Kappetein AP. Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or metabolic syndrome. *Ann Thorac Surg* 2011;**92**:2140–2146.

47. Marso SP, Ellis SG, Tuzcu M, Whitlow PL, Franco I, Raymond RE, Topol EJ. The importance of proteinuria as a determinant of mortality following percutaneous coronary revascularization in diabetics. *J Am Coll Cardiol* 1999;**33**:1269–1277.
48. Mercado N, Brugts JJ, Ix JH, Shlipak MG, Dixon SR, Gersh BJ, Lemos PA, Guarneri M, Teirstein PS, Wijns W, Serruys PW, Boersma E, O'Neill WW. Usefulness of proteinuria as a prognostic marker of mortality and cardiovascular events among patients undergoing percutaneous coronary intervention (data from the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events [EXCITE] trial). *Am J Cardiol* 2008;**102**:1151–1155.
49. Shaw JA, Andrianopoulos N, Duffy S, Walton AS, Clark D, Lew R, Sebastian M, New G, Brennan A, Reid C, Ajani AE. Renal impairment is an independent predictor of adverse events post coronary intervention in patients with and without drug-eluting stents. *Cardiovasc Revasc Med* 2008;**9**:218–223.
50. Genereux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, Lazar D, Jankovic I, Corral MD, Dressler O, Fahy MP, Parise H, Lansky AJ, Stone GW. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv* 2011;**4**:553–561.
51. Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, Lloyd-Jones DM. Distribution of coronary artery calcium scores by framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol* 2011;**57**:1838–1845.
52. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011;**58**:1211–1218.
53. Chen S-L, Chen JP, Mintz G, Xu B, Kan J, Ye F, Zhang J, Sun X, Xu Y, Jiang Q, Zhang A, Stone GW. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *J Am Coll Cardiol Interv* 2010;**3**:632–641.
54. de Boer SP, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma E. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011;**32**:2161–2167.
55. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, Defrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011;**58**:1989–1997.

Combined Anatomical and Clinical Factors for the Long Term Risk Stratification of Patients Undergoing Percutaneous Coronary Intervention: The Logistic Clinical SYNTAX Score

Supplementary Appendix

Table 1

Multivariable associations (odds ratio [95% confidence interval]) between the best performing predictors of 1-year Death and 1-year MACE in the pooled database of 7 contemporary coronary stent trials.

Table 2

Performances of the Logistic Clinical SYNTAX Score (Core and Extended models) at cross validation: models were developed by omitting each study in turn, and validated by each study in turn.

Table 3

Logistic regression formula to predict 1-Year Death

Figures

Figure 1

Plots showing univariate associations between the continuous Core Model predictors and 1-year all-cause Death: a) SYNTAX Score, b) Age, c) Left Ventricular Ejection Fraction and d) Creatinine Clearance. Each panel depicts the risk of 1-year death (solid curve) with 95% CIs (dotted curves).

Figure 2

Receiver-operator characteristic (ROC) curve analysis for the SXscore and the Logistic Clinical SXscore (Core and Extended Model) for 1-year clinical outcomes.

Figure 3

Core and Extended Models of the Logistic Clinical SYNTAX Score for the prediction of 1-Year Death.

Table 1

Multivariable associations (odds ratio [95% confidence interval]) between the best performing predictors of 1-year Death and 1-year MACE in the pooled database of 7 contemporary coronary stent trials

Characteristics	Coding	Death (n=6309)		MACE (n=5048)[1]	
		Core Model	Extended Model	Core Model	Extended Model
CORE MODEL					
SYNTAX Score[†]	23 vs. 8	1.41 (1.15, 1.73)	1.50 (1.17, 1.92)	1.72 (1.54, 1.91)	1.72 (1.55, 1.92)
Age (Years)[†]	72 vs. 56	2.06 (1.51, 2.82)	1.77 (1.20, 2.61)	1.06 (0.92, 1.22)	1.01 (0.87, 1.17)
CrCl (ml/min)[†]	67 vs. 109	1.53 (1.12, 2.09)	1.59 (1.10, 2.30)	1.11 (0.94, 1.31)	1.09 (0.90, 1.32)
LVEF (%)[‡]	40 vs. 50	1.97 (1.61, 2.41)	1.58 (1.21, 2.03)	1.10 (0.93, 1.30)	1.12 (0.96, 1.29)
EXTENDED MODEL					
Presentation	NSTEMI	-	1.33 (0.66, 2.69)	-	-
	STEMI	-	1.80 (1.10, 2.94)	-	-
BMI[†]	30 vs. 25	-	1.27 (1.02, 1.59)	-	-
PVD		-	1.83 (1.08, 3.12)	-	-
Previous MI		-	1.46 (0.95, 2.27)	-	-
Current Smoking		-	1.53 (0.95, 2.46)	-	-
Diabetes	Non-Insulin Treated	-	1.56 (1.09, 2.41)	-	1.27 (1.03, 1.57)
	Insulin Treated	-	2.12 (1.38, 3.15)	-	1.86 (1.44, 2.40)
Hypertension		-	-	-	1.15 (0.96, 1.39)
Stent Generation		-	-	-	1.28 (0.97, 1.69)
Female		-	-	-	1.16 (0.96, 1.39)

[1] n=5048 without STRATEGY/MULTI-STRATEGY[1, 2] and SIRTAX[3] Trials secondary to all-cause revascularisation not being recorded in the trials.

[†]Odds Ratios for continuous variables are given for the interquartile range (indicated in Coding column)

[‡]Odds Ratio for a decrease in 10% for values below 50%

Abbreviations: NSTEMI non ST elevation myocardial infarction, STEMI ST elevation myocardial infarction, BMI body mass index, PVD peripheral vascular disease, MI myocardial infarction, PCI percutaneous coronary intervention, TIA transient ischaemic attack, CVA cerebrovascular accident.

Table 2

Performances of the Logistic Clinical SYNTAX Score (Core and Extended models) at cross validation: models were developed by omitting each study in turn, and validated by each study in turn.

	Death			MACE		
Study	**SYNTAX Score**	**Core Model**	**Extended Model**	**SYNTAX Score**	**Core Model**	**Extended Model**
ARTS II[4]	0.69	0.75	0.80	0.69	0.70	0.71
LEADERS[5]	0.63	0.74	0.74	0.62	0.61	0.60
STRATEGY[2]**/MULTI-STRATEGY**[1]	0.62	0.84	-	-	-	-
RESOLUTE[6]	0.57	0.77	-	0.63	0.63	0.63
SIRTAX[3]	0.64	0.71	0.72	-	-	-
SYNTAX[7]	0.67	0.73	0.76	0.58	0.59	0.61
Overall*	0.660	0.753	0.791[1]	0.605[2]	0.609[2]	0.618[2]

Values are c-statistics for models.

*Pooled population (combining all trials)

[1] n=3880 without STRATEGY/MULTI-STRATEGY and RESOLUTE, secondary to body mass index (BMI) and peripheral vascular disease (PVD) not being recorded in the respective trial.

[2] n=5048 without STRATEGY/MULTI-STRATEGY and SIRTAX secondary to all-cause revascularisation not being recorded in the trial.

Abbreviations: LEADERS, biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation trial;[5] RESOLUTE, RESOLUTE all-comers trial;[6] SIRTAX: the sirolimus-eluting versus paclitaxel-eluting stents for coronary revascularisation trial;[3] SYNTAX: Synergy between PCI with Taxus and cardiac surgery trial;[7] ARTS II: the arterial revascularisation therapies study part II trial;[4] STRATEGY: the single high dose bolus tirofiban and sirolimus eluting stent vs abciximab and bare metal stent in myocardial infarction trial;[2] MULTISTRATEGY: comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction trial.[1]

Table 3

Logistic regression formula to predict 1-Year Death

Logistic Clinical SXscore - Core Model: 1-Year Death Logit (Death) = -7.5478 + 0.0241 * SXscore + 0.0396 * age + 0.0748 * $(50\text{-LVEF})_+$ + 0.0235 * $(90\text{-CrCl})_+$ + 0.3649 * SYNTAX-like
Logistic Clinical SXscore - Extended Model: 1-Year Death Logit (Death) = -9.3818 + 0.0276 * SXscore + 0.0325 * age + 0.0536 * $(50\text{-LVEF})_+$ + 0.0248 * $(90\text{-CrCl})_+$ + 0.5440 * SYNTAX-like + 0.4813 * NSTEMI + 0.7937 * STEMI + 0.0570 * BMI + 0.5689 * PVD + 0.4568* Diabetes + 0.7422* DiabInsul + 0.3673 * PrevMI + 0.4279 * CurrSmok
Risk of 1-Year Death = 1/[1+exp(-Logit(Death)]

Key:

SXscore	= SYNTAX Score
Age	= Age (Years)
LVEF	= Left Ventricular Ejection Fraction
CrCl	= Creatinine Clearance (ml/min)
SYNTAX-like	= SYNTAX Trial Patient (Yes=1/No=0)
NSTEMI	= Non ST-Elevation Myocardial Infarction (Yes=1/No=0)
STEMI	= ST-Elevation Myocardial Infarction (Yes=1/No=0)
BMI	= Body Mass Index (kg/m^2)
PVD	= Peripheral Vascular Disease (Yes=1/No=0)
Diabetes	= Diabetes: Not Insulin Treated (Yes=1/No=0)
DiabInsul	= Diabetes: Insulin Treated (Yes=1/No=0)
PrevMI	= Previous Myocardial Infarction (Yes=1/No=0)
CurrSmok	= Current smoker (Yes=1/No=0)
$(50\text{-LVEF})_+$	indicates 50-LVEF for positive values, 0 for negative values
$(90\text{-CrCl})_+$	indicates 90-CrCl for positive values, 0 for negative values

Figure 1

Plots showing univariate associations between the continuous Core Model predictors and 1-year all-cause Death: a) SYNTAX Score, b) Age, c) Left Ventricular Ejection Fraction and d) Creatinine Clearance. Each panel depicts the risk of 1-year death (solid curve) with 95% CIs (dotted curves).

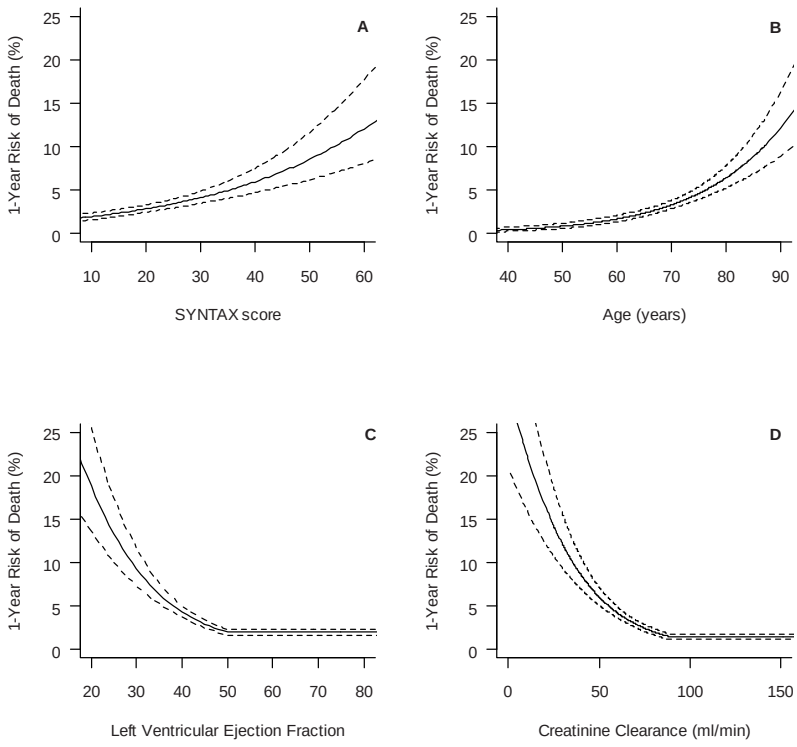


Figure 2

Receiver-operator characteristic (ROC) curve analysis for the SXscore and the Logistic Clinical SXscore (Core and Extended Model) for 1-year clinical outcomes.

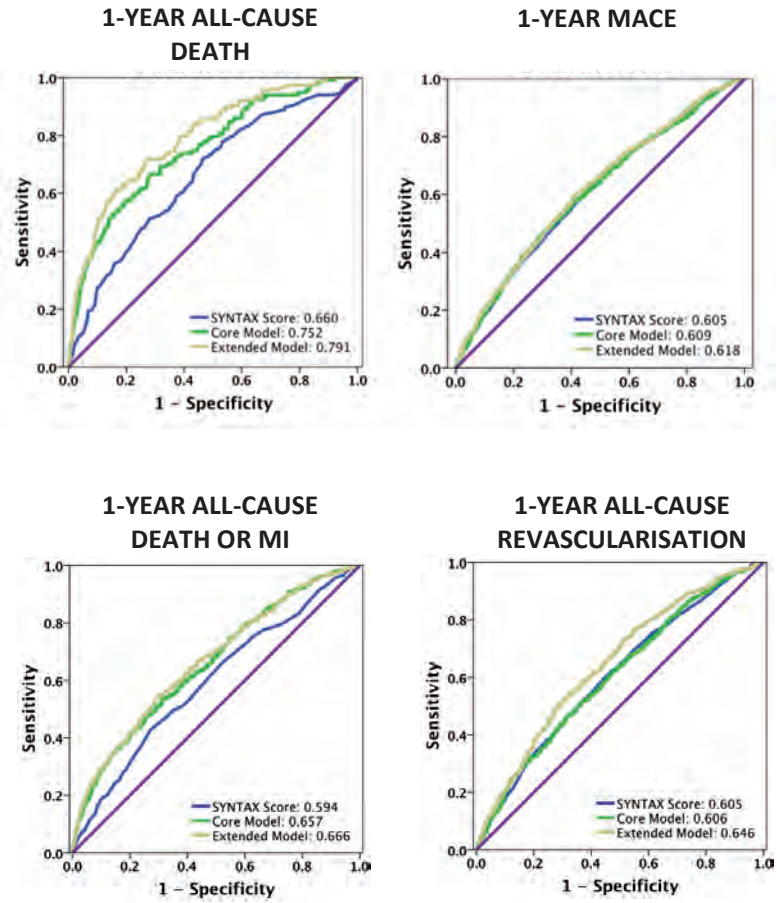
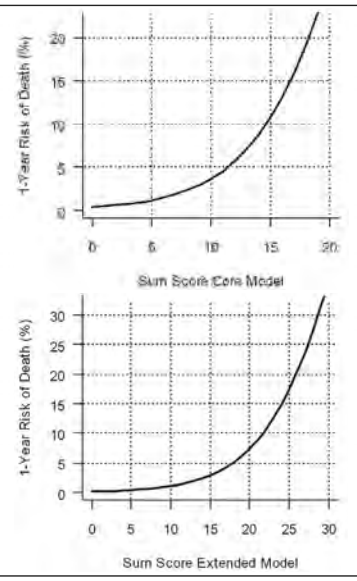


Figure 3

Core and Extended Models of the Logistic Clinical SYNTAX Score for the prediction of 1-Year Death.

	Points	Score
SYNTAX Score	see below	_____
Age (years)	see below	_____
CrCl (ml/min)	see below	_____
LV Ejection Fraction	see below	_____
'SYNTAX-like' Patient*	3	_____
Sum Score Core Model		═══
STEMI	3	_____
NSTEMI	4	_____
BMI	see below	_____
PVD	3	_____
Insulin Treated DM	4	_____
Non Insulin DM	2	_____
Previous MI	2	_____
Current smoking	2	_____
Sub Score Added Predictors		_____ +
Sum Score Extended Model		═══



SYNTAX Score	≤ 17	18-22	23-27	28-32	≥ 33			
	0	**1**	**2**	**3**	**4**			
Age (years)	< 50	50-54	55-59	60-64	65-69	70-74	75-79	≥80
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
CrCl (ml/min)	< 30	30-59	60-89	≥90				
	3	**2**	**1**	**0**				
LV Ejection Fraction (%)	< 30	30-34	35-39	40-44	45-49	≥50		
	10	**8**	**6**	**4**	**2**	**0**		
BMI (kg/m^2)	<20	21-24	25-29	30-34	≥ 35			
	0	**1**	**2**	**3**	**4**			

***SYNTAX-like Patient defined as fulfilling the enrolment criteria for the SYNTAX All-Comers trial i.e. left main stem (isolated or associated with one, two or three vessel disease) or three vessel disease alone.**

Abbreviations. CrCl: creatinine clearance, STEMI: ST elevation myocardial infarction, BMI: body mass index, LV Ejection Fraction: left ventricular ejection fraction, PVD: peripheral vascular disease, DM: diabetes mellitus, MI: myocardial infarction.

Chapter 8.3

Prediction of 1-Year Mortality in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: Validation of the Logistic Clinical SYNTAX Score

Farooq V, Vergouwe Y, Généreux P, Bourantas CV, Palmerini T, Caixeta A, Garcìa-Garcìa HM, Morel MA, McAndrew TC, Kappetein AP, Valgimigli M, Windecker S, Dawkins KD, Steyerberg EW, Serruys PW, Stone GW

JACC Cardiovasc Interv. 2013;6(7):737-45 (Impact Factor: 6.552)

Prediction of 1-Year Mortality in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

Validation of the Logistic Clinical SYNTAX (Synergy Between Percutaneous Coronary Interventions With Taxus and Cardiac Surgery) Score

Vasim Farooq, MBChB,* Yvonne Vergouwe, PhD,† Philippe Généreux, MD,‡ Christos V. Bourantas, MD, PhD,* Tullio Palmerini, MD,‡ Adriano Caixeta, MD,‡ Hector M. Garcìa-Garcìa, MD, PhD,* Roberto Diletti, MD,* Marie-angèle Morel, BSc,§ Thomas C. McAndrew, MS,‡ Arie Pieter Kappetein, MD, PhD,|| Marco Valgimigli, MD,¶ Stephan Windecker, MD,# Keith D. Dawkins, MD,** Ewout W. Steyerberg, PhD,† Patrick W. Serruys, MD, PhD,* Gregg W. Stone, MD‡

Rotterdam, the Netherlands; New York, New York; Ferrara, Italy; Bern, Switzerland; and Natick, Massachusetts

Objectives This study sought to validate the Logistic Clinical SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score in patients with non–ST-segment elevation acute coronary syndromes (ACS), in order to further legitimize its clinical application.

Background The Logistic Clinical SYNTAX score allows for an individualized prediction of 1-year mortality in patients undergoing contemporary percutaneous coronary intervention. It is composed of a "Core" Model (anatomical SYNTAX score, age, creatinine clearance, and left ventricular ejection fraction), and "Extended" Model (composed of an additional 6 clinical variables), and has previously been cross validated in 7 contemporary stent trials (>6,000 patients).

Methods One-year all-cause death was analyzed in 2,627 patients undergoing percutaneous coronary intervention from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. Mortality predictions from the Core and Extended Models were studied with respect to discrimination, that is, separation of those with and without 1-year all-cause death (assessed by the concordance [C] statistic), and calibration, that is, agreement between observed and predicted outcomes (assessed with validation plots). Decision curve analyses, which weight the harms (false positives) against benefits (true positives) of using a risk score to make mortality predictions, were undertaken to assess clinical usefulness.

Results In the ACUITY trial, the median SYNTAX score was 9.0 (interquartile range 5.0 to 16.0); approximately 40% of patients had 3-vessel disease, 29% diabetes, and 85% underwent drug-eluting stent implantation. Validation plots confirmed agreement between observed and predicted mortality. The Core and Extended Models demonstrated substantial improvements in the discriminative ability for 1-year all-cause death compared with the anatomical SYNTAX score in isolation (C-statistics: SYNTAX score: 0.64, 95% confidence interval [CI]: 0.56 to 0.71; Core Model: 0.74, 95% CI: 0.66 to 0.79; Extended Model: 0.77, 95% CI: 0.70 to 0.83). Decision curve analyses confirmed the increasing ability to correctly identify patients who would die at 1 year with the Extended Model versus the Core Model versus the anatomical SYNTAX score, over a wide range of thresholds for mortality risk predictions.

Conclusions Compared to the anatomical SYNTAX score alone, the Core and Extended Models of the Logistic Clinical SYNTAX score more accurately predicted individual 1-year mortality in patients presenting with non–ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention. These findings support the clinical application of the Logistic Clinical SYNTAX score. (J Am Coll Cardiol Intv 2013;6:737–45)

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score is as an objective, anatomical-based tool to determine the complexity of coronary artery disease and guide decision making between cardiac surgery and percutaneous coronary intervention (PCI) (1–5). Since the SYNTAX trial, numerous validation studies have confirmed the SYNTAX score to be an independent predictor of long-term mortality in a broad range of patient types (6–8). The use of the SYNTAX score is now advocated in both the U.S. and European revascularization guidelines (9,10). In addition, the U.S. Food and Drug Administration mandates the SYNTAX score as entry criteria in ongoing contemporary stent and structural heart disease trials, investigating percutaneous left main coronary intervention (EXCEL [Evaluation of XIENCE PRIME Everolimus Eluting Stent System (EECSS) or XIENCE V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularizations] Clinical Trial; NCT01205776) (11) and transcatheter aortic valve implantation (SURTAVI [Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement]; NCT01586910).

Abbreviations and Acronyms

ACS = acute coronary syndromes
BMS = bare-metal stent(s)
CrCl = creatinine clearance
DES = drug-eluting stent(s)
IQR = interquartile range(s)
LVEF = left ventricular ejection fraction
PCI = percutaneous coronary intervention
PVD = peripheral vascular disease

The lack of clinical variables, and the lack of a more individualized approach of the SYNTAX score—with patients categorized as "low," "intermediate," or "high" risk—has recently been shown to be potentially misleading. In a post hoc analysis of the SYNTAX trial (12), relatively higher- and lower-risk patients were identified in the low and high SYNTAX score groups, respectively. The Logistic Clinical SYNTAX score (13) was designed to overcome these limitations, by augmenting the anatomical SYNTAX score with clinical variables, and to individualize long-term (1-year) mortality predictions in patients undergoing contemporary PCI.

The purpose of this study was to validate the Logistic Clinical SYNTAX score in patients with non–ST-segment elevation acute coronary syndromes (ACS), in order to further establish its clinical utility.

Methods

Study population. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial design has previously been described (14). In brief, this was a multicenter, prospective, randomized trial of patients with moderate- and high-risk non–ST-segment elevation ACS, managed with an early invasive strategy. Coronary angiography was performed in all patients within 72 h of randomization to a specific anticoagulation regime undertaken during the intervention. The choice of either bare-metal (BMS) or drug-eluting stents (DES) was per operator discretion; approximately 85% of the PCI population underwent DES implantation. First-generation sirolimus-eluting or paclitaxel-eluting stents were exclusively used if DES was to be implanted. Dual antiplatelet therapy with aspirin and clopidogrel was strongly recommended for at least 1 year. All major adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment. In line with a previous validation study of the anatomical SYNTAX score in the ACUITY trial (8), the subgroup of PCI patients in whom quantitative coronary angiography was performed in the formal angiographic substudy of the ACUITY trial (n = 2,627) was used for validation in the present study (15). All patients underwent anatomical SYNTAX score analyses by 3 interventional cardiologists, appropriately trained for SYNTAX score reading and blinded to the clinical outcomes (16).

Logistic Clinical SYNTAX score. The Logistic Clinical SYNTAX score has previously been developed and cross-validated (13) in a pooled population of 7 contemporary DES trials (n = 6,309) (2,17–23). It is composed of a Core Model (consisting of the anatomical SYNTAX score, age, creatinine clearance [CrCl], and left ventricular ejection fraction [LVEF]), and an Extended Model (consisting of an additional 6 clinical variables) to improve the accuracy of 1-year mortality predictions. During development and cross-validation (13), the Core Model was shown to substantially improve the predictive ability of the anatomical SYNTAX score, with a minor incremental benefit in improving mortality predictions for the Extended Model.

From the *Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; †Department of Public Health, Erasmus University Medical Center, Rotterdam, the Netherlands; ‡Columbia University Medical Center/New York-Presbyterian Hospital, Cardiovascular Research Foundation, New York, New York; §Cardialysis BV, Rotterdam, the Netherlands; ||Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands; ¶Department of Interventional Cardiology, Cardiovascular Institute, University of Ferrara, Ferrara, Italy; #Cardiology Department, Bern University Hospital, Bern, Switzerland; and the **Boston Scientific Corporation, Natick, Massachusetts. Dr. Kappetein has reported that he has served on the Steering Committee of the SYNTAX trial. Dr. Valgimigli has reported that he has received research grants for lectures and advisory boards from Iroko, Eli Lilly, Medtronic, and honoraria for lectures and/or advisory boards from Cordis, Medtronic, Abbott, Eisai, Merck & Co., Inc., AstraZeneca, MedCo, and Terumo. Dr. Windecker has reported that he has received research grants (paid to his institution) from Abbott, Biosensors, Biotronik, Cordis, Boston Scientific, Medtronic, and St. Jude Medical. Dr. Dawkins has reported that he is a full-time employee of Boston Scientific and holds stock in Boston Scientific. Dr. Stone has reported that he has served as a consultant to Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Farooq and Vergouwe contributed equally to this paper. David E. Kandzari, MD, has served as Guest Editor.

Manuscript received March 18, 2013; accepted April 1, 2013.

For validation purposes, all predictor values in the Core Model were present in >85% of patients. For the additional predictors of the Extended Model, all values were present in >90% of patients, except peripheral vascular disease (PVD) (not recorded) and body mass index (weight [100%, n = 2,627], height [36%, n = 945]). The definition of PVD was expanded to include previous transient ischemic attack or cerebrovascular accident, because these variables represented extracardiac arteriopathy. This modification to the variable was rerun in the original development and cross-validation population (13), with no change in predictive performance of the Logistic Clinical SYNTAX score (Fig. 1). Multiple imputation (5×) of missing values was undertaken using an imputation strategy that takes the correlation between all potential predictors into account. The method of chained equations with the Multivariate Imputation by Chained Equations (MICE) algorithm in R software (R Foundation for Statistical Computing, Vienna, Austria) was used (23,24).

Statistical analysis. Continuous variables are expressed as means ±SD or medians and interquartile ranges (IQR), as appropriate. Binary variables are expressed as counts and/or percentages. The possible nonlinearity of the continuous predictors of the Core Model with 1-year all-cause death in the ACUITY trial were assessed with restricted cubic spline functions. These are flexible functions that can accommodate curves in the form of the association to assess the assumption that patient characteristics are linearly related to the log odds of the outcome event (23,25). Statistical analyses were performed with R software (24) and SPSS (version 17.0, SPSS Inc., Chicago, Illinois).

Calibration, discrimination, and clinical usefulness. Calibration, discrimination, and clinical usefulness (23) were assessed for the Logistic Clinical SYNTAX score (Core and Extended Models) and anatomical SYNTAX score in the ACUITY trial. Calibration refers to the agreement between observed and predicted outcomes. The possible over- or underestimation of the predicted risks were graphically

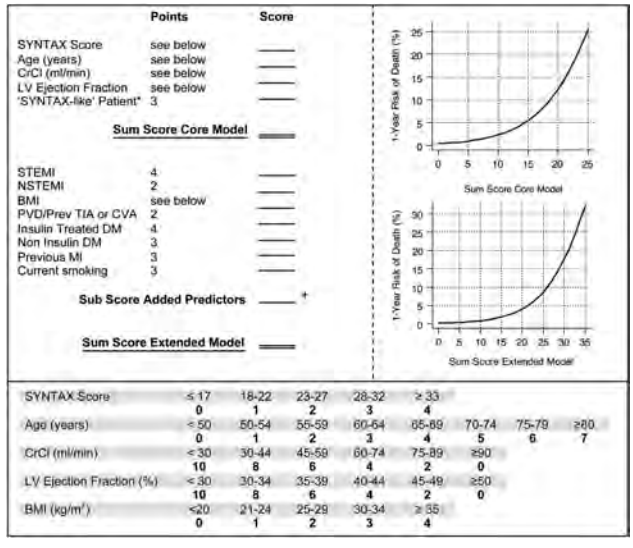


Figure 1. The Logistic Clinical SYNTAX Score for the Prediction of 1-Year Death

Core (incorporating 4 variables) and Extended Model (incorporating a further 6 variables) are illustrated. *SYNTAX-like patient defined as fulfilling the enrollment criteria for the SYNTAX All-Comers trial: that is, left main stem (isolated or associated with 1-, 2-, or 3-vessel disease) or 3-vessel disease alone. Adapted, with permission, from Farooq et al. (13). BMI = body mass index; CrCl = creatinine clearance; CVA = cerebrovascular accident; DM = diabetes mellitus; LV = left ventricular; MI = myocardial infarction; Prev = previous; PVD = peripheral vascular disease; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIA = transient ischemic attack.

assessed with validation plots. Discrimination was studied with the concordance (C) index, which is identical to the area under the receiver-operating characteristic curve. The C-index estimates the probability that, of two randomly chosen patients, the patient with the more favorable prognostic score will outlive the patient with the less favorable prognostic score, and ranges from 0.5 (no discrimination) to a theoretical maximum of 1.

Clinical usefulness was assessed using decision curve analyses (26–29). These analyses estimate a "net benefit" for prediction models that provide individual risk estimates. Patients are classified as high or low risk at a chosen threshold value. The net benefit considers the benefit of the classification (patients correctly classified as dying within 1 year) and the harms (patients wrongly classified as dying within 1 year). The threshold value for classification is used in the decision-curve analysis to weigh correctly classified patients against wrongly classified patients. The references were that everyone was classified as high risk (i.e., died at 1 year), or that everyone was classified as low risk (i.e., alive at 1 year). The interpretation of the decision curve is that the model with the highest net benefit, at a particular threshold value, is the preferred model.

Results

The incidence of all-cause mortality in the quantitative coronary angiography–PCI cohort of the ACUITY trial (n = 2,627) was 2.4% at 1 year (62 deaths). Baseline characteristics are shown in Table 1 (30). The mean age was 60.7 ± 11.7 years; 33% were women; 62% of patients presented with non–ST-segment elevation myocardial infarction and the remainder with unstable angina. Approximately 85% of patients were implanted with DES, and 14% implanted with BMS. The median anatomical SYNTAX score was 9.0 (IQR: 5 to 16) with a maximum value of 59.5. Approximately 40% of the study population had 3-vessel disease, and 28.5% had diabetes mellitus.

The univariate associations of the variables in the Core Model (age, CrCl, LVEF, anatomical SYNTAX score) with 1-year mortality in the ACUITY trial are illustrated in Fig. 2.

Validation of the Logistic Clinical SYNTAX score. CALIBRATION. For the anatomical SYNTAX score, a good agreement was found between observed and predicted mortality outcomes (Fig. 3). For the Logistic Clinical SYNTAX score (Fig. 3), the Core Model demonstrated good agreement between observed and predicted mortality outcomes at the lower risks, with some underestimation at the higher risks (>5%). The Extended Model demonstrated good agreement between observed and predicted mortality outcomes across all recorded risk ranges.

DISCRIMINATION. The area under the receiver-operating characteristic curve demonstrated a substantially higher predictive accuracy of the Core and Extended Models for 1-year all-cause death, compared with the anatomical SYNTAX score in isolation (Fig. 4).

CLINICAL USEFULNESS. The net benefit of the Core and Extended Models, and the anatomical SYNTAX score, are shown on the y-axis on the decision curves (Fig. 5). The net benefit was highest for the Extended Model across all potential threshold values of 1-year mortality. This was followed by the Core Model, and then the anatomical SYNTAX score.

Table 1. Baseline Characteristics of Patients in the ACUITY Trial (N = 2,627)

Clinical characteristics	
Age, yrs	60.7 ± 11.7 (2,627)
Male	67.5 (1,774/2,627)
Diabetes	28.5 (745/2,614)
Insulin-treated diabetes	7.8 (205/2,614)
Hypertension	65.6 (1,718/2,619)
Hyperlipidemia	56.2 (1,454/2,588)
Cerebrovascular event: previous stroke/transient ischemic attack	5.8 (150/2,604)
Creatinine clearance, ml/min	99.2 ± 51.8 (2,458)
History of renal insufficiency	15.5 (381/2,458)
Left ventricular ejection fraction, %	54.5 ± 12.0 (2,231)
Current smoker	35.3 (925/2,618)
Previous PCI	44.0 (1,155/2,623)
Anatomical/procedural characteristics	
Anatomical SYNTAX score	9.0 (IQR 5.0–16.0)*
3-vessel disease	39.7 (1,043/2,627)
Left anterior descending artery involvement	77.5 (2,036/2,627)
Left circumflex involvement	66.1 (1,737/2,627)
Right coronary artery involvement	73.8 (1,939/2,627)
Left main involvement	0.5 (12/2,627)
Bare-metal stent implantation	14.0 (369/2,627)
Drug-eluting stent implantation: Cypher or Taxus†	84.9 (2,230/2,627)
Cypher (sirolimus-eluting stent) only	46.8 (1,043/2,230)
Taxus (paclitaxel-eluting stent) only	49.6 (1,106/2,230)
Cypher and Taxus	1.6 (35/2,230)
Non–ST-segment elevation ACS characteristics	
ST-segment deviation ≥1 mm	25.4 (667/2,627)
Baseline cardiac biomarker elevation	60.2 (1,470/2,442)
Non–ST-segment elevation myocardial infarction	62.2 (1,467/2,358)
Previous myocardial infarction	29.1 (749/2,576)
TIMI risk score (30)	
Low: 0–2	16.2 (345/2,131)
Intermediate: 3–4	59.2 (1,261/2,131)
High: 5–7	24.6 (525/2,131)

Values are mean ± SD (N), % (n/N), or median (IQR). *Data not normally distributed. †The Cypher stent is manufactured by Cordis (Miami Lakes, Florida) and Taxus is manufactured by Boston Scientific (Natick, Massachusetts).

ACS = acute coronary syndromes; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; IQR = interquartile range; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIMI = Thrombolysis In Myocardial Infarction.

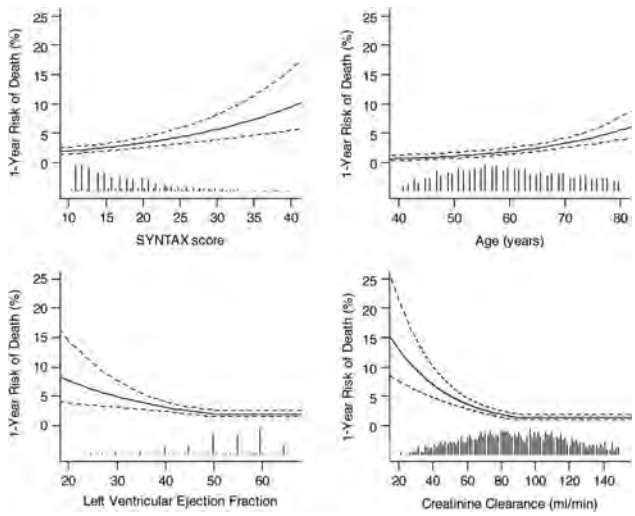


Figure 2. Plots Showing the Form of the Univariate Associations Among the 4 Continuous Core Model Predictors and 1-Year Risk of Death in the ACUITY Trial

Each panel depicts the risk of 1-year death **(solid curve)** with 95% confidence intervals **(dotted curves)**. A histogram illustrating the distribution of the data for each variable in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial is shown below each plot. Due to the rounding of some values of data by the study sites, for example, left ventricular ejection fraction (often to the nearest 5% or 10%), age (nearest whole integer), or the maximum value being a whole or half point (SYNTAX [Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery] score), gaps between the values in the histogram for these variables are seen.

Discussion

In this study, the Logistic Clinical SYNTAX score was validated in a large, prospective, randomized trial of patients with predominantly moderate- and high-risk non–ST-segment elevation ACS undergoing PCI (8). These findings indicate that the Logistic Clinical SYNTAX score is statistically robust, having previously been cross-validated ("internal-external" validation procedure [31]) during development in >6,000 patients in 7 contemporary stent trials (13). The current study provides further legitimacy toward the clinical application of the Logistic Clinical SYNTAX score. In addition, there are several notable findings: 1) In patients with non–ST-segment elevation ACS, both the Core (age, CrCl, LVEF, and anatomical SYNTAX score) and Extended Models (Core Model and additional 6 variables) substantially improved the predictive accuracy of 1-year mortality predictions, compared with the anatomical SYNTAX score alone. 2) The Core and Extended Models were both shown to discriminate well in the study population; the Core Model underestimated mortality predictions in patients at higher risk (>5%), which the Extended Model corrected for. 3) Decision-curve analyses, a method to assess clinical usefulness, confirmed the progressive improvement in 1-year mortality predictions over a wide range of thresholds, with the Extended Model versus the Core Model versus the anatomical SYNTAX score.

One of the main messages of the present study, and of the previous development and cross-validation study of the Logistic Clinical SYNTAX score (13), was that the Core Model was shown to contain most of the predictive information for 1-year mortality. The Extended Model, which incorporates 6 additional clinical variables to the Core Model, including diabetes and peripheral vascular disease, yielded only modest incremental improvement for 1-year mortality predictions. However, the Extended Model proved to be of additional clinical value in patients with non–ST-segment elevation ACS in improving the accuracy of higher risk predictions (>5%), as shown by the validation plots (Fig. 3). In addition, the decision-curve analyses showed that the Extended Model provided additional clinical value compared with the Core Model, by improving the accuracy of 1-year mortality predictions across all considered risk threshold values (Fig. 5).

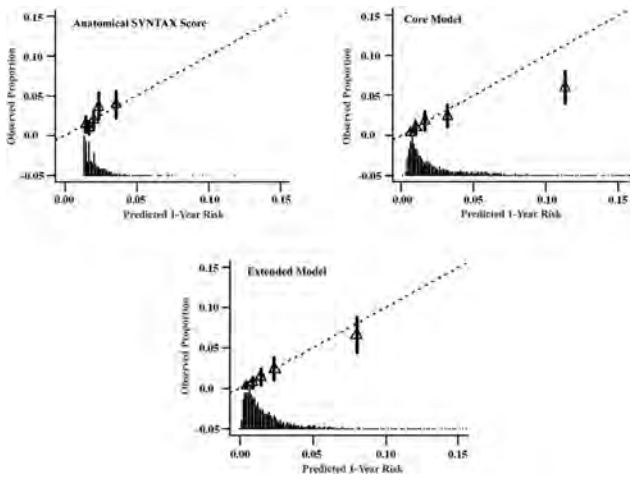


Figure 3. Validation Plots

Validation plots, comparing the anatomical SYNTAX score against the Core and Extended Models of the Logistic Clinical SYNTAX score. A histogram illustrating the distribution of the predicted risks in the ACUITY trial are shown below each plot (scale not shown). The triangles indicate the observed frequencies by quintiles of the predicted 1-year risk. Abbreviations as in Figures 1 and 2.

Decision-curve analyses were recently proposed as an assessment of clinical usefulness and weigh the harms (false positives) against the benefits (true positives) of using a risk score to make treatment decisions (27,29). Comparatively, the C-index is the probability of the correct ordering of risks (i.e., of 2 randomly chosen patients, the patient with the lower prognostic score will outlive the patient with the higher prognostic score), and has previously been suggested to be insensitive in detecting the clinical value of a risk prediction score (23,29,32,33). Indeed, in the present study, only a minor increase in the C-index was observed, when comparing the Extended and Core Models (C-index: Extended Model: 0.77, Core Model: 0.74) (Fig. 4).

Nevertheless, as the Core Model retained a substantial superior ability over the anatomical SYNTAX score in predicting 1-year mortality, the Core Model can be used with reasonable accuracy, with the knowledge that the Extended Model would improve the mortality predictions, particularly in the higher-risk ranges.

Diabetic patients. The FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial has recently reported that diabetics with multivessel disease (predominantly 3- vessel disease, without left main involvement), to confer a mortality benefit in undergoing coronary artery bypass graft surgery compared with PCI with DES (34). The present study provides insights to the potential importance of diabetes as a risk factor for PCI. With the Logistic Clinical SYNTAX score, diabetes added only minor improvement to the predictive accuracy of the Core Model, as 1 of 6 other variables in the Extended Model. Essentially the Core Model captures most of the patient comorbidity, with variables such as CrCl, and is therefore likely to be a reflection of the presence of systemic and coronary atherosclerotic burden. Evidence to support this hypothesis comes from a population-level cohort study, demonstrating that the rate of myocardial infarction was substantially higher in nondiabetics with chronic kidney disease than in diabetics without chronic kidney disease (35). In addition, a recently published large meta-analysis demonstrated the importance of kidney disease as a predictor of clinical outcomes, including mortality, irrespective of the presence or absence of diabetes (36). Thus, the outcomes for patients with diabetes after PCI may be favorable if end-organ manifestations of diabetes are not yet present, such as chronic kidney disease (37).

Study limitations. The ACUITY trial population had relatively low anatomical SYNTAX scores. This is likely to be representative of real-world practice, because other contemporary, all-comer stent trials reported similar mean anatomical SYNTAX scores to those of the ACUITY trial (17,19–22). Despite this limitation, 3-vessel disease still represented approximately 40% of the study population in the ACUITY

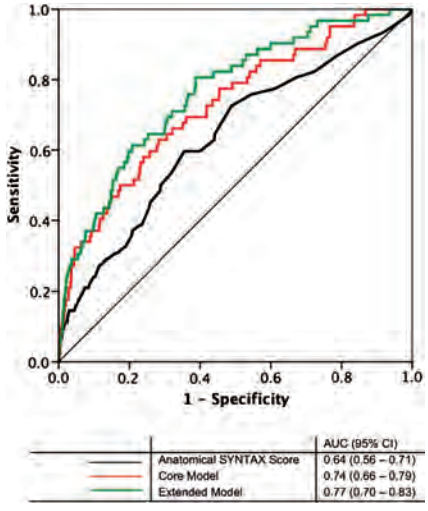


Figure 4. ROC Curves

Receiver-operating characteristic (ROC) curves for the anatomical SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score and the Core and Extended Models of the Logistic Clinical SYNTAX score, predicting 1-year mortality. The combination of variables in the Core **(red)** and Extended **(green)** Models improves the predictive performance of the Logistic Clinical SYNTAX score for 1-year mortality. AUC = area under curve; CI = confidence interval(s).

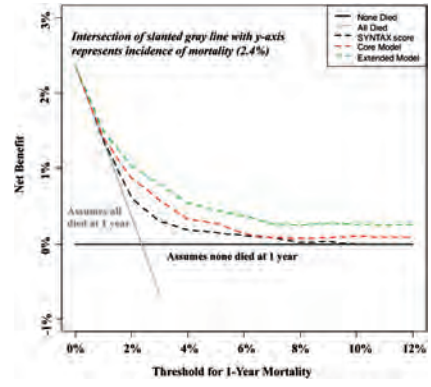


Figure 5. Decision Curves Demonstrating Identification of Patients Who Will Die, Based on 1-Year Mortality Predictions of Logistic Clinical SYNTAX Score, Compared With the Anatomical SYNTAX Score

The x-axis shows threshold values for 1-year mortality risk. The clinician may use the threshold to classify patients as high or low risk at a value to proceed with some action, such as, increased patient monitoring or additional medical therapy. The y-axis represents the net benefit for the different threshold values of 1-year mortality risk. The interpretation of the net benefit is in units of true positives and is the sum of how many patients are correctly identified to be high risk (true positive, i.e., died within 1 year) minus a weighted number of patients incorrectly identified as high risk (false positive, i.e., alive at 1 year). The **slanted gray line** represents the classification of all patients as high risk (i.e., died within 1 year); the horizontal line represents the classification of all patients as low risk (i.e., alive at 1 year), with the latter resulting in a net benefit of 0. The intersection of the y-axis and the **slanted gray line** (as highlighted) represents the overall 1-year mortality risk in the ACUITY trial (2.4%). The prediction models that are the farthest away from the **slanted gray line** (i.e., assume all died within 1 year) and the **horizontal line** (i.e., assume all are alive at 1 year) demonstrate the highest net benefit, namely the Extended Model **(broken green line),** followed by the Core Model **(broken red line),** and then the anatomical SYNTAX score **(broken black line)**. For example, at a threshold value of 3%, the Extended Model would correctly identify an extra 1 in 200 deaths, compared with the anatomical SYNTAX score alone (difference in net benefit is 0.5%). At threshold values of 5% or 10%, this value would be 1 in 300 (difference in net benefit 0.33%). Abbreviations as in Figures 1 and 2.

trial. Second, BMS were used in only 14% of the study population, whereas the Logistic Clinical SYNTAX score was developed and cross-validated in patients undergoing DES implantation (13). The validation process was rerun in the ACUITY trial with BMS patients excluded, and the predictive performance of the Logistic Clinical SYNTAX score did not change (data not shown). Third, because the present study assessed first-generation DES, we cannot exclude the possibility of improved mortality with newer generation DES. In the original development and cross-validation study of the Logistic Clinical SYNTAX score, composed of 7 contemporary stent trials and >6,000 patients, stent generation (first against newer generation) was not shown to have an impact on 1-year mortality (13). Conversely, newer generation DES have been associated with reductions in definite stent thrombosis and composite clinical outcomes; however, improvements in mortality have not been shown (38,39). In addition, we cannot exclude the possibility of newer generation antiplatelet therapy to have had an impact on clinical outcomes (40). Fourth, cardiogenic shock is an important subset of patients that cannot be assessed with the Logistic Clinical SYNTAX score, due to under-recruitment of these patient types in all-comer stent trials, predominantly due to the inability to gain appropriate informed consent (13,41). Lastly, we cannot exclude the possibility of the addition of a functional component to the calculation of the anatomical SYNTAX score to improve the predictive accuracy of the Logistic Clinical SYNTAX score (42).

Conclusions

Compared with the anatomical SYNTAX score alone, the Core and Extended Models of the Logistic Clinical

SYNTAX score more accurately predict individual 1-year mortality in patients presenting with non–ST-segment elevation ACS undergoing PCI. These findings provide further legitimacy toward the clinical application of the Logistic Clinical SYNTAX score.

Acknowledgment
The authors thank all of the study participants whose work made this study possible.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Interventional Cardiology Department, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. SYNTAX Working Group. SYNTAX score calculator. [Online tool]. May 19, 2009. Available at: http://www.syntaxscore.com. Accessed November 1, 2012.
2. Serruys PW, Morice MC, Kappetein AP, et al., for the SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360:961–72.
3. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50–6.
4. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
5. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
6. Garg S, Sarno G, Girasis C, et al. A patient-level pooled analysis assessing the impact of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. J Am Coll Cardiol Intv 2011;4:645–53.
7. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011; 97:1902–13.
8. Palmerini T, Genereux P, Caixeta A, et al. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. J Am Coll Cardiol 2011;57:2389–97.
9. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.
10. Wijns W, Kolh P, Danchin N, et al., for the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
11. Farooq V, Serruys PW, Stone GW, Virmani R, Chieffo A, Fajadet J. Left main coronary artery disease. In: Eeckhout E, Serruys PW, Wijns W, Vahanian A, van Sambeek M, de Palma R, editors. Percutaneous Interventional Cardiovascular Medicine: The PCR-EAPCI Textbook. Part III, Chapter 12. Toulouse, France: PCR Publishing/Europa Edition, 2012:329–405.
12. Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX trial at 3 years. J Am Coll Cardiol Intv 2012;5:606–17.
13. Farooq V, Vergouwe Y, Räber L, et al. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. Eur Heart J 2012;33:3098–104.
14. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial: study design and rationale. Am Heart J 2004;148:764–75.
15. Aoki J, Lansky AJ, Mehran R, et al. Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circulation 2009;119:687–98.
16. Genereux P, Palmerini T, Caixeta A, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. Circ Cardiovasc Interv 2011;4:553–61.
17. Valgimigli M, Percoco G, Malagutti P, et al., for the STRATEGY Investigators. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. JAMA 2005;293:2109–17.
18. Serruys PW, Ong AT, Morice MC, et al. Arterial Revascularisation Therapies Study Part II: sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147–56.
19. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
20. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
21. Valgimigli M, Campo G, Percoco G, et al., for the MULTI-STRATEGY Investigators. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTI-STRATEGY randomized trial. JAMA 2008;299:1788–99.
22. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136–46.
23. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York, NY: Springer, 2009.
24. R Development Core Team. A language and environment for statistical computing. 2006. Available at: http://www.R-project.org/. Accessed August 1, 2011.
25. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. Springer Series in Statistics. New York, NY: Springer, 2001.
26. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128–38.
27. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565–74.
28. Localio AR, Goodman S. Beyond the usual prediction accuracy metrics: reporting results for clinical decision making. Ann Intern Med 2012; 157:294–5.
29. Steyerberg EW, Vickers AJ. Decision curve analysis: a discussion. Med Decis Making 2008;28:146–9.
30. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.
31. Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. Stat Med 2004;23:907–26.
32. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115:928–35.
33. Pepe MS, Janes H, Gu JW. Letter by Pepe et al. regarding article, "Use and misuse of the receiver operating characteristic curve in risk prediction." Circulation 2007;116:e132, author reply e134.
34. Farkouh ME, Domanski M, Sleeper LA, et al., for the FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.
35. Tonelli M, Muntner P, Lloyd A, et al., for the Alberta Kidney Disease Network. Risk of coronary events in people with chronic kidney disease

compared with those with diabetes: a population-level cohort study. Lancet 2012;380:807–14.
36. Fox CS, Matsushita K, Woodward M, et al., for the Chronic Kidney Disease Diagnosis Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380: 1662–73.
37. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50.
38. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393–402.
39. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117,762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873–91.
40. Alexopoulos D, Galati A, Xanthopoulou I, et al. Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. J Am Coll Cardiol 2012;60:193–9.
41. de Boer SP, Lenzen MJ, Oemrawsingh RM, et al. Evaluating the "all-comers" design: a comparison of participants in two "all-comers" PCI trials with non-participants. Eur Heart J 2011;32:2161–7.
42. Nam CW, Mangiacapra F, Entjes R, et al., for the FAME Study Investigators. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. J Am Coll Cardiol 2011;58:1211–8.

Key Words: acute coronary syndrome ■ drug-eluting stents ■ mortality ■ predictions ■ SYNTAX score ■ validation.

APPENDIX

For the logistic regression formula used to predict 1-year death, please see the online version of this paper.

Supplementary Material

Table 1

Logistic regression formula to predict 1-year Death

Logistic Clinical SYNTAX Score - Core Model: 1-Year Death Logit (Death) = -7.5478 + 0.0241 * SYNTAX Score + 0.0396 * age + 0.0748 * (50-LVEF)$_+$ +0.0235 * (90-CrCl)$_+$ + 0.3649 * SYNTAX-like
Logistic Clinical SYNTAX Score - Extended Model: 1-Year Death Logit (Death) = -9.255 + 0.029 * SYNTAX Score + 0.033 * age + 0.050 * (50-LVEF)$_+$ + 0.023 * (90-CrCl)$_+$+ 0.457 * SYNTAX-like + 0.347 * NSTEMI + 0.684* STEMI + 0.051 * BMI + 0.358* PVD/Prev TIA or CVA + 0.457* Diabetes + 0.742* DiabInsul + 0.473 * PrevMI + 0.465 * CurrSmok
Risk of 1-Year Death = 1/[1+exp(-Logit(Death)]

Key:	
Age	= Age (Years)
LVEF	= Left ventricular ejection fraction
CrCl	= Creatinine Clearance (ml/min)
SYNTAX-like	= SYNTAX Trial Patient (Yes=1/No=0)
NSTEMI	= Non ST-elevation myocardial infarction (Yes=1/No=0)
STEMI	= ST-elevation myocardial infarction (Yes=1/No=0)
BMI	= Body mass index (kg/m^2)
PVD/Prev TIA or CVA	= Peripheral vascular disease/Previous transient ischaemic attack/cerebrovascular accident (Yes=1/No=0)
Diabetes	= Diabetes: not insulin treated (Yes=1/No=0)
DiabInsul	= Diabetes: insulin treated (Yes=1/No=0)
PrevMI	= Previous myocardial infarction (Yes=1/No=0)
CurrSmok	= Current smoker (Yes=1/No=0)
(50-LVEF)$_+$	indicates 50-LVEF for positive values, 0 for negative values
(90-CrCl) $_+$	indicates 90-CrCl for positive values, 0 for negative values

Chapter 8.4

Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX Score II

Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW

Lancet 2013;381(9867):639-50 (Impact Factor: 39.060)

Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II

Vasim Farooq, David van Klaveren*, Ewout W Steyerberg, Emanuele Meliga, Yvonne Vergouwe, Alaide Chieffo, Arie Pieter Kappetein, Antonio Colombo, David R Holmes Jr, Michael Mack, Ted Feldman, Marie-Claude Morice, Elisabeth Ståhle, Yoshinobu Onuma; Marie-angèle Morel, Hector M Garcia-Garcia, Gerrit Anne van Es, Keith D Dawkins, Friedrich W Mohr, Patrick W Serruys*

Summary

Background The anatomical SYNTAX score is advocated in European and US guidelines as an instrument to help clinicians decide the optimum revascularisation method in patients with complex coronary artery disease. The absence of an individualised approach and of clinical variables to guide decision making between coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) are limitations of the SYNTAX score. SYNTAX score II aimed to overcome these limitations.

Methods SYNTAX score II was developed by applying a Cox proportional hazards model to results of the randomised all comers SYNTAX trial (n=1800). Baseline features with strong associations to 4-year mortality in either the CABG or the PCI settings (interactions), or in both (predictive accuracy), were added to the anatomical SYNTAX score. Comparisons of 4-year mortality predictions between CABG and PCI were made for each patient. Discriminatory performance was quantified by concordance statistics and internally validated with bootstrap resampling. External validation was done in the multinational all comers DELTA registry (n=2891), a heterogeneous population that included patients with three-vessel disease (26%) or complex coronary artery disease (anatomical SYNTAX score ≥33, 30%) who underwent CABG or PCI. The SYNTAX trial is registered with ClinicalTrials.gov, number NCT00114972.

Findings SYNTAX score II contained eight predictors: anatomical SYNTAX score, age, creatinine clearance, left ventricular ejection fraction (LVEF), presence of unprotected left main coronary artery (ULMCA) disease, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease (COPD). SYNTAX score II significantly predicted a difference in 4-year mortality between patients undergoing CABG and those undergoing PCI ($p_{interaction}$ 0·0037). To achieve similar 4-year mortality after CABG or PCI, younger patients, women, and patients with reduced LVEF required lower anatomical SYNTAX scores, whereas older patients, patients with ULMCA disease, and those with COPD, required higher anatomical SYNTAX scores. Presence of diabetes was not important for decision making between CABG and PCI ($p_{interaction}$ 0·67). SYNTAX score II discriminated well in all patients who underwent CABG or PCI, with concordance indices for internal (SYNTAX trial) validation of 0·725 and for external (DELTA registry) validation of 0·716, which were substantially higher than for the anatomical SYNTAX score alone (concordance indices of 0·567 and 0·612, respectively). A nomogram was constructed that allowed for an accurate individualised prediction of 4-year mortality in patients proposing to undergo CABG or PCI.

Interpretation Long-term (4-year) mortality in patients with complex coronary artery disease can be well predicted by a combination of anatomical and clinical factors in SYNTAX score II. SYNTAX score II can better guide decision making between CABG and PCI than the original anatomical SYNTAX score.

Funding Boston Scientific Corporation.

Introduction

The anatomical SYNTAX score is an important instrument that can help clinicians to establish the optimum revascularisation approach in patients with complex coronary artery disease (with or without unprotected left main coronary artery [ULMCA] involvement).[1–5] It is advocated in both European and US revascularisation guidelines.[6,7] These guidelines also state that clinical variables should be taken into account during discussion between multidisciplinary teams consisting of a clinical cardiologist, cardiac surgeon, and interventional cardiologist (the so-called heart team approach) when deciding the best treatment method; absence of clinical variables is a limitation of the SYNTAX score.

In patients with ULMCA disease, a low-intermediate SYNTAX score (<33) was shown to have much the same long-term clinical outcomes—including all-cause mortality and major cardiovascular and cerebrovascular

Lancet 2013; 381: 639–50

See **Comment** page 605

See **Articles** page 629

*Contributed equally

Thoraxcenter (V Farooq MBChB, Y Onuma MD, H M Garcia-Garcia MD, Prof P W Serruys MD), **Department of Public Health** (D van Klaveren MSc, Prof E W Steyerberg PhD, Y Vergouwe PhD), **and Department of Cardiothoracic Surgery** (Prof A P Kappetein MD) **Erasmus University Medical Center, Rotterdam, Netherlands; AO Ordine Mauriziano Umberto I, Turin, Italy** (E Meliga MD); **San Raffaele Scientific Institute, Milan, Italy** (A Chieffo MD, A Colombo MD); **Mayo Clinic, Rochester, MN, USA** (Prof D R Holmes Jr MD); **Heart Hospital Baylor Plano, Baylor Healthcare System, Dallas, TX, USA** (M Mack MD); **Evanston Hospital, Evanston, IL, USA** (Prof T Feldman MD); **Hôpital Privé Jacques Cartier, Massy, France** (M-C Morice MD); **University Hospital Uppsala, Uppsala, Sweden** (Prof E Ståhle MD); **Cardialysis, Rotterdam, Netherlands** (M-A Morel BSc, H M Garcia-Garcia MD, G A van Es PhD); **Boston Scientific Corporation, Natick, MA, USA** (K D Dawkins MD); **and Herzzentrum Universität Leipzig, Leipzig, Germany** (Prof F W Mohr MD)

Correspondence to:
Prof Patrick W Serruys, Erasmus University Medical Centre, 3015 CE Rotterdam, Netherlands
p.w.j.c.serruys@erasmusmc.nl

For the **SYNTAX score** see http://www.syntaxscore.com

events—with coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) in the SYNTAX trial.[1,4,8] This finding formed the basis for the US Food and Drug Administration's decision to accept a SYNTAX score of less than 33 as an entry criterion to the ongoing international multicentre EXCEL (Evaluation of XIENCE prime versus Coronary artery bypass surgery for Effectiveness of Left main revascularisation) trial, aiming to recruit 2600 patients with ULMCA disease (NCT01205776).[9]

In patients with three-vessel disease, a low SYNTAX score (<23) was shown to have much the same long-term clinical outcomes between CABG and PCI in the SYNTAX trial.[1,8] A substudy of the SYNTAX trial[10] has, however, suggested that patients with high clinical comorbidity (ie, additive EuroSCORE[11] ≥6) with three-vessel disease, irrespective of the anatomical complexity (SYNTAX score), might potentially derive a prognostic benefit from undergoing CABG compared with PCI, provided an acceptable threshold of operative risk is not exceeded. Some researchers have therefore suggested that the SYNTAX score, and other category-based scores[10,12–15] that labelled patients as low risk, intermediate risk, or high risk might be concealing higher risk patients in lower risk groups, or vice versa.

The purpose of our study was to augment the SYNTAX score with prognostically important clinical variables to form SYNTAX score II, to better guide decision making between CABG and PCI. Additionally, SYNTAX score II should provide the basis for individualised decision making between CABG and PCI, by contrast with the present strategy of grouping (low, intermediate, or high) risk to patients.

Methods

SYNTAX trial

The SYNTAX trial was a randomised, prospective, multicentre trial (85 centres in 18 countries) with an allcomers design.[1,5,8] Exclusion criteria were minimal and consisted of previous coronary revascularisation, concomitant cardiac surgery (valve or resection of aortic or left ventricular aneurysm) or acute myocardial infarction, and cardiac enzymes more than twice as high as the normal limit. Patients with ULMCA disease (isolated or associated with one-vessel, two-vessel, or three-vessel disease) or de-novo three-vessel disease were randomised on a 1:1 basis to CABG or PCI with TAXUS Express paclitaxel-eluting stent (Boston Scientific Corporation, Natick, MA, USA; n=1800). Randomisation of patients was stratified by clinical site, absence or presence of ULMCA disease, and medically treated diabetes (requiring oral medications or insulin). Patients deemed unsuitable for randomisation by the cardiologist were nested in registries. An independent clinical events committee reviewed all primary clinical endpoints.[1]

The anatomical SYNTAX score[1–3] combines the importance of a diseased coronary artery segment by vessel-segment weighting (Leaman score), adverse lesion characteristics (American College of Cardiology/American Heart Association lesion classification, and total occlusion characteristics from the European TOTAL Surveillance Study), and the Medina classification system for bifurcation lesions.[14,16–18] Calculation of antomical SYNTAX score was done by the heart team before randomisation, and corroborated by an independent core laboratory (Cardialysis BV, Rotterdam, Netherlands), blinded to treatment assignment. Clinical variables were also prospectively collected as part of the original SYNTAX trial.[1] Chronic obstructive pulmonary disease (COPD) was defined as the long-term use of bronchodilators or steroids for lung disease (EuroSCORE definition[11]). Peripheral vascular disease was defined as aorta and arteries other than coronaries, with exercise-related claudication, or revascularisation surgery, or reduced or absent pulsation, or angiographic stenosis of more than 50%, or combinations of these characteristics (Arterial Revascularisation Therapies Study Part I [ARTS I] definition[19]). Preprocedural left ventricular ejection fraction (LVEF) was taken by transthoracic echocardiography or diagnostic left ventriculography, and categorised as good (≥50%), moderate (30–49%), or poor (<30%). Creatinine clearance, a measure of estimated glomerular filtration rate, was defined by the Cockcroft and Gault formula.[20]

Within the SYNTAX trial, most predictor values were more than 98% complete. Creatinine clearance was 91% complete, LVEF was 98·4% complete when recorded categorically (good, moderate, and poor) and 62·6% complete when recorded continuously (numerical value). An advanced multiple imputation strategy, which takes the correlation between all potential predictors (method of chained equations [Hmisc package version 3.8-3, in R software version 2.13.2]), and sensitivity analyses were done to account for missing values.[21,22] For the multiple imputation of missing values of the continuous variable LVEF, categories of LVEF were additionally considered. All analyses were done for the imputed datasets, and repeated with only complete data, which gave much the same results. The SYNTAX trial is registered with ClinicalTrials.gov, number NCT00114972.

SYNTAX score II

Combination of anatomical SYNTAX score with three simple clinical variables (age, creatinine or creatinine clearance, LVEF) has been shown to contain most of the prognostic information in predicting mortality after PCI (including the SYNTAX score—logistic clinical SYNTAX score[23]) or CABG (excluding the SYNTAX score—ACEF score[24,25]). Consequently, we developed SYNTAX score II on the basis of a core model consisting of anatomical SYNTAX score, age, creatinine clearance, and LVEF. Other common independent predictors of mortality, using the baseline characteristics of the CABG and PCI cohorts of the SYNTAX trial, were screened and identified with a multivariable Cox proportional hazards model

(appendix), the findings of which have been reported.[24] As a result, we added peripheral vascular disease to the core model. Notably, medically treated diabetes—despite being stratified at randomisation in the SYNTAX trial[5] and reported in 26% of patients—was not added to the core model, because it was shown not to be an independent predictor of mortality in the CABG and PCI groups of the SYNTAX trial.[24]

The SYNTAX score aids decision making between CABG and PCI; it is more predictive of clinical outcomes in patients undergoing PCI than in those undergoing CABG, for whom it is not predictive.[2,10] This discrepancy means that the SYNTAX score has a significant interaction effect[25] with CABG and PCI in establishing long-term mortality. Interaction for a particular baseline characteristic was defined as the hazard ratio (HR) of mortality associated with that characteristic among patients undergoing PCI (HR_{PCI}), divided by the HR for the same characteristic among patients undergoing CABG (HR_{CABG})—ie, HR_{PCI}/HR_{CABG}. Consistent with this principle, we screened baseline characteristics (appendix), and added variables to the core model when they showed an interaction between CABG and PCI ($p<0·10$) in affecting 4-year mortality, using a multivariable Cox proportional hazards model. To aid visualisation of the interaction effects, we constructed graphs by plotting the log HR for 4-year mortality (CABG and PCI) on the y axis, and the predictors on the x axis.

Since the SYNTAX trial data originated from 18 countries, we assessed whether between-country heterogeneity existed using gamma frailty in the Cox proportional hazards model.[26] Between-country heterogeneity had a negligible effect on parameter estimates (data not shown). Consequently we present pooled country results.

We constructed scatter plots to visualise how the SYNTAX score II predicted long-term mortality in each individual patient from the CABG and PCI cohorts of the SYNTAX trial (n=1800). On the basis of the Cox proportional hazards model parameter estimates, we made individual risk predictions for each patient as if they had undergone CABG or PCI. The predicted hazards (relative to the average predicted hazard) for CABG versus PCI were plotted. We used a log scale to allow for good separation of individual predicted risks. Bootstrap analyses (1000 resamples with replacement) were done to assess whether individual predictions for CABG were either higher or lower compared with the predictions for PCI with 95% confidence ($p<0·05$), and are highlighted in the scatter plots.[22] Similar scatter plots were produced for the SYNTAX score tertiles[2] and clinical variables in SYNTAX score II to allow judgment of their collective effect on long-term mortality predictions.

We did reclassification analyses (ie, what proportion of patients moved from high to low risk, and from low to high risk) following the principles of Net Reclassification Improvement.[27] The proportion of patients reclassified was calculated with bootstrap analyses (1000 resamples), and are represented in the scatter plots.

See Online for appendix

External validation of SYNTAX score II

External validation was done in the Drug Eluting stent for LefT main coronary Artery disease (DELTA) registry.[28] Briefly, this is a multinational (14 centres in Europe, the USA, and South Korea), non-randomised, allcomers registry (n=2891) of ULMCA disease (isolated, or associated with single or multivessel disease) treated with CABG (n=902, 31·2%) or first generation sirolimus-eluting or paclitaxel-eluting stents (n=1989, 68·8%). SYNTAX scores of 33 or more were reported in 30% (n=871) of the study population and three-vessel disease in 26% (n=744). Previous CABG or PCI was permitted. Follow-up was similar to the SYNTAX trial, with a median period of 3·5 years (IQR 2·5–4·6 years). Data were reported by the study sites in 2039 of 2891 (70·5%) patients for the SYNTAX score, 2785 (96·3%) for age, 2891 (100%) for creatinine (categorical variable [above 150 µmol/L]) and sex, 2747 (95·0%) for LVEF (continuous variable), 1363 (47·1%) for peripheral vascular disease, and 1061 (36·7%) for COPD. Because renal function was collected categorically in the DELTA registry, median renal function from the SYNTAX trial data, with or without a creatinine concentration above 150 µmol/L, was used to replace creatinine with a continuous variable. Since renal function had only a weak interaction effect in affecting mortality between CABG and PCI, this approach was judged to be acceptable. Multiple imputation of missing values and sensitivity analyses, identical to that described earlier, yielded much the same results for the complete dataset. Specifically, sensitivity analyses[21,22,29] testing the robustness of the interaction effects for COPD and peripheral vascular disease gave similar results.

SYNTAX score II assessments

The most important aspects of the SYNTAX score II are the interaction effects, since they drive decision making between CABG and PCI. Other measures are needed to ensure the accuracy of individual mortality predictions for CABG and PCI, and the magnitude of their differences (eg, 10% *vs* 5% or 2% *vs* 1% predicted risks for CABG and PCI), which will further support decision making. These measures include discrimination with the concordance index, and calibration (agreement between predicted and observed risks) with validation plots. The concordance index estimates the probability that, of two randomly chosen patients, the patient with the higher prognostic score will outlive the one with the lower prognostic score.[25] Values of the concordance index range from 0·5 (no discrimination) to a theoretical maximum of 1. The concordance index was internally validated with a bootstrap procedure (100 resamples with replacement) to correct for optimism in parameter estimates.[22]

SYNTAX score II presentation

We present SYNTAX score II as a nomogram, with scores assigned for the presence and magnitude of each predictor directly based on the Cox proportional hazards model coefficients.[22] All statistical analyses were done with Harrell's Regression Modelling Strategies (rms version 3.4-0) package in R software (version 2.13.2).[21,30,31]

Role of the funding source

SYNTAX trial design and conduct was overseen by the SYNTAX steering committee, on which representatives of the study sponsor served. Data analysis and interpretation and writing of the report were independent from the study sponsor. The authors had unrestricted access to the full study database. PWS and EWS took the final responsibility for the decision to submit for publication.

Results

In the randomised SYNTAX population (n=1800), baseline demographics and clinical characteristics for the CABG (n=897) and PCI (n=903) groups were well balanced and have been described previously (appendix).[1] At 4-years follow-up, clinical data were available in 819 of 897 patients in the CABG group and 879 of 903 patients in the PCI group. 178 all-cause deaths were recorded

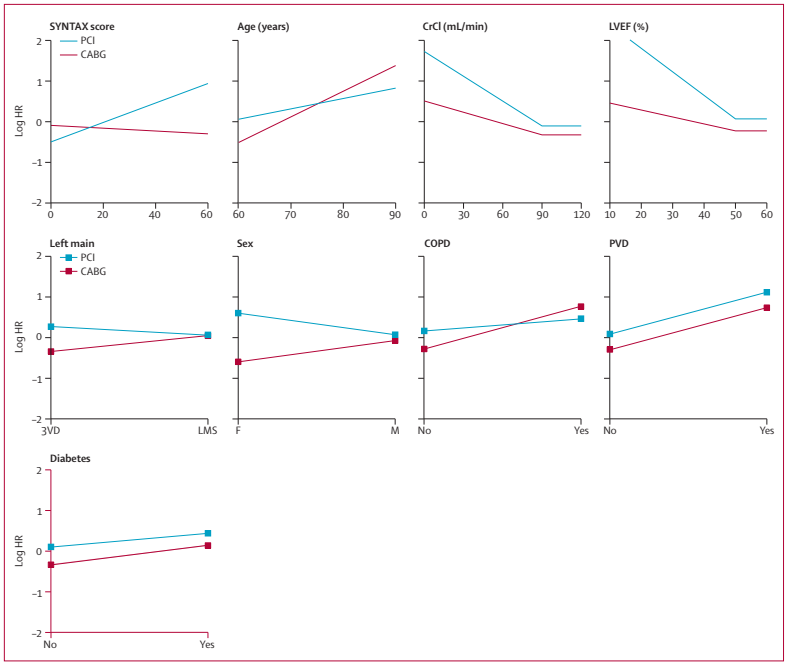


Figure 1: **Predictor effects for CABG and PCI in SYNTAX score II**

Predictor effects are represented visually as a log HR for CABG and PCI on the y-axis for each predictor. Each predictor is expressed on the x-axis continuously (upper panels) or categorically (lower panels), for a person of mean baseline characteristics. Diabetes is included to show its absence of interaction when included in the analyses. Note the differing gradients of the hazards for PCI and CABG, leading to the hazards crossing at an anatomical SYNTAX score of 15. At this cross-over point of hazards, the mortality risk is much the same between CABG and PCI. This threshold of cross-over of hazards will vary according to the level of other variables, namely being lower for female sex, reduced LVEF, and younger age, and higher for COPD, left main disease, and older age. Because both peripheral vascular disease (p=1·00) and diabetes (p=0·67) lacked an interaction effect, as shown by almost parallel HRs (ie, similar increase in mortality risk), their presence would have no effect on decision making between CABG and PCI. Since diabetes was also not an independent predictor of mortality (appendix),[24] it was excluded from SYNTAX score II. CABG=coronary artery bypass surgery. PCI=percutaneous coronary intervention. HR=hazard ratio. CrCl=creatinine clearance. LVEF=left ventricular ejection fraction. Left main=unprotected left main coronary artery disease. 3VD=three-vessel disease. LMS=left main stem. COPD=chronic obstructive pulmonary disease. PVD=peripheral vascular disease.

(CABG 9·0%, 74 all-cause deaths; PCI 11·8%, 104 all-cause deaths, log rank p value=0·063).

The final developed SYNTAX score II consisted of two anatomical (SYNTAX score and ULMCA disease) and six clinical variables (age, creatinine clearance, LVEF, sex, COPD, and peripheral vascular disease). The interaction effect of the SYNTAX score II in collectively affecting long-term mortality predictions between CABG and PCI was significant ($p_{interaction}$=0·0037). Figure 1 shows the interaction effects of the eight SYNTAX score II variables. Six of the eight SYNTAX score II variables—anatomical SYNTAX score, age, LVEF, ULMCA disease, COPD, and female sex—showed a moderate to strong interaction effect in affecting long-term mortality predictions with CABG and PCI ($p_{interaction}$<0·10; table). Creatinine clearance ($p_{interaction}$=0·30) and peripheral vascular disease ($p_{interaction}$=1·00) showed weak or negligible interaction effects. Diabetes was not included in the SYNTAX score II because it was not an independent predictor of mortality[24] and did not have an interaction effect (p=0·67) with CABG and PCI for long-term mortality (figure 1).

Figure 2 shows scatter plots for individual patients in the left main cohort and three-vessel disease cohort of the SYNTAX trial, and by tertiles of the anatomical SYNTAX score. Individual predictions plotted to the left of the diagonal line favoured CABG, and to the right favoured PCI. Individual predictions for CABG and PCI that could not be separated with 95% confidence (ie, p>0·05) are highlighted in grey, and had a similar 4-year mortality in the SYNTAX trial (ie, could not be statistically separated).

For the left main cohort, on the basis of the numerical values of the mortality predictions, CABG was favoured in 50·1% (353) and PCI in 49·9% (352) of the SYNTAX population (figure 2). 62·8% (140) of patients in the low (0–22) SYNTAX score tertile, 61·7% (121) in the intermediate (23–32) tertile, and 31·8% (91) in the high (>32) tertile had numerically lower 4-year mortality predictions for PCI compared with CABG. In 79·7% (562) of patients, 4-year mortality predictions between CABG and PCI could not be significantly separated (p>0·05). 18·8% (42) of patients in the low SYNTAX score tertile had mortality predictions separated with statistical significance (p<0·05) in favour of PCI, and 19·2% (55) of patients in the high SYNTAX score tertile, had statistically significant mortality predictions in favour of CABG.

For the three-vessel disease cohort, on the basis of the numerical values of the mortality predictions, CABG was favoured in 84·2% (922) and PCI in 15·8% (173) of the SYNTAX population (figure 2). 29·1% (103) of patients in the low SYNTAX score tertile (0–22), 12·9% (54) in the intermediate tertile (23–32), and 5·0% (16) in the high tertile (>32) had numerically lower 4-year mortality predictions for PCI compared with CABG. In 58·8% (643) of patients, 4-year mortality predictions between CABG and PCI could not be significantly separated (p>0·05); an effect that was more prevalent in the low to indeterminate SYNTAX score tertiles (0–32). In the high

	Multivariable adjusted HR (95% CI)		Interaction effect (HR_{PCI}/HR_{CABG}); HR (95% CI; p value)
	CABG 4-year mortality	PCI 4-year mortality	
Development population , SYNTAX trial (n=1800)			
Anatomical SYNTAX score (per 10 point increase)	0·97 (0·79–1·18)	1·27 (1·08–1·50)	1·32 (1·01–1·71; p=0·039)
Age (per 10 year increase)	1·88 (1·34–2·64)	1·29 (0·97–1·71)	0·69 (0·44–1·07; p=0·095)
Creatinine clearance† (per 10 mL/min increase)	0·91 (0·77–1·07)	0·82 (0·72–0·93)	0·89 (0·73–1·10; p=0·30)
LVEF (per 10% increase)	0·84 (0·61–1·16)	0·56 (0·43–0·73)	0·67 (0·44–1·00; p=0·053)
Peripheral vascular disease*	2·79 (1·66–4·71)	2·79 (1·72–4·53)	1·00 (0·49–2·04; p=1·00)
ULMCA disease	1·47 (0·93–2·34)	0·82 (0·54–1·23)	0·56 (0·30–1·03; p=0·062)
Women	0·59 (0·32–1·10)	1·70 (1·11–2·60)	2·87 (1·35–6·07; p=0·0059)
COPD	2·84 (1·64–4·90)	1·35 (0·74–2·47)	0·48 (0·21–1·08; p=0·074)
External validation population, DELTA registry (n=2891)			
Anatomical SYNTAX score (per 10 point increase)	1·12 (0·95–1·32)	1·32 (1·20–1·46)	1·18 (0·98–1·42; p=0·083)
Age (per 10 year increase)	1·46 (1·15–1·85)	1·34 (1·19–1·52)	0·92 (0·70–1·21; p=0·56)
Creatinine clearance (per 10 mL/min increase)	0·91 (0·78–1·06)	0·93 (0·86–1·00)	1·02 (0·86–1·21; p=0·82)
LVEF (per 10% increase)	0·59 (0·47–0·75)	0·57 (0·50–0·65)	0·96 (0·72–1·27; p=0·75)
Peripheral vascular disease	1·37 (0·68–2·79)	1·77 (1·01–3·09)	1·29 (0·51–3·22; p=0·59)
Women	0·52 (0·31–0·87)	1·09 (0·82–1·46)	2·09 (1·16–3·76; p=0·014)
COPD	3·63 (1·31–10·04)	1·97 (0·88–4·42)	0·54 (0·20–1·47; p=0·23)

Hazard ratios (HR) in a multivariable Cox proportional hazards model for SYNTAX score II are shown for the CABG and PCI cohorts, followed by the interaction effects (HR_{PCI}/HR_{CABG}) in affecting long-term mortality between CABG and PCI. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. HR=hazard ratio. ULMCA=unprotected left main coronary artery. LVEF=left ventricular ejection fraction. COPD=chronic obstructive pulmonary disease. *Retained in SYNTAX score II to improve the predictive accuracy (discrimination) of the 4-year mortality predictions in the CABG and PCI cohorts.

Table: **Development (SYNTAX Trial) and validation (DELTA Registry) data for SYNTAX score II**

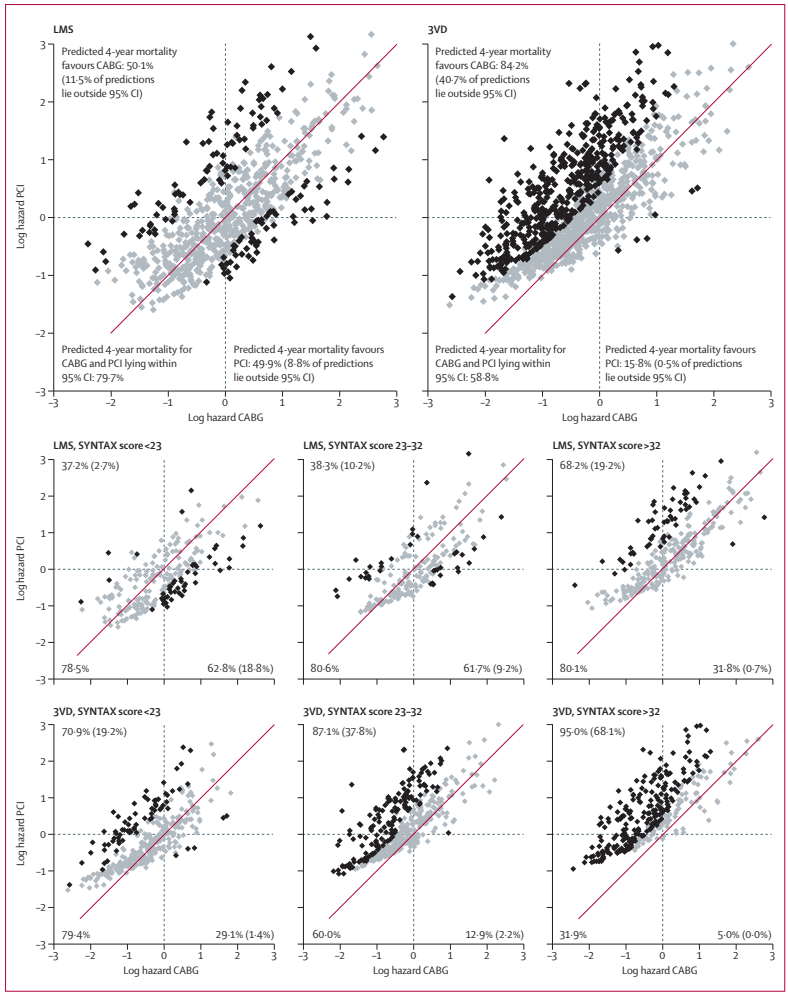


Figure 2: **Mortality predictions for CABG versus PCI for each individual patient in the randomised SYNTAX trial**
The SYNTAX trial included 1800 participants, separated into LMS cohort and 3VD cohort (upper panels), and by tertiles of the anatomical SYNTAX score (lower panels). The diagonal line represents identical mortality predictions for CABG and PCI. Individual predictions plotted to the left of the diagonal line favour CABG (actual percentages shown in top left corner), and to the right favour PCI (actual percentages shown in bottom right corner). Individual mortality predictions for CABG or PCI that could be separated with 95% confidence ($p<0·05$) are coloured black (actual percentage shown in parentheses in respective corners). Mortality predictions that could not be separated with 95% confidence ($p>0·05$) are highlighted in grey, and identify patients with similar 4-year mortality. Percentages of patients in each category are shown. CABG=coronary artery bypass surgery. PCI=percutaneous coronary intervention. LMS=left main stem. 3VD=three-vessel disease.

SYNTAX score tertile (>32), 68·1% (220) of patients had mortality predictions separated with statistical significance (p<0·05) in favour of CABG.

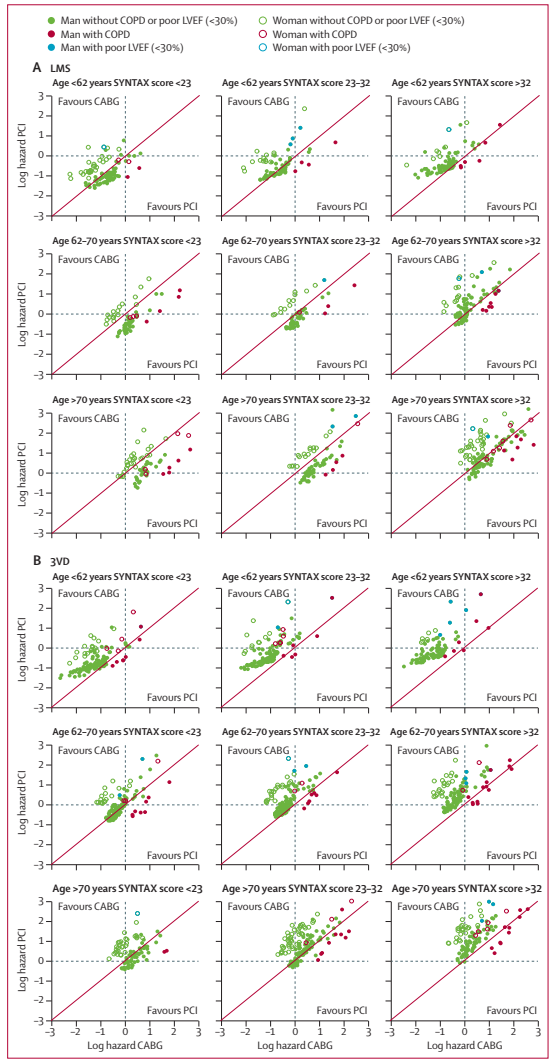
Figure 3 displays scatter plots showing how the anatomical SYNTAX score, presence of ULMCA disease, and clinical variables (tertiles of age, sex, COPD, poor LVEF [<30%]) collectively affect 4-year mortality predictions. On the basis of the crossing of interaction effects between CABG and PCI for the anatomical SYNTAX score shown in figure 1, the presence of specific characteristics of patients altered the threshold value of the anatomical SYNTAX score at which CABG and PCI had much the same 4-year mortality. Younger age, female sex, and reduced LVEF favoured CABG compared with PCI. Thus, in patients with these characteristics, a lower anatomical SYNTAX score (compared with the rest of the population) would be required for the long-term mortality risk to be similar between CABG and PCI. By contrast, older age, COPD, or ULMCA disease favoured PCI compared with CABG and thus, in patients with these characteristics, a higher anatomical SYNTAX score (compared with the rest of the population) would be needed for the long-term mortality risks to be similar. These effects were more prominent in the low-intermediate SYNTAX score tertiles (0–32) than in the high tertile (>32).

On the basis of comparisons of interaction effects (HR_{PCI}/HR_{CABG}), and therefore decision making between CABG and PCI, all variables in the SYNTAX score II interacted in much the same way in the SYNTAX trial and DELTA registry, with the exception of age and LVEF, which had minimal interactions in the DELTA registry. SYNTAX score II discriminated well in all patients who underwent either CABG or PCI, with an internally (SYNTAX trial) validated concordance-index of 0·725 and an externally (DELTA registry) validated concordance-index of 0·716, which were substantially higher than for SYNTAX score alone (internal concordance index 0·567, external concordance index 0·612). The SYNTAX score II was well calibrated (ie, a good agreement between predicted and actual risks) on validation plots in the SYNTAX trial and DELTA registry (appendix). Analyses in the stratum of patients with three-vessel disease (26% of the DELTA registry) yielded much the same results, with a concordance index for the SYNTAX score II of 0·763, and good calibration (expected 4-year survival 88·2%, actual 4-year survival 86·2%).

A nomogram for the bedside application of the SYNTAX score II is detailed in figure 4. The nomogram can be used to obtain long-term mortality predictions for individual patients proposing to undergo CABG or PCI.

Discussion

The main findings of this study are: first, that a personalised, individual assessment of long-term mortality was achievable for patients with complex coronary artery disease (ULMCA or de-novo three-vessel disease) proposing to undergo CABG or PCI; second, that in



Figures 3: **Collective effect of SYNTAX score and other anatomical and clinical variables on mortality predictions**
LMS cohort (A) 3VD cohort (B). Scatter plots are for illustrative purposes only. CABG=coronary artery bypass surgery. PCI=percutaneous coronary intervention. LMS=left main stem. 3VD=three-vessel disease.

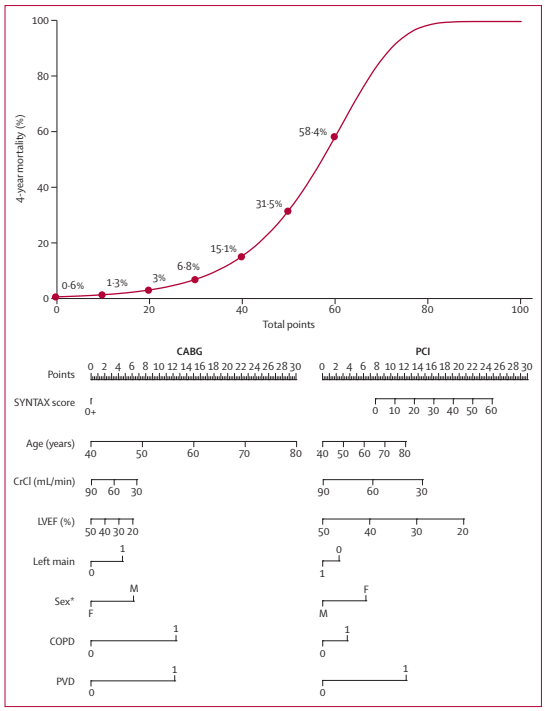


Figure 4: **SYNTAX Score II nomogram for bedside application**

Total number of points for 8 factors can be used to accurately predict 4-year mortality for the individual patient proposing to undergo for CABG or PCI. For example, a 60 year old man with an anatomical SYNTAX score of 30, unprotected left main coronary artery disease, creatinine clearance of 60 mL/min, an LVEF of 50%, and COPD, would have 41 points (predicted 4-year mortality 16·3%) to undergo CABG and 33 points (predicted 4-year mortality 8·7%) to undergo PCI respectively. The same example without COPD included would lead to identical points (29 points) and 4-year mortality predictions (6·3%) for CABG and PCI. COPD defined with EuroSCORE[31] definition, long-term use of bronchodilators or steroids for lung disease. PVD defined according to ARTS I[29] definition, aorta and arteries other than coronaries, with exercise-related claudication, or revascularisation surgery, or reduced or absent pulsation, or angiographic stenosis of more than 50%, or combinations of these characteristics. CABG=coronary artery bypass surgery. PCI=percutaneous coronary intervention. CrCl=creatinine clearance. LVEF=left ventricular ejection fraction. Left main=unprotected left main coronary artery disease. 3VD=three-vessel disease. COPD=chronic obstructive pulmonary disease. PVD=peripheral vascular disease. *Because of the rarity of complex coronary artery disease in premenopausal women, mortality predictions in younger women are predominantly based on the linear relation of age with mortality. The differences in mortality predictions in younger women between CABG and PCI will therefore be affected by larger 95% CIs than those in older women.

addition to the anatomical SYNTAX score, other factors had a direct effect on decision making between CABG and PCI, requiring lower (younger age, female sex, lower LVEF) and higher (older age, COPD, ULMCA disease) SYNTAX scores to achieve similar 4-year mortality, findings that were validated in the DELTA registry, with the exception of age and LVEF; third, the presence of diabetes in itself was shown not to be important for decision making between CABG and PCI; fourth, that the SYNTAX score II clearly identified patients for whom either CABG or PCI had a more favourable long-term outlook, and patients for whom long-term outlooks between CABG and PCI were much the same; and fifth, that the individualised approach of the SYNTAX score II, using anatomical and clinical variables that directly improved decision making between CABG and PCI, was more useful than the anatomical SYNTAX score (panel).

During development of SYNTAX score II, we suggested and then showed that the low, intermediate, and high categories of anatomical complexity in the SYNTAX score were concealing lower risk patients in the higher SYNTAX score groups, and vice versa. This principle is well established in epidemiological literature, and necessitates careful reclassification analyses to ensure that patients with high or low risk are appropriately recategorised.[22,27,37] With the individualised approach of SYNTAX score II, a subset of patients with low (<23), intermediate (23–32), or high (>32) anatomical SYNTAX scores were objectively identified, that would have lower, similar, or higher 4-year mortality predictions for CABG or PCI. Importantly, these findings were validated in the DELTA registry.[28]

Additionally, the present study shows the important principle of combination of anatomical and clinical variables, which interact with CABG and PCI to affect 4-year mortality (ie, are more predictive of mortality in one or the other revascularisation methods), and therefore drive decision making between CABG and PCI. The presence of ULMCA disease drove mortality predictions in favour of PCI, requiring higher anatomical SYNTAX scores among PCI patients to achieve similarity in long-term prognosis between CABG and PCI. The main explanation for this finding is that a sizeable proportion of the SYNTAX score can be attributed to the presence of the left main disease. Conversely, in patients with three-vessel disease and no left main involvement, the SYNTAX score would represent more complex downstream coronary anatomical disease, compared with a left main patient with an identical anatomical SYNTAX score, and therefore patients with three-vessel disease would derive a greater prognostic benefit in undergoing CABG.[9,10]

Notably, diabetes was not a useful variable in the SYNTAX score II, despite medically treated diabetes being stratified at randomisation in the SYNTAX trial and reported in more than a quarter of patients. Several reasons might explain this apparent paradox. First, diabetes in itself did not produce an interaction effect in affecting long-term mortality between CABG and PCI (figure 1). Second, diabetes is a metabolic, systemic disorder, the severity and duration of which has a specific effect on organs such as the heart, detected by complex coronary anatomy (anatomical SYNTAX score) and LVEF;

the brain, detected by the presence of peripheral vascular disease, a sign of systemic atherosclerosis; kidney function, detected by the creatinine clearance; and age, older patients are representative of a longer duration of diabetes and its consequent multiorgan effect. The risk factors in the SYNTAX score II (predominantly the core model: SYNTAX score, age, creatinine clearance, and LVEF) are the dimensions that are relevant for the outlook for the patient, and are why diabetes falls out of the multivariable model. Although diabetes is the common denominator, it cannot be regarded as the one, direct, causative factor, in view of the many other risk factors associated with coronary artery disease, such as hypercholesterolaemia and hypertension. These findings are exemplified by diabetes previously being shown not to be an independent predictor of mortality in the CABG and PCI groups of the SYNTAX trial,[24] and in a pooled analysis of seven contemporary stent trials (n>6000), after SYNTAX score, age, creatinine clearance, and LVEF were accounted for.[23] Additionally, a large population-based cohort study and meta-analysis involving 128 505 individuals with diabetes showed that individuals without diabetes but with chronic kidney disease and proteinuria had a stronger association with the risk of myocardial infarction, and a higher rate of mortality, compared with those with diabetes,[38] and that the relative risk of long-term mortality associated with chronic kidney disease was "much the same irrespective of the presence or absence of diabetes."[39] Third, two meta-analyses of randomised controlled trials[40,41] comparing CABG against PCI before drug-eluting stents were available (balloon angioplasty or bare metal stents) have shown a survival advantage for individuals with diabetes undergoing CABG (compared with PCI) at 4 years (but not at 6·5 years) in one study,[40] and at a median follow up of 5·9 years in the other study.[41] Importantly, significant selection bias in recruiting patients before randomisation occurred in most of these studies (eg, 2–12% of screened patients were randomised in most studies), whereas in the SYNTAX trial, selection of patients was mandated to be allcomers to overcome these issues. Furthermore, in these two meta-analyses,[40,41] most patients had substantially less complex coronary artery disease compared with those in the SYNTAX trial, with single or double vessel disease occurring in almost two-thirds[41] of patients (without left main involvement). Consequently, most of these patients probably would have had anatomical SYNTAX scores that lay below the cross-over point of 15 for the hazards for CABG and PCI (figure 1) in the present study.

Since drug-eluting stents became available, the FREEDOM Trial (n=1900)[42] has shown a mortality benefit for CABG compared with drug-eluting stents in individuals with diabetes with predominantly three-vessel disease (without left main involvement) at a median follow-up of 3·8 years (minimum 2 years). Notably, FREEDOM showed an apparent absence of association of SYNTAX score with 5-year mortality. However, these analyses were underpowered to assess anatomical SYNTAX score, since the numbers at 5 year follow-up were less than a quarter (n=440) of the study population. Therefore, a significant subset of lower risk patients might exist in FREEDOM, and in other reported studies examining multivessel disease (ASCERT registry[43]), in whom CABG and PCI would have much the same long-term clinical outcomes.

Female sex was shown to have a significant interaction effect in the development (SYNTAX trial) and validation (DELTA registry) populations, requiring lower anatomical SYNTAX scores for women to achieve similar long-term mortality after CABG or PCI. Notably, female sex was recently reported to be an independent predictor of long-term mortality in the PCI group of the SYNTAX trial, despite adjustment for risk factors,[24] and contrary to reported scientific literature.[44,45] The main hypotheses put forward were that women in the SYNTAX trial had substantially higher anatomical SYNTAX scores (mean 26·5, SD 11·9), and therefore plaque burden, compared with contemporary stent trials (12·9, 8·4),[45] and that the plaque burden might be associated with more unfavourable plaque composition.[24,46] Another perspective is that, because women with complex coronary artery disease are more likely to have greater clinical comorbidity,[44] then a lower anatomical SYNTAX score is needed for women to achieve similar long-term mortality between CABG and PCI, as shown by the interaction analyses (figure 1).

SYNTAX score II provides an impartial, evidence-based assessment[47] of the decision making process for clinicians weighing anatomical and clinical factors to establish the optimum revascularisation technique for individual patients with complex coronary artery disease. Such an instrument might help to more clearly and objectively define the often uncertain line that separates patients for whom PCI or CABG should be considered, as reported in appropriate-use criteria for coronary revascularisation.[48] SYNTAX score II should be used by multidisciplinary teams consisting of a clinical cardiologist, cardiac surgeon, and interventionalist to comply with international revascularisation guidelines (class 1 indication),[6,7] and to remove any possibility of individual bias in interpretation.

Importantly, SYNTAX score II was externally validated in the DELTA registry (n=2891), a heterogeneous population that included patients with complex coronary artery disease (anatomical SYNTAX score ≥33 existed in 30% of the DELTA registry) who would have not been suitable for enrolment in the EXCEL trial,[9] and three-vessel disease (26% of the DELTA registry). Additionally, all the variables in SYNTAX score II, with the exception of age and LVEF, were externally validated in the DELTA registry. One of the major limitations, inherent to all observational registry studies, is that decision making between CABG and PCI had already been done by clinicians. These decisions, although not objective, are based on the clinical judgment of cardiologists and

***Panel:* Research in context**

Systematic review

We searched PubMed using the terms "drug-eluting stents" and "coronary artery bypass graft surgery" and "randomised controlled trials" or "registries," with the last search done in January, 2013. Search results were filtered by hand and targeted studies which validated a score that stratified the long-term risk for patients undergoing PCI or CABG, or that could potentially help with decision making between these procedures in patients with complex coronary artery disease. Most studies validated the anatomical SYNTAX score as an instrument to guide decision making between PCI and CABG in the context of unprotected left main or multivessel coronary artery disease.[14,32] Two studies did not,[33,42] but seemed to be underpowered to allow for such assessment.[9,37,34] Other studies amalgamated the anatomical SYNTAX score with cardiac-surgery-based risk scores to guide decision making between PCI and CABG.[10,12,14,35] These studies were, however, limited by using risk scores previously developed for predicting in-hospital mortality after cardiac surgery. Additionally, they did not use an individualised approach to decision making between PCI and CABG, and instead were reliant on categorising risk into low, intermediate, or high-risk groups, which has previously been shown to be potentially misleading.[10,35] Other studies focused on improvement of longer term clinical predictions in patients undergoing either PCI or CABG, without being specifically developed to directly improve decision making between these procedures.[13,23,35,36]

Interpretation

Decision making between PCI and CABG with drug-eluting stents has traditionally been an area free from a compelling evidence base. The SYNTAX trial established that anatomical complexity—as assessed by the SYNTAX score—helped to guide decision making between PCI and CABG. The SYNTAX score II further improved decision making between PCI and CABG by augmenting the anatomical SYNTAX score with anatomical and clinical variables that would change the threshold value of the anatomical SYNTAX score in which PCI and CABG would offer comparable long-term mortality. Such a score would provide more objective, evidence-based decision making between PCI and CABG, when undertaken during multidisciplinary discussions between clinical cardiologists, cardiac surgeons, and interventional cardiologists, in working out the best possible revascularisation method in patients with complex coronary artery disease.

cardiac surgeons, and thus lead to (often appropriate) selection bias. Evidence to support this notion comes from Hannan and colleagues[49] who examined the New York State registries and showed much the same mortality outcomes between CABG and PCI with drug-eluting stents in patients with multivessel disease when the data were not adjusted for baseline characteristics.[49,50] Notably, after adjustment of the data for baseline characteristics, which included all clinical variables recorded in the SYNTAX score II, a mortality benefit was shown for CABG. The inherent, unavoidable (and often appropriate) selection bias in registries might therefore be the predominant reason for not identifying an interaction effect for age and LVEF in the DELTA registry.

Future validation studies of the SYNTAX score II should ideally be done in sufficiently powered, randomised, allcomers studies comparing CABG against PCI with drug-eluting stents, in which selection bias would be minimised. Such so-called mega-trials are at present rare, and include the recently reported FREEDOM Trial (n=1900)[42] and the ongoing EXCEL trial investigating ULMCA disease (n=2600).[9] Prospective trials are being planned that will use SYNTAX score II to recruit patients, and include its further validation as one of the endpoints.

The SYNTAX score II nomogram (figure 4) provides individual mortality predictions for CABG and PCI, and a measure of the magnitude of their differences, with clinically applicable accuracy. It is, however, currently limited by being unable to provide an indicator as to whether the mortality predictions can be statistically separated. An online version of the SYNTAX score II is under development, which will provide this additional information. Some of the incomplete data in the DELTA registry might have affected validation of certain variables. This effect would have been minimised since multiple imputation and sensitivity analyses were done,[22,29] as evidenced by COPD being shown to have similar interaction coefficients in the SYNTAX trial and DELTA registry, and peripheral vascular disease not to have had an interaction effect in either study. Despite the SYNTAX trial being the only randomised, sufficiently powered, allcomers trial comparing CABG with PCI, with long-term follow-up, we cannot exclude the possibility that a larger sample size might have had an effect on interaction effects between CABG and PCI for certain factors. This uncertainty includes diabetes, although medically treated diabetes was prestratified at randomisation as a powered subgroup in the SYNTAX trial, and was present in more than a quarter of the study patients (26%). Because of the rarity of complex coronary artery disease in premenopausal women, mortality predictions in younger women with the SYNTAX score II are predominantly based on the linear association between age with mortality. The differences in mortality predictions in younger women between CABG and PCI will therefore be affected by larger 95% CIs. The interobserver variability of the SYNTAX score can potentially affect the mortality predictions. Appropriate training has been shown to limit this occurrence.[51] Work is underway to develop a non-invasive calculated anatomical SYNTAX score, using multislice CT that will incorporate non-invasive functional assessment of lesions.[14,52] The possibility of improved mortality cannot be excluded with newer generation drug-eluting stents, particularly since improvements in drug-eluting stent design have shown reductions in the incidence of stent thrombosis and composite clinical outcomes.[53,54] These findings should be balanced by a study of a pooled analysis of more than 6000 patients in seven contemporary drug-eluting stent trials,[23] showing stent generation (newer generation *vs* first generation) not to be a predictor of mortality. Additionally, when deaths associated with the Academic Research Consortium[55] definition of definite or probable stent thrombosis were removed from the SYNTAX trial (on the basis of the assumption that these patients would be alive), there was a 0·45% (definite stent thrombosis) or 1·5% (definite and probable stent thrombosis) reduction in mortality

(appendix). In view of the relative infrequency of these deaths, it is unlikely that they would have had a significant effect on the coefficients for the SYNTAX score II and its ability to affect decision making. The allcomers concept of the SYNTAX trial, although representative of contemporary clinical practice, might be unavoidably limited by the inability to gain appropriate informed consent or refusal to participate from consecutive patients.[56]

Contributors

VF, DvK, EWS, and PWS undertook the study design, analysis, interpretation of data, and writing of the manuscript. HMG-G and YV provided additional support in the study design and interpretation of the data. In the SYNTAX trial, FWM, M-CM, APK, TEF, ES, MJM, ACo, DRH, M-aM, GAvE, KDD, and PWS participated in study design, enrolled patients, contributed to data collection, and participated in data analysis and interpretation. In the DELTA registry, ACh, EM, and ACo were the principal investigators, and YO collected and interpreted data. EM provided technical assistance in analysing the data from the DELTA registry. All authors critically reviewed and approved the final version of the manuscript for submission.

Conflicts of interest

KDD is a full-time employee of, and holds stock in, Boston Scientific. MM has served on the speaker's bureau of Boston Scientific, Cordis, and Medtronic. TF has served on the speaker's bureau of Boston Scientific; has received grant support from Abbott, Atritech, Boston Scientific Corporation, Edwards, and Evalve; and has worked as a consultant for Abbott, Coherex, Intervalve, Square One, and WL Gore. MM's institution has received a research grant from Boston Scientific. The other authors declare that they have no conflicts of interest.

Acknowledgments

We thank all the study centres and participants whose work made this study possible. We also thank Jian Huang and Peggy Pereda (Boston Scientific Corporation, Natick, MA, USA) for their invaluable technical support in accessing the study database.

References

1 Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360:** 961–72.
2 Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009; **5:** 50–56.
3 Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005; **1:** 219–27.
4 Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 2010; **121:** 2645–53.
5 Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006; **151:** 1194–204.
6 Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010; **31:** 2501–55.
7 Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011; **58:** e44–122.
8 Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013; **381:** 629–38.
9 Farooq V, Serruys PW, Stone GW, Virmani R, Chieffo A, Fajadet J. Left main coronary artery disease. Percutaneous interventional cardiovascular medicine. In: The PCR-EAPCI Textbook, EUROPA edn. Toulouse, France: PCR Publishing, 2012: 329–405.
10 Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX trial at 3 years. *JACC Cardiovasc Interv* 2012; **5:** 606–17.
11 Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J* 2003; **24:** 881–82.
12 Garg S, Sarno G, Garcia-Garcia HM, et al. A new tool for the risk stratification of patients with complex coronary artery disease: the clinical SYNTAX score. *Circ Cardiovasc Interv* 2010; **3:** 317–26.
13 Chen S-L, Chen JP, Mintz G, et al. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *J Am Coll Cardiol Interv* 2010; **3:** 632–41.
14 Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart* 2011; **97:** 1902–13.
15 Capodanno D, Miano M, Cincotta G, et al. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J* 2010; **159:** 103–09.
16 Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981; **63:** 285–99.
17 Medina A, Suarez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol* 2006; **59:** 183.
18 Hamburger JN, Serruys PW, Scabra-Gomes R, et al. Recanalization of total coronary occlusions using a laser guidewire (the European TOTAL Surveillance Study). *Am J Cardiol* 1997; **80:** 1419–23.
19 Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001; **344:** 1117–24.
20 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16:** 31–41.
21 Harrell FE Jr, et al. Hmisc: Harrell Miscellaneous. R package version 3.8-3. 2012. http://CRAN.R-project.org/package=Hmisc.
22 Steyerberg EW. Clinical prediction models. a practical approach to development, validation, and updating. New York: Springer, 2009.
23 Farooq V, Vergouwe Y, Raber L, et al. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the logistic clinical SYNTAX score. *Eur Heart J* 2012; **33:** 3098–104.
24 Farooq V, Serruys PW, Bourantas C, et al. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 2012; **33:** 3105–13.
25 Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer-Verlag, 2001.
26 Hougaard P. Frailty models for survival data. *Lifetime Data Anal* 1995; **1:** 255–73.
27 Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; **27:** 157–72.
28 Chieffo A, Meliga E, Latib A, et al. Drug-eluting stent for left main coronary artery disease: the DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Intv* 2012; **5:** 718–27.
29 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; **367:** 1355–60.
30 R Development Core Team. R: a language and environment for statistical computing. 2011. http://www.R-project.org.
31 Harrell FE Jr. rms: Regression Modeling Strategies. R package version 3.4-0. 2012. http://CRAN.R-project.org/package=rms.

32 Head S, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. *Heart* (in press).

33 Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 2011; **364:** 1718–27.

34 Serruys PW, Farooq V. Is FREEDOM casting doubt on the SYNTAX score? *N Engl J Med* (in press).

35 Singh M, Holmes DR, Lennon RJ, Rihal CS. Development and validation of risk adjustment models for long-term mortality and myocardial infarction following percutaneous coronary interventions —clinical perspective. *Circ Cardiovasc Interv* 2010; **3:** 423–30.

36 Shahian DM, O'Brien SM, Sheng S, et al. Predictors of long-term survival after coronary artery bypass grafting surgery: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (the ASCERT study). *Circulation* 2012; **125:** 1491–500.

37 Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010; **21:** 128–38.

38 Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 2012; **380:** 807–14.

39 Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012; **380:** 1662–73.

40 Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol* 2003; **41:** 1293–304.

41 Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; **373:** 1190–97.

42 Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; **367:** 2375–84.

43 Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies. *N Engl J Med* 2012; **366:** 1467–76.

44 Chieffo A, Hoye A, Mauri F, et al. Gender-based issues in interventional cardiology: a consensus statement from the Women in Innovations (WIN) initiative. *EuroIntervention* 2010; **5:** 773–79.

45 Stefanini GG, Kalesan B, Pilgrim T, et al. Impact of sex on clinical and angiographic outcomes among patients undergoing revascularization with drug-eluting stents. *JACC Cardiovasc Interv* 2012; **5:** 301–10.

46 Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *JACC Cardiovasc Imaging* 2012; **5** (suppl 3)**:** S62–72.

47 Ellis J, Mulligan I, Rowe J, Sackett DL. Inpatient general medicine is evidence based. A-Team, Nuffield Department of Clinical Medicine. *Lancet* 1995; **346:** 407–10.

48 Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012; **59:** 857–81.

49 Hannan EL, Wu C, Walford G, et al. Drug-eluting stents *vs* coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008; **358:** 331–41.

50 Daemen J, Kukreja N, Serruys PW. Drug-eluting stents *vs* coronary-artery bypass grafting. *N Engl J Med* 2008; **358:** 2641–42.

51 Genereux P, Palmerini T, Caixeta A, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv* 2011; **4:** 553–61.

52 Papadopoulou SL, Girasis C, Dharampal A, et al. Tomography (MSCT) SYNTAX Score: a feasibility and reproducibility study. *JACC Imaging* (in press).

53 Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; **379:** 1393–402.

54 Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011; **378:** 1940–48.

55 Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115:** 2344–51.

56 de Boer SP, Lenzen MJ, Oemrawsingh RM, et al. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011; **32:** 2161–67.

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013; **381:** 639–50.

Web Extra Material

Table 1

Baseline characteristics in the randomised SYNTAX Trial (n=1800).[1]

Baseline Characteristic	PCI (N=903)	CABG (N=897)	P Value
Age (years)	65.2±9.7	65.0±9.8	0.55
Male gender	76.4	78.9	0.20
Female gender	33.6	21.1	0.20
Body-mass index (weight [kg]/height [metres])	28.1±4.8	27.9±4.5	0.37
Diabetes	28.2	28.5	0.89
Medically treated diabetes* (%)			
Any	25.6	24.6	0.64
Requiring insulin	9.9	10.4	0.72
Metabolic syndrome (%)	46.0	45.5	0.86
Current smoker (%)	18.5	22.0	0.06
Previous myocardial infarction (%)	31.9	33.8	0.39
Previous cerebrovascular accident (CVA) (%)	3.9	4.8	0.33
Previous transient ischemic attack (TIA) (%)	4.3	5.1	0.46
Peripheral vascular disease (%)**	9.1	10.6	0.28
Blood pressure ≥130/85 mm Hg (%)	68.9	64.0	0.03
Chronic obstructive pulmonary disease (COPD)***	7.9	9.3	0.29
Congestive heart failure (%)	4.0	5.3	0.18
Hyperlipidemia (%)	78.7	77.2	0.44
Angina (%)			
Stable (%)	56.9	57.2	0.91
Unstable (%)	28.9	28.0	0.66
Silent ischaemia	8.2	8.2	0.97
Left ventricular ejection fraction (continuous) (%)	59.9±12.9	58.3±13.2	0.32
Creatinine clearance (ml/min) (Cockcroft and Gault[2])	86.7±35.6	85.6±29.4	0.49
Anatomical SYNTAX Score[3-6]	28.4±11.5	29.1±11.4	0.19
Unprotected left main coronary artery disease (%)	39.5	38.8	0.76
De novo three vessel disease (without left involvement)	60.5	61.2	0.76

Continuous variables are expressed as means±SD. Categorical variables are expressed as percentages.

*Medically treated diabetes was defined as diabetes for which the patient was receiving oral hypoglycaemic agents or insulin at the time of enrolment.
**Aorta and arteries other than coronaries, with exercise related claudication, and/or revascularization surgery and/or reduced or absent pulsation and/or angiographic stenosis of more than 50% (ARTS I definition[7]).
***Long term use of bronchodilators or steroids for lung disease (EuroSCORE definition[8]).

Tables 2a-2b

Independent predictors of 4-year mortality in the CABG (upper) and PCI (lower) cohorts. An entry/exit criteria of 0.05/0.05 were used in a Cox proportional hazards model. These findings have previously been reported.[9] Used with permission from Farooq et al.[9]

CABG Cohort (n=897) **Independent Correlates of 4-Year Mortality** *(Variables with a p value >0.05 italicised)*	**Hazard Ratio**	**95% C.I.**	**p-value**
Lack of discharge aspirin	3.56	2.04, 6.21	<0.001
Peripheral vascular disease	2.65	1.49, 4.72	0.001
COPD	2.44	1.30, 4.60	0.006
History of GI bleeding or peptic ulcer disease	*2.14*	*0.90, 5.07*	*0.085*
Age per increase in 10 years	1.95	1.41, 2.69	<0.001
Pre-procedural poor LVEF	*1.86*	*0.65, 5.33*	*0.25*
Amiodarone therapy on discharge	*1.79*	*0.95, 3.35*	*0.070*
Serum creatinine (mg/dL)	1.47	1.17, 1.84	0.001
Hypertension	*1.28*	*0.62, 2.67*	*0.51*
Lack of pre-procedural aspirin	*1.18*	*0.64, 2.19*	*0.59*

PCI Cohort (n=903) **Independent Correlates of 4-Year Mortality** *(Variables with a p value >0.05 italicised)*	**Hazard Ratio**	**95% C.I.**	**p-value**
No post-procedural antiplatelet therapy*	152.16	53.57, 432.22	<0.001
Amiodarone therapy on discharge	4.49	1.36, 14.83	0.014
Pre-procedural poor LVEF	3.31	1.03, 10.64	0.045
History of GI bleeding or peptic ulcer disease	2.93	1.41, 6.12	0.004
Peripheral vascular disease	2.13	1.26, 3.60	0.005
Age per increase in 10 years	1.62	1.26, 2.09	<0.001
Female gender	1.60	1.01, 2.56	0.048
Serum creatinine	*1.28*	*0.95, 1.72*	*0.11*
Diabetes	*1.28*	*0.83, 2.00*	*0.27*
SYNTAX Score per increase in 10 points	1.25	1.06, 1.47	0.007

* Neither aspirin nor thienopyridine

Abbreviations: CABG coronary artery bypass graft surgery; COPD chronic obstructive pulmonary disease; CI confidence interval; GI gastrointestinal; LVEF left ventricular ejection fraction; PCI percutaneous coronary intervention.

Figure 1

Title: Validation plots for the SYNTAX Score II
Legend: Validation plots in the development (SYNTAX Trial[1]) (**a**) and validation (DELTA Registry[10]) populations (**b**). The SYNTAX Score II was well calibrated in the SYNTAX Trial and DELTA Registry, as indicated by a good correlation between predicted and observed 4-year mortality. c-indices for the anatomical SYNTAX Score and SYNTAX Score II are indicated in each population (consisting of CABG and PCI treated patients).

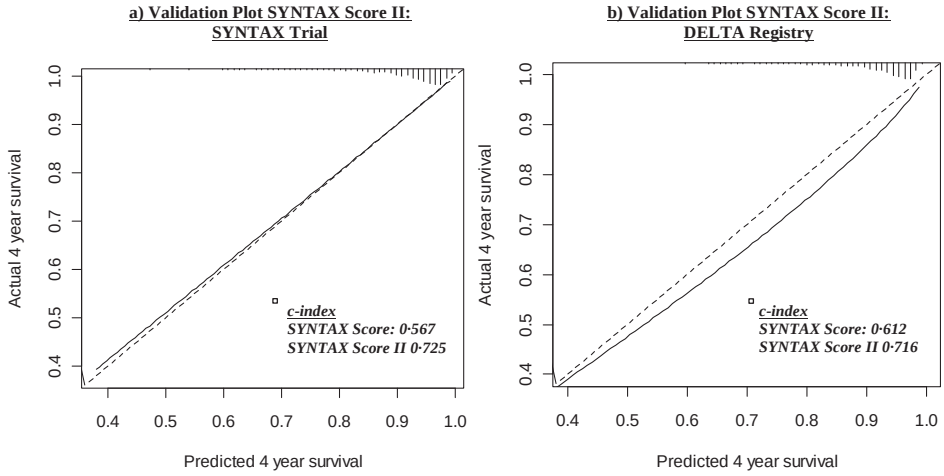
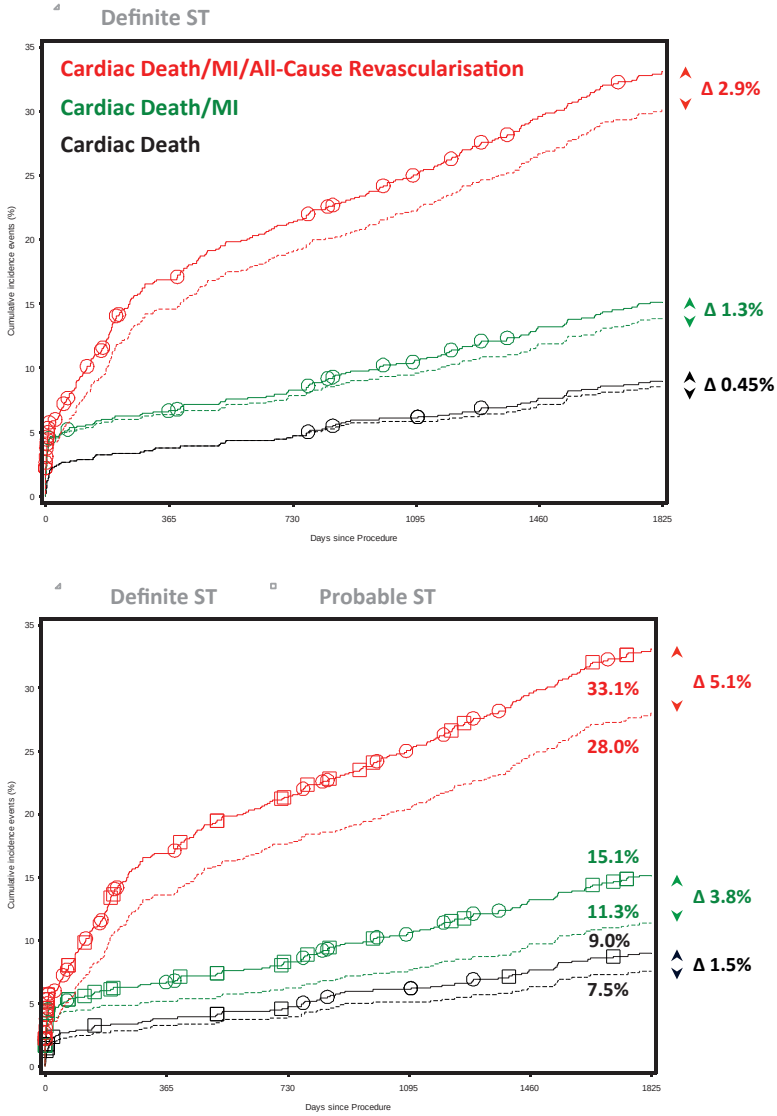


Figure 2

Title: Corrected Kaplan-Meier curves for ARC Definition stent thrombosis
Legend: Kaplan-Meier estimates of cardiac death (black lines), cardiac death or myocardial infarction (MI) (green lines), and cardiac death, MI, or all cause revascularization, according to Academic Research Consortium (ARC)[11] definition (reported by the Clinical Events Committee). Broken lines indicate corrected KM curves after ST related clinical event excluded. Definite stent thrombosis (ST) is superimposed on the Kaplan-Meier curves as a circle and probable ST as a square. If all these ST-related events had been eliminated (broken lines), using ARC definite (upper) and ARC definite/probable (lower), the incidence of cardiac mortality would have decreased by 0.45% (definite ST) and 1.5% (definite/probable ST). Methodology adapted from Serruys et al.[12]



References

1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009; **360**(10): 961-72.
2. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; **16**(1): 31-41.
3. Sianos G, Morel MA, A.P. K, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention; 2005 p. 219-27.
4. SYNTAX score calculator: http://www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.
5. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention. 2009; **5**(1): 50-6.
6. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart. 2011; **97**(23): 1902-13.
7. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med. 2001; **344**(15): 1117-24.
8. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. European Heart Journal. 2003; **24**(9): 881-2.
9. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, et al. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial. Eur Heart J. 2012 [Epub ahead of print].
10. Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P, et al. Drug-Eluting Stent for Left Main Coronary Artery Disease: The DELTA Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment. JACC Cardiovasc Interv. 2012; **5**(7): 718-27.
11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; **115**(17): 2344-51.
12. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice M-C, et al. 5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions. J Am Coll Cardiol. 2010; **55**(11): 1093-101.

Chapter 8.5

SYNTAX Score II – Authors' reply

Farooq V, van Klaveren D, Steyerberg EW, Serruys PW

Lancet; 2013;381(9881):1899-900 (Impact Factor: 39.06)

SYNTAX score II

Vasim Farooq and colleagues[1] (Feb 23, p 639) developed and validated a new score (SYNTAX II) for the prediction of mortality after coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) in patients with complex coronary artery disease. They added clinical characteristics to the anatomical SYNTAX score to improve individualised treatment decisions. They conclude that the new score can better guide the choice between CABG and PCI. It is very valuable that they used the SYNTAX trial not only to compare the treatment groups but also to develop a decision rule to guide treatment choice.

However, we have concerns about the use of the conventional measures of discrimination, calibration, and reclassification to assess this score. These conventional statistics were developed to evaluate risk predictions under a single treatment or no treatment: discrimination, for example, tells us to what extent those who died had higher calculated mortality risks than those who survived. Here there is not one but two treatment options. To decide which of the two is preferable for a patient, one needs to estimate the mortality risk after CABG and the mortality risk after PCI for that individual, and then compare the two. The difference between these two risks is the estimated benefit from one treatment compared with the other, and performance measures should assess how accurate the model is in predicting this benefit.[2,3] Using conventional statistics of model performance to assess the value of the model in estimating treatment benefit and guiding treatment decisions could be potentially misleading.

The score should be evaluated for outcome improvement. It would have been informative if the authors had presented results obtained using the new score versus those obtained with the original score for treatment decisions. To what extent does survival improve with the new score?[4] New purposes for prediction models require new performance statistics.

We declare that we have no conflicts of interest.

*Parvin Tajik, Katrien Oude Rengerink, Ben Willem Mol, Patrick M Bossuyt
p.tajik@amc.uva.nl

Department of Clinical Epidemiology, Biostatistics and Bioinformatics (PT, PMB), and Department of Obstetrics and Gynaecology (PT, KOR, BWM), Academic Medical Centre, University of Amsterdam, Amsterdam 1105 AZ, The Netherlands

1 Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013; **381:** 639–50.
2 Janes H, Pepe MS, Bossuyt PM, Barlow WE. Measuring the performance of markers for guiding treatment decisions. *Ann Intern Med* 2011; **154:** 253–59.
3 Huang Y, Gilbert PB, Janes H. Assessing treatment-selection markers using a potential outcomes framework. *Biometrics* 2012; **68:** 687–96.
4 Song X, Pepe MS. Evaluating markers for selecting a patient's treatment. *Biometrics* 2004; **60:** 874–83.

Authors' reply

We welcome the opportunity to expand on how to assess the performance of the SYNTAX score II.[1]

First, interactions in the SYNTAX score II are central to more personalised decision making—ie, specific anatomical or clinical factors to be more predictive of mortality with percutaneous coronary intervention (PCI) compared with coronary artery bypass graft (CABG) surgery, or vice versa. All variables in the SYNTAX score II were validated, with the exception of age and left ventricular ejection fraction, which might relate to selection bias inherent to all registries. Hence randomised validation was proposed.[1] Currently, validation of the SYNTAX score II is prespecified as an endpoint in the ongoing randomised EXCEL trial (NCT01205776), and the planned SYNTAX trial II which will use the SYNTAX score II to recruit patients on the grounds of patient safety.

Second, substantial differences in treatment assignment (CABG or PCI) were evident using reclassification analyses—ie, comparisons between the SYNTAX score II and conventional tertiles of the anatomical SYNTAX score.[2] These were quantified and presented in the manuscript, and cannot be deemed misleading, because they are an accepted and important step in assessing performance.[3]

A further step to quantify effect on survival of the population under study requires a clear decision rule. If we simply select CABG or PCI based on a higher or lower expected survival (Kaplan-Meier analyses) with the SYNTAX score II, irrespective of the margin of difference, 4-year mortality would be 7·5% compared with 8·4% using the anatomical SYNTAX score with existing myocardial revascularisation guidelines[4] (equivalent to using the SYNTAX score II in only 111 patients [100/0·9%] to have one more patient alive at 4 years). Similar analyses selecting CABG or PCI based on statistical comparisons of expected survival showed that 4-year mortality remained unaltered at 8·2%. Notably, using either approach to decision making with the SYNTAX score II resulted in a similar 4-year survival (Kaplan-Meier analyses) between CABG and PCI in both the development and validation populations. Additionally, and contrary to current myocardial revascularisation guidelines,[4] patients were identified in all tertiles of the anatomical SYNTAX score who would be potentially suitable for CABG, PCI, or both.

The choice between CABG and PCI would thus be down to individual patient preference, their perception of short-term and long-term risk, and health economics. We agree that the practical applications of performance statistics are complex, and future work in this evolving field will prove to be of additional value in upcoming validation studies.


Antonia Reeve/Science Photo Library

For more on **expected survival** see www.syntaxscore.com

We declare that we have no conflicts of interest.

*Vasim Farooq, David van Klaveren, Ewout W Steyerberg, *Patrick W Serruys*
p.w.j.c.serruys@erasmusmc.nl

Thoraxcenter, Erasmus University Medical Centre, Rotterdam 3015 GD, The Netherlands (VF, PWS); and Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands (DvK, EWS)

1 Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013; **381:** 639–50.
2 Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360:** 961–72.
3 Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis research strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013; **10:** e1001381.
4 Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010; **31:** 2501–55.

Neuroprosthetic control and tetraplegia

The neuroprosthetic achievements reported by Jennifer Collinger and colleagues (Feb 16, p 557)[1] are remarkable. The diagnosis of the tetraplegic patient of the study is, however, puzzling. The patient has spinocerebellar ataxia without cerebellar features. Material available elsewhere[2,3] suggests that her symptoms began rather suddenly 13 years before taking part in the study. She describes relapsing weakness, has normal looking hands, and, head rest excepted, no symptoms above the neck. This is unusual for spinocerebellar ataxia, which typically has slow onset with gradual deterioration.

One of several alternative explanations for this clinical picture, including cervical spinal cord pathology, is that the patient has a functional (psychogenic) tetraplegia, a common and genuine cause of physical disability.[4]

The diagnosis could affect the generalisability of these techniques. It might be harder for a patient with a brain disease to control a neuroprosthetic device than someone with a structurally normal brain. Furthermore, someone with a functional tetraplegia, and an abnormal body image, might have superior ability to control a neuroprosthetic device compared with an amputee or spinal cord injured patient in whom neuroprosthetic ability must be superimposed over a potentially intact cognitive body image.

We do not detract from the authors considerable technical achievements, nor are we suggesting that this patient's disability is anything other than genuine. However, clinical characterisation is essential in understanding the potential of this technology for patients with brain disease compared with patients with other causes of severe disability.

We declare that we have no conflicts of interest.

*Jon Stone, William Landau
jon.stone@ed.ac.uk

Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK (JS); and Washington University, School of Medicine, St Louis, MO, USA (WL)

1 Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* 2013; **381:** 557–64.
2 University of Pittsburgh Medical Center. One giant bite. https://www.youtube.com/watch?v=76lIQtE8oDY (accessed March 13, 2013).
3 60 Minutes. http://www.cbsnews.com/video/watch/?id=50137987n (accessed March 13, 2013).
4 Stone J, Warlow C, Sharpe M. The symptom of functional weakness: a controlled study of 107 patients. *Brain* 2010; **133:** 1537–51.

Authors' reply

Jon Stone and William Landau's main concern is the possibility that the patient's disorder might be functional (psychogenic) tetraplegia.

We welcome the opportunity to present details of the patient's diagnosis, which were not included in our report[1] due to space limitations. The patient was thoroughly evaluated before enrolment, including a case review with her treating neurologist (GM) of more than 14 years. The patient first noted stiffness in her legs at age 36 years, 17 years before enrolment. Over several months, stiffness progressed to fatigue, weakness in the legs, and then to weakness in the arms over the following year. 3 years after symptom onset, the patient was too weak to walk and used a wheelchair full time; she had also developed subtle sensory symptoms and urinary retention.

Upon presentation at the University of Pittsburgh, 4 years after symptom onset, pertinent examination findings were left lateral gaze-evoked jerk nystagmus, mild left arm weakness, and severe right arm weakness. In the leg, there was complete paralysis except for knee flexion, which was near normal, and hip flexion, which showed severe weakness. She had increased tone in the legs with bilateral plantar reflexes present. She had mild to moderate vibratory sense loss to the knees, without pinprick loss. There were no cerebellar signs in the arm that moved and no obvious truncal ataxia for a patient who could not stand. She had no history of depression or significant pain. She progressed with primarily motor dysfunction and became tetraplegic. Testing, at that time, failed to reveal a genetic disorder. After thorough evaluation for central and peripheral nervous system diseases, resulting in an unknown aetiology, it was determined she had a degenerative disorder diagnosed as spinal cerebellar syndrome. Her father had a very similar set of symptoms, with the addition of ataxia, and more recently, two of her siblings were diagnosed with multiple sclerosis.

At the time of enrolment in the study,[1] she had 0/5 motor strength in all extremities, preserved—although subjectively slightly diminished—sensation, and decreased tone.

PART IX

Viewpoint

Chapter 9.1

Revascularization strategies in patients with diabetes

Serruys PW, Farooq V

N Engl J Med. 2013;368(15):1454-5 (Impact Factor: 51.658)

Revascularization Strategies in Patients with Diabetes

TO THE EDITOR: In reporting the results of the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, Farkouh et al. (Dec. 20 issue)[1] suggest that in patients with diabetes and advanced coronary artery disease, coronary-artery bypass grafting (CABG) was superior to percutaneous coronary intervention (PCI). The benefit of CABG was driven by differences in rates of myocardial infarction and death from any cause. However, rates of cardiovascular death were similar in the two groups, whereas the rate of stroke was significantly higher after CABG.[1] At 30 days, the primary outcome had occurred in fewer patients after PCI. The main driver of the difference in the primary composite outcome was the higher incidence of myocardial infarction after PCI. However, beyond 30 days after any revascularization procedure, myocardial infarction was defined as only a typical increase in the troponin level (more than one value exceeding the necrosis boundary).[1,2] Most of these late myocardial infarctions (accounting for 82% of those seen in the PCI group) might actually have been relatively minor episodes of myonecrosis. The clinical relevance of these events, as compared with other major components of the primary outcome, including stroke, remains largely speculative. Accordingly, additional information on the types of myocardial infarction in the two groups would be critical to better interpret the study. Otherwise, the superiority of CABG over PCI could be questioned, even in this challenging scenario.

Fernando Alfonso, M.D.
Rosana Hernandez, M.D.

Clínico San Carlos University Hospital
Madrid, Spain
falf@hotmail.com

No potential conflict of interest relevant to this letter was reported.

1. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.
2. Farkouh ME, Dangas G, Leon MB, et al. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial. Am Heart J 2008;155:215-23.

DOI: 10.1056/NEJMc1301244

TO THE EDITOR: The conclusion of Farkouh et al. that CABG was superior to PCI was driven by the difference in rates of myocardial infarction and death from any cause (with a substantial proportion of deaths that occurred from cardiovascular causes) at 5 years after randomization. PCI was performed with the use of first-generation sirolimus-eluting stents in 51% of the patients and paclitaxel-eluting stents in 43% of the patients.

To extrapolate the findings of the FREEDOM trial for current clinical practice, the incidence of cardiovascular death and myocardial infarction adjudicated to be due to probable or definite stent thrombosis is of great interest; PCI with contemporary stents might reduce the incidence of fatal or nonfatal stent thrombosis. We concur with the accompanying editorial by Hlatky[1] that both revascularization strategies should be weighed by a multidisciplinary heart team to assess the benefit:risk ratio of each form of treatment. Patients with diabetes and multivessel disease should be informed about expected long-term results after CABG (as shown in this trial) and about the estimated results after PCI with contemporary stent technology.

Jan J. Piek, M.D., Ph.D.
Robbert J. de Winter, M.D., Ph.D.
Jan G.P. Tijssen, Ph.D.
Academic Medical Center
Amsterdam, the Netherlands
j.j.piek@amc.uva.nl

No potential conflict of interest relevant to this letter was reported.

1. Hlatky MA. Compelling evidence for coronary-bypass surgery in patients with diabetes. N Engl J Med 2012;367:2437-8.

DOI: 10.1056/NEJMc1301244

TO THE EDITOR: Although they appear to show the superiority of CABG over multivessel PCI in patients with diabetes, the data presented in the article by Farkouh et al. suggest incomplete revascularization in patients treated by means of PCI. In this group, the average number of lesions was 5.65 per patient, whereas the average number of lesions stented was 3.5 per patient. The completeness of revascularization in the CABG group was not reported. Incomplete revascularization is known to be associated with an increased risk of myocardial infarction, repeat revascularization,[1] and cardiovascular death[2] and may have contributed to the worse outcomes in the PCI group in this trial. This issue needs to be clarified to be able to interpret this trial properly.

Alisdair Ryding, Ph.D.
Norfolk and Norwich University Hospital
Norwich, United Kingdom
alisdair.ryding@nnuh.nhs.uk

No potential conflict of interest relevant to this letter was reported.

1. Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circulation 2012;125:2613-20.
2. Vieira RD, Hueb W, Gersh BJ, et al. Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. Circulation 2012; 126:Suppl 1:S158-S163.

DOI: 10.1056/NEJMc1301244

TO THE EDITOR: The suggestion of a lack of association of the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score (www.syntaxscore.com)[1] with clinical outcomes in the FREEDOM trial should be interpreted with caution. Such conclusions are not consistent with the large volume of evidence that validates the SYNTAX score.[2-5] Can the authors elaborate on how the SYNTAX score was used, since it became operational during the FREEDOM trial? Were the clinician and persons who conducted the core laboratory readings unaware of the clinical outcomes? Furthermore, because of the numbers of patients at risk in the analysis of 5-year outcomes according to the SYNTAX score in the FREEDOM trial, the study was underpowered to draw any conclusions, since these patients composed less than a quarter (440 patients) of the study population (1900 patients). The results of the FREEDOM trial are nevertheless consistent with the results in the subgroup of patients with diabetes and three-vessel disease in the SYNTAX trial (Fig. 1): namely, that in patients with a low SYNTAX score (i.e., ≤22), there was a minimal difference in long-term clinical outcomes between cardiac surgery and PCI with first-generation drug-eluting stents. Consequently, no conclusions can yet be drawn from the FREEDOM trial with respect to how the SYNTAX score can influence decision making on the most appropriate form of revascularization in patients with diabetes and complex coronary artery disease (without left main coronary stenosis).

Patrick W. Serruys, M.D., Ph.D.
Vasim Farooq, M.B., Ch.B.
Erasmus University Medical Center
Rotterdam, the Netherlands
p.w.j.c.serruys@erasmusmc.nl

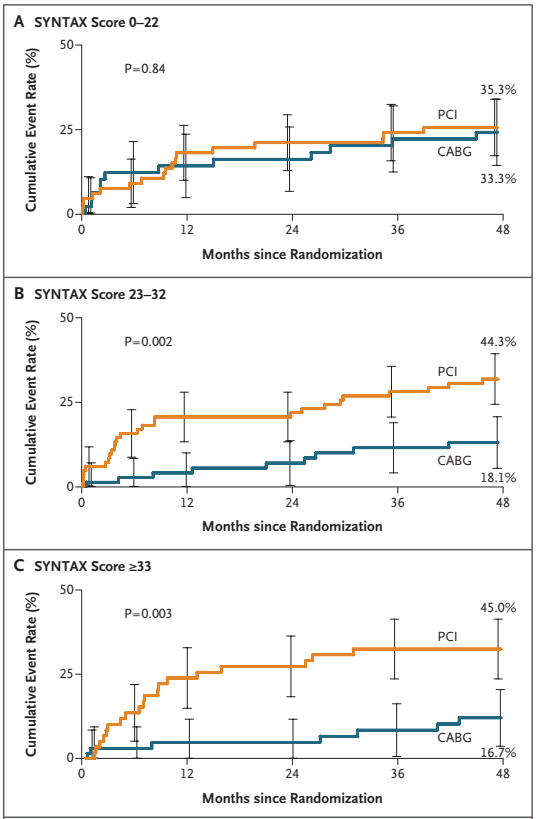


Figure 1. Clinical Outcomes, According to Categories of the Anatomical SYNTAX Score.

Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) scores in the subgroup of 297 patients with medically treated diabetes and three-vessel disease in the randomized SYNTAX trial are shown. The SYNTAX score categories are the following: 0 to 22, low anatomical complexity (Panel A); 23 to 32, intermediate anatomical complexity (Panel B); and ≥33, high anatomical complexity (Panel C). Cumulative event rates of the composite outcome of major adverse cardiovascular and cerebrovascular events (death from any cause, myocardial infarction, revascularization for any cause, or stroke) are shown. I bars indicate 95% confidence intervals. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention. Data are from the SYNTAX trial investigators.

No potential conflict of interest relevant to this letter was reported.

1. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.
2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72. [Erratum, N Engl J Med 2013;368:584.]
3. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;97:1902-13.
4. Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. JACC Cardiovasc Interv 2012;5:606-17.
5. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639-50.

DOI: 10.1056/NEJMc1301244

THE AUTHORS REPLY: Alfonso and Hernandez state that more analysis of the data on myocardial infarction is needed to interpret the results of the FREEDOM trial. This simply is not the case. Our randomized, controlled trial showed that survival among patients with diabetes and multivessel coronary disease who require revascularization is increased if they undergo CABG rather than PCI. There is no complexity to this result, and no amount of analysis of the data on myocardial infarction will change the fact that patients who met the criteria for randomization in our trial were more likely to die sooner if they underwent PCI rather than CABG.

Piek and colleagues suggest that the use of newer stents could alter the outcome of our trial. The performance of the newer stents as compared with earlier stents has been studied.[1] The results of these analyses suggest, at most, very small absolute improvement in outcomes — far too little to affect the conclusions of the trial. The message of the trial is clear and actionable; speculation regarding the superiority of newer stents in producing the opposite result to that of our trial is not.

As Ryding points out, substantial data exist to suggest that more complete revascularization

improves outcomes as compared with less complete revascularization.[2] However, our trial involved highly experienced interventional cardiologists and surgeons who attempted to maximize the completeness of revascularization. Substantially more complete PCI-based revascularization is therefore unlikely in other institutions.

Serruys and Farooq suggest that the SYNTAX score may have had a role in selecting patients in the FREEDOM trial in whom PCI may have been an appropriate procedure. In the group of patients with a low SYNTAX score, the incidence of the primary outcome of death, myocardial infarction, or stroke at 6 months was 6 percentage points lower in the CABG group than in the PCI group. In addition, the test for heterogeneity was nonsignificant and suggests that there was no significant interaction with the SYNTAX score in the comparison of PCI with CABG. Since the point estimates of all subgroups in Figure 2 of the article are trending in the same direction, the finding of the superiority of CABG is robust. Of course, subgroups can be defined for which inadequate power is available to fully study the question posed. Serruys and Farooq have defined such a subgroup.[3] Even here, the data are consistent with the results in the full FREEDOM cohort.

Michael E. Farkouh, M.D.
Michael Domanski, M.D.
Valentin Fuster, M.D., Ph.D.
Icahn School of Medicine at Mount Sinai
New York, NY
valentin.fuster@mssm.edu

Since publication of their article, the authors report no further potential conflict of interest.

1. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873-91.
2. Vieira RD, Hueb W, Gersh BJ, et al. Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. Circulation 2012;126: Suppl 1:S158-S163.
3. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.

DOI: 10.1056/NEJMc1301244

Chapter 9.2

'Cherry-picking' patients for randomised controlled trials - reliving the past…

Farooq V, Serruys PW

J Am Coll Cardiol. 2013;61(24):2492 (Impact Factor: 14.086)

"Cherry-Picking" Patients for Randomized, Controlled Trials—Reliving the Past. . .

We read with interest the VA CARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes) study (1) comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in subjects with diabetes. In our opinion, the most notable finding of the study is not the outcome of the trial, but the actual study design itself, that is, the stringent angiography- and clinically based inclusion and exclusion criteria, which makes application of the study's findings to real-world contemporary clinical practice highly questionable. Notably, of the 6,678 diabetic patients screened for this study, a staggering 6,080/6,678 (91%) of screened subjects did not meet angiographic requirements for the study, and only 198 subjects (3%) were randomly assigned to either CABG (n = 97, 1.5%) or PCI with drug-eluting stents (DESs) (n = 101, 1.5%) and completed the 2-year follow-up. Such a trial design is reminiscent of the PCI versus CABG randomized trials undertaken before the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial (2,3), where "cherry-picking" of patients before randomization was a major confounding issue (2% to 12% of screened patients were randomized in most trials) that effectively invalidated the results of these trials (4,5). The SYNTAX trial was designed to overcome these limitations by incorporating an all-comers design in which practically no patient was refused entry, with subjects either randomized (if determined by the Heart Team to achieve "equivalent anatomical revascularization" between CABG and PCI) or nested in registries (2,3). This was at the insistence of 7 cardiac surgeons (dubbed the "magnificent 7") during the design of SYNTAX to prevent selection bias, a view that was fully endorsed by the clinical and interventional cardiologists at the time. To give an example of the potential dangers of using highly selected populations in a clinical trial design, a recent meta-analysis of randomized trials undertaken before SYNTAX comparing PCI with CABG (6) showed CABG to be favored in older subjects and PCI to be favored in younger subjects, findings that have since been directly contradicted by the all-comers SYNTAX trial (where the opposite was shown) (7). In addition, the analyses demonstrating the anatomic SYNTAX score in the VA CARDS study not to show any treatment effect between CABG and PCI warrant specific mention in that they were severely underpowered to draw any conclusions, even if considered hypothesis generating (8). Specifically, the majority of subjects in the VA CARDS study had low (≤22) (CABG: n = 47 vs. PCI: n = 59) SYNTAX scores, with few subjects in the intermediate (23 to 32) (CABG: n = 33 vs. PCI: n = 24) or high (≥33) (CABG: n = 13 vs. PCI: n = 12) SYNTAX scores, presumably due to the overwhelmingly restrictive angiographic inclusion and exclusion criteria of the study as described earlier, thus making any comparisons of the low with the higher SYNTAX score tertiles practically meaningless. Even within the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, (9) analyses based on the SYNTAX score tertiles appear to have been limited by power and were contradicted by those reported in the pre-stratified and powered diabetic subgroup of SYNTAX (10). The real lesson of the VA CARDS study is that randomization of subjects in a clinical trial is not enough and that an all-comers clinical trial design is warranted. Anything less will take us back to the confusing era of randomized trials performed before SYNTAX and will serve to cloud the medical literature.

Vasim Farooq, MBChB
***Patrick W. Serruys, MD, PhD**

*Erasmus Medical Center
's-Gravendijkwal 230
3015 CE Rotterdam
the Netherlands
E-mail: p.w.j.c.serruys@erasmusmc.nl

http://dx.doi.org/10.1016/j.jacc.2013.03.018

Please note: Steven Nissen, MD, served as Guest Editor for this letter.

REFERENCES

1. Kamalesh M, Sharp TG, Tang XC, et al. Percutaneous coronary intervention versus coronary bypass surgery in United States Veterans with diabetes. J Am Coll Cardiol 2013;61:808–16.
2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
3. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381:629–38.
4. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;82:1966–75.
5. Taggart DP. CABG or stents in coronary artery disease: end of the debate?. Lancet 2013;381:605–7.
6. Flather M, Rhee JW, Boothroyd DB, et al. The effect of age on outcomes of coronary artery bypass surgery compared with balloon angioplasty or bare-metal stent implantation among patients with multivessel coronary disease. A collaborative analysis of individual patient data from 10 randomized trials. J Am Coll Cardiol 2012;60: 2150–7.
7. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50.
8. Ellis SG. Coronary revascularization for patients with diabetes: updated data favor coronary artery bypass grafting. J Am Coll Cardiol 2013;61:817–9.
9. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.
10. Serruys PW, Farooq V. Revascularization strategies in patients with diabetes. N Engl J Med 2013;368:1454–5.

Reply

In the letter about our paper (1), Drs. Farooq and Serruys make the assertion that the VA CARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes) study is not applicable to contemporary coronary revascularization based on: 1) the angiographic inclusion criteria being too strict; 2) the small percentage of screened patients who were enrolled; and 3) that our study was underpowered to evaluate SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores. The letter completely misses important aspects of our study.

Our angiographic criteria were based on subsets of patients known to have better survival with surgery than with medical treatment. We deliberately excluded patients when the primary role of revascularization would be symptom relief. These patients were extensively studied in COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (Bypass versus Angioplasty Revascularization Intervention 2 Diabetes) (2,3). Including these subsets would have increased enrollment but also would have diluted the power of the study to find survival differences.

Our screened patients included *all patients* with diabetes referred for a diagnostic angiogram *for any reason*. To compare VA-CARDS to SYNTAX, we need to know the total number of patients having diagnostic angiography at the 85 sites over their 2-year enrollment (4). An average of 500 diagnostic angiograms per year per SYNTAX site would yield a total of 85,000 diagnostic coronary angiograms. The 1,800 patients enrolled in SYNTAX would then represent 2.1% of this total, which is *lower* than our study.

Our study was not designed or powered to examine SYNTAX score subgroups. The SYNTAX scores in our study merely show that there was no systematic bias in the distribution of scores to explain the observed survival difference. If anything, low SYNTAX scores were more frequent for PCI than surgery. It is important to note in this discussion that the SYNTAX trial itself was not powered to compare small subgroups based on SYNTAX terciles. There is no SYNTAX score that leads to an absolute improvement in outcome for percutaneous coronary intervention over surgery among patients with 3-vessel coronary disease. The failure to find a significant p value in the subanalysis of 352 patients with low SYNTAX scores and 3-vessel coronary artery disease is likely to represent a type II error (5). The SYNTAX investigators need to report a power analysis of each of the subgroups that they analyze. The assumption that the failure to find a difference means that there is no difference is misleading.

***Masoor Kamalesh, MD**
Thomas Sharp, MD

*Krannert Institute of Cardiology
1481 West 10th Street
Indianapolis, Indiana 46202
E-mail: mkamales@iupui.edu

http://dx.doi.org/10.1016/j.jacc.2013.03.017

REFERENCES

1. Kamalesh M, Sharp TG, Tang XC, et al. Percutaneous coronary intervention versus coronary bypass surgery in United States Veterans with diabetes. J Am Coll Cardiol 2013;61:808–16.
2. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
3. The BARI 2D Study Group A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–15.
4. Serruys PW, Morice MC, Kappetein AP. et al. SYNTAX Investigators Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
5. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.

Chapter 9.3

Observations from the CREDO-Kyoto three-vessel disease registry: can one adjust for the unadjustable?

Farooq V, Serruys PW

EuroIntervention. 2013;22;9(4):419-21 (Impact Factor: 3.173)

Observations from the CREDO-Kyoto three-vessel disease registry: can one adjust for the unadjustable?

Vasim Farooq, MBChB, MRCP; Patrick W. Serruys*, MD, PhD

Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands

In this issue of EuroIntervention, results from the long-awaited three-vessel-disease (3VD) subset of the CREDO-Kyoto PCI/CABG registry cohort-2 (CREDO-Kyoto registry) are published[1]. These findings were first presented at the European Society of Cardiology Congress in Paris, France, in August 2011, and were controversial. Although the registry was retrospective in nature, given its size, the results are difficult to ignore, particularly the apparent finding of CABG being "best" for 3VD in lower SYNTAX-score patients[2].

Over a three-year period (2005-2007), 15,939 consecutive patients were enrolled in 26 centres in Japan, of whom 2,981 patients were identified with 3VD (PCI: n=1,825; CABG: n=1,156), and an impressive 2,812 patients (PCI: n=1,792; CABG: n=1,020) underwent retrospective SYNTAX score calculations. As expected, the adjusted primary endpoint of all-cause death, MI, or stroke was significantly lower in CABG-treated patients compared to PCI-treated patients, reflecting recent findings from the ASCERT registry[3], and the randomised, all-comers SYNTAX trial[4].

Interestingly, in the CREDO-Kyoto registry, unadjusted all-cause death was significantly greater for PCI compared to CABG (PCI: 11.7% vs. CABG: 9.3%, p=0.046), whereas unadjusted cardiac death was similar (PCI: 5.6% vs. CABG: 5.4%, p=0.41). Adjusted all-cause death (p=0.005) remained significantly in favour of CABG, whereas adjusted cardiac death remained neutral between CABG and PCI (p=0.28).

The results stratified by the presence of tertiles of the SYNTAX score in the CREDO-Kyoto registry are of additional interest, since the European revascularisation guidelines[5] advocate that, for 3VD disease with a low SYNTAX score (0-22), PCI is given a class IIA recommendation (weight of evidence/opinion in favour of usefulness/efficacy). This recommendation is based primarily on the results of the SYNTAX trial[4]. Conversely, for 3VD associated with higher SYNTAX scores (>22), PCI is given a class III recommendation (not useful/effective and possibly harmful). Yet in the low SYNTAX score subset (0-22) of the CREDO-Kyoto study, the adjusted risk of the primary endpoint was higher for PCI compared to CABG (HR 1.66 [1.04-2.65], p=0.03), whereas the unadjusted risk of the primary endpoint was similar between CABG and PCI (HR 1.26 [0.86-1.925], p=0.24). Findings in the higher SYNTAX score tertiles were mixed, with only a high SYNTAX score (≥33) showing a trend towards treatment benefit for CABG compared to PCI on adjusted analyses (p=0.051). Given these contradictory findings, how is one to interpret them, particularly in the context of the current published evidence?

Interpreting the CREDO-Kyoto study

The main observation of the CREDO-KYOTO study is that the authors attempt to equalise the two treatment groups (CABG and PCI), through adjustment of data with simple clinical variables, and then undertake sensitivity analyses using propensity score matching to confirm the findings. What should be highlighted is that the authors endeavour to adjust an unadjustable characteristic, namely the clinical judgement and decision-making process of the Heart Team in selecting the most appropriate revascularisation modality[6]. As the authors appropriately highlight in the limitations section, selection bias due to unmeasured confounders, such as patient frailty, cognitive dysfunction, active malignancy, and systemic infection, could not be controlled for, and may offer an explanation why all-cause death was higher for PCI, whereas cardiac death was similar between CABG and PCI, even after adjustment for baseline factors.

Evidence to support these statements comes from the New York State registry[6,7], in which survival after CABG or PCI was similar in unadjusted curves, but showed a mortality benefit favouring CABG after adjustment for risk factors **(Figure 1)**. Excessive comorbidities make CABG less attractive due to the operative risk, which can be prohibitive. In such scenarios, PCI becomes the default approach. In the SYNTAX trial, these types of patients were not randomised, since CABG and PCI could not be offered equally, and they were therefore nested in a PCI registry (n=198). Strikingly, at five years, the nested PCI registry of the SYNTAX trial reported a mortality rate of 30%[4]. By comparison, in the randomised SYNTAX trial, five-year all-cause mortality was 11.4% in the CABG arm and 13.9% in the PCI arm (p=0.10). The reasons to explain the more than doubling of mortality in the PCI registry of the SYNTAX trial may be related to a greater occurrence of incomplete revascularisation due to severe anatomical complexity, and the associated negative impact on long-term survival[8,9], high EuroSCORE subjects being shown to have an excess of mortality after PCI[10,11], and the hypothesis[12] that bypass grafts "protect" coronary vessels from future cardiac events for the lifespan of the graft, whereas PCI treats individual lesions

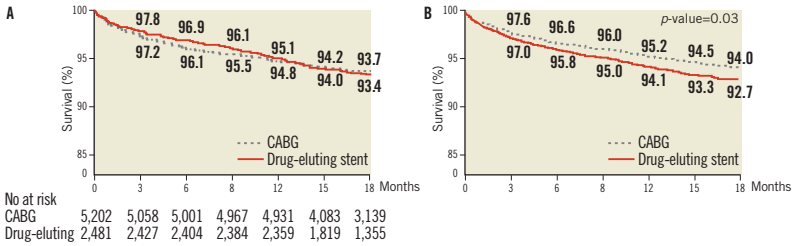


Figure 1. *Unadjusted (A) and adjusted (B) Kaplan-Meier curves for survival from the New York State registry[7]. Adjusted survival curves (B) are for age, sex, ejection fraction, haemodynamic state, history or no history of myocardial infarction before the procedure, the presence or absence of cerebrovascular disease, peripheral arterial disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes, renal failure, and involvement of the proximal left anterior descending artery. Reprinted with permission from Massachusetts Medical Society, Hannan et al[7].*

– particularly in very high-risk subjects where the chances of a future clinical event are likely to be substantial.

In the higher SYNTAX scores in the CREDO-Kyoto study, at least a trend for a treatment benefit of CABG was seen in the high SYNTAX score tertile (>32). This is likely to be related to the data being underpowered, confounded by selection bias as discussed.

SYNTAX score II

Recently, the SYNTAX score II was proposed and validated[13], whereby the anatomical SYNTAX score was combined with clinical variables shown directly to affect decision making between CABG and PCI based on interactions **(Figure 2)**. For example, the anatomical SYNTAX score aids decision making between CABG and PCI because it is more predictive of clinical outcomes in patients undergoing PCI, compared to patients undergoing CABG (where it is not predictive). Based on this principle, other factors were included in the SYNTAX score II, that were shown to alter the threshold value of the anatomical SYNTAX score that would lead to similar long-term mortality between CABG and PCI.

In essence, the SYNTAX score II adjusts the individual patient anatomical and clinical characteristics to aid objective decision making between CABG and PCI for the Heart Team. In addition, by individualising risk, the SYNTAX score II was shown to be able to identify higher and lower-risk subjects in all tertiles of the anatomical SYNTAX score who had a long-term mortality that favoured either CABG or PCI, or both revascularisation modalities. As compared to existing revascularisation guidelines using the conventional SYNTAX score, the selection of subjects based on a higher or lower expected survival using the SYNTAX score II was recently reported to be necessary only in approximately 110 patients in order to have one more patient alive at four years[14].

Conclusion

What is required for validation of the effectiveness of the SYNTAX score and SYNTAX score II in decision making are prospectively run studies, or randomised validation studies, free from selection bias. Registry data, no matter how large, are confounded by (often appropriate) decision-making processes, and should therefore be interpreted with caution, as exemplified in the CREDO-Kyoto registry. The take-home message from the CREDO-Kyoto study is that the results actually appear to support current revascularisation guidelines, particularly with respect to the low SYNTAX score group, provided both anatomical and clinical factors are accounted for, as demonstrated in the SYNTAX score II.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

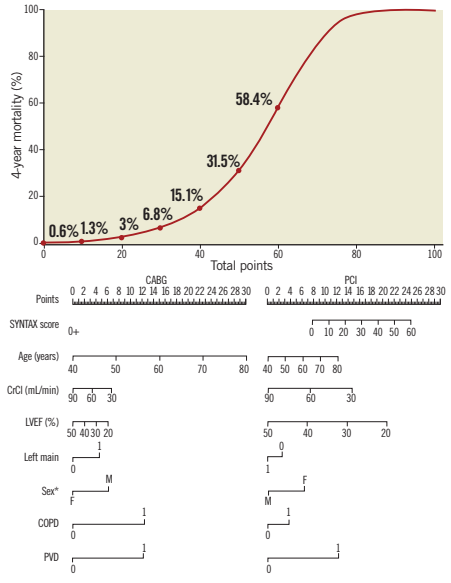
1. Tazaki J, Shiomi H, Morimoto T, Imai M, Yamaji K, Sakata R, Okabayashi H, Hanyu M, Shimamoto M, Nishiwaki N, Komiya T, Kimura T; on behalf of the CREDO-Kyoto PCI/CABG registry cohort-2 investigators. Three-year outcome after percutaneous coronary intervention and coronary artery bypass grafting in patients with triple-vessel coronary artery disease: observations from the CREDO-Kyoto PCI/CABG registry cohort-2. *EuroIntervention.* 2013;9:437-45.

2. CREDO-Kyoto: CABG best for three-vessel disease in lower-SYNTAX-score patients? http://www.theheart.org/article/1270587.do Accessed 11th May 2013.

3. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, Zhang Z, Klein LW, Shaw RE, McKay C, Ritzenthaler LL, Popma JJ, Messenger JC, Shahian DM, Grover FL, Mayer JE, Shewan CM, Garratt KN, Moussa ID, Dangas GD, Edwards FH. Comparative effectiveness of revascularization strategies. *N Engl J Med.* 2012;366:1467-76.

4. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629-38.

5. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous



*Due to the rarity of complex coronary artery disease in pre-menopausal women, mortality predictions in younger women are predominantly based on the linear relationship of age with mortality The differences in mortality predictions in younger women between CABG and PCI will therefore be affected by larger 95% confidence intervals than those in older women but will be equally valid.

Figure 2. *The SYNTAX score II nomogram for bedside application. Total number of points for 8 factors can be used for accurate prediction of 4-year mortality for the individual patient proposing to undergo CABG or PCI. Younger age, female gender and reduced LVEF favoured CABG compared to PCI on long-term prognostic grounds. Thus, in such patients a lower anatomical SYNTAX score would be required in order for the long-term mortality risk to be similar between CABG and PCI. By contrast, older age, chronic obstructive pulmonary disease or ULMCA disease favoured PCI compared to CABG. Thus, in this type of patient, a higher anatomical SYNTAX score would be needed for the long-term mortality risks to be similar. For example, a 60-year-old male with an anatomical SYNTAX score of 30, ULMCA disease, CrCl 60 ml/min, a LVEF of 50%, and COPD would have 41 points (predicted 4-year mortality: 16.3%) and 33 points (predicted 4-year mortality: 8.7%) to undergo CABG and PCI, respectively. The same example, without COPD included, would lead to identical points (29 points) and 4-year mortality predictions (6.3%) for CABG and PCI. Legend and image modified and reproduced with permission from Farooq et al[11]. CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; CrCl: creatinine clearance (Cockcroft and Gault formula); LVEF: left ventricular ejection fraction; Left main: unprotected left main coronary artery disease; COPD: chronic obstructive pulmonary disease (long-term use of bronchodilators or steroids for lung disease [EuroSCORE definition]); PVD: peripheral vascular disease (aorta and arteries other than coronaries, with exercise-related claudication, and/or revascularisation surgery and/or reduced or absent pulsation and/or angiographic stenosis of more than 50%).*

Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501-55.

6. Daemen J, Kukreja N, Serruys PW. Drug-eluting stents vs. coronary-artery bypass grafting. *N Engl J Med.* 2008;358:2641-2; author reply 2643-4.

7. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med.* 2008;358:331-41.

8. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol.* 2013;61:282-94.

9. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of Incomplete Revascularisation and its Association with Five-Year Mortality in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score. *Circulation.* 2013 Jun 13 [Epub ahead of print].

10. Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart.* 2009;95:43-8.

11. Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR Jr, Kappetein AP, Mack MJ, Feldman T, Morice MC, Stahle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv.* 2012;5:606-17.

12. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. *Ann Thorac Surg.* 2006;82:1966-75.

13. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet.* 2013;381:639-50.

14. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW. SYNTAX score II - Authors' reply. *Lancet.* 2013;381:1899-900.

Chapter 9.4

Response to Letter Regarding Article, "Quantification of Incomplete Revascularization and Its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial: Validation of the Residual SYNTAX Score".

Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Ståhle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW.

Circulation. 2014;129(8):e355-6 (Impact Factor 15.202).

Letter by Carnero-Alcázar et al Regarding Article, "Quantification of Incomplete Revascularization and Its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial: Validation of the Residual SYNTAX Score"

To the Editor:

We read with interest the article by Farooq et al, "Quantification of Incomplete Revascularization and Its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial: Validation of the Residual SYNTAX Score,"[1] in which the authors investigated the effect on long-term outcomes of the randomized patients receiving percutaneous coronary intervention in the SYNTAX study according to the SYNTAX score (SS) of the residual coronary lesions once subjects had been revascularized (residual SS). They concluded that a residual SS >8 was associated with increasing adverse long-term clinical outcomes, including mortality. On the other hand, residual SS ≤8 was associated with long-term mortality comparable with that of patients with complete revascularization (residual SS=0).

SS was used to stratify the comparison between coronary artery bypass graft and percutaneous coronary intervention in the SYNTAX trial,[2] so that apparently the benefits of coronary artery bypass graft over percutaneous coronary intervention remained only in the highest SS tertiles. We cannot forget that these subgroup comparisons were performed post hoc and with small sample sizes. Furthermore, the alternative hypothesis had not been demonstrated. Therefore, we believe subgroup analysis results could be interpreted only as being hypothesis originating.[2] On the other hand, SS reproducibility is limited. The SYNTAX Investigators assessed the reliability of SS by comparing the score obtained by different well-trained observers when calculating the SS for the same angiography.[3] The weighted κ measures the agreement between ≥2 observations. Weighted κ >0.75 represents excellent agreement beyond chance; 0.40 to 0.75, fair to good agreement; and <0.40, poor agreement. In that study, Serruys et al[3] reported a weighted κ for the observations of the global score of 0.45; the weighted κ for the number of lesions was 0.59; and weighted κ for bifurcations was 0.41. Although the weighted κ values were >0.4, in our opinion, the degree of agreement was still lower than desired.

Given the limited power of the SS to predict outcomes after coronary artery bypass graft or percutaneous coronary intervention, SS II was developed by the SYNTAX Investigators.[4] This new score added to the original SS some clinical items to improve the risk prediction among patients with complex coronary disease. Although it demonstrated an accurate prediction of 4-year mortality (greater than the original SS), SS II was complex to calculate and, like the SS, had poor reproducibility. The more variables it has, the greater its complexity is, and the less parsimonious a score is, the less useful it becomes.

Before the present article by Farooq et al,[1] a basic principle of coronary revascularization remained unchanged: Complete revascularization is always better. After performing a (once again) nonrandomized subgroup analysis with limited sample sizes (and thus limited statistical power to detect differences), the authors concluded that some degree of incompleteness of revascularization (residual SS ≤8) might be acceptable. We should be cautious when assuming these conclusions because they are, once again, hypothesis generating.

Although the 3 scores mentioned before are widely used in everyday practice, we believe the decision on the optimal revascularization treatment must not completely rely on these scores yet. Further studies must be performed to prospectively assess their true accuracy and reproducibility

Disclosures

None.

Manuel Carnero-Alcázar, MD, PhD
Luis Carlos Maroto-Castellanos, MD, PhD
José Enrique Rodríguez-Hernández, MD
Cardiac Surgery Department
Hospital Clínico San Carlos
Madrid, Spain

References

1. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Ståhle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial: validation of the residual SYNTAX score. *Circulation*. 2013;128:141–151.
2. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack M, Stahle E, Feldman T, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Eng J Med*. 2009;360:961–972.
3. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention*. 2009;5:50–56.
4. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639–650.

Response to Letter Regarding Article, "Quantification of Incomplete Revascularization and Its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial: Validation of the Residual SYNTAX Score"

We thank Carnero-Alcázar and colleagues for their comments concerning our article.[1]

First, the readership should be reminded that the anatomic Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score was designed before the SYNTAX trial as a tool to force the interventional cardiologist and cardiac surgeon to systematically analyze the coronary angiogram and agree that "equivalent anatomic revascularization" could be achieved on the basis of a vessel size of 1.5 mm. A vessel size of 1.5 mm was selected as this was the size of the vessel the cardiac surgeon stated they could revascularize. Before the SYNTAX trial, the SYNTAX score was tested in the Arterial Revascularization Therapies Study (ARTS) II Study.[2] In the SYNTAX trial protocol, outcomes related to the SYNTAX score were prespecified. Since the SYNTAX trial, numerous studies have validated the SYNTAX score.[3]

Second, criticisms related to the reproducibility of the SYNTAX score appear excessive. The simple interpretation of a coronary angiogram, on which most contemporary revascularization practice is based, has been reported as far back as the 1970s to have substantial intraobserver and interobserver variability in visual estimation (SD up to 18%),[4] findings that are simply reflected in the SYNTAX score calculation. Suitable training to undertake the SYNTAX score, quantitative coronary angiography, and functional guidance have been shown to limit this issue.[3] A semiautomated, computed tomography–derived functional SYNTAX score is currently in development and is expected to further minimize this concern.[3]

Third, it is important to highlight that the SYNTAX score II is built on the principle of parsimony. The core factors in the SYNTAX score II (SYNTAX score and ACEF [age, creatinine clearance, and left ventricular ejection fraction]) contain the bulk of the prognostic information for predicting long-term mortality after coronary artery bypass graft surgery or percutaneous coronary intervention.[3] The remaining factors added to the SYNTAX score II were based on the principle that they were shown to alter the threshold value of the SYNTAX score (interactions) for equipoise to be achieved between coronary artery bypass graft surgery and percutaneous coronary intervention for long-term mortality, thereby aiding decision making between revascularization modalities. An online calculator to simplify the calculation of the SYNTAX score II is planned for public release shortly (www.syntaxscore.com).

Finally, the authors assert that complete revascularization (CR) is always better. On which definition of CR is this assumption being made? This is particularly pertinent given the multiple definitions of CR that exist in the literature. Although too extensive incomplete revascularization is likely to have a negative impact on long-term clinical outcomes, too extensive surgical revascularization has been associated with the occurrence of major perioperative complications and acute myocardial infarction, with evidence to support a reasonable incomplete revascularization approach.[5,6] Even within the SYNTAX trial, despite CR being mandated by the heart team, the reality was somewhat different, with only 56.7% and 63.2% of the percutaneous coronary intervention and coronary artery bypass graft surgery cohorts, respectively, achieving CR. In addition, CR is a clinical outcome, not a baseline characteristic. Therefore, conducting a randomized trial directly examining this issue is difficult, particularly because incomplete revascularization was shown to be a surrogate marker for sicker patients, with a greater burden and complexity of coronary disease and clinical comorbidity.[1]

We fully agree that further prospective validation of these SYNTAX-based tools is required to further legitimize their use in clinical practice. This is currently occurring in the ongoing EXCEL (Evaluation of XIENCE PRIME Everolimus Eluting Stent System [EECSS] or XIENCE V® EECSS or XIENCE Xpedition EECSS or XIENCE PRO EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and SYNTAX II trials investigating unprotected left main and 3-vessel disease, respectively.[3]

Disclosures

Dr Feldman reported serving on the speaker's bureau for Boston Scientific; receiving grant support from Abbott, Atritech, BSC, Edwards, and Evalve; and consulting for Abbott, Coherex, Intervalve, Square One, and W.L. Gore. Dr Mack has served on the speaker's bureau for Boston Scientific, Cordis, and Medtronic. Dr Morice reported that her institution has received a research grant from Boston Scientific. Dr Dawkins is a full-time employee of and holds stock in Boston Scientific. The other authors report no conflicts.

Vasim Farooq, MBChB, MRCP
Patrick W. Serruys, MD, PhD
Christos V. Bourantas, MD
Yaojun Zhang, MD
Takashi Muramatsu, MD
Department of Interventional Cardiology
Erasmus University Medical Centre
Thoraxcenter
Rotterdam, The Netherlands

Ted Feldman, MD
Evanston Hospital
Evanston, IL

David R. Holmes, MD
Mayo Clinic
Rochester, MN

Michael Mack, MD
Medical City Dallas Hospital
Dallas, Texas

Marie Claude Morice, MD
Institut Jacques Cartier
Massy, France

Elisabeth Ståhle, MD
University Hospital Uppsala
Uppsala, Sweden

Antonio Colombo, MD
San Raffaele Scientific Institute
Milano, Italy

Ton de Vries, MA
Marie-angèle Morel, BSc
Cardialysis BV
Rotterdam, The Netherlands

Keith D. Dawkins, MD
Boston Scientific Corp
Natick, MA

Arie Pieter Kappetein, MD, PhD
Department of Cardiothoracic Surgery
Erasmus University Medical Centre
Thoraxcenter
Rotterdam, The Netherlands

Friedrich W. Mohr, MD
Herzzentrum
Leipzig, Germany

References

1. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Ståhle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial: validation of the residual SYNTAX score. *Circulation*. 2013;128:141–151.
2. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Schuijer M, Rademaker T, Wittebols K, Stoll HP; ARTS II Investigators. 5-Year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol*. 2010;55:1093–1101.
3. Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX score. *Heart*. 2014;100:276–287.
4. Serruys PW, Foley D, De Feyter PJ, eds. *Quantitative Coronary Angiography in Clinical Practice*. Dordrecht, Netherlands: Kluwer Academic; 1994.
5. Alamanni F, Dainese L, Naliato M, Gregu S, Agrifoglio M, Polvani GL, Biglioli P, Parolari A; Monzino OPCAB Investigators. On- and off-pump coronary surgery and perioperative myocardial infarction: an issue between incomplete and extensive revascularization. *Eur J Cardiothorac Surg*. 2008;34:118–126.
6. Rastan AJ, Walther T, Falk V, Kempfert J, Merk D, Lehmann S, Holzhey D, Mohr FW. Does reasonable incomplete surgical revascularization affect early or long-term survival in patients with multivessel coronary artery disease receiving left internal mammary artery bypass to left anterior descending artery? *Circulation*. 2009;120(suppl): S70–S77.

Chapter 9.5

Complex Coronary Artery Disease: Would Outcomes From the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Trial Have Differed With Newer-Generation Drug-Eluting Stents?

Farooq V, Serruys PW

JACC Cardiovasc Interv. 2013;6(10):1023-5 (Impact Factor: 6.552)

EDITORIAL COMMENT

Complex Coronary Artery Disease

Would Outcomes From the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Trial Have Differed With Newer-Generation Drug-Eluting Stents?*

Vasim Farooq, MB, ChB,
Patrick W. Serruys, MD, PhD

Rotterdam, the Netherlands

Newer-generation drug-eluting stents (DES) have unequivocally led to significant improvements in safety compared with first-generation DES (1–8). Given the substantial clinical benefits attained with newer-generation DES, the obvious question remains—would outcomes from the landmark SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (9–12) have differed with newer-generation DES?

In this issue of *JACC: Cardiovascular Interventions*, Ribichini et al. (13) present important findings from the randomized, multicenter EXECUTIVE (Evaluating Xience-V in Multi-Vessel Disease) pilot trial, comparing the newer-generation everolimus-eluting stent (EES) (Xience V, Abbott Vascular, Santa Clara, California) against the first-generation paclitaxel-eluting stent (PES) (Taxus Express, Boston Scientific, Natick, Massachusetts) in the treatment of multivessel coronary artery disease. The primary outcome was angiographic, namely, late lumen loss, and demonstrated the superiority of EES (all lesions late lumen loss: EES 0.05 ± 0.51 mm vs. PES 0.24 ± 0.50 mm, $p < 0.001$). Although the study was clearly underpowered for clinical outcomes, observations of numerical differences in 1-year major adverse cardiac events of 11.1% in the randomized EES arm, and 16.5% in the randomized PES arm are difficult to ignore, and offer a unique insight into the potential benefit of newer-generation DES in the treatment of multivessel disease.

There are, however, a number of caveats to the EXECUTIVE trial that should be highlighted. Firstly, in keeping with the U.S. and European revascularization guidelines (14–16), the EXECUTIVE trial focused primarily on low SYNTAX score (<23) (11,17,18) subjects, having been recruited in approximately 95% of the EES and PES treatment arms (mean SYNTAX score: 12.7 ± 5.2). How generalizable the results of the EXECUTIVE trial are to subjects with more complex multivessel disease, therefore, remains unclear. Secondly, the EXECUTIVE trial lacked an all-comers design, with clinical and angiographic inclusion and exclusion criteria, which somewhat limits translation of the study's findings to contemporary clinical practice, even in low SYNTAX score subjects. For example, a history of congestive cardiac failure or a left ventricular ejection <30%—factors previously shown to alter the threshold value of the SYNTAX score in favor of coronary artery bypass grafting (CABG) (19)—were exclusion criteria. In the pre-SYNTAX era, such restrictive trial designs comparing CABG with percutaneous coronary intervention (PCI) were heavily criticized for "cherry-picking" patients for randomization, despite the randomized nature of these studies (20,21). Thirdly, the EXECUTIVE trial was clearly underpowered to assess clinical outcomes, and showed numerical differences in clinical outcomes that could not be statistically corroborated. Fourthly, the fact that complete revascularization almost uniquely appeared to have been achieved in all randomized patients, with consequent favorable outcomes (22,23), and that an arbitrarily defined limit of 4 planned stents per patient was placed in the angiographic inclusion criteria, does imply a further amount of selection bias in recruiting subjects.

The improved clinical outcomes with the EES in multivessel disease (despite the described shortcomings of the EXECUTIVE trial), coupled with similarly reported data from the FLM Taxus (French Left Main Taxus) and the LEMAX (LEft MAin Xience) registries, investigating left main stenting with EES (24,25), and the known reductions in stent thrombosis (ST) of newer-generation DES (1–8), does imply that if newer-generation DES had been used in the SYNTAX trial, there would have been a significant reduction in clinical events, particularly repeat revascularization and myocardial infarction.

As to whether reductions in mortality would be seen with newer-generation DES in patients undergoing contemporary PCI is entirely plausible (8). Large-scale reductions in ST and their clinical sequelae with newer-generation DES are firmly established in the literature, although the expected reduction in mortality awaits confirmation from randomized trials (1–7). Conversely, in the SYNTAX trial, if the cardiac mortality events related to ST were removed, based on Academic Research Consortium (26) definitions of ST, there would have been only a modest reduction in cardiac mortality at 5 years. Namely, for definite ST, 5-year cardiac mortality would be reduced from 9% to 8.5%, and for

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

definite and probable ST, from 9% to 7.5% (27). The main reason to account for this phenomenon may relate to the hypothesis that bypass grafts protect coronary vessels from future myocardial events for the lifespan of the graft, particularly in more complex coronary artery disease where the plaque burden and risk of a future cardiac event would potentially be higher, compared with a subject with less complex coronary artery disease. Conversely, stents would only treat individual lesions (21,28).

The potential reduction in mortality with newer-generation DES in the SYNTAX trial would therefore be unlikely to bridge the gap between CABG and PCI, particularly with more complex coronary artery disease. This is exemplified in the SYNTAX score II (19,29), in which the SYNTAX score was combined with clinical variables that were shown to alter the threshold value of the SYNTAX score so that equipoise was achieved between CABG and PCI for long-term mortality. Notably, subsets of patients were identified across all tertiles of the SYNTAX score who would have a mortality benefit from undergoing CABG or PCI (Fig. 1). It should, however, be emphasized that increasing anatomical complexity, particularly in subjects with 3-vessel disease, lead to a greater likelihood of a mortality benefit to be attained with CABG over PCI (Fig. 1).

In both the ongoing EXCEL (Evaluation of XIENCE PRIME Everolimus Eluting Stent System [EECSS] or XIENCE V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (NCT01471522), investigating the treatment of unprotected left main coronary artery disease, and the

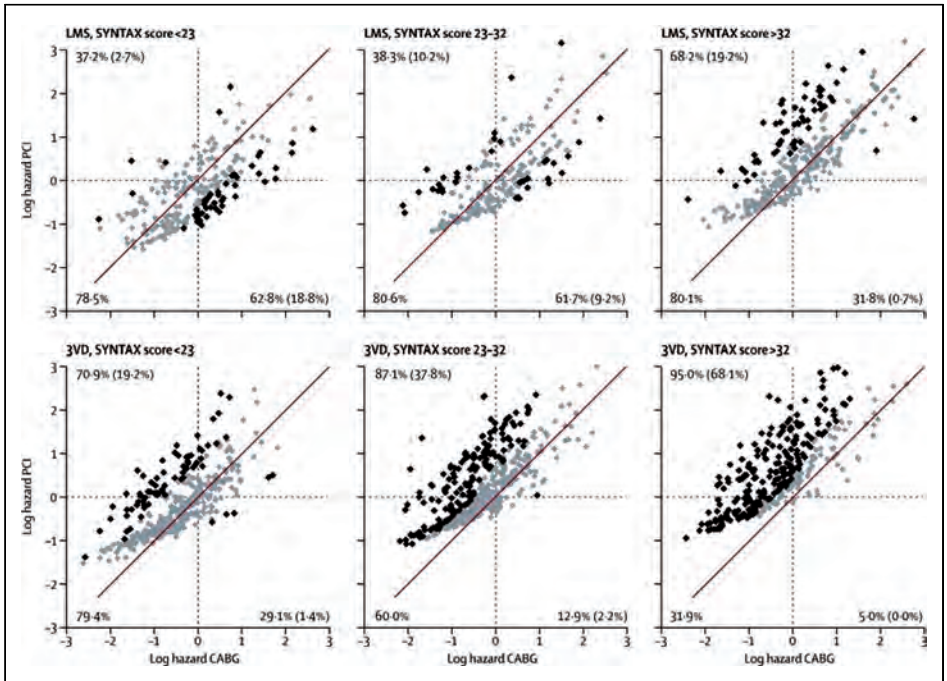


Figure 1. Scatter Plots for Individual Patients in the Left Main and 3-Vessel Disease Cohorts of the Randomized SYNTAX Trial (N = 1,800)

The scatter plots for the left main and 3-vessel disease cohorts of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial are based on the SYNTAX score II. The **diagonal line** represents identical mortality predictions for CABG and PCI. Individual mortality predictions plotted to the **left of the diagonal line** favor CABG (actual percentages shown in **top left corner**), and to the **right** favor PCI (actual percentages shown in **bottom right corner**). Individual mortality predictions for CABG or PCI that could be statistically separated with 95% confidence ($p < 0.05$) are colored **black** (actual percentage shown in parentheses in respective corners). Mortality predictions that could not be statistically separated with 95% confidence ($p > 0.05$) are highlighted in **gray**, and identify patients with similar 4-year mortality. 3VD = 3-vessel disease; CABG = coronary artery bypass grafting; LMS = left main stem; PCI = percutaneous coronary intervention. Legend and image are adapted and reproduced, with permission, from Farooq et al. (19).

planned SYNTAX Trial II, investigating the treatment of de novo 3-vessel disease, the SYNTAX score and SYNTAX score II, respectively, are being used to recruit subjects on the grounds of patient safety (30). Further delineating the boundaries between CABG and PCI is where further study is heading to help best define the optimal revascularization modality for individual patients with complex coronary artery disease.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Erasmus Medical Centre, 's-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393–402.
2. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873–91.
3. Meredith IT, Verheye S, Dubois CL, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol 2012;59:1362–70.
4. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. J Am Coll Cardiol Intv 2013; 6:777–89.
5. Planer D, Smits PC, Kereiakes DJ, et al. Comparison of everolimus- and paclitaxel-eluting stents in patients with acute and stable coronary syndromes: pooled results from the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) trials. J Am Coll Cardiol Intv 2011;4:1104–15.
6. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
7. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010; 363:136–46.
8. Sarno G, Lagerqvist B, Frobert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J 2012;33:606–13.
9. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629–38.
10. Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;32:2125–34.
11. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
12. Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151:1194–204.
13. Ribichini F, Romano M, Rosiello R, et al. A clinical and angiographic study of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with multivessel coronary artery disease. The EXECUTIVE (EXecutive RCT: Evaluating XIENCE V in a Multi-Vessel Disease) trial. J Am Coll Cardiol Intv 2013;6:1012–22.
14. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58: e44–122.
15. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:e123–210.
16. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
17. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50–6.
18. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. Heart 2013 Mar 28 [E-pub ahead of print].
19. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50.
20. Farooq V, Serruys PW. "Cherry-picking" patients for randomized, controlled trials: reliving the past [letter]. J Am Coll Cardiol 2013;61:2492.
21. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;82:1966–75.
22. Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial: validation of the residual SYNTAX score. Circulation 2013;128:141–51.
23. Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013;61:282–94.
24. Moynagh A, Salvatella N, Harb T, et al. Two-year outcomes of everolimus vs. paclitaxel-eluting stent for the treatment of unprotected left main lesions: a propensity score matching comparison of patients included in the French Left Main Taxus (FLM Taxus) and the LEft MAin Xience (LEMAX) registries. EuroIntervention 2013;9:452–62.
25. Farooq V, Serruys PW, Stone GW, Virmani R, Chieffo A, Fajadet J. Left main coronary artery disease. In: Eeckhout E, Serruys PW, Wijns W, Vahanian A, van Sambeek M, De Palma R, editors. Percutaneous Interventional Cardiovascular Medicine. The PCR-EAPCI Textbook. Vol. 2, part III. Toulouse, France: PCR publishing and Europa Edition, 2012:407–45.
26. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
27. Farooq V, Serruys PW, Zhang Y, et al. Short and long term clinical impact of stent thrombosis and graft occlusion in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery trial: the SYNTAX trial at 5 years. J Am Coll Cardiol 2013. In press.
28. Serruys PW, Farooq V, Vranckx P, et al. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX trial at 3 years. J Am Coll Cardiol Intv 2012;5:606–17.
29. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW. SYNTAX score II: authors' reply [letter]. Lancet 2013;381:1899–900.
30. Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX Score. Heart 2013 Jul 22 [E-pub ahead of print].

Key Words: CABG ■ left main ■ multivessel disease ■ PCI ■ SYNTAX.

PART X

Summary and Conclusions
Samenvatting en Conclusies
Acknowledgements
Curriculum Vitae
List of Publications
Appendix

Summary and Conclusions
Samenvatting en Conclusies

Summary and Conclusions

As a direct result of the all-comers SYNTAX Trial, the boundaries between a percutaneous and a surgical based approach to coronary revascularisation in subjects with complex coronary artery disease has more clearly been defined. The present thesis has allowed for a greater understanding of the results of this landmark trial, and has developed/ validated several SYNTAX based tools to allow application of the findings to clinical practice, as summarised in Chapter 10. Within the Appendix is enclosed the SYNTAX II trial protocol, investigating the management of de novo three vessel disease, and will use the SYNTAX Score II as a tool to recruit subjects on the grounds of patient safety. As to whether the boundaries between the two revascularisation modalities will change with advances in technology with either technique is the subject of ongoing and future trials. Irrespective of the results of these trials, it should be emphasised that treatment recommendations for patients with complex coronary artery disease needs to be made by a heart team, in open dialogue with the patient, rather than an individual practitioner.

Samenvatting en Conclusies

Als direct gevolg van de 'all-comers' SYNTAX Trial zijn de grenzen tussen een percutane en chirurgische benadering van coronaire revascularisatie bij patiënten met complexe kransslagaderziekte duidelijker gedefinieerd. Dit proefschrift heeft geleid tot een beter begrip van de resultaten van deze baanbrekende trial. De verschillende SYNTAX gebaseerde tools, die zijn ontwikkeld en gevalideerd voor toepassing van de bevindingen in de klinische praktijk, zijn samengevat in hoofdstuk 10. Het SYNTAX II onderzoeksprotocol in de appendix stuurt de behandeling van 'de novo three vessel disease' en gebruikt de SYNTAX Score II als een instrument voor selectie van patiënten die adequaat en veilig percutaan behandeld kunnen worden. De vraag of de grenzen tussen de twee revascularisatie technieken zullen verschuiven met de vooruitgang in beide technieken is het onderwerp van lopende en toekomstige trials. Ongeacht de resultaten van deze trials, moet worden benadrukt dat de aanbevelingen voor behandeling van patiënten met complexe kransslagaderziekte moeten worden gedaan door een hart team, in open dialoog met de patiënt, in plaats van door een individuele arts.

Chapter 10

Widening Clinical Applications of the SYNTAX Score

Farooq V, Head S, Kappetein AP, Serruys PW

Heart 2014;100(4):276-87 (Impact Factor: 5.014)

Widening clinical applications of the SYNTAX Score

Vasim Farooq,[1] Stuart J Head,[2] Arie Pieter Kappetein,[2] Patrick W Serruys[1]

[1]Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands
[2]Department of Cardiothoracic Surgery, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, The Netherlands

Correspondence to
Professor Patrick W Serruys, Department of Interventional Cardiology, Erasmus MC, 's-Gravendijkwal 230, Rotterdam 3015 CE, The Netherlands; p.w.j.c.serruys@erasmusmc.nl

Received 13 May 2013
Revised 24 June 2013
Accepted 25 June 2013
Published Online First 22 July 2013

ABSTRACT
The SYNTAX Score (http://www.syntaxscore.com) has established itself as an anatomical based tool for objectively determining the complexity of coronary artery disease and guiding decision-making between coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI). Since the landmark SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Trial comparing CABG with PCI in patients with complex coronary artery disease (unprotected left main or de novo three vessel disease), numerous validation studies have confirmed the clinical validity of the SYNTAX Score for identifying higher-risk subjects and aiding decision-making between CABG and PCI in a broad range of patient types. The SYNTAX Score is now advocated in both the European and US revascularisation guidelines for decision-making between CABG and PCI as part of a SYNTAX-pioneered heart team approach. Since establishment of the SYNTAX Score, widening clinical applications of this clinical tool have emerged. The purpose of this review is to systematically examine the widening applications of tools based on the SYNTAX Score: (1) by improving the diagnostic accuracy of the SYNTAX Score by adding a functional assessment of lesions; (2) through amalgamation of the anatomical SYNTAX Score with clinical variables to enhance decision-making between CABG and PCI, culminating in the development and validation of the SYNTAX Score II, in which objective and tailored decisions can be made for the individual patient; (3) through assessment of completeness of revascularisation using the residual and post-CABG SYNTAX Scores for PCI and CABG patients, respectively. Finally, the future direction of the SYNTAX Score is covered through discussion of the ongoing development of a non-invasive, functional SYNTAX Score and review of current and planned clinical trials.

INTRODUCTION

The SYNTAX Score (http://www.syntaxscore.com) has emerged as an anatomically based tool for objectively determining the complexity of coronary artery disease and guiding decision-making between coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI).[1–4] Since the landmark SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Trial[5–7] comparing CABG with PCI in patients with complex coronary artery disease (unprotected left main coronary artery (ULMCA) or de novo three vessel disease (3VD)), numerous validation studies have confirmed the clinical validity of the SYNTAX Score for identifying higher-risk subjects and aiding decision-making between CABG and PCI in a broad range of patient types.[4 8] The SYNTAX Score is now advocated in both the European and US revascularisation guidelines[9–11] as part of the SYNTAX-pioneered heart team approach.[12] In addition, the US Food and Drug Administration mandates the SYNTAX Score as an entry criterion in ongoing contemporary stent and structural heart disease trials—namely, the EXCEL (Evaluation of XIENCE PRIME or XIENCE V Everolimus Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation) Trial (ClinicalTrials.gov identifier: NCT01205776)[13] and SURTAVI (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) Trial (ClinicalTrials.gov identifier: NCT01586910).

Since establishment of the SYNTAX Score, widening clinical applications of this clinical tool have emerged (table 1). The purpose of this review is to give the clinician a concise overview of the widening applications of the SYNTAX Score, from improving its diagnostic accuracy by incorporation of a functional component, augmenting the anatomical SYNTAX Score with clinical variables to enhance decision-making between CABG and PCI, moving towards individualised decision-making between CABG and PCI, to assessment of the completeness of revascularisation and its prognostic implications. Lastly, the future direction of the SYNTAX Score is explored.

ANATOMICAL AND FUNCTIONAL APPROACH

SYNTAX Score

The SYNTAX Score was developed during the design of the SYNTAX Trial as a tool to force the interventional cardiologist and cardiac surgeon to systematically analyse the coronary angiogram and to specify the number of coronary lesions requiring treatment, their angiographic location and anatomical complexity.[1–5 8] The SYNTAX Score combines the importance of a diseased coronary artery segment in terms of its severity (ie, obstructive or occlusive), anatomical location and importance in supplying blood to the myocardium ('vessel-segment weighting' based on the Leaman Score[14]), adverse lesion characteristics (American College of Cardiology (ACC)/American Heart Association (AHA) lesion classification),[15] bifurcation lesion characteristics (Medina classification[16]) and total occlusion characteristics from the European TOTAL Surveillance Study.[17] Each vessel segment, 1.5 mm in diameter or greater (figure 1A, labelled 1–16), with a ≥50% diameter stenosis by visual estimation, is awarded a multiplication factor related to coronary lesion location and severity (figure 1A). Further characterisation of the coronary lesions leads to the addition of more points (figure 1B), which includes features of total occlusions (duration, length, blunt stump, presence of bridging collaterals or side branch), bifurcation

To cite: Farooq V, Head SJ, Kappetein AP, *et al*. *Heart* 2014;**100**:276–287.

Table 1 Outline of the SYNTAX Score and how it has progressed since its inception

	Year 'conceived'	Structure	Remarks
Anatomical SYNTAX Score[5–8]	2006	Score of angiographic variables—that is, anatomical complexity. Developed during the design of the SYNTAX Trial[3 5] as a tool to force the heart team to systematically analyse the coronary angiogram and agree that equivalent anatomical revascularisation (CABG and PCI) could be achieved	First reported to be useful for decision-making between CABG and PCI in the SYNTAX Trial in 2009.[5] Categories of anatomical complexity (low, intermediate and high), no clinical variables, no individual predictions. Adding a functional component shown to improve accuracy.[20] Non-invasive multislice CT anatomical SYNTAX Score in development,[58] with integration of a non-invasive functional component[4]
'Development phase'—augmenting the anatomical SYNTAX Score with clinical variables and the move towards individualised decision-making			
ACEF[23]	2009	Age, creatinine, ejection fraction	Predicted individual in-hospital operative mortality after CABG. Shown to be at least comparable to the EuroSCORE (composed of 17 variables) in predicting operative risk.[21–23] Shown to aid in long-term predictions of mortality after PCI or CABG[36]
Clinical SYNTAX Score[29]	2010	Amalgamation of SYNTAX Score with modified ACEF Score (creatinine replaced with CrCl, as shown to be more predictive of mortality)	Similar to the SYNTAX Score; categorised patient risk. Could only identify a high-risk group in PCI-treated patients. Provided little help in decision-making between CABG and PCI. Not individualised
Global Risk[31 36]	2010	Amalgamation of SYNTAX Score with surgical EuroSCORE (composed of 17 variables)	Similar to the SYNTAX Score; categorised patient risk. Could identify a low-risk group with comparable outcomes to CABG and PCI in left main and 3VD patients. Not individualised. High EuroSCORE patients identified to have a prognostic benefit in undergoing CABG compared with PCI irrespective of the SYNTAX Score, provided that an acceptable threshold of operative risk not exceeded
Logistic Clinical SYNTAX Score[32 33]	2011	Combination of age, SYNTAX Score, age, CrCl, LVEF shown to contain the majority of the prognostic information for 1-year mortality predictions after PCI	Individual 1-year mortality predictions in all PCI patients (STEMI, NSTEMI) irrespective of clinical presentation (except cardiogenic shock). Not designed for decision-making between CABG and PCI. Cross-validated in seven contemporary stent trials and >6000 patients[32] and further externally validated[33]
End result of this process leading to the development of the SYNTAX Score II			
SYNTAX Score II[38 40]	2012	Augmenting SYNTAX Score with clinical variables—based on the principle that age, CrCl, LVEF and SYNTAX Score contained the majority of the long-term prognostic information in CABG and PCI patients. Additional variables added that directly influenced decision-making between CABG and PCI	Individualised approach. Threshold of the SYNTAX Score in guiding decision-making between CABG and PCI shown to alter based on the presence of other risk factors. Validated in the DELTA Registry,[41] containing left main and 3VD (quarter of population), with a third (30%) of the population with highly complex disease (SYNTAX Scores $\geq$33). Prospective validation studies underway in the EXCEL Trial (left main) and planned SYNTAX II Trial (de novo 3VD)
Use of the SYNTAX Score as an objective marker of completeness of revascularisation			
Residual SYNTAX Score[47 48]	2012	Recalculation of the SYNTAX Score after PCI	Developed and validated in the ACUITY[47] and SYNTAX[47 48] Trials respectively. A residual SYNTAX Score >8 was shown to have an adverse effect on long-term prognosis at up to 5 years follow-up. Further prospectively run validation studies are awaited
Post-CABG SYNTAX Score[51 52]	2013	Recalculation of the SYNTAX Score after CABG, with points deducted on the basis of importance of the diseased coronary artery segment (Leaman Score[14]) in patients who have a functioning bypass graft anastomosed distally	Pilot study in angiographic substudy of the SYNTAX Trial demonstrated the feasibility of this approach in identifying subjects after CABG with an adverse long-term (5 year) prognosis.[51 52] Validation studies are awaited

3VD, three vessel disease; ACUITY, Acute Catheterisation and Urgent Intervention Triage Strategy; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

(Medina classification[16]) or trifurcation (number of diseased branches involved), side branch angulation, aorto-ostial lesion, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus, and diffuse or small vessel disease. An online SYNTAX Score algorithm[1] automatically summates each of these features to calculate the total SYNTAX Score.

Based primarily on the results of the SYNTAX Trial,[5–7] current European revascularisation guidelines[9] give subjects with 3VD and low SYNTAX Scores (0–22) a level of evidence of IA for CABG and IIa B for PCI. In subjects with ULMCA disease and low to intermediate SYNTAX Scores (<33), a level of evidence of IA is given for CABG and IIb B for PCI. Furthermore, US guidelines now give surgical revascularisation for ULMCA disease a Class 1B recommendation,[10 11] compared with a Class 1A recommendation in previous guidelines.[18]

Functional SYNTAX Score

PCI guided by the assessment of the functional significance of a lesion using fractional flow reserve (FFR) has been shown to improve clinical outcomes.[19] The functional SYNTAX Score uses the principle of the functional assessment of coronary lesions to determine the SYNTAX Score, rather than the angiographic determination of the SYNTAX Score based on visual assessment, as is undertaken in conventional SYNTAX Score calculations. In a retrospective sub-analysis of almost 500 patients (n=497) from the FFR-guided arm of the FAME (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) Study, the primary benefit was reclassifying higher-risk groups into lower-risk categories without any adverse sequelae in terms of major adverse cardiac events (MACE) and death or myocardial infarction (MI) at 1 year.[20]

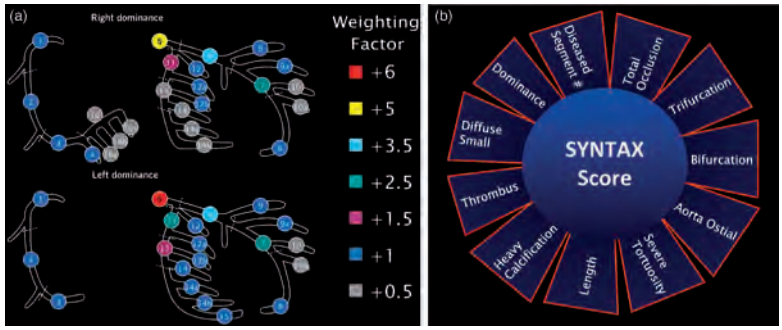


Figure 1 Coronary tree segments and their importance in supplying blood flow to the left ventricle (vessel segment weighting—weighting factors—Leaman Score[14]) based on the presence of a right or left dominant system (A). A multiplication factor of ×2 is used for non-occlusive (50–99% diameter stenosis) lesions and ×5 for occlusive (100% diameter stenosis) lesions. For example, a stenotic proximal LAD lesion (segment 6) would have a weighting factor of 3.5×2 (7 points), and an occlusive proximal LAD lesion a weighting factor of 3.5×5 (17.5 points). Other adverse lesion characteristics considered in the SYNTAX score have an additive value (B). Images used with permission from the SYNTAX Trial Investigators.

It should be emphasised that subjects in the FAME Study had substantially less complex coronary artery disease (mean±SD SYNTAX Score 14.8±6.0) compared with the PCI arm of the SYNTAX Trial (mean±SD SYNTAX Score 28.4±11.5), and that subjects with left main coronary artery disease were not investigated. Prospective validation studies of the functional SYNTAX Score in complex coronary artery disease are awaited at the time of writing.

AUGMENTING THE ANATOMICAL SYNTAX SCORE WITH CLINICAL FACTORS AND THE PERSONALISATION OF DECISION-MAKING: DEVELOPMENT OF THE SYNTAX SCORE II

Since the SYNTAX Score was developed, limitations of this scoring system in aiding decision-making between CABG and PCI has become evident—namely, the lack of clinical variables and lack of a personalised approach to decision-making. Below is a brief overview of the 'development phase' leading to the SYNTAX Score II, which was designed to overcome these limitations (table 1).

The law of 'parsimony' and 'ACEF'

ACEF

Ranucci *et al*[21–23] developed a simple risk model consisting of only three clinical variables (age, serum creatinine and left ventricular ejection fraction (LVEF)), for assessing operative mortality risk in elective cardiac operations (ACEF Score—figure 2A). Based on the 'law of parsimony' or 'the Ockham razor' concept, whereby a simple model can explain a phenomenon with the same level of accuracy as complex models, ACEF was shown to be least comparable to the EuroSCORE (composed of 17 variables)[24 25] in predicting in-hospital mortality after CABG.[22 23]

The three risk factors used in ACEF are natural continuous variables that are objectively defined and not subject to personal estimation (eg, is the patient diabetic? does the patient have extra cardiac arteriopathy?). In addition, the variables of ACEF are known independent risk factors for mortality, and it was subsequently shown that the end organ manifestations of the risk factor (as identified in ACEF) are more important than the actual presence of the risk factor for predicting long-term prognosis.[21 26–28]

Clinical SYNTAX Score/Logistic Clinical SYNTAX Score

Based on the principle of ACEF, the Clinical SYNTAX Score,[29–31] and subsequently the Logistic Clinical SYNTAX Score (figure 2B),[32 33] were developed and validated. Both the Clinical SYNTAX Score and Logistic Clinical SYNTAX Score combined ACEF with the SYNTAX Score, and were shown to improve mortality predictions compared with the SYNTAX Score alone in subjects with complex coronary artery disease.[29–33] Similar to the conventional SYNTAX Score, the Clinical SYNTAX Score relied on categorisation of risk (low, intermediate and high) and was able to only identify a high-risk group after PCI.[29–31] The Logistic Clinical SYNTAX Score was designed to individualise risk and provide 1-year mortality predictions in an all-comers PCI population irrespective of clinical presentation (except cardiogenic shock).[32 33]

The Logistic Clinical SYNTAX Score was developed and cross-validated ('internal–external' validation procedure[34]) in >6000 subjects from seven contemporary coronary stent trials,[32] and further externally validated in 2627 subjects presenting with non-ST elevation acute coronary syndrome and undergoing PCI from the Acute Catheterisation and Urgent Intervention Triage Strategy (ACUITY) Trial.[33] Notably, the addition of a further six additional clinical variables, including diabetes, to the Logistic Clinical SYNTAX Score led to only a minor incremental improvement in risk predictions.[32 33] Thus, the Logistic Clinical SYNTAX Score was shown to follow the law of parsimony, as seen with the surgical ACEF model discussed above[21–23]—namely, the end organ manifestations of the risk factor were more important than the actual presence of the risk factor for predicting long term prognosis.

Global risk

In the SYNTAX Trial, it was shown that, as well as the SYNTAX Score in PCI subjects, the EuroSCORE (a surgery-based risk score composed of 17 variables designed to predict in-hospital mortality after CABG[24 25]) was an independent predictor of MACE in subjects undergoing surgery- or percutaneous-based

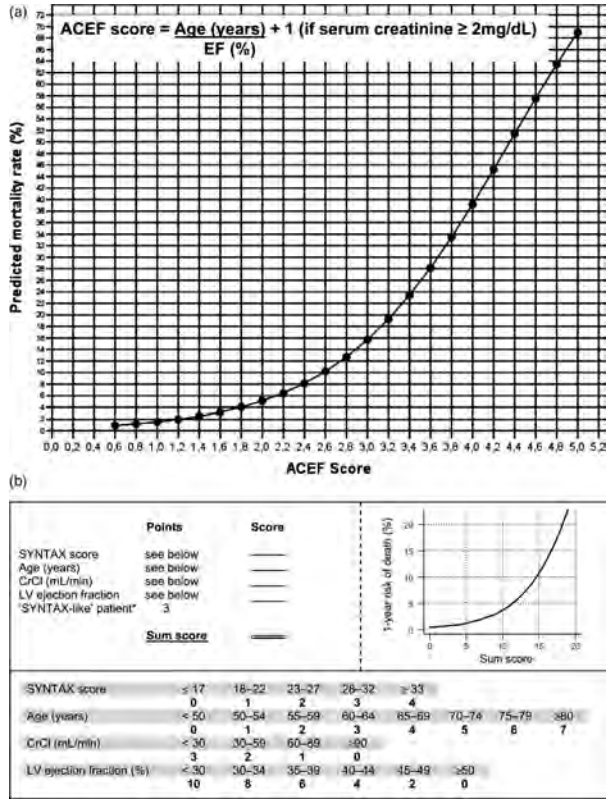


Figure 2 Side by side comparisons of ACEF (A) and the Logistic Clinical SYNTAX Score (B). Images used with permission from Ranucci *et al*[23] and Farooq *et al*.[32] *SYNTAX-like patient defined as fulfilling the enrolment criteria for the SYNTAX All-Comers trial, i.e. left main stem (isolated or associated with one-, two-, or three-vessel disease) or three-vessel disease alone. CrCl, creatinine clearance, LV ejection fraction, left ventricular ejection fraction.

revascularisation. Subsequently, it was hypothesised that the amalgamation of the SYNTAX Score with the EuroSCORE could improve decision-making between CABG and PCI.[4 5] The feasibility of this 'Global Risk' approach was demonstrated in a registry of 255 subjects with left main coronary artery disease using tertiles of the SYNTAX Score and tertiles of the additive EuroSCORE that reflected their study population.[35] Subsequently, the Global Risk was validated in the SYNTAX Trial using conventional tertiles of the SYNTAX Score and EuroSCORE,[36] and was shown to substantially enhance the identification of low-risk patients with ULMCA disease or de novo 3VD who could safely and efficaciously be treated with CABG or PCI, compared with the SYNTAX Score alone.

One of the unexpected findings from the Global Risk was that higher-risk subjects (high additive EuroSCORE ≥6) in all tertiles of the SYNTAX Score (low, intermediate or high) were shown to have a potential prognostic benefit from undergoing CABG compared with PCI, irrespective of the SYNTAX Score, provided that an acceptable threshold of operative risk was not exceeded.[36] For example, in the 3VD cohort of the SYNTAX Trial, the 3-year mortality of subjects with a low SYNTAX Score (<23) and a high EuroSCORE (≥6) was doubled when undergoing PCI (15.9%) compared with CABG (8.2%). One hypothesis used to explain these findings is that the bypass graft would potentially 'protect' the entire treated coronary vessel from future cardiac events for the lifespan of the graft in high-risk subjects compared with PCI, which would treat the individual lesion.[37] On the basis of these observations, it was hypothesised by the investigators that potentially low (or high) risk subjects were potentially concealed by high (or low) risk subjects in all tertiles of the SYNTAX Score. This hypothesis is what prompted the investigators to develop a more individualised approach to decision-making between CABG and PCI, and subsequently led to the development of the SYNTAX Score II,[38] as detailed below.

SYNTAX Score II

As previously discussed, the combination of the anatomical SYNTAX Score with ACEF contained most of the prognostic information for predicting mortality after CABG (excluding the anatomical SYNTAX Score[21–23 36]) or PCI (including the anatomical SYNTAX Score[32 36]). The SYNTAX Score II was built on the ACEF 'skeleton', with the addition of risk factors that were shown to directly affect decision-making between CABG

and PCI—that is, interaction effects, namely a risk factor being more predictive of mortality in patients undergoing PCI compared with CABG, or vice versa (figure 3).[38] For example, the anatomical SYNTAX Score aids decision-making between CABG and PCI because it is more predictive of clinical outcomes in patients undergoing PCI than in patients undergoing CABG (where it is not predictive). On the basis of this principle, younger age, female gender and reduced LVEF favoured CABG over PCI on long-term prognostic grounds. Thus, in such patients, a lower anatomical SYNTAX Score would be required in order for the long-term mortality risk to be similar between CABG and PCI. In contrast, older age, chronic obstructive pulmonary disease (COPD) or ULMCA disease favoured PCI over CABG, and thus, in this type of patient, a higher anatomical SYNTAX Score would be needed for the long-term mortality risks to be similar.

By adopting the individualised approach of the SYNTAX Score II, augmented by clinical variables, it was shown that subsets of patients existed in all tertiles of the SYNTAX Score in which CABG or PCI would confer a mortality benefit, or offer similar long-term prognosis.[38] A nomogram was developed (figure 4) that allowed an accurate individualised prediction of 4-year mortality in patients proposing to undergo CABG or PCI, to objectively aid decision-making. For example, a 60-year-old man with an anatomical SYNTAX Score of 30, ULMCA disease, CrCl of 60 mL/min, a LVEF of 50%, and COPD would have 41 points (predicted 4-year mortality 16.3%) and 33 points (predicted 4-year mortality 8.7%) for CABG and PCI, respectively. The same example, without COPD included, would lead to identical points (29 points) and identical 4-year mortality predictions (6.3%) for CABG and PCI. An online version of the SYNTAX Score II will soon appear alongside the original SYNTAX Score calculator (http://www.syntaxscore.com).

Diabetics

Notably, diabetes was not included in the final SYNTAX Score II, despite medically treated diabetes being prestratified at randomisation as a powered subgroup in the SYNTAX Trial, and present in over a quarter of the study patients (26%). This in spite of diabetics being perceived as a specific high-risk group potentially warranting a different treatment strategy compared with patients with other risk factors.[9–11 39]

The primary reason for the non-inclusion of diabetes in the SYNTAX Score II was that it was shown to be equally predictive of mortality in the CABG and PCI cohorts of the SYNATX Trial, after adjustment for other risk factors (figure 3) —that is, diabetes lacked an interaction effect and was therefore not

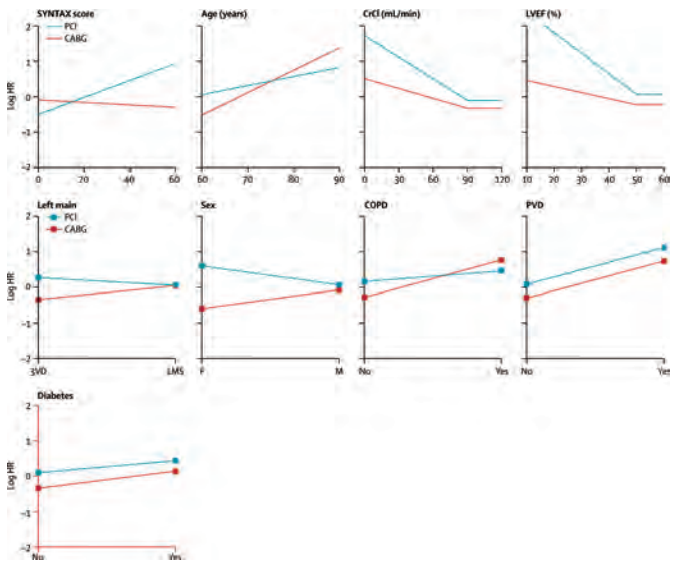


Figure 3 Predictor effects for coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) in the SYNTAX Score II. These are represented visually as log HR for CABG and PCI on the y-axis for each predictor. Each predictor is expressed on the x-axis continuously (upper) or categorically (lower), for a person of mean baseline characteristics. Diabetes is included (highlighted in red) to illustrate its absence of interaction when included in the analyses. Note the different gradients of the hazards for PCI and CABG, leading to the hazards crossing at an anatomical SYNTAX Score of 15. At this 'cross-over' point of hazards, the mortality risk is comparable between CABG and PCI. This threshold of cross-over of hazards will vary according to the level of other variables, namely being lower for female gender, reduced left ventricular ejection fraction (LVEF) and younger age, and higher for chronic obstructive pulmonary disease (COPD), unprotected left main coronary artery disease and older age. As both PVD (p=1.00) and diabetes (p=0.67) lacked an interaction effect, as indicated by almost parallel HRs (ie, comparable increase in mortality risk), their presence would have no effect on decision-making between CABG and PCI. Legend and image reproduced with permission from Farooq *et al*.[3 38] 3VD three vessel disease; LMS left main stem; CrCl creatinine clearance; COPD chronic obstructive pulmonary disease; PVD peripheral vascular disease.

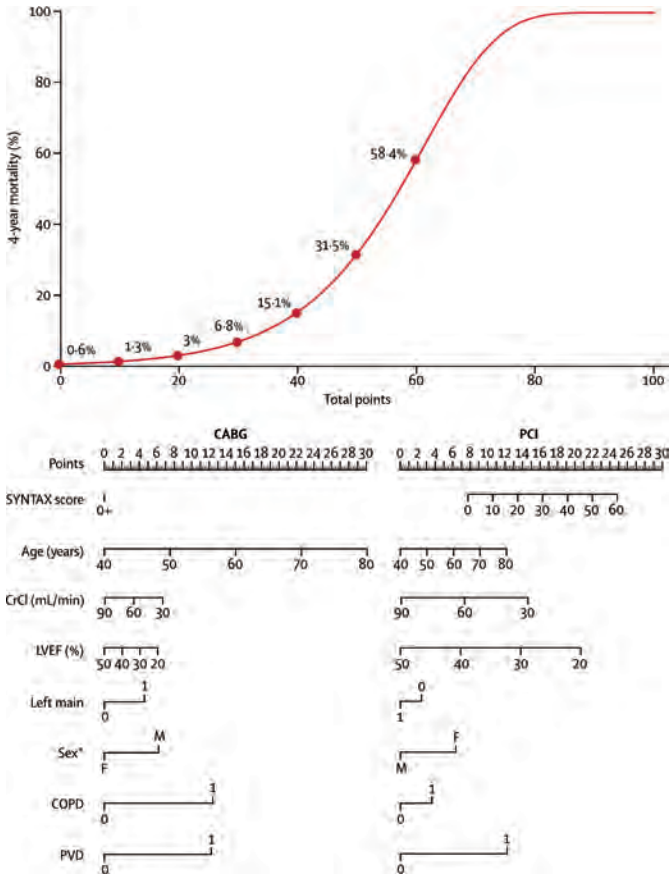


Figure 4 The SYNTAX Score II nomogram for bedside application. The total number of points for eight factors can be used to accurately predict 4-year mortality for the individual patient proposing to undergo coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). Image reproduced with permission from Farooq *et al*.[38] *Due to the rarity of complex coronary artery disease in pre-menopausal women, mortality predictions in younger women are predominantly based on the linear relationship of age with mortality. The differences in mortality predictions in younger women between CABG and PCI will therefore be affected by larger 95% confidence intervals than those in older women but will be equally valid. 3VD three vessel disease; LMS left main stem; CrCl creatinine clearance; LVEF left ventricular ejection fraction; COPD chronic obstructive pulmonary disease; PVD peripheral vascular disease.

important for decision-making between CABG and PCI (after adjustment for the end organ manifestations of the risk factors). As previously discussed for ACEF, the end organ manifestation of diabetes was what affected long-term mortality in CABG and PCI populations[21–23 28 32]—and therefore decision-making between CABG and PCI in the SYNTAX Score II—and not the actual presence of the risk factor. The findings of the lack of inclusion of diabetes in the SYNTAX Score II are supported by epidemiological data, in which non-diabetics with chronic kidney disease and proteinuria had a stronger association with the risk of MI, and a higher mortality, than diabetics, and that the relative risk of long-term mortality associated with chronic kidney disease was 'much the same irrespective of the presence or absence of diabetes'.[26 27]

Validation of the SYNTAX Score II

As compared with existing revascularisation guidelines using the anatomical SYNTAX Score,[9–11] it was shown that, if CABG or PCI was selected on the basis of a higher or lower expected survival (irrespective of the margin of difference) with the SYNTAX Score II in the SYNTAX Trial, the SYNTAX Score II would only need to be used in 110 patients to have one more patient alive at 4 years.[40]

External validation of the SYNTAX Score II[38] was performed in the multinational Drug Eluting stent for Left main coronary Artery disease (DELTA) Registry (14 centres in Europe, USA and South Korea),[41] composed of subjects with ULMCA disease associated with or without multivessel disease (26% of the study population had 3VD). All variables in the SYNTAX Score II interacted in a similar way, and therefore influenced decision-making between CABG and PCI, in the SYNTAX Trial and DELTA Registry, with the exception of age and LVEF, which had minimal interactions in the DELTA Registry—findings that may relate to the unavoidable selection bias inherent to all registries, since decision-making between CABG and PCI has already been made and would be difficult to control for.[42] Even randomised trials lacking an all-comers design, with restrictive inclusion and exclusion criteria, can potentially make application to clinical practice questionable.[37 43 44] This is exemplified in a recent meta-analysis of randomised trials undertaken before SYNTAX comparing PCI with CABG, where in most trials 2–12% of screened subjects were randomised because of the highly restrictive inclusion and exclusion criteria.[45] In this meta-analysis, CABG was shown to be favoured in older subjects, and PCI in younger subjects[45]—findings that have since been directly contradicted by the SYNTAX Score II in the all-comers SYNTAX Trial (where the opposite was shown).[38] Hence 'randomised' validation of the SYNTAX Score II was proposed,[38] in which its further validation would be conducted in randomised controlled trials or prospectively run studies, as discussed below under Future directions.

TOOLS FOR ASSESSMENT OF COMPLETENESS OF REVASCULARISATION

Interpreting the long-term prognostic impact of incomplete revascularisation in patients with complex coronary artery disease has historically been difficult.[46] The lack of standardised definitions of incomplete revascularisation has confounded this issue and made comparisons between studies difficult. The residual and post-CABG SYNTAX Score were designed to overcome this limitation as detailed.

Residual SYNTAX score

The residual SYNTAX Score is based on the principle of being a measure of the myocardial ischaemia burden, dependent on the location of the coronary disease, its importance in supplying blood to the myocardium, and the anatomical complexity (eg, calcification, bifurcation, long lesion) associated with the obstructive disease. The residual SYNTAX Score is essentially the SYNTAX Score recalculated after the PCI procedure, and provides an objective, quantitative measure of the degree and complexity of residual stenosis after revascularisation. More proximal coronary artery disease scores more highly on the residual SYNTAX Score since this is dependent on the vessel-segment weighting as previously discussed (figure 1), particularly if the obstructive disease is more complex.[47 48]

Genereux *et al*[47] first demonstrated that a residual SYNTAX Score of >8.0 after PCI was associated with adverse 1-year mortality, in a post hoc analysis of the ACUITY Trial. The ACUITY Trial consisted of subjects with moderate- to high-risk acute coronary syndrome undergoing PCI, and substantially less complex coronary artery disease (median SYNTAX Score 9.0, IQR 5.0–16.0) compared with the SYNTAX Trial (median SYNTAX Score 28, IQR 20.0–36.0).

The residual SYNTAX Score was subsequently validated in the randomised, all-comers SYNTAX Trial, consisting of subjects with complex coronary artery disease (ULMCA or de novo 3VD) at the final 5-year follow-up.[48] The previous finding of a residual SYNTAX Score of >8 being associated with adverse long-term clinical outcomes in the ACUITY Trial[47] was found to be equally of importance in SYNTAX patients who underwent a 5-year follow-up. Notably, as the baseline SYNTAX Score increased, the frequency of a residual SYNTAX Score >8 increased in unison, with an associated increase in long-term mortality (figure 5). In addition, progressively higher residual SYNTAX Scores were shown to be a surrogate marker of sicker patients,[49] with greater baseline clinical comorbidity and anatomical complexity, with consequent adverse long-term clinical outcomes, including all-cause mortality.

Stratified analyses in the powered subgroups of ULMCA disease and medically treated diabetes showed a residual SYNTAX Score of >8 to be associated with adverse long-term clinical outcomes, including mortality. Stratified analyses in subjects with reduced LVEF also showed the results to be equally applicable, whereas, in subjects with total occlusions, a more modest effect was shown that did not reach statistical significance. The latter perhaps implied that appropriate viability assessment was required to ensure that revascularisation of the total occlusion was appropriate and clinically justified.[50]

In summary, the residual SYNTAX Score allowed the quantification of the degree of revascularisation, and the determination of an objective level of reasonable incomplete revascularisation,[46] whereby a threshold value could be determined (≤8) that would not have a negative effect on long-term mortality and other clinical outcomes.

Post-CABG SYNTAX Score

The CABG equivalent of the residual SYNTAX Score—post CABG SYNTAX Score—has recently been shown to be linked to adverse 5-year clinical outcomes, including mortality, in the angiographic substudy of the SYNTAX Trial (SYNTAX-LE MANS) (figure 6A).[51 52] Owing to the inherently different mechanisms of treatment of coronary artery disease with CABG and PCI, calculation of the residual SYNTAX Score (ie, burden of coronary disease removed by PCI) differs from that of the post-CABG SYNTAX Score (ie, coronary disease bypassed with a graft). The basic principle of the post-CABG SYNTAX Score is that it deducts points from the 'native' baseline SYNTAX Score based on the level of 'protection' conferred by the bypass grafts, through deduction of the vessel-segment weighting (Leaman Score[14]—figure 1) that the bypass graft provides (figure 6B). Since the post-CABG SYNTAX Score is based on validated physiological principles of blood flow (Leaman Score[14]), it does not arbitrarily deduct points for the type of bypass graft anastomosed. Points related to native coronary disease (eg, bifurcation disease, calcification, total occlusions, long lesions, diffuse disease) remain unaltered.

Historical evidence to back up the findings from the post-CABG SYNTAX Score being linked to adverse long-term prognosis comes from the CASS (Coronary Artery Surgery Study)[53] and Rotterdam[54] registries. First, in both studies, more extensive preoperative coronary artery disease was linked to the higher prevalence and severity of other clinical risk factors and adverse long-term prognosis, compared with subjects with less complex coronary artery disease. Second, 5 years follow-up of the Bypass Angioplasty Revascularisation Investigation (BARI) Trial demonstrated that native coronary disease progression (and not the extent of initial revascularisation) was the predominant determinant of the recurrence of angina and jeopardised myocardium in percutaneous and surgically revascularised subjects.[55] Lastly, coronary artery calcification has been linked to adverse all-cause mortality at 10 years, independent of other risk

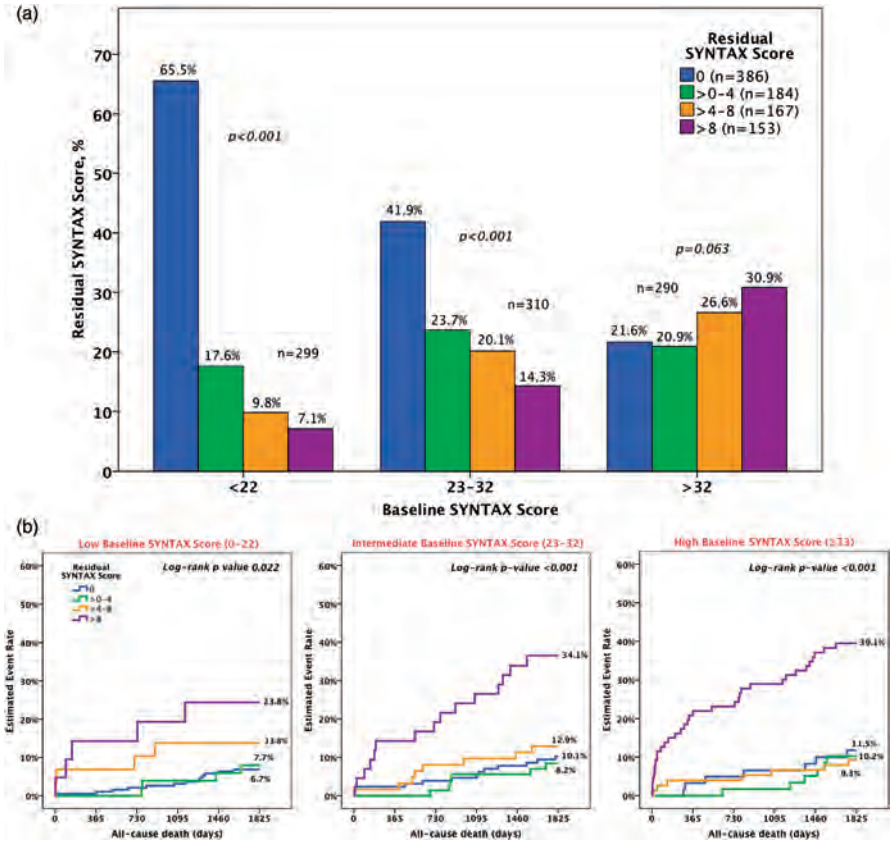


Figure 5 The residual SYNTAX Score in the SYNTAX Trial. Complete (residual SYNTAX Score 0) and incomplete (tertiles of the residual SYNTAX Score (residual SYNTAX Score >0)) revascularisation, stratified according to tertiles of the baseline SYNTAX Score (A). Kaplan–Meier curves showing cumulative event rates through to 5 years, based on complete (residual SYNTAX Score 0) and incomplete (tertiles of residual SYNTAX Score) revascularisation, in the low (0–22), intermediate (23–32) and high (≥33) baseline SYNTAX Scores (B). Note the progressive increase in the frequency of a residual SYNTAX Score >8 across the tertiles of the baseline SYNTAX Score (A) and its association with adverse long-term mortality (B). Legend and image reproduced with permission from Farooq *et al*.[48]

factors.[56 57] Validation studies of the post-CABG SYNTAX Score are awaited at the time of writing.

FUTURE DIRECTIONS

Non-invasive SYNTAX Score

Multislice CT SYNTAX Score

Papadopoulou *et al*[58] first described the feasibility and reproducibility of a multislice CT (MSCT)-derived SYNTAX Score in 80 consecutive patients with symptomatic angina, using definitions of the angiographically defined SYNTAX Score adapted for the MSCT capabilities. The underlying concept was to allow the SYNTAX Score to be calculated before the intervention, to potentially aid decision-making and optimise patient management. In this study, the MSCT SYNTAX Score was shown to be feasible, with results comparable to the SYNTAX Score calculated with conventional coronary angiography. While this study was shown to be highly reproducible,[58] a subsequent validation study of similar size (n=104) found only fair agreement between MSCT and angiography-derived SYNTAX Scores,[59] although this did improve substantially when analyses were restricted to good quality MSCT. Notably, both studies investigated subjects with predominantly less complex coronary artery disease (low SYNTAX Scores <23).[58 59] Larger scale validation studies, particularly in more complex 'SYNTAX-like' patients, are awaited.

Non-invasive FFR

The addition of a non-invasive FFR component (Heartflow, Redwood City, California, USA) has the potential to allow the

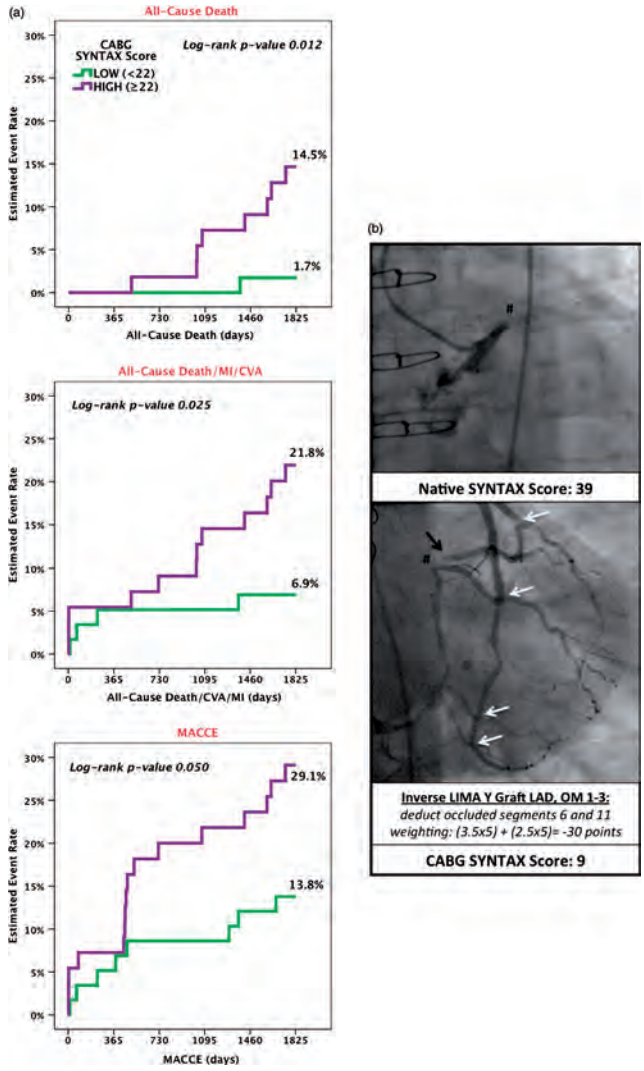


Figure 6 (A) The post-coronary artery bypass graft (CABG) SYNTAX Score in the angiographic substudy of the SYNTAX Trial (SYNTAX-LE MANS). Outcomes (Kaplan–Meier curves) separated by the median of the post-CABG SYNTAX Score into low (0–21; n=58) and high (≥22; n=55) score groups. At 5 years, significantly greater all-cause mortality, significantly greater all-cause death/CVA/myocardial infarction (MI) and major adverse cardiovascular and cerebrovascular events (MACCE) were evident in the high post-CABG SYNTAX Score group compared with the low post-CABG SYNTAX Score group. Note the peak in MACCE at approximately 18 months secondary to patients undergoing scheduled coronary angiography, the findings of which triggered repeat revascularisation. (B) Example of the calculation of the post-CABG SYNTAX Score. Occluded left main (#) in a left dominant system gave a native SYNTAX Score of 39 (upper image). A patent left internal mammary artery (LIMA) inverse Y graft anastomosed to the mid LAD (upper white arrow), with sequential anastomoses to the 1st, 2nd and 3rd obtuse marginal (OM) branches (lower three white arrows) are shown. Based on the vessel segment weighting (refer to figure 1), 17.5 (occluded proximal LAD) and 12.5 (occluded proximal left circumflex (LCx)) points were deducted from the native SYNTAX Score. Post-CABG SYNTAX Score was therefore 39−17.5 −12.5=9 points. Legend and images reproduced with permission from Farooq *et al*.[51 52]

non-invasive calculation of a functionally based MSCT SYNTAX Score. This technology is based on using computational fluid dynamic techniques applied to the MSCT angiography.[58] Validation data from the non-invasive FFR MSCT have been reported in the DISCOVER FLOW and multicentre DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) Trials.[4 60–62] In both studies, non-invasive FFR MSCT was shown to substantially improve the diagnostic accuracy in detecting haemodynamically significant coronary artery disease in subjects with suspected coronary artery disease. Application of this technology in subjects with more complex coronary artery disease has recently been undertaken (figure 7). At the time of writing, work to derive a non-invasive functional MSCT SYNTAX Score using this technology is in progress.

Ongoing and future studies

EXCEL Trial

The ongoing international multicentre EXCEL Trial is aiming to recruit 2600 patients with ULMCA disease and a SYNTAX

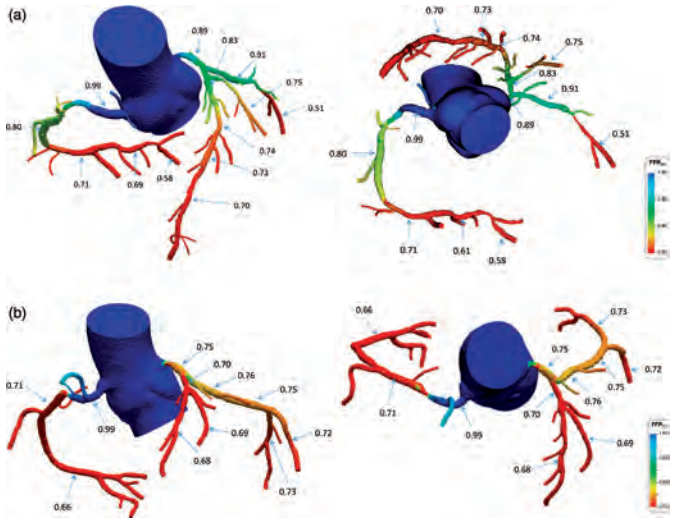


Figure 7 Application of non-invasive fractional flow reserve (FFR) technology during multislice CT (MSCT) in subjects with complex coronary artery disease, namely multivessel (A) and left main and multivessel (B) coronary artery disease. Values shown are the non-invasive calculated FFR in all major epicardial vessels and side branches.

Score <33, randomised to CABG (n=1300) or PCI with contemporary stents (n=1300).[13] The primary end point is a composite measure of all-cause death, MI or stroke 3 years after revascularisation. As part of the EXCEL Trial, validation of the SYNTAX Score II has recently been prespecified as an end point.

SYNTAX II trial

The planned SYNTAX II single-arm trial will use the SYNTAX Score II[38] as a tool to recruit subjects with de novo 3VD (without left main involvement) on the grounds of patient safety —that is, subjects with a similar long-term mortality between CABG and PCI, as determined by the SYNTAX Score II in conjunction with the heart team. Notably, subjects from all tertiles of the SYNTAX Score will be eligible. The PCI procedure will be guided by a functional assessment of all three vessels (functional SYNTAX Score[20]), a newer generation stent platform with a biodegradable polymer,[63 64] and intravascular ultrasound-guided stent implantation.[65] The PCI and CABG arms of the SYNTAX Trial[5–7] will act as control arms. Validation of the SYNTAX Score II will be prespecified as an end point. Recruitment of patients is expected to begin towards the end of the year.

SUMMARY

Since the founding of the original SYNTAX Score, a multitude of clinical applications have emerged as discussed in this review. It is, however, important to recognise that randomised trials lacking an all-comers trial design, and registries (however well designed), have their inherent limitations as discussed, and further validation of SYNTAX-based tools in these populations should be interpreted with caution. So-called 'randomised validation' may prove to be the better technique in further validating these tools to remove any form of selection bias, particularly in registries, where decision-making between CABG and PCI has already been undertaken. Moreover, the move away from categorisation of risk (ie, low, intermediate or high) to individual risk profiling, culminating in the development of the SYNTAX Score II, is a significant step forward, provided that it is undertaken in the context of the heart team in open dialogue with the patient, whose individual perception of short- and long-term risk would prove to be an important factor in decision-making. SYNTAX-based tools (residual and post-CABG SYNTAX Scores), as measures of completeness of revascularisation, show significant promise, and may aid the heart team in determining a reasonable level of revascularisation. The ongoing development of a non-invasive functional SYNTAX Score would undoubtedly prove to be a significant development in streamlining and simplifying the heart team process.

Contributors VF and PWS critically reviewed the literature and cowrote the manuscript. SH and APK critically reviewed the manuscript.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1 SYNTAX Score calculator. http://www.syntaxscore.com. SYNTAX working-group. Launched 19 May 2009.
2 Sianos G, Morel MA, Kappetein AP, *et al*. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;1:219–27.
3 Serruys PW, Onuma Y, Garg S, *et al*. Assessment of the SYNTAX Score in the Syntax study. *EuroIntervention* 2009;5:50–6.
4 Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart* 2011;97:1902–13.
5 Serruys PW, Morice MC, Kappetein AP, *et al*. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961–72.
6 Kappetein AP, Feldman TE, Mack MJ, *et al*. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011;32:2125–34.

7 Mohr FW, Morice MC, Kappetein AP, *et al*. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;381:629–38.
8 Head SJ, Farooq V, Serruys PW, *et al*. The SYNTAX Score and its clinical implications. *Heart* 2013 Mar 28. [Epub ahead of print].
9 Wijns W, Kolh P, Danchin N, *et al*. Guidelines on myocardial revascularization. *Eur Heart J* 2010;31:2501–55.
10 Levine GN, Bates ER, Blankenship JC, *et al*. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44–122.
11 Hillis LD, Smith PK, Anderson JL, *et al*. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;58:e123–210.
12 Head SJ, Kaul S, Mack MJ, *et al*. The rationale for Heart Team decision-making for patients with stable complex coronary artery disease. *Eur Heart J* 2013 Feb 26. [Epub ahead of print].
13 Farooq V, Serruys PW, Stone GW, *et al*. Left main coronary artery disease. In: Eeckhout E, Serruys PW, Wijns W, Vahanian A, Sambeek Mv, Palma Rd, eds. *Percutaneous interventional cardiovascular medicine. The PCR-EAPCI Textbook*. Europa edition. Toulouse, France: PCR publishing, 2012: Part 3, Chapter 12:407–45.
14 Leaman DM, Brower RW, Meester GT, *et al*. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981;63:285–99.
15 Smith SC Jr, Feldman TE, Hirshfeld JW Jr, *et al*. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006;47:e1–121.
16 Medina A, Suarez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol* 2006;59:183.
17 Hamburger JN, Serruys PW, Scabra-Gomes R, *et al*. Recanalization of total coronary occlusions using a laser guidewire (the European TOTAL Surveillance Study). *Am J Cardiol* 1997;80:1419–23.
18 Kushner FG, Hand M, Smith SC Jr, *et al*. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2009;54:2205–41.
19 De Bruyne B, Pijls NH, Kalesan B, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991–1001.
20 Nam CW, Mangiacapra F, Entjes R, *et al*. Functional SYNTAX Score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011;58:1211–18.
21 Ranucci M, Castelvecchio S. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. *EuroIntervention* 2010;6:549–53.
22 Ranucci M, Castelvecchio S, Conte M, *et al*. The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29,659 patients undergoing elective cardiac surgery. *J Thorac Cardiovasc Surg* 2011;142:581–6.
23 Ranucci M, Castelvecchio S, Menicanti L, *et al*. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 2009;119:3053–61.
24 Nashef SA, Roques F, Michel P, *et al*. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9–13.
25 Roques F, Michel P, Goldstone AR, *et al*. The logistic EuroSCORE. *Eur Heart J* 2003;24:881–2.
26 Tonelli M, Muntner P, Lloyd A, *et al*. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 2012;380:807–14.
27 Fox CS, Matsushita K, Woodward M, *et al*. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;380:1662–73.
28 Farooq V, Serruys PW, Bourantas C, *et al*. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 2012;33:3105–13.
29 Garg S, Sarno G, Garcia-Garcia HM, *et al*. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 2010;3:317–26.
30 Wykrzykowska JJ, Garg S, Onuma Y, *et al*. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. *Circ Cardiovasc Interv* 2011;4:47–56.
31 Capodanno D, Caggegi A, Miano M, *et al*. Global risk classification and clinical SYNTAX (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) score in patients undergoing percutaneous or surgical left main revascularization. *J Am Coll Cardiol Intv* 2011;4:287–97.
32 Farooq V, Vergouwe Y, Raber L, *et al*. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the logistic clinical SYNTAX Score. *Eur Heart J* 2012;33:3098–104.
33 Farooq V, Vergouwe Y, Genereux P, *et al*. Prediction of 1-year mortality in patients with acute coronary syndromes undergoing percutaneous coronary intervention: validation of the logistic clinical SYNTAX Score. *JACC Interv* 2013. In press.
34 Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 2004;23:907–26.
35 Capodanno D, Miano M, Cincotta G, *et al*. EuroSCORE refines the predictive ability of SYNTAX Score in patients undergoing left main percutaneous coronary intervention. *Am Heart J* 2010;159:103–9.
36 Serruys PW, Farooq V, Vranckx P, *et al*. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv* 2012;5:606–17.
37 Taggart DP, Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. *Ann Thorac Surg* 2006;82:1966–75.
38 Farooq V, van Klaveren D, Steyerberg EW, *et al*. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX Score II. *Lancet* 2013;381:639–50.
39 Farkouh ME, Domanski M, Sleeper LA, *et al*. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375–84.
40 Farooq V, van Klaveren D, Steyerberg EW, *et al*. SYNTAX Score II—Authors' reply. *Lancet* 2013;381:1899–900.
41 Chieffo A, Meliga E, Latib A, *et al*. Drug-eluting stent for left main coronary artery disease: the DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 2012;5:718–27.
42 Farooq V, Serruys PW. Observations from the CREDO-Kyoto three-vessel disease registry: can one adjust for the unadjustable? *EuroIntervention* 2013. In press.
43 Farooq V, Serruys PW. 'Cherry-picking' patients for randomized, controlled trials-reliving the past. *J Am Coll Cardiol* 2013;61:2492.
44 Hlatky MA, Boothroyd DB, Baker L, *et al*. Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention: a cohort study. *Ann Intern Med* 2013;158:727–34.
45 Flather M, Rhee JW, Boothroyd DB, *et al*. The effect of age on outcomes of coronary artery bypass surgery compared with balloon angioplasty or bare-metal stent implantation among patients with multivessel coronary disease. A collaborative analysis of individual patient data from 10 randomized trials. *J Am Coll Cardiol* 2012;60:2150–7.
46 De Bruyne B. Multivessel disease: from reasonably incomplete to functionally complete revascularization. *Circulation* 2012;125:2557–9.
47 Genereux P, Palmerini T, Caixeta A, *et al*. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol* 2012;59:2165–74.
48 Farooq V, Serruys PW, Bourantas CV, *et al*. Quantification of incomplete revascularisation and its association with five-year mortality in the synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX Score. *Circulation* 2013 Jun 13. [Epub ahead of print].
49 Farooq V, Serruys PW, Garcia-Garcia HM, *et al*. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (synergy between percutaneous coronary intervention with Taxus and cardiac surgery) trial. *J Am Coll Cardiol* 2013;61:282–94.
50 Fiocchi F, Sgura F, Di Girolamo A, *et al*. Chronic total coronary occlusion in patients with intermediate viability: value of low-dose dobutamine and contrast-enhanced 3-T MRI in predicting functional recovery in patients undergoing percutaneous revascularisation with drug-eluting stent. *Radiol Med* 2009;114:692–704.
51 Farooq V, Girasis C, Magro M, *et al*. The CABG SYNTAX Score—an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX left main angiographic (SYNTAX-LE MANS) substudy. *EuroIntervention* 2013;8:1277–85.
52 Farooq V, Girasis C, Magro M, *et al*. Letter to the Editor. The coronary artery bypass graft SYNTAX Score: five year outcomes from the SYNTAX-LE MANS left main angiographic sub-study. *EuroIntervention* 2013 Apr 30. pii: 20130103-03. [Epub ahead of print].

53 Myers WO, Blackstone EH, Davis K, *et al*. CASS Registry long term surgical survival. Coronary Artery Surgery Study. *J Am Coll Cardiol* 1999;33:488–98.

54 van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. *Eur Heart J* 2009;30:453–8.

55 Alderman EL, Kip KE, Whitlow PL, *et al*. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 2004;44:766–74.

56 Budoff MJ, Shaw LJ, Liu ST, *et al*. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 2007;49:1860–70.

57 Okwuosa TM, Greenland P, Ning H, *et al*. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol* 2011;57:1838–45.

58 Papadopoulou SL, Girasis C, Dharampal A, *et al*. CT-SYNTAX Score: a feasibility and reproducibility Study. *JACC Cardiovasc Imaging* 2013;6:413–15.

59 Kerner A, Abadi S, Abergel E, *et al*. Direct comparison between coronary computed tomography and invasive angiography for calculation of SYNTAX Score. *EuroIntervention* 2013;8:1428–34.

60 Serruys PW, Girasis C, Papadopoulou SL, *et al*. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. *EuroIntervention* 2012;8:511–19.

61 Koo BK, Erglis A, Doh JH, *et al*. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve) study. *J Am Coll Cardiol* 2011;58:1989–97.

62 Min JK, Leipsic J, Pencina MJ, *et al*. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;308:1237–45.

63 Wilson GJ, Huibregtse BA, Pennington DE, *et al*. Comparison of the SYNERGY with the PROMUS (XIENCE V) and bare metal and polymer-only Element control stents in porcine coronary arteries. *EuroIntervention* 2012;8:250–7.

64 Meredith IT, Verheye S, Dubois CL, *et al*. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. *J Am Coll Cardiol* 2012;59:1362–70.

65 Zhang Y, Farooq V, Garcia-Garcia HM, *et al*. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention* 2012;8:855–65.

Acknowledgements

Getting to Rotterdam

My decision to enter interventional cardiology happened more by chance than actual planning. Shortly after I graduated, personal events drew me towards realising that cardiology, and at that interventional cardiology, was where my career ambitions firmly lay. I still vividly remember being amazed at the immediate impact that the insertion of a small piece of metal (coronary stent) had in the treatment of a myocardial infarction.

"You must do the thing you think you cannot do." [Eleanor Roosevelt]
Several years later I picked up the PhD thesis of an ex fellow of Professor Serruys on coronary bifurcations and chronic total occlusions at a PCI meeting in Leeds UK, and literally read it cover to cover. I still remember saying to myself, don't even bother trying to get to Rotterdam, it's too far away, and I won't be good enough…

"Expect the best, prepare for the worst." [Muhammad Ali Jinnah]
My decision to come to Rotterdam again happened more by chance rather than actual planning. I was extremely motivated to undertake interventional research, particularly in relation to the bioabsorbable scaffolds – the so called next 'revolution' in interventional cardiology – and was going through the process of writing research grants to set up a project up in the UK. We were however struggling to secure the backing of industry on which the foundations of the project lay.

"Screw it, Let's do it!" [Sir Richard Branson]
Towards the end of 2009, several of my colleagues suggested I should write to Professor Serruys about an interventional research fellowship at the Thoraxcenter in Rotterdam. Rather unexpectedly I got an immediate offer of a series of interviews, which I attended in December 2009 at the Thoraxcenter. I had very little expectation at the interviews and remember telling myself, you have nothing to lose, just go for it... I had interviews firstly with the late Professor Willem van der Giessen, Dr Eric Duckers, Dr Peter de Jaegre, and at the end of the day, Professor Serruys, who were all very enthusiastic and positive. This was subsequently followed up by a personal phone call from Professor Serruys inviting me to join his team at Rotterdam. I still remember, I rather embarrassingly repeatedly asked (in more than one phone call when I was dealing with the logistics in coming to Thoraxcenter) "are you really offering me a position?"

At the time of accepting the position to come to Rotterdam, I was working at Manchester Royal Infirmary. I am grateful to the entire team here for their advice and support during this period, in particular, Faz, Doug, Magdi, Raj, Bernard, Mahadevan, Helen and Mamas. In addition, I am grateful to Dr Lawrence Cotter and Dr Ngozi Edi-Osagie, past

and present chairman of The Dickinson Trust Traveling Scholarship Fund, Manchester Royal Infirmary, the Dickinson Trustees, Michael Pate, and Salley Hussey, for a financial grant that contributed to supporting my time in Rotterdam. I am grateful to Dr Peter Clarkson, Dr Amir Zaidi, and Dr Andy Jones from the North Western Deanery for their support in allowing me to take time out of my interventional cardiology training in Manchester to go to Rotterdam.

Rotterdam

"Attitude is a little thing that makes a big difference." [Sir Winston Churchill]
I settled in a modest place in Rotterdam in Aug 2010 with the invaluable assistance of my dear brother Javad who took time out of his busy job abroad to help me with the move. I remember turning up to work for the first time and meeting the Professor. His enthusiasm was unbounded and he literally threw me into multiple meetings and research proposals. As the professor used to say, "total immersion" in all the fields was required. At first it was overwhelming. The best analogy is being a novice swimmer and being politely nudged in at the deep end and just expected to swim! Of course the support was there – I just had not yet realised…

"Never, never, never give up." [Sir Winston Churchill]
The beginning was however tough. I had to learn to develop a thick skin and take criticism and rejections constructively. Professor Serruys used to advise me, no one knows "who this Vasim Farooq is," and that you are "travelling in well chartered waters." In my first 18 months I made steady progress, and had the pleasure to work with multiple teams on various projects ranging from preclinical to clinical research. In addition, we formed a friendly collaboration with Professor Ewout Steyerberg and his team (Yvonne and David).

"Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won't come in." [Isaac Asimov]
At each stage, our knowledge and understanding of the field continued to evolve, previously held assumptions challenged, and we collectively went on to prove our hypotheses. The frequent occasions to personally present our work at major international meetings, such as the European Society of Cardiology (ESC), American College of Cardiology (ACC), EuroPCR, Transcatheter Cardiovascular Therapeutics (TCT) congresses, followed by acceptance in reputable scientific journals proved to be a major vindication of our efforts.

"Alone we can do so little; together we can do so much…" [Helen Keller]
There are multiple people I need to thank for my time in Rotterdam, far too many to list below. If I have missed anyone of – I apologise. I truly believe that the friends I made in Rotterdam were like an extended family and still regard the city as my second home…

Thoraxcenter and Department of Public Health, Erasmus MC

I am indebted to Professor Patrick Serruys and Professor Felix Zijlstra to allow me the honour of undertaking and continuing my fellowship at the Thoraxcenter, Rotterdam. Hector's wise counsel, friendship and frequent dinners with his family; the energy and vibrancy of my good friend Pascal Vranckx – a rare breed of being an interventionalist, an intensivist and a thoroughly nice chap; Yoshi – in particular for his passion of all things interventional – and for just being Yoshi (he will understand); Osama – your friendship, good humour, unique insights into all things TAVI, and regular socialising; the guidance and kind words of Carl Schultz and Nicolas van Mieghem; the counsel of the late Professor Willem van der Giessen, Robert-Jan van Geuns, Arie-Pieter Kappetein, Eric Duckers, Pim J. de Feyter; the invaluable help from Jurgen Ligthart and colleagues; the collaboration with Heleen van Beusekom, Koen Nieman and Eric Boersma; the friendship and good humour of Joost Daemen and Nico Bruining; the unique opportunity to collaborate with my other mentor and friend Professor Ewout Steyerberg – from our very first meeting your enthusiasm was limitless, your unwavering support appreciated; Yvonne Vergouwe – with her rather large motorcycle…I do miss our regular meetings; my dear friend David van Klaveren, your professionalism and friendship are something I miss dearly.

Interventional Fellows (in order of meeting) – a truly international team!

Josep Gomez Lara (Spain), Joanna Wykrzykowska (US), Roberto Diletti (Italy), Bill "Vasileios" Gogas (and his wife Katerina) (Greece), Salvatore Brugaletta (Italy), Juan Luis Gutiérrez Chico (Spain), Maria Radu (Denmark), Chrysafios Girasis and Stella-Lida (Greece), Michael Magro (Malta), Cihan Simsek (The Netherlands), Stuart Head (The Netherlands), Nienke van Ditzhuijzen (The Netherlands), Jung Ho Heo (South Korea), Lorenz Räber (Switzerland), Takashi Muramatsu (and his wife Yuko) (Japan), Il Soo Lee (and his wife Mijung) (South Korea), Alexander Kharlamov (Russia), Christos Bourantas and Thekla Geragotou (Greece), Yaojun Zhang (China), Javaid Iqbal (UK), Shimpei Nakatani (Japan), Carlos Campos (Brazil).

It is difficult to know where to start in acknowledging the countless fellows I had the pleasure to work with and can truly call my friends. We shared the highs and lows of research together, we learnt from each other, we socialised together, travelled to national

and international congresses together, we spent so much time together that it was practically like an extended family. It was always difficult when friends returned to their mother countries; this was however offset by the new blood that inevitably occurred.

I can never forget the first social event in Rotterdam. A delicious Spanish meal at Hector's house, with paella prepared by my Spanish friends; countless lunch and evening meals at each others apartments; the culinary and somewhat odd linguistic skills of Josep (I think he had similar views about my English accent…); the passion of my Italian and Spanish friends Roberto, Salvatore and Juan Luis; larger than life, straight-talking Bill and his music and friendship; my dear friends Maria and Lorenz – your good humour and friendship are sorely missed; Chrysafios (Chris) and my Maltese friend Michael, we worked extremely well together, I still have the recording of the only time Chris ever admitted he was wrong!; my Dutch friends Stuart, Cihan, and Nienke – as you may well know at first Rotterdam did not quite agree with me, but I grew to love the city (similar to the feelings I had when I first went to Manchester); the hospitality and friendship of Jung Ho and Il Soo – Jung Ho the busy researcher/photographer and Il Soo, the gentle, man of peace – I pray your son (Sang Joon) continues to make a speedy recovery; Takashi (and Yuko) – at first we did not understand what each other were saying, yet after 3 months we passed that barrier and became great friends (I later found it took you 6 months before you finally understood my English accent! – qualities that simply underlie the true gentleman that you are…); my dear friends Chris Bourantas (with whom I had briefly met in the UK many years previously at the start of my training in cardiology) and Thekla – your wedding in an olive garden in Athens was inspirational…truly unforgettable… your country beautiful…and I even managed a Greek dance (albeit very poorly as the videos well prove!); Yaojun, your enthusiasm and energy were inexhaustible; my dear friend Javaid, am sure you have now settled in Rotterdam; Shimpei and Carlos, I only briefly met you before I left Rotterdam but could see we would have been great friends.

Cardialysis

I must consider the organizer as more important than the discoverer. [Carl Wilhelm Wolfgang Ostwald]

Gerritt-Anne van Es, Coen van Kalken, Hanny Boutkan, Marie-angèle Morel, Teun Smits, Ana Guimaraes (and her little ones), Ton de Vries, Jolanda de Groot, Glenda van Bochove, Linda Korthout, Ravindra Pawar, Jamal, Bianca Backx, Anne-Marie Bruinsma, Anne-Marie Hoogenboom, Yvonne, Arja, Eliane Lopes dos Santos, Marije, Marieke Tuinman, Peter Paul Kint, Mandy Hartwig, Janette Symons, Linda Roest, Monique Schuijer, Jeannette

Fong-Pien-Joe, Ad Meijer, Andre Boogaards, Tessa Rademaker, Michael Swart, Marco Bressers, Eric van Remortel, Wietze Lindeboom, Pierre Gobbens.

It is difficult to know where to start thanking the people of Cardialysis for their time and hospitality. All I can say is that they are a truly wonderful, friendly, and highly professional team. I learnt so much from you all, and left regarding many of you as my friends. You are all missed.

Gerritt-Anne, a personal thank you for your support during my time in Rotterdam. Teun, Ana and Marie-angèle – I do miss our daily early morning banter, Teun your dry sense of humour was unforgettable, and I was truly flattered by your leaving present, Ana it was always a real delight talking to you and seeing your little ones – thank you for introducing me to haring at Schmidt's place and the good advice of the need to chew the haring to prevent any sickness…; Ton, Tessa, Michael, Marco, Eric, Wietze and Pierre – in my eyes the "magnificent seven" who I learnt so much from and was truly a wonderful experience working with; Ton even in times of tight deadlines you were always a great friend and a true gentlemen, you would always make time to help us out with problems no matter how busy you were; Glenda you were always great company, a dear friend, and would provide us with invaluable technical support – you were very missed when you left Cardialysis to pursue your dreams; Jolanda you were always great company and your countless trips to the pub quiz and odd times to the Pleinbioscoop with Marie-angèle and the team looked forward to; Ravindra, Jamal, Yvonne, Marieke and Marije, your warm and friendly nature, good humour and patience were greatly appreciated; Monique, Bianca, Linda, Eliane, Anne Marie, Janette, and others – it was always a real delight working with you individually on differing trials; Ad I always appreciated your friendliness and ability to solve multiple problems – thank you; Peter Paul your warm and friendly nature was always appreciated; the list of personal thanks could go on and on…

*Pub (O'Sheas) quiz team: "Cardiac B*stards"*

Our pub quiz team name was dreamt up by my good friend master Ton de Vries, in recognition of the film "Inglorious B*stards," a name that admittedly took a while to grow on me... I looked forward to going to the weekly pub quizzes, particularly in my last 6 months at Rotterdam, it was a welcome break from everything. We formed a great team, and if I remember correctly, the highest position we got was second, which was fantastic considering the team that beat us were made up of die-hard quiz fanatics. Everything from elephants being unable to jump, eclectic music (Ton and Andre), contemporary music (Sylvie), sports and football (Marie-angèle), knowledge of travel and just odd facts (Jolanda, Linda, Janette, Eliane), always being invited but never actually making it to

the quiz because of her little ones (Ana), being always highly confident in her answers whether right or wrong but great fun all the same (Jolanda), never 100% sure of any answer (me), forgetting the name of the main street in central Paris by the only Parisienne on the team (name withheld)...

EuroIntervention/Europa Organisaton

It was a great pleasure to be part of the editorial board with the EuroIntervention team in Rotterdam, in particular, Paul Cummins, Sylvie L'Hoste, Wendel van der Sluis, and the editor-in-chief Professor Serruys. My lasting impression of Paul is a work hard, play hard, electric guitar playing, Guinness loving Irish friend. Sylvie, my gratitude to you is detailed below. The calm Wendel – in the short time I met you we became good friends – thank you for the book you gave me when I left, I am still reading it! Warm thanks go to William Wijns, Frédéric Doncieux and Rodney de Palma for their friendliness and invaluable reviews of the two chapters we co-authored in the PCR-EAPCI Textbook.

Hanny, Sylvie and Marie-angèle

My three 'rocks' in Rotterdam. I am enormously grateful for all the help, support and friendship we shared together in Rotterdam, you were all there from the very beginning, during the low and high times. Firstly the wonderful Hanny, thank you for just being Hanny – I am not sure what I would have done without you. Your cheerfulness, good humour and philosophy are something I miss very much. What can I say but you were always there, even during the times when you were off work…thank you! I still have your leaving card with your famous last words of wisdom written on it *"The way is the GOAL… because very often the goal is IN THE WAY."* Secondly, my dear friend Mademoiselle Perdue (Sylvie) what can I say, I would have been 'lost' without you. I will never forget when you took the entire team out for a day in the windmills in Rotterdam, the concert where Paul Cummins was the lead guitarist, your tireless efforts in helping us make the illustrations for the left main chapter of the PCR - EAPCI textbook in collaboration with Catherine Meunier (French illustrator) and putting up with me in the process, the frequent socialising with the team, and er… your driving skills… merci beaucoup! Thirdly, the delightful Marie-angèle Morel, senior author of the BENESTENT trial, 'queen' of the SYNTAX Score, a wealth of new ideas, a problem solver (no matter how big or small), football – Feyenoord – crazy, and wonderful company. The move of the local Rotterdam footballer Robin Van Persie to Manchester United cemented our friendship. When I could not get home for New Year's day in my last 6 months in Rotterdam, you threw us an amazing New Year Eve's party... Dank u to you all, Hanny, Sylvie and Marie-angèle, the leaving party you

threw me was unforgettable, the Feyenoord van Persie shirt unique, you truly are all very special, and I miss you all very dearly.

SYNTAX Investigators

"There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance." [Hippocrates]

Patrick W Serruys, Marie-Claude Morice, Arie-Pieter Kappetein, Antonio Colombo, David R. Holmes, Michael J. Mack, Elisabeth Ståhle, Ted E. Feldman, Marie-angèle Morel, Keith D. Dawkins, and Friedrich W. Mohr.

I am grateful to all the SYNTAX Investigators for their friendly and helpful advice, support and critical review of all the manuscripts based on the SYNTAX Trial. Indeed, it was a great honour and privilege to work alongside such a unique and inspirational team. Special thanks go to Dr Keith Dawkins for his advice, support, frank and honest reviews of our manuscripts, and unique insights into the SYNTAX Trial – they were always very well received and appreciated; Professor Kappetein, I enjoyed our friendly debates on all things SYNTAX; Professor Mohr, I had the unique opportunity to present alongside you at the ESC Congress in Munich on the SYNTAX Trial, and was very flattered by your personal invite to present at the "Hands Across the Ocean" conference in Leipzig last December – and was simply blown away by the friendliness and hospitality in Leipzig; Dr Colombo, we were truly humbled by your enthusiasm of the SYNTAX Score II and demonstration of its first public clinical use with Alaide Chieffo during a live case on board the SS Rotterdam; Dr Morice, Dr Holmes, Dr Mack, Dr Ståhle and Dr Feldman – your kind and learned comments were always very much appreciated, whenever we received your positive comments we always knew we were winning…

Industry

"Research is four things: brains with which to think, eyes with which to see, machines with which to measure, and fourth, money." [Albert Szent-Gyorgyi]

I am grateful to Boston Scientific for their unwavering support, in particular, Keith Dawkins, Peggy Pereda, Jian Huang, Vicki Houle, Kristine Roy, and Nic van Dyck; Michel Lussier and Egon Wülfert of Volcano Corporation; the friendly support of John Stevens and Campbell Rogers of Heartflow, Inc; the multiple face to face meetings and support of Abbott whilst working on the ABSORB programme, in particular Richard Rapoza, Susan Veldhof, Ann Snoeijs, Laura Perkins, Jennifer Powers; the enthusiasm and support of Dragica Paunovic of Terumo, in particular when working in the evolving field

of three-dimensional optical coherence tomography; Susanne Meis and colleagues of Biosensors; Manish Doshi of Envision Scientific.

My Mentors

"If I have seen further it is by standing on the shoulders of Giants." [Sir Isaac Newton]
Professor Steyerberg. I am grateful for all your support and mentorship you provided during my time in Rotterdam. From our very first meeting it was clear that we would work tremendously well together. You were always extremely enthusiastic and encouraging, would never allow us accept defeat, and pushed us to excel. We were uniquely privileged to work alongside your gifted team, in particular my dear friends Yvonne and David, and to allow us to brainstorm thoughts and ideas in meetings with your entire department. Special thanks go out to Sanne in dealing with the all-important logistics. If ever there was an example of a warm and friendly collaboration this was it. I still have your famous book you loaned to me – I promise to return it very soon!

Professor Serruys. It is difficult to know where to acknowledge my gratitude for the unique opportunity and mentorship you provided to me in Rotterdam. As you know I came to Rotterdam to work on the bioresorbable scaffold programme, which I achieved, but simultaneously got working in SYNTAX (forming the basis of my thesis), intravascular imaging, contemporary coronary stents, and multiple other branches of interventional cardiology – such was the philosophy you instilled to us of being positive, enthusiastic, a team player, open to new ideas and the pursuit of the truth, however difficult it was to find. Sometimes I felt like a piece of metal being hammered into shape, but realise this was simply the nature of research and the need to reach the very highest standards. Special thanks also go out to your amazing wife Danielle, her strength and courage are an inspiration to us all. Danielle was always welcoming on the countless visits to your home in the evenings and weekends, particularly on those cold winter days, when Rotterdam was hit by snow blizzards and under a blanket of snow. Professor Serruys you gave me, a simple interventional fellow, the unique opportunity to share thoughts and ideas with cardiologists and cardiac surgeons from around the world. Your mentorship and guidance culminated in me unexpectedly winning the Thomas J. Linnemeier Spirit of Interventional Cardiology Young Investigator Award at the TCT 2013 in San Francisco, United States. Looking ahead, I am uniquely privileged to continue to working with you on the SYNTAX II Trial. Thank you for opening my eyes…thank you for everything!

Future

"Learn from yesterday, live for today, hope for tomorrow. The important thing is to not stop questioning." [Albert Einstein]

I got to Rotterdam, not really knowing what to expect, unsettled and uneasy of the future; its ironic that on leaving Rotterdam and returning home, I felt exactly the same way. It's a great feeling and I wouldn't change it for the world…

Final words

"I sustain myself with the love of family." [Maya Angelou]

Final words go to my family, in particular my mother and father, all I can say is thank you…

Vasim Farooq, 17th February 2014

Curriculum Vitae

Personal Details

Name	Vasim Farooq
Place of Birth	Farnworth, Bolton, United Kingdom
Email	vasimfarooq@icloud.com
Date of birth	8th September 1975
Age	38
Nationality	British
General Medical Council (GMC) Registration	Reference Number: 4710480 Full registration: August 2001
Current employment	Specialist Registrar in Interventional Cardiology, Manchester Royal Infirmary, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom

Qualifications

Member of the Royal College of Physicians (MRCP) United Kingdom,	2004
MB ChB Medicine University of Manchester	2000
ALS Advanced Life Support	2013
Good Clinical Practice Course	2013
British Society Echocardiography Accreditation in Transthoracic Echocardiography	2008
ATLS Advanced Trauma Life Support	2001

Awards

Thomas J Linnemeier Spirit of Interventional Cardiology Young Investigator Award Transcatheter Cardiovascular Therapeutics (TCT) 2013, San Francisco, United States.
Reviewer of the Year, EuroPCR 2012, Paris, France.

Other Academic and Professional Activities

1) On the steering committee for the SYNTAX II Trial, investigating the management of three vessel disease with newer generation drug eluting stents
2) International associate editor: EuroIntervention

Current & Previous Employments

Specialist Registrar Interventional Cardiology	• Manchester Royal Infirmary, Central Manchester University Hospitals NHS Foundation Trust, Manchester	02/14 – Present
	• University Hospital Of South Manchester NHS Foundation Trust, Wythenshawe Hospital, Manchester	08/13 – 02/14
	• Blackpool Teaching Hospitals Lancashire Cardiac Centre, Blackpool	02/13 – 08/13
Research Fellow Interventional Cardiology	• Thoraxcenter, Erasmus Medical Centre Rotterdam, The Netherlands	08/10 – 02/13
Specialist Registrar Interventional Cardiology	• Central Manchester and Manchester Children's University Hospitals, Manchester Heart Centre, Manchester Royal Infirmary	08/09 – 08/10
	• Blackpool Teaching Hospitals Lancashire Cardiac Centre, Blackpool	02/08 – 08/09
	• District Hospital: Royal Albert Edward Infirmary, Wigan	08/07 – 02/08
Cardiology Research Registrar	• University of Hull Academic Department of Cardiology, Hull and East Yorkshire Hospitals	03/07 – 07/07
Specialist Registrar Cardiology (LAT)	• District Hospital: Tameside Hospital, Manchester	08/06 – 02/07
	• University Teaching Hospital, Hope Hospital, Salford Royal NHS Foundation Trust, Manchester	08/05 – 08/06
Clinical Fellow Cardiology	• University Hospital Of South Manchester NHS Foundation Trust, Wythenshawe Hospital	02/05 – 08/05
	• District Hospital: Leighton Hospital, Cheshire	09/04 – 02/05

Senior House Officer (SHO)	• University Teaching Hospital, Hope Hospital, Salford Royal NHS Foundation Trust, Manchester o Medical rotation (neurology, stroke medicine, care of the elderly medicine, gastroenterology, haematology. nephrology). • District Hospital: Hinchingbrooke Hospital, Huntingdon, Cambridgeshire o Accident & Emergency Medicine	08/01 – 08/04
Pre-Registration House Officer (PRHO)	• District Hospital: Royal Oldham Hospital, Oldham o Adult Medicine • Christie University Hospital and University Hospital Of South Manchester NHS Foundation Trust, Wythenshawe Hospital o General/Upper GI/Oncological Surgery	08/00 – 08/01

List of Publications

SECTION I: SYNTAX RELATED PUBLICATIONS

Widening Clinical Applications of the SYNTAX Score
Farooq V, Head S, Kappetein AP, Serruys PW
Heart 2014;100(4):276-87

The SYNTAX score and its clinical implications
Head SJ, **Farooq V,** Serruys PW, Kappetein AP
Heart. 2014;100(2):169-77

Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX Score II
Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW
Lancet. 2013;381(9867):639-50 (Impact Factor: 39.060)

SYNTAX Score II – Authors' reply
Farooq V, van Klaveren D, Steyerberg EW, Serruys PW
Lancet. 2013;381(9881):1899-900

Quantification of Incomplete Revascularisation and its Association with Five-Year Mortality in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score
Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Ståhle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW
Circulation. 2013;128(2):141-51

Short-Term and Long-Term Clinical Impact of Stent Thrombosis and Graft Occlusion in the SYNTAX Trial at 5 Years: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial
Farooq V, Serruys PW, Zhang Y, Mack M, Ståhle E, Holmes DR, Feldman T, Morice MC, Colombo A, Dawkins KD, Kappetein AP, Mohr FW
J Am Coll Cardiol. 2013;62(25):2360-9

The Negative Impact of Incomplete Angiographic Revascularization on Clinical Outcomes and Its Association With Total Occlusions: The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) Trial
Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Ståhle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E
J Am Coll Cardiol. 2013;61(3):282-94

Revascularization strategies in patients with diabetes
Serruys PW, **Farooq V**
N Engl J Med. 2013;368(15):1454-5

'Cherry-picking' patients for randomised controlled trials - reliving the past…
Farooq V, Serruys PW
J Am Coll Cardiol. 2013;61(24):2492

Complex Coronary Artery Disease: Would Outcomes From the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Trial Have Differed With Newer-Generation Drug-Eluting Stents?
Farooq V, Serruys PW
JACC Cardiovasc Interv. 2013 Oct;6(10):1023-5

Observations from the CREDO-Kyoto three-vessel disease registry: can one adjust for the unadjustable?
Farooq V, Serruys PW
EuroIntervention. 2013;22;9(4):419-21

The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy
Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia-Garcia HM, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Ståhle E, James S, Carrié D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW
EuroIntervention. 2013;8(11):1277-85

The coronary artery bypass graft SYNTAX Score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy
Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia Garcia HM, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Ståhle E, James S, Carrié D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW
EuroIntervention. 2013;9(8):1009-1010

Incidence, correlates, and significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous based revascularisation: A substudy from the Synergy between Percutaneous Coronary Interventions with Taxus and Cardiac Surgery (SYNTAX) Trial
Farooq V, Serruys PW, Vranckx P, Bourantas CV, Girasis C, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, Dawkins KD, Mohr FW, James S, Ståhle E
Int J Cardiol. 2013;168(6):5287-92

CT-SYNTAX score: a feasibility and reproducibility Study
Papadopoulou SL, Girasis C, Dharampal A, **Farooq V,** Onuma Y, Rossi A, Morel MA, Krestin GP, Serruys PW, de Feyter PJ, Garcia Garcia HM
JACC Cardiovasc Imaging. 2013;6(3):413-5

Prediction of 1-Year Mortality in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: Validation of the Logistic Clinical SYNTAX Score
Farooq V, Vergouwe Y, Généreux P, Bourantas CV, Palmerini T, Caixeta A, Garcìa-Garcìa HM, Morel MA, McAndrew TC, Kappetein AP, Valgimigli M, Windecker S, Dawkins KD, Steyerberg EW, Serruys PW, Stone GW
JACC Cardiovasc Interv. 2013;6(7):737-45

Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial
Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Ståhle E
Eur Heart J. 2012;33(24):3105-13

Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score
Farooq V, Vergouwe Y, Räber L, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW
Eur Heart J. 2012;33(24):3098-104

A Global Risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years
Serruys PW, **Farooq V,** Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR Jr, Kappetein AP, Mack MJ, Feldman T, Morice MC, Ståhle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW
JACC Cardiovasc Interv. 2012;5(6):606-17

Left main coronary intervention: are we moving too quickly without the appropriate evidence base?
Farooq V, Serruys PW
Catheter Cardiovasc Interv. 2012;80(2):213-4

Plaque compositional Syntax score: combining angiography and lipid burden in coronary artery disease
Brugaletta S, Magro M, Simsek C, Heo JH, de Boer S, Ligthart J, Witberg K, **Farooq V,** van Geuns RJ, Schultz C, van Mieghem N, Regar E, Zijlstra F, Duckers HJ, de Jaegere P, Muller JE, van der Steen AF, Boersma E, Garcia-Garcia HM, Serruys PW
JACC Cardiovasc Imaging. 2012;5(3 Suppl):S119-21

Contemporary and evolving risk scoring algorithms for percutaneous coronary Intervention
Farooq V, Brugaletta S, Serruys PW.
Heart. 2011;97(23):1902-13

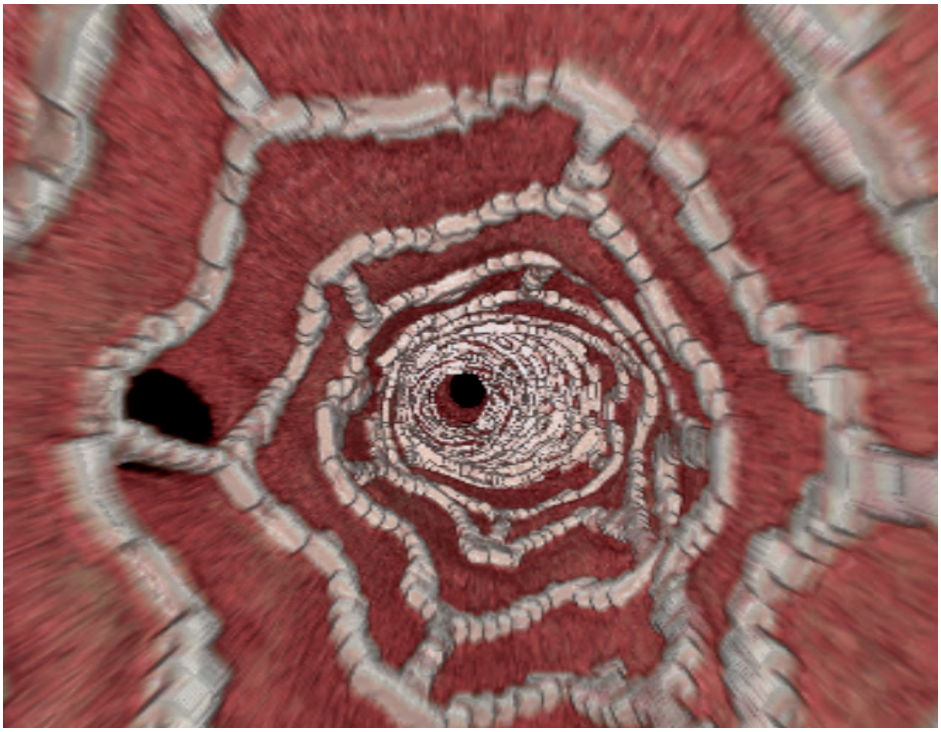
The SYNTAX score and SYNTAX-based clinical risk scores
Farooq V, Brugaletta S, Serruys PW
Semin Thorac Cardiovasc Surg. 2011;23(2):99-105

Tools & techniques: risk stratification and diagnostic tools in left main stem intervention
Farooq V, Heo JH, Räber L, Brugaletta S, Radu M, Gogas BD, Diletti R, Onuma Y, Garcia-Garcia HM, Serruys PW
EuroIntervention. 2011;7(6):747-53

Utilizing risk scores in determining the optimal revascularization strategy for complex coronary artery disease
Farooq V, Brugaletta S, Serruys PW
Curr Cardiol Rep. 2011;13(5):415-23

A guide to interpreting and assessing the performance of prediction models
Farooq V, Brugaletta S, Vranckx P, Serruys PW
EuroIntervention. 2011;6(8):909-12

SECTION II: BIORESORBABLE VASCULAR SCAFFOLDS



Intracoronary Optical Coherence Tomography and Histology of Overlapping Everolimus Eluting Bioresorbable Vascular Scaffolds in a Porcine Coronary Artery Model: The Potential Implications for Clinical Practice

Farooq V, Serruys PW, Heo JH, Gogas BD, Onuma Y, Perkins LE, Diletti R, Radu MD; Räber L, Bourantas CV, Zhang Y, van Remortel E, Pawar R, Rapoza RJ, Powers JC, van Beusekom H, Garcìa-Garcìa HM, Virmani R

JACC Cardiovasc Interv. 2013;6(5):523-532

Clinical and intravascular imaging outcomes at 1 and 2 years after implantation of absorb everolimus eluting bioresorbable vascular scaffolds in small vessels. Late lumen enlargement: does bioresorption matter with small vessel size? Insight from the ABSORB cohort B trial

Diletti R, **Farooq V,** Girasis C, Bourantas C, Onuma Y, Heo JH, Gogas BD, van Geuns RJ, Regar E, de Bruyne B, Dudek D, Thuesen L, Chevalier B, McClean D, Windecker S, Whitbourn RJ, Smits P, Koolen J, Meredith I, Li X, Miquel-Hebert K, Veldhof S, Garcia-Garcia HM, Ormiston JA, Serruys PW

Heart. 2013;99(2):98-105

In vivo assessment of the three-dimensional haemodynamic micro-environment following drug-eluting bioresorbable vascular scaffold implantation in a human coronary artery: fusion of frequency domain optical coherence tomography and angiography

Papafaklis MI, Bourantas CV, **Farooq V,** Diletti R, Muramatsu T, Zhang Y, Fotiadis DI, Onuma Y, Garcia Garcia HM, Michalis LK, Serruys PW

EuroIntervention. 2013;9(7):890

Incidence and short-term clinical outcomes of small side branch occlusion after implantation of an everolimus-eluting bioresorbable vascular scaffold: an interim report of 435 patients in the ABSORB-EXTEND single-arm trial in comparison with an everolimus-eluting metallic stent in the SPIRIT first and II trials.

Muramatsu T, Onuma Y, García-García HM, **Farooq V,** Bourantas CV, Morel MA, Li X, Veldhof S, Bartorelli A, Whitbourn R, Abizaid A, Serruys PW; ABSORB-EXTEND Investigators.

JACC Cardiovasc Interv. 2013 Mar;6(3):247-57

Assessment of plaque evolution in coronary bifurcations located beyond everolimus eluting scaffolds: serial intravascular ultrasound virtual histology study

Lee IS, Bourantas CV, Muramatsu T, Gogas BD, Heo JH, Diletti R, **Farooq V,** Zhang Y, Onuma Y, Serruy PW, Garcia-Garcia HM

Cardiovasc Ultrasound. 2013;11:25

Bioresorbable scaffolds in the treatment of coronary artery disease

Zhang Y, Bourantas CV, **Farooq V,** Muramatsu T, Diletti R, Onuma Y, Garcia-Garcia HM, Serruys PW

Med Devices (Auckl). 2013;6:37-48

Proximal and distal maximal luminal diameters as a guide to appropriate deployment of the ABSORB everolimus-eluting bioresorbable vascular scaffold: a substudy of the ABSORB Cohort B and the on-going ABSORB EXTEND Single Arm Study
Farooq V, Gomez-Lara J, Brugaletta S, Gogas BD, Garcìa-Garcìa HM, Onuma Y, van Geuns RJ, Bartorelli A, Whitbourn R, Abizaid A, Serruys PW
Catheter Cardiovasc Interv. 2012;79(6):880-8

ABSORB II randomized controlled trial: a clinical evaluation to compare the safety, efficacy, and performance of the Absorb everolimus-eluting bioresorbable vascular scaffold system against the XIENCE everolimus-eluting coronary stent system in the treatment of subjects with ischemic heart disease caused by de novo native coronary artery lesions: rationale and study design
Diletti R, Serruys PW, **Farooq V,** Sudhir K, Dorange C, Miquel-Hebert K, Veldhof S, Rapoza R, Onuma Y, Garcia-Garcia HM, Chevalier B
Am Heart J. 2012;164(5):654-63

Angiographic maximal luminal diameter and appropriate deployment of the everolimus-eluting bioresorbable vascular scaffold as assessed by optical coherence tomography: an ABSORB cohort B trial sub-study
Gomez-Lara J, Diletti R, Brugaletta S, Onuma Y, **Farooq V,** Thuesen L, McClean D, Koolen J, Ormiston JA, Windecker S, Whitbourn R, Dudek D, Dorange C, Veldhof S, Rapoza R, Regar E, Garcia-Garcia HM, Serruys PW
EuroIntervention. 2012;8(2):214-24

Endothelial-dependent vasomotion in a coronary segment treated by ABSORB everolimus-eluting bioresorbable vascular scaffold system is related to plaque composition at the time of bioresorption of the polymer: indirect finding of vascular reparative therapy?
Brugaletta S, Heo JH, Garcia-Garcia HM, **Farooq V,** van Geuns RJ, de Bruyne B, Dudek D, Smits PC, Koolen J, McClean D, Dorange C, Veldhof S, Rapoza R, Onuma Y, Bruining N, Ormiston JA, Serruys PW
Eur Heart J. 2012;33(11):1325-33

Vascular response of the segments adjacent to the proximal and distal edges of the ABSORB everolimus-eluting bioresorbable vascular scaffold: 6-month and 1-year follow-up assessment: a virtual histology intravascular ultrasound study from the first-in-man ABSORB cohort B trial
Gogas BD, Serruys PW, Diletti R, **Farooq V,** Brugaletta S, Radu MD, Heo JH, Onuma Y, van Geuns RJ, Regar E, De Bruyne B, Chevalier B, Thuesen L, Smits PC, Dudek D, Koolen J, Windecker S, Whitbourn R, Miquel-Hebert K, Dorange C, Rapoza R, Garcia-Garcia HM, McClean D, Ormiston JA
JACC Cardiovasc Interv. 2012;5(6):656-65

The edge vascular response following implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold and the XIENCE V metallic everolimus-eluting stent. First serial follow-up assessment at six months and two years: insights from the first-in-man ABSORB Cohort B and SPIRIT II trials
Gogas BD, Bourantas CV, Garcia-Garcia HM, Onuma Y, Muramatsu T, **Farooq V,** Diletti R, van Geuns RJ, De Bruyne B, Chevalier B, Thuesen L, Smits PC, Dudek D, Koolen J, Windecker S, Whitbourn R, McClean D, Dorange C, Miquel-Hebert K, Veldhof S, Rapoza R, Ormiston JA, Serruys PW
EuroIntervention. 2013;9(6):709-20

Vascular compliance changes of the coronary vessel wall after bioresorbable vascular scaffold implantation in the treated and adjacent segments
Brugaletta S, Gogas BD, Garcia-Garcia HM, **Farooq V,** Girasis C, Heo JH, van Geuns RJ, de Bruyne B, Dudek D, Koolen J, Smits P, Veldhof S, Rapoza R, Onuma Y, Ormiston J, Serruys PW
Circ J. 2012;76(7):1616-23

Bioresorbable scaffolds: current evidence and ongoing clinical trials
Bourantas CV, Zhang Y, **Farooq V,** Garcia-Garcia HM, Onuma Y, Serruys PW
Curr Cardiol Rep. 2012;14(5):626-34

Bioresorbable scaffolds: Current knowledge, potentialities and limitations experienced during their first clinical applications
Bourantas CV, Onuma Y, **Farooq V,** Zhang Y, Garcia-Garcia HM, Serruys PW
Int J Cardiol. 2013;167(1):11-21

The ABSORB bioresorbable vascular scaffold: an evolution or revolution in interventional cardiology?
Gogas BD, **Farooq V,** Onuma Y, Serruys PW
Hellenic J Cardiol. 2012;53(4):301-9

Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap the plaque?
Brugaletta S, Radu MD, Garcia-Garcia HM, Heo JH, **Farooq V,** Girasis C, van Geuns RJ, Thuesen L, McClean D, Chevalier B, Windecker S, Koolen J, Rapoza R, Miquel-Hebert K, Ormiston J, Serruys PW
Atherosclerosis. 2012;221(1):106-12

Serial in vivo intravascular ultrasound-based echogenicity changes of everolimus-eluting bioresorbable vascular scaffold during the first 12 months after implantation insights from the ABSORB B trial
Brugaletta S, Gomez-Lara J, Serruys PW, **Farooq V,** van Geuns RJ, Thuesen L, Dudek D, Koolen J, Chevalier B, McClean D, Windecker S, Smits PC, de Bruyne B, Whitbourn R, Meredith I, van Domburg RT, Sihan K, de Winter S, Veldhof S, Miquel-Hebert K, Rapoza R, Garcia-Garcia HM, Ormiston JA, Bruining N
JACC Cardiovasc Interv. 2011;4(12):1281-9

Head-to-head comparison of the neointimal response between metallic and bioresorbable everolimus-eluting scaffolds using optical coherence tomography
Gomez-Lara J, Brugaletta S, **Farooq V,** Onuma Y, Diletti R, Windecker S, Thuesen L, McClean D, Koolen J, Whitbourn R, Dudek D, Smits PC, Chevalier B, Regar E, Veldhof S, Rapoza R, Ormiston JA, Garcia-Garcia HM, Serruys PW
JACC Cardiovasc Interv. 2011;4(12):1271-80

Analysis of 1 year virtual histology changes in coronary plaque located behind the struts of the everolimus eluting bioresorbable vascular scaffold
Brugaletta S, Gomez-Lara J, Garcia-Garcia HM, Heo JH, **Farooq V,** van Geuns RJ, Chevalier B, Windecker S, McClean D, Thuesen L, Whitbourn R, Meredith I, Dorange C, Veldhof S, Rapoza R, Ormiston JA, Serruys PW
Int J Cardiovasc Imaging. 2012;28(6):1307-14

Serial analysis of the malapposed and uncovered struts of the new generation of everolimus-eluting bioresorbable scaffold with optical coherence tomography
Gomez-Lara J, Radu M, Brugaletta S, **Farooq V,** Diletti R, Onuma Y, Windecker S, Thuesen L, McClean D, Koolen J, Whitbourn R, Dudek D, Smits PC, Regar E, Veldhof S, Rapoza R, Ormiston JA, Garcia-Garcia HM, Serruys PW
JACC Cardiovasc Interv. 2011;4(9):992-1001

Optical coherence tomography (OCT) of overlapping bioresorbable scaffolds: from benchwork to clinical application
Farooq V, Onuma Y, Radu M, Okamura T, Gomez-Lara J, Brugaletta S, Gogas BD, van Geuns RJ, Regar E, Schultz C, Windecker S, Lefèvre T, Brueren BR, Powers J, Perkins LL, Rapoza RJ, Virmani R, García-García HM, Serruys PW
EuroIntervention. 2011;7(3):386-99

6-month clinical outcomes following implantation of the bioresorbable everolimus-eluting vascular scaffold in vessels smaller or larger than 2.5 mm
Diletti R, Onuma Y, **Farooq V,** Gomez-Lara J, Brugaletta S, van Geuns RJ, Regar E, de Bruyne B, Dudek D, Thuesen L, Chevalier B, McClean D, Windecker S, Whitbourn R, Smits P, Koolen J, Meredith I, Li D, Veldhof S, Rapoza R, Garcia-Garcia HM, Ormiston JA, Serruys PW
J Am Coll Cardiol. 2011;58(3):258-64

Angiographic geometric changes of the lumen arterial wall after bioresorbable vascular scaffolds and metallic platform stents at 1-year follow-up
Gomez-Lara J, Brugaletta S, **Farooq V,** van Geuns RJ, De Bruyne B, Windecker S, McClean D, Thuesen L, Dudek D, Koolen J, Whitbourn R, Smits PC, Chevalier B, Morel MA, Dorange C, Veldhof S, Rapoza R, Garcia-Garcia HM, Ormiston JA, Serruys PW
JACC Cardiovasc Interv. 2011;4(7):789-99

Comparison of in vivo eccentricity and symmetry indices between metallic stents and bioresorbable vascular scaffolds: insights from the ABSORB and SPIRIT trials
Brugaletta S, Gomez-Lara J, Diletti R, **Farooq V,** van Geuns RJ, de Bruyne B, Dudek D, Garcia-Garcia HM, Ormiston JA, Serruys PW
Catheter Cardiovasc Interv. 2012;79(2):219-28

Agreement and reproducibility of gray-scale intravascular ultrasound and optical coherence tomography for the analysis of the bioresorbable vascular scaffold

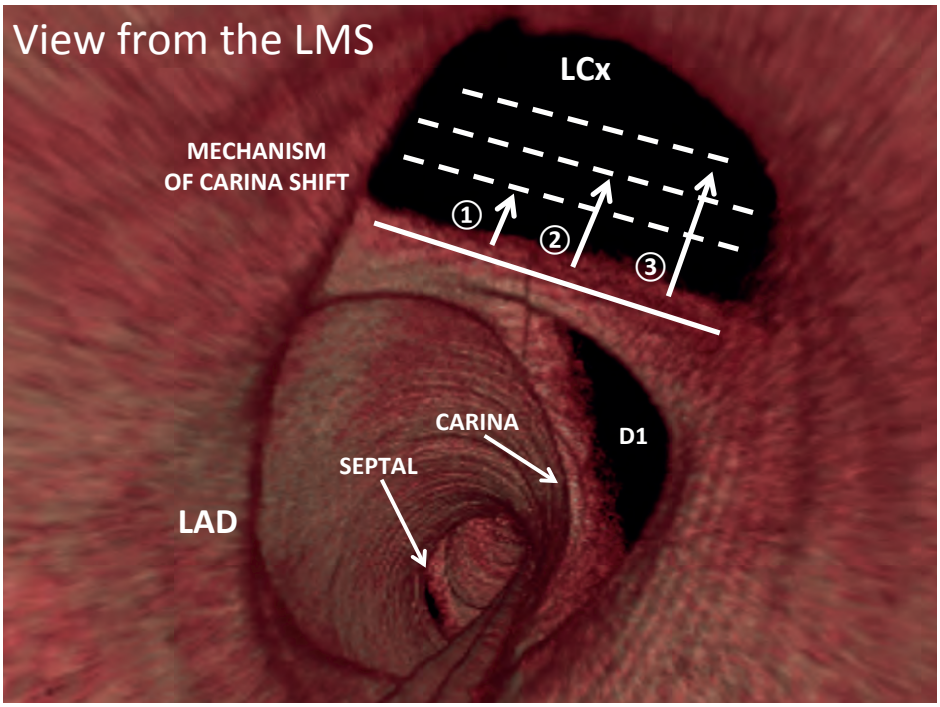
Gómez-Lara J, Brugaletta S, Diletti R, Gogas BD, **Farooq V,** Onuma Y, Gobbens P, Van Es GA, García-García HM, Serruys PW
Catheter Cardiovasc Interv. 2012;79(6):890-902

Evaluation with in vivo optical coherence tomography and histology of the vascular effects of the everolimus-eluting bioresorbable vascular scaffold at two years following implantation in a healthy porcine coronary artery model: implications of pilot results for future pre-clinical studies
Gogas BD, Radu M, Onuma Y, Perkins L, Powers JC, Gomez-Lara J, **Farooq V,** Garcia-Garcia HM, Diletti R, Rapoza R, Virmani R, Serruys PW
Int J Cardiovasc Imaging. 2012;28(3):499-511

Effect of the Endothelial Shear Stress Patterns on Neointimal Proliferation Following Drug-Eluting Bioresorbable Vascular Scaffold Implantation
An Optical Coherence Tomography Study
Bourantas CV, Papafaklis MI, Kotsia A, **Farooq V,** Muramatsu T, Gomez-Lara J, Zhang Y, Iqbal J, Kalatzis FG, Naka KK, Fotiadis DI, Dorange C, Wang J, Rapoza R, Garcia-Garcia HM, OnumaY, Michalis LK, Serruys PW.
JACC Cardiovasc Interv. 2014 [Epub ahead of print]

Short- and long-term implications of a bioresorbable vascular scaffold implantation on the local endothelial shear stress patterns.
Bourantas CV, Papafaklis MI, Garcia-Garcia HM, **Farooq V,** Diletti R, Muramatsu T, Zhang Y, Kalatzis FG, Naka KK, Fotiadis DI, Onuma Y, Michalis LK, Serruys PW
JACC Cardiovasc Interv. 2014;7(1):100-1

SECTION III: INTRAVASCULAR IMAGING



Three-dimensional optical frequency domain imaging in conventional percutaneous coronary intervention: the potential for clinical application
Farooq V, Gogas BD, Okamura T, Heo JH, Magro M, Gomez-Lara J, Onuma Y, Radu MD, Brugaletta S, van Bochove G, van Geuns RJ, Garcìa-Garcìa HM, Serruys PW
Eur Heart J. 2013;34(12):875-85

In vivo three dimensional optical coherence tomography. A novel imaging modality to visualize the edge vascular response
Gogas BD, Muramatsu T, Garcia-Garcia HM, Bourantas CV, Holm NR, Thuesen L, **Farooq V,** Onuma Y, Serruys PW
Int J Cardiol. 2013;164(3):e35-7

Revisiting: "Comparison of intravascular ultrasound versus angiography guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients"
Zhang YJ, Garcia-Garcia HM, **Farooq V,** Bourantas CV, Serruys PW, Chen SL
EuroIntervention. 2013;9(7):891-2

Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients
Zhang Y, **Farooq V,** Garcia-Garcia HM, Bourantas CV, Tian N, Dong S, Li M, Yang S, Serruys PW, Chen SL
EuroIntervention. 2012;8(7):855-65

Serial 2- and 3-dimensional visualization of side branch jailing after metallic stent implantation: to kiss or not to kiss...?
Diletti R, **Farooq V,** Muramatsu T, Gogas BD, Garcia-Garcia HM, van Geuns RJ, Serruys PW
JACC Cardiovasc Interv. 2012;5(10):1089-90

Unravelling the complexities of the coronary bifurcation: is this raising a few eyebrows?
Farooq V, Okamura T, Onuma Y, Gogas BD, Serruys PW
EuroIntervention. 2012;7(10):1133-41

Three-dimensional coronary tomographic reconstructions using in vivo intracoronary optical frequency domain imaging in the setting of acute myocardial infarction: the clinical perspective
Gogas BD, **Farooq V,** Serruys PW
Hellenic J Cardiol. 2012;53(2):148-51

New insights into the coronary artery bifurcation hypothesis-generating concepts utilizing
3-dimensional optical frequency domain imaging
Farooq V, Serruys PW, Heo JH, Gogas BD, Okamura T, Gomez-Lara J, Brugaletta S, Garcìa-Garcìa HM, van Geuns RJ
JACC Cardiovasc Interv. 2011;4(8):921-31

3D reconstructions of optical frequency domain imaging to improve understanding of conventional PCI
Farooq V, Okamura T, Gogas BD, Heo JH, Magro M, Gomez-Lara J, Brugaletta S, Onuma Y, Radu M, Garcìa-Garcìa HM, Serruys PW
JACC Cardiovasc Imaging. 2011;4(9):1044-6

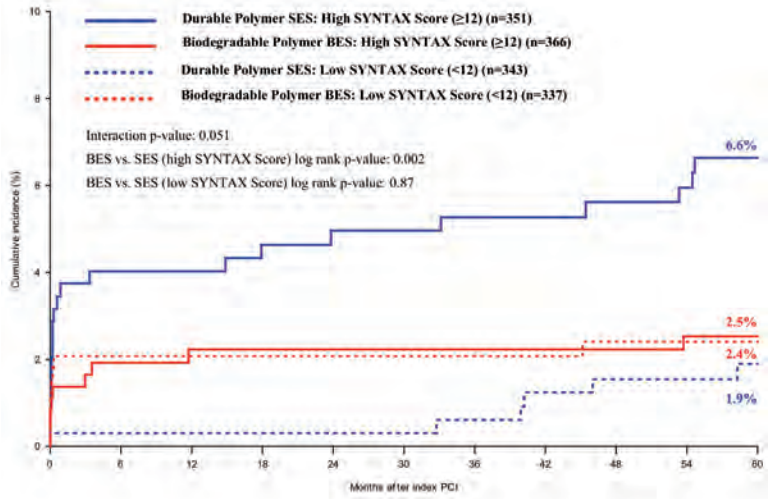
Three-dimensional reconstruction of the post-dilated ABSORB everolimus-eluting bioresorbable vascular scaffold in a true bifurcation lesion for flow restoration
Gogas BD, van Geuns RJ, **Farooq V,** Regar E, Heo JH, Ligthart J, Serruys PW
JACC Cardiovasc Interv. 2011;4(10):1149-50

3-dimensional optical frequency domain imaging for the evaluation of primary percutaneous coronary intervention in ST-segment elevation myocardial infarction
Gogas BD, **Farooq V,** Onuma Y, Magro M, Radu MD, van Geuns RJ, Regar E, Serruys PW
Int J Cardiol. 2011;151(1):103-5

3-Dimensional reconstruction of a bifurcation lesion with double wire after implantation of a second generation everolimus-eluting bioresorbable vascular scaffold
van Geuns RJ, Gogas BD, **Farooq V,** Regar E, Serruys PW
Int J Cardiol. 2011;153(2):e43-5

Assessment of coronary atherosclerosis by IVUS and IVUS-based imaging modalities: progression and regression studies, tissue composition and beyond
Gogas BD, **Farooq V,** Serruys PW, Garcìa-Garcìa HM
Int J Cardiovasc Imaging. 2011;27(2):225-37

SECTION IV: CONTEMPORARY STENT TRIALS



Improved safety and reduction in stent thrombosis associated with biodegradable polymer based biolimus-eluting stents versus durable polymer based sirolimus-eluting stents in patients with coronary artery disease. Final 5-year report of the Limus Eluted From A Durable Versus ERodabale Stent Coating (LEADERS) randomised, non-inferiority trial

Serruys PW, **Farooq V,** Kalesan B, de Vries T Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker T, van Es GA, Meier B, Jüni P, Windecker S

JACC Cardiovasc Interv 2013;6:777-89

Impact of overlapping newer generation drug-eluting stents on clinical and angiographic outcomes: pooled analysis of five trials from the international Global RESOLUTE Program

Farooq V, Vranckx P, Mauri L, Cutlip DE, Belardi J, Silber S, Widimsky P, Leon M, Windecker S, Meredith I, Negoita M, van Leeuwen F, Neumann FJ, Yeung AC, Garcia-Garcia HM, Serruys PW

Heart. 2013;99(9):626-33

Clinical and angiographic characteristics of patients likely to have vulnerable plaques: Analysis from the PROSPECT study
Bourantas CV, Garcia-Garcia HM, **Farooq V,** Maehara A, Généreux P, Diletti R, Muramatsu T, Fahy M, Weisz G, Stone GW, Serruys PW
JACC Cardiovasc Imaging. 2013;6(12):1263-72

Clinical outcomes of patients with stable ischemic heart disease as compared with acute coronary syndromes after percutaneous coronary interventions
Vranckx P, Kalesan B, Stefanini GG, **Farooq V,** Onuma Y, Silber S, de Vries T, Jüni P, Serruys PW, Windecker S
EuroIntervention. 2013 [Epub ahead of print]

Clinical Outcomes after Zotarolimus and Everolimus Drug Eluting Stent Implantation in Coronary Artery Bifurcation Lesions. Insights from the RESOLUTE All Comers trial
Diletti R, Garcia-Garcia HM, Bourantas CV, van Geuns RJ, van Mieghem NM, Vranckx P, Zhang Y, **Farooq V,** Iqbal J, Wykrzykowska J, de Vries T, Swart M, Teunissen Y, Negoita M, van Leeuwen F, Silber S, Windecker S, Serruys PW
Heart. 2013;99(17):1267-74

Coronary evaginations are associated with positive vessel remodelling and are nearly absent following implantation of newer-generation drug-eluting stents: an optical coherence tomography and intravascular ultrasound study
Radu MD, Räber L, Kalesan B, Muramatsu T, Kelbæk H, Heo J, Jørgensen E, Helqvist S, **Farooq V,** Brugaletta S, Garcia-Garcia HM, Jüni P, Saunamäki K, Windecker S, Serruys PW
Eur Heart J. 2013 [Epub ahead of print]

Natural history of optical coherence tomography-detected non-flow-limiting edge dissections following drug-eluting stent implantation
Radu MD, Räber L, Heo J, Gogas BD, Jørgensen E, Kelbæk H, Muramatsu T, **Farooq V,** Helqvist S, Garcia-Garcia HM, Windecker S, Saunamäki K, Serruys PW
EuroIntervention. 2014;9(9):1085-9

Progress in Treatment by Percutaneous Coronary Intervention: The Stent of the Future
Muramatsu T, Onuma Y, Zhang YJ, Bourantas CV, Kharlamov A, Diletti R, **Farooq V,** Gogas BD, Garg S, García-García HM, Ozaki Y, Serruys PW.
Rev Esp Cardiol. 2013;66(6):483-96.

Clinical and angiographic outcomes following first-in-man implantation of a novel thin-strut low-profile fixed-wire stent: the Svelte Coronary Stent Integrated Delivery System first-in-man trial
Diletti R, Garcia-Garcia HM, Bourantas CV, van Geuns RJ, Van Mieghem NM, Agostoni P, Muramatsu T, **Farooq V,** Spencer R, De Schepper J, Pomeranz M, Stella P, Serruys PW
EuroIntervention. 2013;9(1):125-34

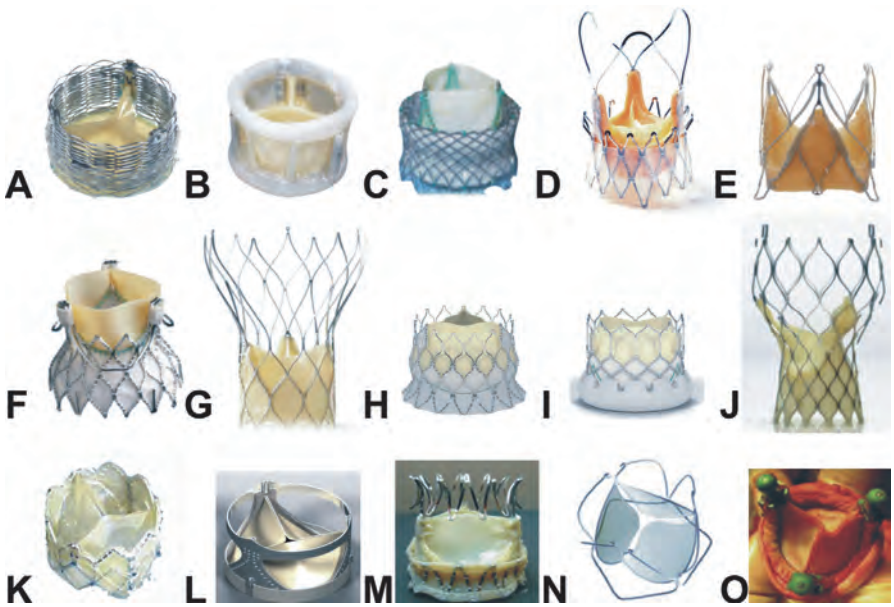
Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting
Vranckx P, **Farooq V,** Garg S, Van Es GA, Silber S, Windecker S, Stone GW, Serruys PW
Heart. 2012;98(19):1424-30

Use of the Sideguard (Cappella) stent in bifurcation lesions: a real-world experience
Mamas MA, **Farooq V,** Latib A, Sastry S, D'Souza S, Williams P, Wiper A, Neyses L, El-Omar M, Fraser DG, Fath-Ordoubadi F
EuroIntervention. 2012 Feb;7(10):1170-80

Relationship between palpography and virtual histology in patients with acute coronary syndromes
Brugaletta S, Garcia-Garcia HM, Serruys PW, Maehara A, **Farooq V,** Mintz GS, de Bruyne B, Marso SP, Verheye S, Dudek D, Hamm CW, Farhat N, Schiele F, McPherson J, Lerman A, Moreno PR, Wennerblom B, Fahy M, Templin B, Morel MA, van Es GA, Stone GW
JACC Cardiovasc Imaging. 2012;5(3 Suppl)

Angiographic and histological results following implantation of a novel stent-on-a-wire in the animal model
Diletti R, Garcia-Garcia HM, van Geuns RJ, **Farooq V,** Bailey L, Rousselle S, Kopia G, Easterbrook W, Pomeranz M, Serruys PW
EuroIntervention. 2012;8(3):390-9

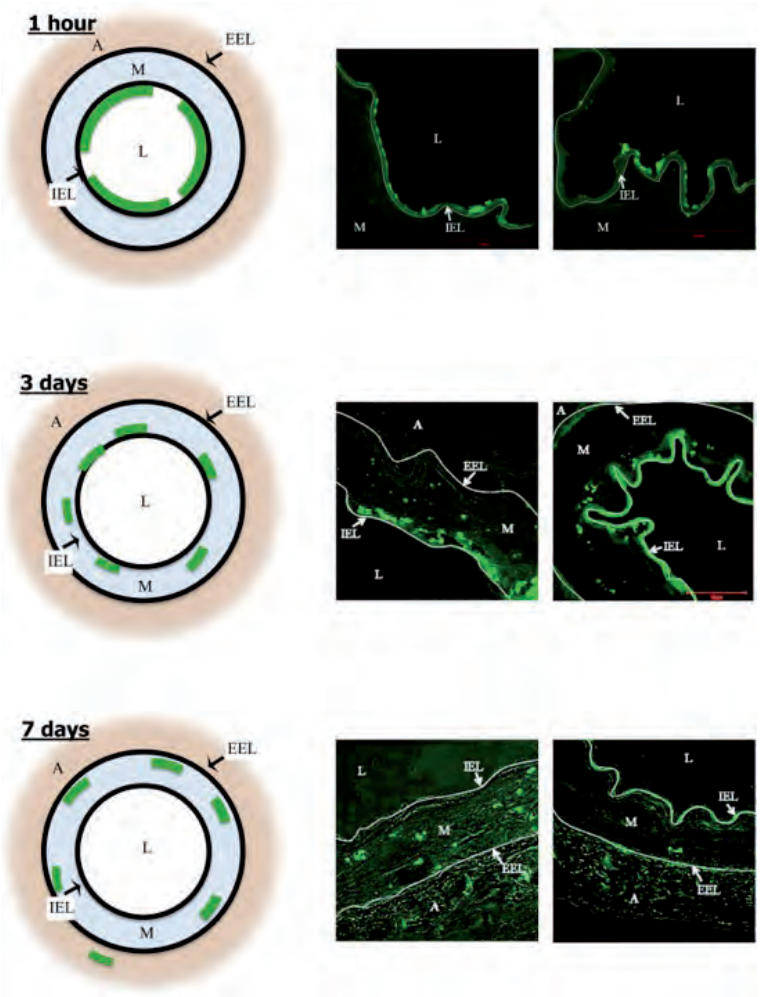
SECTION V: TRANSAORTIC VALVE IMPLANTATION



Future perspectives in transcatheter aortic valve implantation
Bourantas CV, van Mieghem NM, **Farooq V,** Soliman OI, Windecker S, Piazza N, Serruys PW
Int J Cardiol. 2013;168(1):11-8

Transcatheter aortic valve implantation: new developments and upcoming clinical trials
Bourantas CV, **Farooq V,** Onuma Y, Piazza N, Van Mieghem NM, Serruys PW
EuroIntervention. 2012;8(5):617-27

SECTION VI: OTHER



Emerging technologies: polymer-free phospholipid encapsulated sirolimus nano-carriers for the controlled release of drug from a stent-plus-balloon or a stand-alone balloon catheter

Lemos PA, **Farooq V,** Takimura CK, Gutierrez PS, Virmani R, Kolodgie F, Christians U, Kharlamov A, Doshi M, Sojitra P, van Beusekom HM, Serruys PW

EuroIntervention. 2013;9(1):148-56

Lipid core burden index and Framingham score: can a Systemic Risk Score predict lipid core burden in non-culprit coronary artery?
Heo JH, Garcia-Garcia HM, Brugaletta S, de Boer S, Simsek C, **Farooq V,** Boersma E, Serruys PW
Int J Cardiol. 2012;156(2):211-3

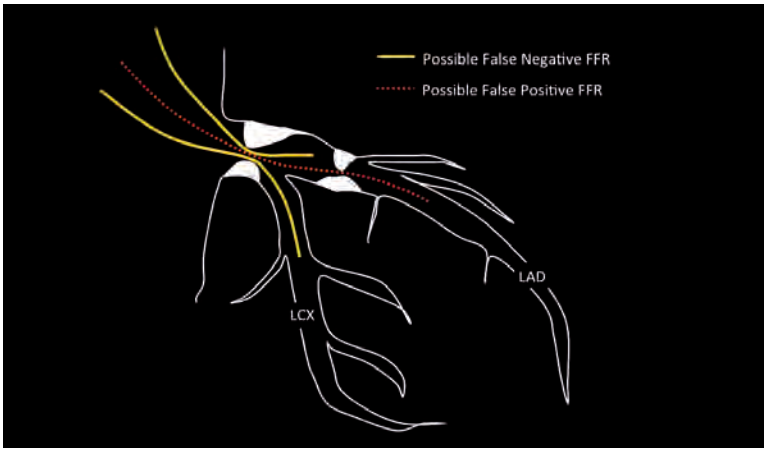
Restenosis: delineating the numerous causes of drug-eluting stent restenosis
Farooq V, Gogas BD, Serruys PW
Circ Cardiovasc Interv. 2011;4(2):195-205

The use of a guide catheter extension system as an aid during transradial percutaneous coronary intervention of coronary artery bypass grafts
Farooq V, Mamas MA, Fath-Ordoubadi F, Fraser DG
Catheter Cardiovasc Interv. 2011;78(6):847-63

Serious adverse incidents with the usage of low molecular weight heparins in patients with chronic kidney disease
Farooq V, Hegarty J, Chandrasekar T, Lamerton EH, Mitra S, Houghton JB, Kalra PA, Waldek S, O'Donoghue DJ, Wood GN
Am J Kidney Dis. 2004;43(3):531-7

The severity of muscle ischemia during intermittent claudication
Egun A, **Farooq V,** Torella F, Cowley R, Thorniley MS, McCollum CN
J Vasc Surg. 2002;36(1):89-93

SECTION VII: BOOK CHAPTERS



Left main coronary artery disease
Farooq V, Serruys PW, Stone GW, Virmani R, Chieffo A, Fajadet J.
Volume II. Part III. Chapter 12.
Percutaneous Interventional Cardiovascular Medicine. The PCR-EAPCI Textbook.

In-stent restenosis
Farooq V, Raber L, Gogas BD, Serruys PW.
Volume II. Part III. Chapter 26.
Percutaneous Interventional Cardiovascular Medicine. The PCR-EAPCI Textbook.

3D-Optical Coherence Tomography
Farooq V, Okamura T, Foin N, Muramatsu T, Alegría-Barrero E, Di Mario C, Serruys PW.
The Clinical Atlas of Intravascular Optical Coherence Tomography. Europa Edition

Risk-benefit analysis
Brugaletta S, Serruys PW, **Farooq V,** Kappetein AP, Stearns SC.
Volume IV. Part IV. Chapter 8.
Percutaneous Interventional Cardiovascular Medicine. The PCR-EAPCI Textbook.

Appendix
SYNTAX-II Clinical Investigational Plan

A single-arm trial to evaluate the effectiveness of PCI of de novo 3 vessel disease applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance, using an everolimus eluting stent with biodegradable abluminal coating

ECRI-002

SYNTAX-II Clinical Investigational Plan

A single-arm trial to evaluate the effectiveness of PCI of de novo 3-vessel disease applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance, using an everolimus-eluting stent with biodegradable abluminal coating

Version 2.0, November 27th, 2013

Sponsor:

European Cardiovascular Research Institute (ECRI)

Westblaak 92

3012 KM Rotterdam

The Netherlands

CRO:

Cardialysis

Westblaak 92

3012 KM Rotterdam

The Netherlands

Protocol approval page

A single-arm trial to evaluate the effectiveness of PCI of *de-novo* 3-vessel disease applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance, using an everolimus-eluting stent with a biodegradable abluminal coating

Protocol version: 2.0, dated 27 November 2013

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

Patrick W. Serruys, Erasmus MC Rotterdam Steering Committee Member, *Chairman*	Date
Javier Escaned, Hospital San Carlos Madrid Steering Committee Member, *Principal Investigator*	Date
Adrian Banning, John Radcliffe Hospital, Oxford Steering Committee Member, *Principal Investigator*	Date
Vasim Farooq, Manchester Royal Infirmary Steering Committee Member, Deputy Study Chair	Date
Gerrit-Anne van Es Managing Director, ECRI-Trials B.V.	Date

Other Steering Committee members:

Arie-Pieter Kappetein, Erasmus MC Rotterdam, *Co-Principal Investigator*

David Taggart, John Radcliffe Hospital, Oxford, *Co-principal Investigator*

Robert-Jan van Geuns, ErasmusMC, Rotterdam, The Netherlands

Hector Garcia, Cardialysis, Rotterdam The Netherlands

TABLE OF CONTENTS

1 PROTOCOL SYNOPSIS

Protocol Number	ECRI-002
Title	A single-arm trial to evaluate the effectiveness of PCI of de novo 3-vessel disease applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance, using an everolimus-eluting stent with a biodegradable abluminal coating.
Objective	• To evaluate the effectiveness of contemporary PCI treatment of de novo 3-vessel disease following the heart team selection applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance (SYNTAX II strategy) • To establish superiority of the SYNTAX II strategy compared to the PCI arm of the SYNTAX I study (Primary endpoint) • To prospectively assess the effectiveness of the SYNTAX Score II for heart team decision making • To prospectively validate the SYNTAX Score II for all-cause death at 1 and 2 year and 5 year follow-up; • To retrospectively validate the residual SYNTAX Score (academic research)
Treatment	SYNTAX II strategy consists of contemporary PCI of de novo 3-vessel disease following the heart team consensus applying the SYNTAX Score II for the heart team selection of patients, pressure wire functional assessment of lesions and IVUS optimization of DES implantation.
Study design	The SYNTAX II Trial is a multicenter, 3-vessel disease, all-comers, open-label, single-arm trial of approximately 450 patients in approximately 25 interventional cardiology centres in Europe. All patients will be treated with an everolimus-eluting stent with a biodegradable abluminal coating. Comparisons will be undertaken using the completed SYNTAX I Trial as a control: Primary endpoint: comparison with PCI (TAXUS Express^2);.
Number of Subjects	450 subjects in total
Investigational Sites	Up to approximately 25 sites in Europe
Follow-up	In-hospital and additional follow-up visits at 1 month, 6 months and 12 months after enrolment.

	In addition, patients will be contacted annually by telephone up to 5 years to check survival status and other MACCE components (patient reported).
Primary Endpoint	The primary endpoint is a composite of MACCE rate (all-cause death, cerebrovascular event (stroke), documented myocardial infarction, or all-cause revascularization) at 1 year follow-up (SYNTAX I definition) compared to PCI arm of the SYNTAX I Trial (Patient Oriented Clinical Endpoint).
Secondary Endpoints	• Composite of all-cause death, cerebrovascular event (stroke), documented myocardial infarction at 1 year follow-up compared to the PCI arm of SYNTAX I; (Safety Endpoint) • Composite of cardiovascular death, documented target-vessel myocardial infarction and repeat target lesion revascularization at 1 year follow-up compared to the PCI arm of SYNTAX I; (Device Oriented Clinical Endpoint) • Rates of individual components of MACCE (all-cause death, cerebrovascular event (stroke), documented myocardial infarction and repeat revascularization) at 1 year; • The composite of MACCE and its individual components at 2-5 years follow-up (patient reported); • Myocardial Infarction – according to Universal MI definition 2012 at all timepoints; • Stent Thrombosis – according to ARC definitions at all timepoints;
Exploratory Endpoint	• Composite of MACCE (all-cause death, cerebrovascular event [stroke], documented myocardial infarction or all-cause revascularization) at 5 years follow-up compared to CABG arm of the SYNTAX I Trial.
General Inclusion and Exclusion Criteria	**Inclusion Criteria:** 1. At least 1 stenosis (angiographic, visually determined de novo lesions with ≥50% DS) in all 3 major epicardial territories (LAD and/or side branch, CX and/or side branch, RCA and/or side branch) supplying viable myocardium without left main involvement; (Patients with ostial LAD *or* ostial CX - Medina 0,0,1 *or* Medina 0,1,0 – may be enrolled)

	2. Patients with hypoplastic RCA with absence of descending posterior and presence of a lesion in the LAD and CX territories may be included in the trial as a 3VD equivalent; 3. Vessel size should be at least 1.5 mm in diameter as visually assessed in diagnostic angiogram; 4. Patients with a) stable (Canadian Cardiovascular Society Class 1, 2, 3 or 4) angina pectoris; b) or unstable (Braunwald class IB, IC, IIB, IIC, IIIB, IIIC) angina pectoris and ischemia; c) or patients with atypical chest pain or those who are asymptomatic provided they have myocardial ischemia (e.g. treadmill exercise test, radionuclide scintigraphy, stress echocardiography); 5. All anatomical SYNTAX Scores are eligible for initial screening with the SYNTAX Score II; 6. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee of the respective clinical site; 7. Signed Heart Team Decision Form between local cardiologist and surgeon that the selected case meets all of the inclusion and exclusion criteria; **Exclusion Criteria:** Candidates will be ineligible for enrolment in the study if any of the following conditions apply: 1. Under the age of 21 years; 2. Known pregnancy at time of enrolment. Female of childbearing potential (and last menstruation within the last 12 months), who are not taking adequate contraceptives. Female who is breastfeeding at time of enrolment; 3. Prior PCI or CABG; 4. Ongoing acute myocardial infarction and enzymes CKMB >2x upper limit of normal; 5. Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement); 6. Single or two-vessel disease (at time of Heart Team consensus);

	7. Participation or planned participation in another cardiovascular clinical study before one year follow up is completed; 8. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language barrier such that the patient is unable to give informed consent and potential for non-compliance towards the requirement in the study protocol.
Antiplatelet Medication	Dual Antiplatelet treatment is mandatory for at least 6 months; aspirin indefinitely. *Loading dose:* • All patients must receive aspirin ≥300 mg/day starting 12-24 hours prior to the procedure (even if the subject is on chronic aspirin therapy). • Clopidogrel loading dose must be 600 mg, starting 12-24 hours prior to the procedure (even if the subject is on chronic clopidogrel therapy). Alternatively: • Prasugrel 60 mg >1 hr before PCI; or • Ticagrelor 180 mg >1 hr before PCI if approved by the local regulatory authorities during the enrolment period of this protocol. *Maintenance dose:* Starting from the day after the procedure, aspirin 75-100 mg/day will be prescribed to all patients indefinitely. Additionally, all patients must receive platelet aggregation inhibition therapy for at least 6 months as currently recommended by the ESC/AHA/ACC guidelines which includes: • Clopidogrel 75 mg once daily. Alternatively: • Prasugrel 10 mg once daily; or (The dose of prasugrel may be decreased to 5mg od in patients with a weight <60 kg or age >75 years). • Ticagrelor (90mg bid)

2 INTRODUCTION

The anatomical-based SYNTAX Score (http://www.syntaxscore.com) has established itself as a tool to aid the Heart Team consensus in determining the optimal revascularization modality in patients with unprotected left main coronary artery (ULMCA) disease or de novo three vessel disease (3VD).[1-10] The anatomical based SYNTAX Score was designed and implemented in the landmark SYNTAX Trial,[4, 7, 10] as an instrument to force the interventional cardiologist and cardiac surgeon to examine the coronary angiogram, and agree that equivalent anatomical revascularisation could be achieved. Only after the publication of the SYNTAX Trial did the importance of the anatomical SYNTAX Score become clear. Namely, in appropriately guiding decision making between coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) for the treatment of complex coronary artery disease. Since publication of the SYNTAX Trial, the anatomical-based SYNTAX Score, has been validated in multiple studies, and has recently been advocated in both the US and European revascularization guidelines, as a tool to guide the clinician in determining the optimal revascularization modality (CABG or PCI) in patients with complex coronary artery disease.[8, 9, 11-13]

Dedicated studies in the post SYNTAX Trial era investigating 3VD remain scarce. As of present, current revascularization guidelines recommend that a low SYNTAX Score (0-22) may offer similar clinical outcomes between percutaneous coronary intervention (PCI) with drug eluting stents (DES) and coronary artery bypass graft (CABG) surgery.[11-13]

Diabetes

Outcomes in diabetic patients have historically lacked suitably powered randomized trials. Meta-analyses of trials comparing CABG against PCI in the pre-DES era (balloon angioplasty and bare metal stents) have shown a potential prognostic advantage of CABG compared to PCI.[14, 15] A major limitation of these studies were however that the studies were not all-comers in design, with patients ‘cherry-picked’ for randomisation based on restrictive inclusion and exclusion criteria, making application to clinical practice questionable.[16, 17]

In the DES era, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial,[18, 19] consisting of 1900 patients with two or 3VD, randomised to CABG or PCI with first generation DES, showed a prognostic advantage for CABG at a median follow up of 3.8 years. At 5 years follow up, only 678/1900 patients reached this time point, with 197 deaths recorded. In this subset of patients, there was no interaction between the SYNTAX Score and treatment (p=0.58). There was however a stepwise increase in death, MI, or stroke in patients that underwent PCI (low SYNTAX Score: 19.4%, intermediate SYNTAX Score: 22.2%, high SYNTAX Score: 31.0%), but not in those treated with CABG (low SYNTAX Score: 20.1%, intermediate SYNTAX Score: 21.5%, high SYNTAX Score: 16.0%). The FREEDOM Trial was however underpowered to assess the SYNTAX Score at 5 years.[9, 20]

Conversely, diabetics in the SYNTAX Trial (a pre-stratified powered subgroup), has shown that low SYNTAX Scores to be associated with comparable long term mortality and composite clinical outcomes (major adverse cardiac and cerebrovascular events [MACCE]).[20-22]

Left Main Coronary Artery Disease

Based on the results of the SYNTAX Trial, in which short and long term outcomes were similar between CABG and PCI in subjects with unprotected left main coronary artery (ULMCA) disease with an anatomical SYNTAX Score <33,[4, 7, 10] the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was conceived (ClinicalTrials.gov Identifier: NCT01205776). EXCEL is an ongoing, international, multicentre trial, aiming to recruit 2600 patients with ULMCA disease and a SYNTAX Score <33 – randomized to surgical (n=1300) or percutaneous (with the XIENCE PRIME or XIENCE V DES [n=1300]) revascularization.[23] Notably the US Food and Drug Administration (FDA) mandated the anatomical-based SYNTAX Score as entry criteria within the EXCEL Trial.

SYNTAX Score II

The category based risk approach of the anatomical-based SYNTAX Score – i.e. "low", "intermediate," or "high" SYNTAX Scores – to guide decision making between CABG or PCI, has been shown to be potentially misleading in a post hoc analysis of the SYNTAX Trial.[24] Within this study, it was shown that low and high risk subjects existed in higher and lower SYNTAX Score tertiles, which appeared to have implications for the most appropriate revascularisation modality (CABG and PCI); e.g. there was a doubling of 3-year mortality in subjects with 3VD – with a low SYNTAX Score (<23) and a high additive EuroSCORE (≥6) – who underwent PCI compared to CABG.[24] In addition, a recent study pooling over 6000 PCI subjects treated with DES, demonstrated that the addition of clinical variables to the anatomical SYNTAX Score, substantially increased the accuracy of identifying low (and high) risk patients compared to the anatomical SYNTAX Score alone.[25]

The SYNTAX Score II[26, 27] was designed to improve decision making between CABG and PCI, by allowing for a long term, individualized risk assessment of patients with complex coronary artery disease. The SYNTAX Score II combined the anatomical based SYNTAX Score with clinical variables, that were shown to alter the threshold value of the SYNTAX Score so that equipoise was achieved between CABG and PCI for long term mortality. These included the presence of unprotected left main coronary artery disease, female gender,[28] chronic obstructive pulmonary disease, age and left ventricular ejection fraction. The SYNTAX Score II was developed in the randomized SYNTAX Trial (n=1800), and validated in the multicentre Drug Eluting stent for LefT main coronary Artery disease (DELTA) Registry (n=2891).[29] Importantly the DELTA Registry was a multinational, non-randomised, all-comers registry, conducted in 14 centres in Europe, US and South Korea. The study population was heterogeneous, and included complex coronary artery disease – anatomical SYNTAX Score ≥33 existed in 30%, and 3VD in 26%, of the DELTA Registry.

During development and validation of the SYNTAX Score II, it was shown that diabetes did not improve decision making between CABG and PCI. Findings that were consistent with a previous study of over 6000 patients treated with DES, where it was shown that the presence of diabetes minimally affected long term mortality predictions after PCI with DES, when age, kidney

function and left ventricular ejection fraction were accounted for.[25] Subsequent epidemiology/population based studies have further supported these findings.[30, 31]

By utilizing the individualized approach of the SYNTAX Score II, in contrast to the anatomical-based SYNTAX Score tertiles, a subset of patients with low, intermediate or high SYNTAX Scores were identified, that would have lower, similar, or higher 4-year mortality predictions for CABG or PCI. Specifically for 3VD, approximately 80%, 60% and 30% of patients in the respective low, intermediate and high SYNTAX Score tertiles of the randomised SYNTAX population would have similar long-term mortality between CABG and PCI (**Appendix II**).

Contemporary PCI Practice and the SYNTAX Trial

Overall, the amount of information gathered in the SYNTAX Trial has helped shape both clinical practice and international guidelines in the management of complex coronary artery disease. The conclusions drawn in the SYNTAX Trial since its publication do however not take into account areas in which the progress has been made in more contemporary interventional practice. Some of these are discussed in the following paragraphs:

1) ***Chronic total occlusion recanalization:*** In SYNTAX, the presence of a (chronic) total occlusion (C)TO was identified to be the strongest independent predictor of incomplete revascularisation in the PCI arm of the SYNTAX Trial.[32, 33] Over the last 10 years the practice of (C)TO recanalization has been largely modified by the systematisation in the approach to (C)TO recanalization and the development of new devices. Although acquaintance with these techniques is still limited among interventional cardiologists, international registries have consistently reported that skilled, dedicated (C)TO operators have success rates of 85-95%, a much higher success rate that that observed in SYNTAX operators (approximately 50%).[34] Major technical improvements include the development of new coronary wires, dedicated intracoronary cathethers (Corsair,® Tornus,® CrossBoss™) and re-entry devices (The Stingray™ CTO Re-Entry System).[35] Contemporary (C)TO procedures are performed both in anterograde or retrograde fashion (through collateral channels), frequently with the concourse of IVUS imaging. Virtually all these developments were not applied to (C)TO recanalization in SYNTAX. It will therefore be encouraged that each participating centre should select an expert

in (C)TO revascularisation who should be involved in the procedure whenever a (C)TO is involved.

2) ***Ischemia-driven revascularisation****:* A large body of evidence, largely based on the use of fractional flow reserve (FFR), has demonstrated that, compared with angiography, decision making of coronary revascularisation based on physiological assessment of stenosis severity results in improved patient outcomes.[36-39] Recalculation of the SYNTAX score by incorporating FFR-derived information of stenosis severity (functional SYNTAX score[40]) may decrease the number of higher-risk patients with multivessel disease undergoing PCI and contribute to a better discrimination of risk for adverse events in this subset of patients. A new pressure-derived index, instantaneous wave-free ratio (iFR), that allows faster adenosine-free assessment may be more ideally suited for multiple measurements performed in the context of multivessel disease.[41]

3) ***Imaging guidance of PCI procedures****:* While the proposal of using intravascular ultrasound (IVUS) to tackle restenosis made in the bare metal stent (BMS) era was virtually abandoned with the arrival of drug eluting stents (DES), a growing body of evidence suggests that DES implantation with IVUS guidance in complex anatomical subsets may contribute to better patient outcomes. Specifically, a recent meta-analysis of IVUS guided DES implantation in almost 20 000 subjects has reported significantly reductions in stent thrombosis and mortality.[42, 43]

4) ***Newer generation DES****:* Compared to first generation DES, newer generation DES have proven reductions in stent thrombosis and other clinical outcomes. This has largely been through the design of more biocompatible polymers, biodegradable polymers, limus based drugs, thinner stent struts through the incorporation of metallic alloys with greater radial strength, and increased deliverability of the devices.[44-49] Outcomes of the SYNTAX Trial related to newer generation DES are therefore unknown and will be investigated in the current study.

Purpose of Study

The purpose of the planned SYNTAX II Trial is to investigate the management of de-novo 3VD in order to prospectively assess which patients would have at least comparable short and long term clinical outcomes between CABG and PCI, using contemporary PCI practice. In SYNTAX II the effectiveness of a contemporary stent (the new generation SYNERGYTM DES, designed with thinner struts, biocompatible and biodegradable polymer, and a limus based drug50, 51), the use of pressure wire assessment of lesions to allow for ischemia-driven revascularisation, IVUS guidance to optimise DES deployment, and the treatment of (C)TO lesions with contemporary techniques, will be compared against PCI practice in the original SYNTAX trial. The proposed study would involve the SYNTAX Score II to prospectively recruit subjects on the grounds of patient safety.26, 27

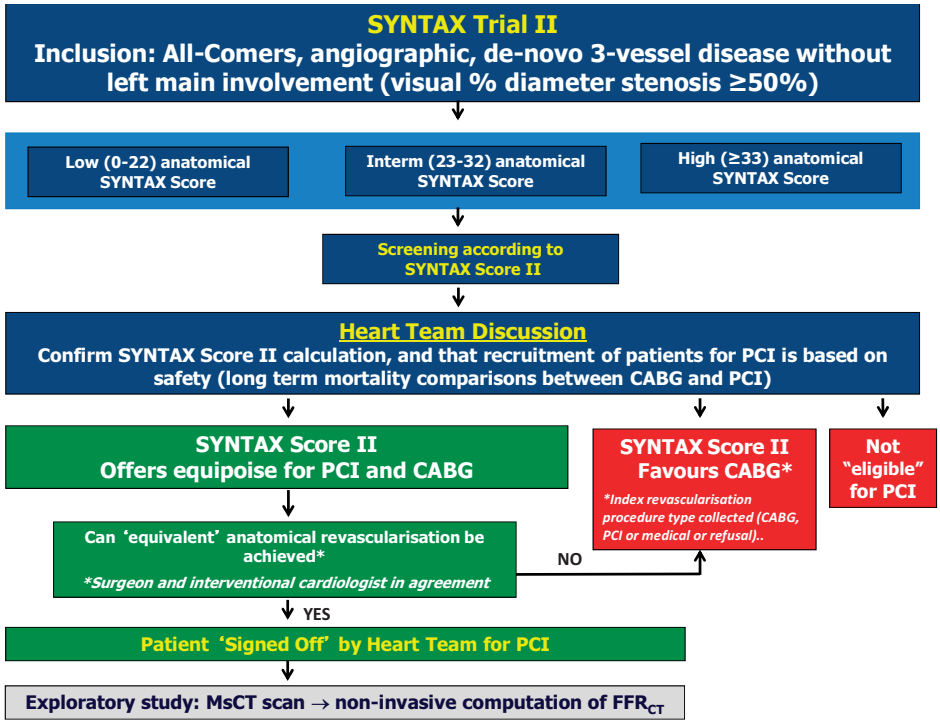
3 OBJECTIVE

- To evaluate the effectiveness of contemporary PCI treatment of de novo 3-vessel disease following the heart team selection applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance (SYNTAX II strategy).
- To establish superiority of the SYNTAX II strategy compared to the PCI arm of the SYNTAX I study (Primary Endpoint).
- To prospectively assess the effectiveness of SYNTAX Score II for heart team decision making.
- To prospectively validate the SYNTAX Score II for all-cause death at 1 and 2 year and 5 year follow-up.
- To retrospectively validate the residual SYNTAX Score (academic research)[52, 53].

Comparisons will be undertaken using the completed SYNTAX I Trial as a historical control:4 Primary Endpoint – PCI cohort (TAXUS Express2);

4 STUDY DESIGN

The SYNTAX-II Trial is a multicenter, 3-vessel disease, all-comers, open-label, single arm trial of approximately 450 patients in approximately 25 interventional cardiology centres in Europe. All patients will be treated with the Boston Scientific SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System.



Study Flowchart: Part-1: Heart Team algorithm

1. All patients with *de-novo* 3-vessel disease (DS ≥50%), with no left main involvement, will be screened by the local Heart Team (interventional cardiologist and cardiac surgeon). Initial enrolment criteria will be unrestrictive and similar to the SYNTAX Trial.[3, 4] As per the original SYNTAX Trial, prior CABG or PCI will be one of the very few exclusion criteria.
2. All patients will have anatomical SYNTAX Scores and EuroSCOREs (I and II)[54-58] undertaken, and will undergo further assessment by the Heart Team for enrolment in the study.
3. All patients will have the SYNTAX Score II prospectively determined by the Heart Team using an online calculator (**Appendix III**). The SYNTAX Score II will be used to objectively determine if the patient is suitable for PCI, CABG, or both revascularization modalities. Based on SYNTAX Score II in the SYNTAX Trial, approximately 80%, 60% and 30% of patients in the low, intermediate and high SYNTAX Score tertiles respectively, would have at least similar long-term mortality between CABG and PCI (**Appendix II**). Patients not suitable for PCI based on the SYNTAX Score II assessment will undergo CABG, unless contraindicated. In patients not eligible for SYNTAX II trial, the index revascularisation procedure type will be collected (i.e. CABG, PCI, medical treatment or refusal).

Equivalent Anatomical Revascularization

As per the SYNTAX Trial, patients must be able to undergo "*equivalent anatomical revascularization*," based on the SYNTAX Trial definition of 1.5 mm vessels being revascularised, as agreed by the cardiac surgeon and interventional cardiologist during the Heart Team meeting.[3] Patients not suitable for equivalent anatomical revascularization will undergo CABG, unless contraindicated. For patients not eligible for SYNTAX II trial, the index revascularisation procedure type will be collected (i.e. CABG, PCI, or medical treatment or refusal).

Exploratory sub-study

After the Heart Team consensus, but prior to PCI procedure, a multislice computed tomography (MSCT) scan should be obtained (documentary only). MSCT will not be used in process of Heart Team discussion. The MSCT scan will be processed by HeartFlow Inc. (Redwood city, California, USA). HeartFlow's technology enables the computation of FFR_{CT} in a non-invasive manner.[8, 59-62] Results will only become available after completion of the SYNTAX II study.

Reporting of Study Endpoints

The primary endpoint will be reported at 1 year. At 2-5 years follow-up, all patients will be contacted by telephone to check survival status and other MACCE components (patient reported). From all screened patients the index treatment type (i.e. CABG, PCI, medical, other) will be collected.

Clinical data will be adjudicated by an independent Clinical Event Committee (CEC). Ongoing safety monitoring will be performed by a Data Safety Monitoring Board (DSMB).

4.1 Risk Factor Modification

Tight control of risk factors will be mandated in line with the European and US revascularisation guidelines.[11, 12] Cholesterol reduction, with a LDL ≤1.8, will be an additional protocol defined target the operator will be recommended to record and control.

In summary, patients (de-novo 3VD) will be treated according to ACC/AHA/ESC guidelines, i.e. Heart Team discussion (Ia); functional evaluation for diagnosis in absence of objective evidence of ischemia (Ia); and LDL levels ≤1.8mmol (Ia).

5 ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is a composite of MACCE at 1 year follow-up compared to PCI arm of the SYNTAX I Trial (acting as a historical control) (Patient Oriented Clinical Endpoint)

MACCE is defined as: all-cause death; cerebrovascular event (stroke); documented myocardial infarction or all-cause revascularization).

5.2 Secondary endpoints

Secondary endpoints of this study are to assess:

- Composite of all-cause death, cerebrovascular event (stroke), documented myocardial infarction at 1 year follow-up compared to the PCI arm of SYNTAX I; (Safety Endpoint)
- Composite of cardiovascular death, documented target-vessel myocardial infarction and repeat target lesion revascularization at 1 year follow-up compared to the PCI arm of SYNTAX I; (Device Oriented Clinical Endpoint)
- Rates of individual components of MACCE (all-cause death, cerebrovascular event (stroke), documented myocardial infarction and repeat revascularization) at 1 year;
- The composite of MACCE rate and its individual components at 2-5 years follow-up (patient reported);
- Myocardial Infarction – according to Universal MI definition 2012 at all timepoints;
- Stent Thrombosis – according to ARC definitions at all timepoints;

5.3 Exploratory endpoint

- Composite of MACCE (all-cause death, cerebrovascular event (stroke), documented myocardial infarction or all-cause revascularization) at 5 years follow-up compared to CABG arm of the SYNTAX I Trial

6 SUBJECT SELECTION

Patient selection will be from all-comers de novo 3VD patients. Anatomical SYNTAX and SYNTAX II Scores, will be undertaken to objectively determine if CABG or PCI offer a least similar long term mortality.

Approximately 450 3-vessel disease all-comers patients will be enrolled. The recruitment will be competitive.

6.1 Inclusion Criteria

1. At least 1 stenosis (angiographic, visually determined de novo lesions with ≥50% DS) in all 3 major epicardial territories (LAD and/or side branch, CX and/or side branch, RCA and/or side branch) supplying viable myocardium without left main involvement;
   (Patients with ostial LAD *or* ostial CX - Medina 0,0,1 *or* Medina 0,1,0 – may be enrolled)
2. Patients with hypoplastic RCA with absence of descending posterior and presence of a lesion in the LAD and CX territories may be included in the trial as a 3VD equivalent;
3. Vessel size should be at least 1.5 mm in diameter as visually assessed in diagnostic angiogram;
4. Patients with
   a) stable (Canadian Cardiovascular Society Class 1, 2, 3 or 4) angina pectoris;
   b) or unstable (Braunwald class IB, IC, IIB, IIC, IIIB, IIIC) angina pectoris and ischemia;
   c) or patients with atypical chest pain or those who are asymptomatic provided they have myocardial ischemia (e.g. treadmill exercise test, radionuclide scintigraphy, stress echocardiography);
5. All anatomical SYNTAX Scores are eligible for initial screening with the SYNTAX Score II;
6. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee of the respective clinical site;
7. Signed Heart Team Decision Form between local cardiologist and surgeon that the selected case meets all of the inclusion and exclusion criteria;

6.2 Exclusion Criteria

Candidates will be ineligible for enrolment in the study if any of the following conditions apply:

1. Under the age of 21 years;

2. Known pregnancy at time of enrolment. Female of childbearing potential (and last menstruation within the last 12 months), who are not taking adequate contraceptives. Female who is breastfeeding at time of enrolment;

3. Prior PCI or CABG;

4. Patients with ongoing acute myocardial infarction and enzymes CKMB >2x upper limit of normal;

5. Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement);

6. Single or two-vessel disease at the time of Heart Team consensus;

7. Participation or planned participation in another cardiovascular clinical study before one year follow up is completed;

8. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language barrier such that the patient is unable to give informed consent and potential for non-compliance towards the requirement in the study protocol.

7 STUDY PROCEDURES

7.1 Patient Information and Informed Consent

All potential subjects must be consented prior to undergoing any study-specific procedures. Once the subject's general eligibility for the study is met, the background of the proposed study and the benefits and risks of the procedures and study must be explained to the subject prior to obtaining informed consent. Only those subjects who sign the Ethics Committee approved informed consent form prior to any study-specific procedures are candidates for actual enrolment in the study. Failure to provide written informed consent renders the subject ineligible for the study.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It is the investigator's responsibility to ensure that the informed consent process is performed in accordance with ISO14155, EC requirements and country specific regulations.

7.2 Baseline evaluation

The following routine tests will be performed:

a) Routine laboratory tests prior to the procedure according to local hospital practice. Creatinine and creatinine clearance (Cockcroft and Gault[63]) are mandated to be performed prior to procedure. Cardiac enzymes must be sampled prior to the PCI procedure in order to detect acute myocardial infarction (AMI) patients. Prior to the PCI procedure the cardiac enzymes (CK-MB or Troponin) must be less than 2-times the upper limit of normal (<ULN).
b) 12-lead electrocardiogram pre, and post procedure and at discharge

7.3 Anatomical, residual and functional SYNTAX Scores

The baseline anatomical SYNTAX Score and SYNTAX Score II will be recorded in the eCRF. All procedural coronary angiograms will be collected and allowances made for the export of this data to Cardialysis, Rotterdam. No analyses will be performed by the Core Laboratory. At a later stage post hoc analysis of the baseline anatomical SYNTAX Score, residual SYNTAX Score[52, 53] and functional SYNTAX Score[40] will be undertaken (academic research).

7.3.1 EuroSCORE and EuroSCORE II

EuroSCORE and EuroSCORE II will be collected and recorded in the eCRF.

7.4 Patient Allocation

Calculation of the SYNTAX Score II and prognostic outcomes (mortality predictions) following CABG or PCI will be determined at 4 years using the SYNTAX Score II online calculator. Individual mortality predictions for CABG and PCI that can be separated with 95% confidence (ie, that can be statistically separated, $p<0{\cdot}05$) will have a treatment recommendation for either CABG alone or PCI alone. Individual mortality predictions for CABG and PCI that cannot be separated with 95% confidence (i.e., could not be statistically separated, $p>0{\cdot}05$) will have a treatment recommendation for either CABG or PCI.

Comparisons of 4 year mortality predictions will be undertaken using the SYNTAX Score II online calculator, which will incorporate statistical comparisons of mortality predictions for CABG and PCI (as previously highlighted). The online calculator will provide the heart team with an objective treatment recommendation, namely, CABG is recommended, PCI is recommended, or either CABG or PCI is recommended. Final decision of treatment recommendation will be left at the discretion of the heart team after formal dialogue with the patient and provision of the prognostic information. The heart team may overrule the treatment recommendation made by the online calculator. Reasons for undertaking this should be clearly documented in the eCRF.

Having established that the patient could be potentially recruited based on the SYNTAX Score II on the grounds of patient safety, subjects will be assessed by the heart team as to whether *"equivalent anatomical revascularization"* could be potentially achieved between CABG and PCI. Secondly, the heart team must clearly establish that both CABG and PCI would be equally offered to the patient. If the patient fulfils both criteria then the patient may be recruited in the SYNTAX II Trial.

The decision for the subject's inclusion into SYNTAX II will be documented and *'signed off'* by both members of the local Heart Team (Heart Team Worksheet) - subsequently investigator will receive patient allocation number.

7.5 MSCT

After Heart Team consensus, but prior to the planned PCI procedure, a MSCT scan should be obtained (documentary only). Refer to Appendix VI for MSCT acquisition protocol. The MSCT results and results of MSCT-derived FFR will only become available after completion of the SYNTAX II study, and therefore investigators will be blinded to its results during the study. Furthermore, the analysis of MSCT and FFR_{CT} will be performed by analysts blinded to iFR/FFR and angiographic data.

7.5.1 MSCT and angiographic SYNTAX Score: Exploratory Endpoint

- To prospectively examine the value of an objective anatomic SYNTAX Score based on non-invasive MSCT imaging - compared to conventional angiographic SYNTAX Score as visually assessed by the Heart Team.

7.5.2 MSCT and non-invasive FFR_{CT}: Exploratory Endpoints

- To prospectively compare, in a population of patients with multi-vessel disease, functional stenosis severity assessed with non-invasive FFR_{CT} with invasive functional assessment with iFR/FFR, using per-vessel comparisons. Per vessel analysis will be performed to calculate the percentage of vessels properly classified by MSCT-FFR, in terms of haemodynamic stenosis severity, compared to invasive iFR/FFR measurements.
- To prospectively compare, in a population of patients with multi-vessel disease, functional SYNTAX scores calculated from a) multi-slice computed tomography coronary angiography and non-invasive FFR, and b) conventional angiography and iFR/FFR. In both a) and b), functional SYNTAX score is defined as anatomical SYNTAX scoring limited to vessels with haemodynamically significant stenoses (as estimated by HeartFlow [non-invasive functional SYNTAX score] or iFR/FFR [invasive functional SYNTAX score])

7.6 Index Procedure

7.6.1 iFR/FFR

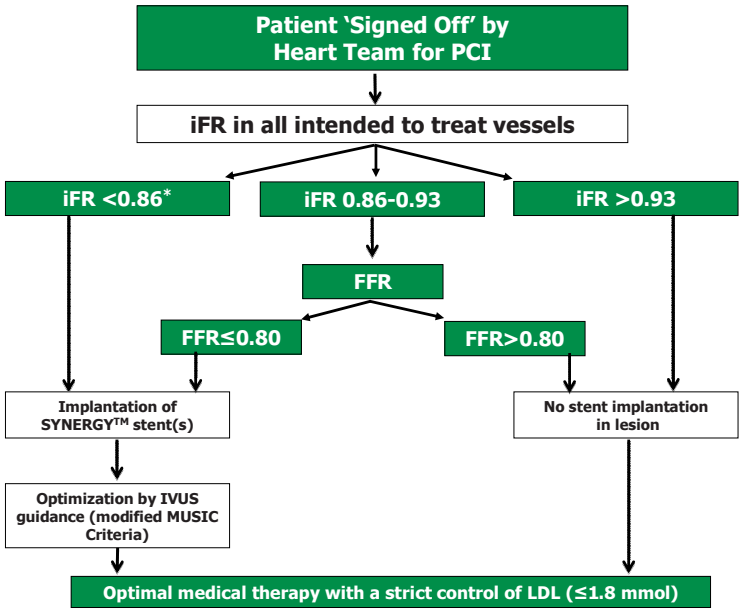
All centres must be experienced in PCI of complex coronary artery disease, utilizing functional (iFR/FFR) and IVUS guidance.

iFR is a recently introduced pressure-derived index for the assessment of coronary stenosis severity that, at difference to FFR, does not require adenosine administration and provides an estimation of stenosis severity a few seconds after crossing the stenosis with the pressure guide-wire.[41] These characteristics make iFR a more ideal method to apply ischemia driven revascularisation in patients with 3VD, in whom multiple measurements are required.

The subject will undergo invasive adenosine-free iFR® assessment of all 3 major epicardial vessels. All lesions intended to be treated should be interrogated, including side-branches. Total occlusions and culprit lesions of acute coronary syndromes[64-66] preclude iFR measurements. iFR values will be collected with the PrimeWire Prestige Plus with Accuesense™ technology. In

place of the PrimeWire Prestige Plus wire, the Verrata™ wire will be permitted to be used in the study once the wire has received an expected CE-mark.

In SYNTAX II ischemia driven revascularisation will be performed following a hybrid decision-making strategy of coronary revascularisation with iFR and FFR.[67] The use of a hybrid iFR/FFR approach, currently undergoing testing in the ADVISE II study (ClinicalTrials.gov Identifier: NCT01740895) has the potential of significantly reducing the need for adenosine administration, whilst maintaining a 95% classification agreement to the FFR-only strategy.[67]



**** Consider FFR pullback with sequential lesions***

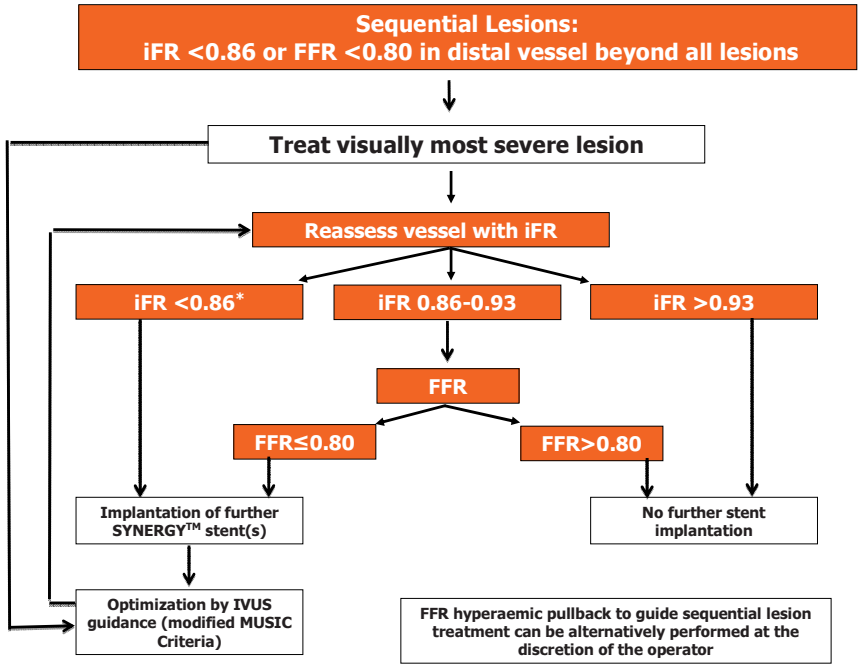
Study Flowchart: Part-2: PCI procedure

iFR values will be collected with the PrimeWire Prestige Plus (or Verrata™ wire) with Accusense™ technology.

In case of iFR <0.86 the lesion will be treated by PCI. If iFR is ≥0.86 and ≤0.93, FFR is mandated to be measured using i.v. or i.c. adenosine, and the decision to treat will be based on an FFR cutoff of 0.80. iFR >0.93 the stenosis should not be treated.

In subjects with contraindications to adenosine administration, revascularisation will be performed using iFR as a dichotomous index, using most recently reported cutoff value of iFR <0.89 for haemodynamic significance.[67]

In case of sequential lesions, the procedure depicted in the flowchart should be followed.



Study Flowchart: Part-2a: PCI procedure (sequential lesions)

iFR/FFR values will be recorded in the eCRF. No analysis will be performed by the core laboratory. Export of recordings to Cardialysis will be performed for post hoc analysis at a later stage (academic research).

7.6.2 Stent implantation

Stent implantation will be performed according to routine local clinical practice using the femoral, brachial or radial approach with the intention of achieving equivalent anatomical revascularization to CABG. The radial approach, although not mandated, will be strongly recommended.[68]

Patients will exclusively be implanted with the SYNERGY™ stent.[50, 51] Stenting should be attempted for each lesion in a vessel with a >1.5 mm in diameter as assessed on the diagnostic angiogram and agreed to be revascularised by the Heart Team in order to achieve equivalent anatomical revascularization.

IVUS use at pre-PCI is left to the discretion of the investigator. IVUS assessment post stent implantation for optimisation of stent deployment is mandated (see part 7.5.3).

If the implantation of the SYNERGY stent was not successful, the reason should be recorded in the CRF.

7.6.2.1 Treatment of Bifurcations

All types of bifurcation may need stenting of the main vessel, and/or the side branch, followed by kissing balloon post-implantation if a two stent approach is adopted. The treatment goal is to avoid gaps whenever more than one stent is used. Bifurcation techniques will be selected depending on the anatomy and morphology, although it is expected that most lesions would require a simple (provisional) approach, in keeping with recommendations from the European Bifurcation Club.[69, 70]

Stent sizing in bifurcation stenoses should take into account vessel diameter mismatch between mother and daughter vessels, following the recommendations of the European Bifurcation Club[69, 70] (see also Appendix V for detailed treatment of bifurcations – mandated and recommended strategies).

7.6.2.2 Treatment of Total Occlusions

It has recently been shown that the presence of a total occlusion (TO) to be the strongest independent predictor of incomplete revascularisation in the PCI arm of the SYNTAX Trial.[32, 33] Operator skill and use of specific techniques and devices are key determinants PCI success in CTOs.[34] A dedicated chronic total occlusion (CTO) operator is recommended to be made available in all participating centres. Staging of the revascularisation procedure should be encouraged, to ensure CTOs are appropriately revascularised. CTO recanalization can be performed using the antegrade or retrograde approach, as well as using specific re-entry techniques such as the StingRay device [71] Selection of stent length can be based on IVUS imaging. Viability assessment of total occlusions will be left at the discretion of the operator.[72-77] A tolerant attitude, refraining stenting towards moderate stenoses located distal to the occluded segment should be followed, on the grounds of important vessel diameter shift after vessel recanalization.[78]

7.6.3 Intravascular Ultrasound (IVUS)

In SYNTAX II Trial, mechanical IVUS catheters (Revolution® Rotational Imaging Catheter / Volcano Therapeutics or Atlantis™ SR Pro or SR Pro2 Imaging Catheter or Opticross™ / Boston Scientific Corp) or phase array IVUS catheters (EagleEye® Platinum Digital IVUS Catheter / Volcano Therapeutics) will be used to guide SYNERGY implantation. Use of either motorised or manual IVUS pullback will be allowed, although motorised pullback is recommended.

Both Boston and Volcano IVUS consoles have incorporated simplified software algorithms into their consoles to allow for the operator to undertake these calculations, and allow export of the data for post hoc analysis at a later stage. The following are the recommendations made on the grounds of evidence collected in the DES era:

- **Plaque preparation based on pre-procedural IVUS.** Rotational atherectomy or cutting balloon should be considered if a >270° arc of superficial calcium is evident in IVUS.[79] Pre-procedural IVUS is left to the discretion of the investigator (not mandatory).
- **Selection of SYNERGY dimensions.** Separate recommendations are given for selecting SYNERGY stent diameter in bifurcation and non-bifurcation stenoses.
    - In ***non-bifurcation*** stenoses: stent diameter matching distal vessel diameter or area (See table in **Appendix IV**).
    - In ***bifurcation*** stenoses: stent diameter matching distal (daughter) branch, with mandatory post-dilation of the proximal (mother) segment and polygon of confluence (POC) with a larger balloon size according to IVUS imaging. Regarding stent length, IVUS can be useful in outlining the presence of significant neighbour stenoses that might cause in-flow or out-flow narrowing after DES implantation, a very common finding in cases of DES thrombosis that is believed to be causative.
    - **Incomplete stent *expansion*:** See IVUS criteria **Appendix IV**.
    - **Incomplete stent *apposition*.** A non-compliant balloon sized with IVUS to vessel luminal diameter or area will be used in segments with malapposition (See table in Appendix IV)

No analyses will be performed by the Core Laboratory. However, allowances will be made for export of IVUS data to Cardialysis, Rotterdam for potential post hoc analysis at later stage (academic research).
The operator will record the numerical values of the IVUS targets in the eCRF.

7.6.4 Staged procedures

Staged procedures are permitted, and will be encouraged for more complex cases – e.g. revascularization of total occlusions – to increase the likelihood of complete revascularization and to decrease the risk of contrast induced nephropathy.

The recommended timing of a planned elective staged second PCI procedure is within 2 weeks post index procedure (with an upper limit allowed for 4 weeks in exceptional circumstances). The need for staging, and all specific lesions planned to be treated during the staged procedure should be captured beforehand in the eCRF. Staged procedures are only allowed in non-target vessels. Stented index segments or immediately adjacent segment(s), including adjacent branch segment(s) should not be manipulated again. The staged procedures will not affect the original follow-up schedule. Staged procedures should be performed in the exact same manner as the index procedure, including iRF/FFR, IVUS, medications, etc.

7.7 Concomitant Medications

Optimal medical therapy will be mandated in all patients and will be assessed at clinical follow-up visits.

7.7.1 Anti-Platelet Medication

Dual antiplatelet (aspirin + clopidogrel/ticagrelor/prasugrel) will be mandated for at least 6 months, aspirin indefinitely. Ticagrelor therapy will be encouraged to be continued in patients already receiving this therapy, based on this regime having been shown to have the best safety to efficacy ratio.[80, 81]

Loading dose:

- All patients must receive aspirin ≥300 mg/day starting 12-24 hours prior to the procedure (even if the subject is on chronic aspirin therapy).
- Clopidogrel loading dose must be 600 mg, starting 12-24 hours prior to the procedure (even if the subject is on chronic clopidogrel therapy).

On the rare occasion of a patient not receiving aspirin or clopidogrel as outlined above, the procedure is to be deferred until appropriate administration of antiplatelet therapy has been attained. Loading of antiplatelet therapy immediately prior to PCI should be discouraged, since lack of pre-procedural anti-platelet therapy was linked to creatine kinase (CK) cardiac enzyme rises >2 x upper limit of normal post PCI and adverse mortality in the SYNTAX Trial.[28, 82]

Alternatively:

- Prasugrel 60 mg >1 hr before PCI; or
- Ticagrelor 180 mg >1 hr before PCI if approved by the local regulatory authorities during the enrolment period of this protocol.

Maintenance dose:

Starting from the day after the procedure, aspirin 75-100 mg per will be prescribed to all patients indefinitely.

Additionally, all patients must receive platelet aggregation inhibition therapy for at least 6 months as currently recommended by the ESC/AHA/ACC guidelines which includes:

- Clopidogrel 75 mg once daily.

Alternatively:

- Prasugrel 10 mg once daily; or
  (The dose of prasugrel may be decreased to 5mg od in patients with a weight <60 kg or age >75 years).
- Ticagrelor (90 mg bid)

7.7.2 Other medication

- Unless contraindicated, peri-procedural IIb/IIIa inhibitor will be given according to the guidelines.[11-13]
- The use of other medications (e.g. beta-blockers, ACE inhibitors) should be given in accordance to the guidelines.[11-13]

7.7.3 PCI Statin therapy

Optimal medical therapy with strict control of LDL (target of ≤1.8 mmol/l) is strongly recommended, along with optimization of all medical therapy – rosuvastatin/atorvastatin (according to the guidelines). Strict control of LDL levels is recommended aiming for a target of ≤1.8 mmol.

Several randomized trials have demonstrated that high dose statin therapy decreases PCI-related myonecrosis in subjects undergoing stent implantation, whether or not the subject is already taking chronic statin therapy.[83-87] Therefore, in the absence of absolute contraindications to statin use (e.g. severe allergy with prior use), one of the following statin regimens must be administered at least 12 hours (at least one dose) before the PCI, regardless of LDL level and history of prior statin use.

- atorvastatin 80 mg daily
- rosuvastatin 40 mg daily

Risk Factor Modification

Tight control of risk factors will be mandated in line with the European and US revascularisation guidelines.[11-13] Cholesterol reduction, with a LDL ≤1.8, will be an additional protocol defined target the operator will be recommended to record and control.

In summary, patients (de novo 3VD) will be treated according to ACC/AHA/ESC guidelines, i.e. Heart Team discussion (Ia); functional evaluation for diagnosis in absence of objective evidence of ischemia (Ia); and LDL levels ≤1.8mmol (Ia).

7.8 Hospital Discharge (post-PCI to hospital discharge)

At discharge from the hospital where the index procedure took place, an assessment of the patient's clinical status will be performed. Assessment of the cardiovascular drug use and any Serious Adverse Events will be recorded. An ECG will be performed and an anonymised copy of the ECG (showing patient ID and recording date) should be sent to the CRO.

7.9 Follow-up Period

7.9.1 Hospital visits at 1 month (± 7 days), 6 months (± 14 days) and 1 year (± 30 days) post-procedure

An assessment of the angina status, cardiovascular drug use and any Serious Adverse Events will be recorded during clinical follow-up visits.

An anonymised copy of the ECG (showing patient ID and recording date) should be sent to the CRO.

7.9.2 Telephone contacts at 2 years (± 30 days), 3 years (± 30 days), 4 years (± 30 days) and 5 years (± 30 days)

During these telephone contacts information from the patient will be gathered on any Major Adverse Cardiac or Cerebrovascular Events (MACCE). Patients will also be asked for angina status and cardiovascular drug use.

7.10 Withdrawal from the Study

After entering into the study, the patients are asked to complete all scheduled follow-up visits. Patients will be exempt from follow-up only if they withdraw their consent.

All subjects should be encouraged to remain in the study until he/she has completed the protocol requirements during the 5-year follow-up period.

Possible reasons for premature discontinuation may include, but are not limited to, the following:

- Withdrawal of consent: Patient decides to withdraw from the study. The decision must be an independent decision that is documented in the patient study files.
- Physician discretion: The investigator may choose to withdraw a patient from the study if he/she considers follow-up too burdensome for the patient.
- Lost to follow-up: All patients should be encouraged to return for all scheduled follow-up visits, and to provide appropriate contact information to accommodate completion of required telephone follow-ups. The investigator will attempt to contact the patient at each follow-up

visit, independent of any missed follow-ups. The investigator should make 3 documented attempts per required follow-up visit.

Patients who have discontinued the trial prematurely will not be replaced.

8 STATISTICAL DESIGN AND ANALYSIS

8.1 Introduction

This trial is a non-randomized single arm study that aims to perform a comparative analysis with historical controls. Patient recruitment in the current trial will be using the SYNTAX Score II, and the historical control will be with similarly selected patients from the randomised SYNTAX Trial.

The analytical plan will be split into two sections:

1. Descriptive statistical methodology: to describe the results of the current trial by itself.
2. Comparative statistical methodology: to describe the comparison between the SYNERGY™ Everolimus Eluting Stent (EES) results of this trial and similar selected patients from the PCI and CABG cohorts of the randomised SYNTAX Trial.

8.2 Patient Selection

Patients will be prospectively recruited in the current trial with the SYNTAX Score II. Similarly selected subjects (using the SYNTAX Score II) will be undertaken from the PCI and CABG cohorts of the randomised SYNTAX Trial and will act as control groups for the current trial.

The study populations of SYNTAX II and the de-novo 3-vessel disease patients of SYNTAX I will be ‘matched’ based on the SYNTAX Score II. During the recruitment of the SYNTAX II study it will be monitored whether the populations sufficiently overlap.

No reference data for multivessel disease can be found in the published literature for the SYNERGY EES; thus the data is inferred from the Italian EXECUTIVE Pilot Trial (Ribichini et al)[88] in which the XIENCE EES was compared to the Taxus Liberte (paclitaxel eluting stent [PES]) in multivessel coronary disease. In the current trial, EES will be compared to the selected PES arm (superiority) and the selected CABG arm (non inferiority) of the SYNTAX Trial.

8.3 Assumptions for comparative analysis

In the EXECUTIVE Trial, the PES arm had an event rate for MACE (major adverse cardiac events) at 1 year of 16.5%, and 11.1% for the EES arm. This implies a ratio of 11.1/16.5 i.e. 0.67.

We assume the same ratio as the margin of effect of the new device in the current trial. We assume the incidence of stroke will be low and unchanged in the current trial as compared to the SYNTAX Trial, therefore the outcome of major adverse cardiac and cerebrovascular events (MACCE) will be assessed in order to allow comparisons with the CABG arm. The incidence of MACCE at 1 year for the selected PES arm was 17.1%; assuming a ratio of 0.67, we estimate 11.5% as the incidence of MACCE in the current trial. The incidence of MACCE at 1 year for the selected CABG arm was 10.8%. In our assumptions - as factor of benefit - we only considered the hazard ratio of Synergy vs. Taxus. We did not introduce reduction in the hazard ratio due to functional/IVUS assessment.

SYNTAX II will not consider CABG as a separate arm and therefore we need to define the uncertainty margins in advance. The point estimate of 10.8% for the selected CABG arm is accompanied with a 95% confidence interval of 7.7-14.6% (Clopper-Pearson Exact Test). It is assumed that there have been minimal changes of CABG over the time since the recruitment of the SYNTAX Trial.

8.4 Sample size

8.4.1 Superiority testing (PCI) for the primary endpoint

A sample size of 416 patients will guarantee a power of 90% to show superiority of the EES arm of the current trial to the historical PES control group. The assumptions used are:

1) a 5% 2-sided level of significance (alpha)
2) a 11.5% MACCE rate at 360 days for the EES arm, compared to the historical control of 17.1% in the selected patients from the PES arm of the SYNTAX Trial.

8.4.2 Non-inferiority testing (CABG) for the exploratory endpoint

A sample size of 416 patients will guarantee a power of 80% to show non-inferiority of the EES arm of the current trial to the historical CABG control group. The assumptions used are:

1) a 5% 1-sided level of significance (alpha)
2) a 11.5% MACCE rate at 360 days for the EES arm, compared to the historical control of 10.8% in the selected patients from the CABG arm of the SYNTAX Trial
3) a non-inferiority margin of 5%, as was used in the SYNTAX Trial.

8.4.3 Sample size justification

For the comparison with the selected PCI arm a sample size of 450 patients is chosen to obtain a power of at least 90%.

8.5 Analytical plan

The primary analysis will be based on the intention-to-treat principle. More details will be described in the statistical analysis plan.
All statistical analyses will be done using the SAS System software, version 9.2 or above (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

8.5.1 Descriptive statistical methodology

Continuous variables will be presented using mean, standard deviation, median, minimum and maximum. Discrete variables will be presented in terms of frequencies and percentages.

8.5.2 Comparative statistical methodology

For the primary endpoint (MACCE at 360 days) the log rank test will be applied to compare the SYNTAX II with the historical control of the selected PCI arm.

For the comparison to the selected CABG arm a 90% CI for the incidence of MACCE at 360 days will be constructed. If the upper limit of 90% CI in the current trial is less than 15.8%, the SYNERGY EES will be declared non-inferior to the selected CABG arm.

For the current trial day 0 will be the day of patient allocation, i.e. the day of patient “signed off” by the Heart Team.

8.6 Validation of SYNTAX Score II

Prospective validation of the SYNTAX Score II for all-cause death at 1, 2 and 5 year will be undertaken.

9 SAFETY REPORTING

The investigator will monitor the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after patient has signed Informed Consent.

An SAE form should be completed within 24 hours of the investigator's and study staff's awareness of the event.

9.1 Serious Adverse Events (SAEs) Definitions

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

An AE is classified as "serious" if the event:

- Led to death;
- Led to serious deterioration in the health of a patient that:
  - Resulted in a life threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in patients hospitalisation or prolongation of existing hospitalisation;
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

All SAEs will be followed until the event has been resolved (with or without sequelae).

9.2 Anticipated Adverse Device Effects

Anticipated adverse device effects for Synergy, IVUS, iFR/FFR procedures are described in the Instructions For Use (IFU).

If the investigator observes device malfunctions that led or might have led to a death or serious deterioration in health of a patient, user or other person or has complaints with regard to defects in the medical devices, the investigator shall, within 24 hours of such observation, report such device malfunction or complaint to the device company. Company shall be responsible for handling all complaints and reported device malfunctions in respect of the quality of medical devices, for determining the measures to be taken due to such observations or complaints and for ensuring that all necessary actions are taken including, but not limited to, any necessary action in connection with the recall of the medical devices or the reporting of incidents to competent authorities if deemed appropriate by the Company. Discussions regarding such device malfunction or complaints will be held between the Company and the Participating Site.

9.3 Reporting to Ethics Committee (EC)

Safety reporting to local ECs will be in accordance with the “guidelines on a medical device vigilance system” by the European Commission (MEDDEV2.12 rev 6, Dec 2009) and in compliance with local country law.

If an event fulfils the criteria for SAE, then this shall be reported in the eCRF within 24 hours of the clinic study staff having become aware of this. At the time the event is reported in the eCRF, no event-supporting source documentation needs to be sent. Event supporting source documents will be requested by the sponsor (via monitoring organisation and/or CRO) for the purpose of clinical event adjudication.

Clinical study staf must report device malfunctions directly to the manufacturer, who will then perform vigilance reporting to Competent Authorities, if applicable.

All (S)AEs will be MedDRA coded by the Safety Group. This allows categorising them by body system, which facilitates their reporting as frequency counts to local ethics committees, as well as to the Data Safety Monitoring Board (DSMB).

9.4 Data Safety Monitoring Board (DSMB)

Serious adverse events (events leading to serious disability or admission to hospital, life-threatening events or death) will be periodically reviewed and analysed by an independent DSMB. Members of this board are not affiliated with any (interventional) cardiology site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise.

The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB Charter. Based on safety data, the DSMB may recommend that the Steering Committee modify or stop the clinical trial. All final decisions regarding clinical trial/investigation modifications, however, rest with the Steering Committee.

All analyses are carried out aiming to protecting the safety of the trial participants. If the data at hand suggests a substantial safety concern about the experimental treatment strategy, the DSMB will carefully balance the observed risk profile against possible signs of improved efficacy.

9.5 Risk Analysis

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. Known adverse events that may result from stent intervention (incorporating IVUS/FFR assessments) include but may not be limited to:

- Allergic reaction or hypersensitivity to device material and its degredants (everolimus, platinum, chromium, poly-lactide-co-glycolide (PLGA))
- Shortness of breath/dyspnea
- Distal embolism (air, tissue, or thrombotic)
- Nausea/Vomiting
- Coronary and stent thrombosis
- Coronary and stent embolism
- Coronary dissection
- Total coronary occlusion
- Abrupt coronary closure/threatened abrupt closure
- Coronary injury
- Coronary spasm
- Coronary perforation
- Coronary rupture
- Pseudoaneurysm
- Angina (stable or unstable)
- Urgent or non-urgent coronary artery bypass graft surgery
- Vascular complications including at the entry site which may require vessel repair and vessel dissection
- Hematoma
- Respiration cease
- Hypertension
- Death

- Bleeding
- Bleeding complication (that may require transfusion)
- Shock
- Myocardial ischemia
- Cardiac enzyme level elevation
- Myocardial infarction
- Cardiac tamponade
- Cardiac arrest
- ECG change
- Heart failure
- Renal failure
- Stent implanted in unintended location
- Restenosis of lesion/vessel treated with stent
- Access site infection or pain
- Access site hematoma or bleeding
- Cerebral stroke/cerebral vascular accident (CVA)
- Hypotension
- Palpitation
- Aneurysm
- Arteriovenous fistula
- Pulmonary edema
- Fever
- Arrhythmia (atrial or ventricular)
- Peripheral ischemia (due to vascular injury)
- Adverse reaction to drug (to everolimus, antiplatelets or contrast agent)

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB). The study will be performed in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP).

The trial will only start at a clinical site after written approval of the study has been obtained from the appropriate national EC/IRB.

10.2 Data Recording

It is the expectation of the Sponsor that all data entered into the eCRF has source documentation available at the clinical site. The site must implement processes to ensure this happens.

10.3 Quality Assurance and Monitoring

Monitoring the clinical investigation at the study site is the responsibility of the monitoring organisation through trained and qualified Clinical Research Associates (CRAs).

A baseline monitoring visit will be scheduled when first patients have been enrolled and data have been entered into the eCRF. This serves to confirm the quality of site study execution and to discuss practicalities with the site study staff. During on-site monitoring, the Informed Consent Forms will be checked and a sample of clinical data will be verified against eCRF data. Subject confidentiality will be maintained at all time. Emphasis will be on the complete reporting by the study staff of SAEs as well as the availability of baseline angiograms, iFR, IVUS recordings and per protocol required 12-lead ECGs.

Each clinical site will be visited several times during the study to ensure a high degree of data quality. These site monitoring visits will be conducted to verify that the data are authentic, accurate and complete, that the safety and rights of subjects are protected, that the study is conducted according to the protocol, and that any other study agreements, GCP and all

applicable regulatory requirements are met. The investigator and the head of the medical institution (where applicable) agree to allow the CRA direct access to all relevant documents. It is important that the investigator and the study staff are available during the monitoring visit and possible audits and that sufficient time is devoted to the process. Findings from the review and source documents will be discussed with the investigator. The number of monitoring visits will depend on Key Performance Indicators (KPI) derived from data management.

Remote site monitoring will also be performed to ensure complete quality study data and patient adherence to the protocol. On a regular basis, the monitoring organisation will contact each site to discuss the progress of the study with respect to patient enrolment, timely attendance of patients to their follow-up visits and other relevant study aspects such as data query resolution.

Each participating clinic will receive a close-out visit to resolve any outstanding issues and to perform the final source data verification.

There will be regular teleconferences between the Sponsor and the monitoring organisation to discuss site management issues.

10.4 Quality Assurance and Data management

The data collection will be performed through an electronic CRF (eCRF). The investigator or an authorised member of the investigational team must sign all completed eCRFs by using an electronic signature (a password will be provided by the data management centre at the start of the study).

Clinical data management will be performed in accordance with data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. angiographies, ECGs, etc.). Appropriate computer edit programs will be run to verify the accuracy of the database. The investigator will be queried on incomplete, inconsistent or missing data.

10.5 On-site Audits

To ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit, may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide may inspect the investigator during and after the study. The investigator should contact the sponsor immediately if this occurs, and must cooperate with the regulatory authority inspections as required.

11 ORGANISATION

11.1 Sponsor

In this investigator-initiated trial, the European Cardiovascular Research Institute (ECRI) will act as Sponsor (ECRI-Trials B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands,). The Sponsor's responsibilities are described in chapter 18.

11.2 Steering Committee

The Steering Committee is responsible of the overall management of the study at the highest level. The Steering Committee is comprised of a Chairman, Deputy Study Chair, PIs, Co-PIs, ECRI). Their names, roles and responsibilities are described in a separate Steering Committee Charter.

11.3 Clinical Event Committee (CEC)

The composition, events to be adjudicated, the minimum amount of data required, and the algorithm followed in order to classify the events are described in a separate CEC Charter.

11.4 Data Safety Monitoring Board (DSMB)

The composition, guiding policies and operating procedures governing the DSMB are described in a separate DSMB Charter.

11.5 Data Management

Data management will be conducted by the Clinical Research Organisation (CRO) Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands).

11.6 Site Management and Monitoring

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) will be responsible for site management and monitoring.

11.7 Safety Reporting

Sites are responsible for reporting of incidents, including device malfunctions, to the manufactures. Manufacturers are responsible for vigilance reporting of device malfunctions to competent authorities according to the “guidelines on medical devices vigilance system” by the European Commission (MEDDEV2.12 rev 6, Dec 2009).

No expedited safety reporting is foreseen.

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for event reporting to the EC/IRB according to local and national requirements.

11.8 Statistical Analysis

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for the statistical analysis.

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation (SD)

Regulations require that investigators maintain information in the patient's medical records that corroborate data collected in the electronic Case Report Form (eCRF). In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained and made available as required by monitors and/or regulatory inspectors:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify investigational plan entry criteria;
- Dated and signed notes on the day of entry into the study, protocol number, clinical site, patient number assigned and a statement that informed consent was obtained;
- Notations on abnormal lab results;
- Adverse events reported and their resolution, including supporting documents such as discharge summaries, cath lab reports, ECGs, lab results;
- Study patient's condition upon completion of or withdrawal from the study.

12.2 Case Report Form Completion

All required data will be accurately recorded by authorised personnel documented on the authorised signature log in the eCRF.

12.3 Record Retention

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator according to the national requirements following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer

location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian.

13 PUBLICATION POLICY

The Steering Committee and investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings.

The SYNTAX II trial is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with Boston Scientific and Volcano. All public presentations and manuscript generation and submissions will be led under the auspices of the Principal Investigators who will organise and lead a Publications Committee. However, this study represents a joint effort between investigators, ECRI and collaborators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

The final locked database will be housed at the data management centre, Cardialysis. Cardialysis will not publicly release data or study-related material, presentations, or manuscripts without the express permission of the Principal Investigators. All Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-centre results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted. All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the Publications Committee for review and approval prior to submission for publication or presentation.

The Steering Committee will receive any proposed publication and/or presentation materials prior to submission of the presentation or the initial submission of the proposed publication in order for the materials to be timely reviewed by all parties.

14 INVESTIGATOR RESPONSIBILITIES

14.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly. This study will be conducted in accordance the Declaration of Helsinki and other applicable regulatory requirements or any conditions of approval imposed by the IRB/EC or regulatory authorities.

14.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to patient enrolment:

- Signed Protocol Signature Page
- Recent signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Copy of the written confirmation of the EC/IRB regarding approval of the protocol including version number and date, patient information sheet and informed consent form, including version and date and other adjunctive patient material.
- List of EC/IRB members, including name, title, occupation and any institutional affiliation of each member. If the EC/IRB member list is not available, the General Assurance or EC/IRB Recognition Number should be provided.
- Signed Investigator Site Agreement.

14.3 Ethics Committee (EC) / Institutional Review Board (IRB) Approval

According to the local regulations, the investigator must have all necessary approvals, including written approval from the EC/IRB of the clinical site or other accepted EC/IRB prior to enrolling patients in the study. A copy of the written approval must be provided to Sponsor and should include the following:

- Statement of EC/IRB approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval
- Identification of the approved Primary Investigator
- Signature of the EC/IRB chairperson
- Acknowledgement of the Co-Investigators
- EC/IRB approval of the informed consent form (if applicable)
- EC/IRB approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC/IRB and written approval obtained prior to implementation. Minor changes which do not affect the subject's safety will be subject to notification.

Serious Adverse Event (SAE) reports will be submitted to the EC/IRB as requested by the Sponsor, EC/IRB and/or local regulations. Annual and final reports will be provided to the EC/IRB as required.

14.4 Informed Consent

Study subjects must provide written informed consent using an EC/IRB-approved informed consent form. The study must be explained to the study subjects in lay language. The investigator, or representative, must be available to answer all of the study subject's study-related questions. Study subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

14.5 Protocol Deviation

The CRA/monitor will report all protocol deviations to the Sponsor. The investigator will review all protocol deviations and will inform the EC/IRB according to the EC/IRB requirement.

14.6 Reporting Requirements

The investigator should notify the EC/IRB in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to Competent Authority where required.

Site responsibilities for submitting data and reports:

Type of CRF/Report	**Completed by Site Within**	**Process**
Serious Adverse Event Notification eCRF (including death, MACE)	24 hours	Enter eCRF pages within 24 hours of knowledge of event
eCRF (Baseline, In-hospital summary, Follow-up, Patient Withdrawal)	Ongoing basis	Collected in the eCRF
Angiographic Films, ECGs, IVUS and iFR/FFR recordings. MSCT scans (if applicable).	Ongoing basis	Collected by site and shipped to Core lab within 7 days
Device malfunctions	Ongoing basis	Collected by site and provided to manufacturer
Annual Reports	Forward as requested by EC/IRB	Copy provided by Sponsor to be send to EC/IRB
Final Report	Forward within 3 months of study completion or termination	Copy provided by Sponsor to be send to EC/IRB

14.7 Audits / Inspection

In the event that audits are initiated by the Sponsor (or its designee) or national/international regulatory authorities, the investigator allows access to the original medical records and provides all requested information. In the event that audits are initiated by a regulatory authority, the investigator will immediately notify the Sponsor.

15 SPONSOR RESPONSIBILITIES

15.1 Role of ECRI

As Sponsor, ECRI has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant competent authorities.

General duties

Prior to allowing the sites to start enrolling patients into the study, the Sponsor is responsible for selecting investigators, ensuring EC/IRB approvals are obtained where applicable, and signing the Investigator Site Agreement with the investigators and/or hospitals. It is the Sponsor's responsibility to ensure that the study is conducted according to ISO 14155, the Declaration of Helsinki, and other applicable regulatory requirements, the study protocol, and any conditions of approval imposed by the EC/IRB or regulatory authorities. Additionally, the Sponsor will ensure proper clinical site monitoring.

Selection of clinical investigators and sites

The Sponsor together with the Steering Committee will select qualified investigators and facilities which have adequate study patient population to meet the requirements of the investigation.

Training of investigator and site personnel and site monitoring

The training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor, or designee, and may be conducted during an investigator meeting, a site initiation visit, or other appropriate training sessions.
Periodic monitoring visits will be conducted frequently enough to ensure that all clinical patient data are properly documented and that the study is properly conducted.

Documentation

The Sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents;

- All study relevant documents (protocol, EC/IRB approval and comments, patient information and informed consent template, relevant correspondence, etc.)
- Signed and dated Case Report Form
- Records of any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

15.2 Supplemental Applications

As appropriate, the Sponsor will submit changes to the study protocol to the investigators to obtain EC/IRB re-approval.

15.3 Submitting Reports

The Sponsor will submit the appropriate reports identified by the regulations. This includes withdrawal of any EC/IRB approval, interim (if any) and final reports.

15.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, SAEs and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator Site Agreements according to requirements set forth by ISO14155.

All Core Laboratories and clinical sites will maintain study records according to local requirements for this type of study.

15.5 Audit

The Sponsor is responsible for auditing the study to ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit and may arrange to conduct an on-site audit to assess the performance of the study at the study site and of the study documents originating there.

15.6 Confidentiality

All data and information collected during this study related to the participating subject will comply with the standards for protection of privacy based on applicable local/ national requirements for subject's confidentiality. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study subjects' names. Access to study subject files will be limited to authorised personnel of the Sponsor, the investigator, and research staff. Authorised regulatory personnel have the right to inspect and copy all records pertinent to this study, but all efforts must be made to remove the subject's personal data.

16 REFERENCES

1. SYNTAX score calculator: www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.
2. Sianos G, Morel MA, A.P. K, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. (2005) The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*.
3. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. American heart journal 2006;**151**(6):1194-204.
4. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;**360**(10):961-72.
5. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;**5**(1):50-6.
6. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation 2010;**121**(24):2645-53.
7. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;**32**(17):2125-34.
8. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;**97**(23):1902-13.
9. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. Heart 2013.
10. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;**381**(9867):629-38.
11. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. Eur Heart J 2010;**31**(20):2501-55.
12. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID,

Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;**58**(24):e44-122.
13. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM, Jr., Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;**58**(24):e123-210.
14. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, CarriÈ D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, K‰ohler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. The Lancet 2009;**373**(9670):1190-1197.
15. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. Journal of the American College of Cardiology 2003;**41**(8):1293-304.
16. Farooq V, Serruys PW. "Cherry-picking" patients for randomized, controlled trials-reliving the past. J Am Coll Cardiol 2013;**61**(24):2492.
17. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;**82**(6):1966-75.
18. Farkouh ME, Dangas G, Leon MB, Smith C, Nesto R, Buse JB, Cohen DJ, Mahoney E, Sleeper L, King S, 3rd, Domanski M, McKinlay S, Fuster V. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) Trial. Am Heart J 2008;**155**(2):215-23.
19. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, 3rd, Bertrand M, Fuster V. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;**367**(25):2375-84.
20. Serruys PW, Farooq V. Revascularization strategies in patients with diabetes. N Engl J Med 2013;**368**(15):1454-5.
21. Banning AP, Westaby S, Morice MC, Kappetein AP, Mohr FW, Berti S, Glauber M, Kellett MA, Kramer RS, Leadley K, Dawkins KD, Serruys PW. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. Journal of the American College of Cardiology 2010;**55**(11):1067-75.
22. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ. Treatment of complex coronary artery disease in patients with diabetes: 5-year results

comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg 2013;**43**(5):1006-13.
23. Farooq V, Serruys PW, Stone GW, Virmani R, Chieffo A, Fajadet J. Left main coronary artery disease. Percutaneous Interventional Cardiovascular Medicine. The PCR-EAPCI Textbook. PCR publishing / EUROPA EDITION, Toulouse, France, 2012: Part 3, Chapter 12: 407-445.
24. Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR, Jr., Kappetein AP, Mack MJ, Feldman T, Morice MC, Stahle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. JACC Cardiovasc Interv 2012;**5**(6):606-17.
25. Farooq V, Vergouwe Y, Raber L, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. Eur Heart J 2012;**33**(24):3098-104.
26. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr., Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;**381**(9867):639-50.
27. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW. SYNTAX score II - Authors' reply. Lancet 2013;**381**(9881):1899-900.
28. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Stahle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. Eur Heart J 2012;**33**(24):3105-13.
29. Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P, Valgimigli M, Jegere S, Makkar RR, Palacios IF, Kim YH, Buszman PE, Chakravarty T, Sheiban I, Mehran R, Naber C, Margey R, Agnihotri A, Marra S, Capodanno D, Leon MB, Moses JW, Fajadet J, Lefevre T, Morice MC, Erglis A, Tamburino C, Alfieri O, Serruys PW, Colombo A. Drug-Eluting Stent for Left Main Coronary Artery Disease: The DELTA Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment. JACC Cardiovasc Interv 2012;**5**(7):718-27.
30. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;**380**(9854):1662-73.
31. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;**380**(9844):807-14.

32. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013;**61**(3):282-94.
33. Head SJ, Mack MJ, Holmes DR, Jr., Mohr FW, Morice MC, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. Eur J Cardiothorac Surg 2012;**41**(3):535-41.
34. Thompson CA, Jayne JE, Robb JF, Friedman BJ, Kaplan AV, Hettleman BD, Niles NW, Lombardi WL. Retrograde techniques and the impact of operator volume on percutaneous intervention for coronary chronic total occlusions an early U.S. experience. JACC Cardiovasc Interv 2009;**2**(9):834-42.
35. Whitlow PL, Burke MN, Lombardi WL, Wyman RM, Moses JW, Brilakis ES, Heuser RR, Rihal CS, Lansky AJ, Thompson CA. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. JACC Cardiovasc Interv 2012;**5**(4):393-401.
36. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. Journal of the American College of Cardiology 2010;**55**(25):2816-21.
37. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. Journal of the American College of Cardiology 2010;**56**(3):177-84.
38. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;**367**(11):991-1001.
39. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;**360**(3):213-24.
40. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. J Am Coll Cardiol 2011;**58**(12):1211-8.
41. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-

intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;**59**(15):1392-402.
42. Zhang Y, Farooq V, Garcia-Garcia HM, Bourantas CV, Tian N, Dong S, Li M, Yang S, Serruys PW, Chen SL. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. EuroIntervention 2012;**8**(7):855-65.
43. Zhang YJ, Garcia-Garcia HM, Farooq V, Bourantas CV, Serruys PW, Chen SL. Revisiting: "Comparison of intravascular ultrasound versus angiography guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients". EuroIntervention 2013.
44. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;**56**(10 Suppl):S43-78.
45. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;**56**(10 Suppl):S1-42.
46. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;**368**(3):254-65.
47. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;**379**(9824):1393-402.
48. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;**125**(23):2873-91.
49. Farooq V, Gogas BD, Serruys PW. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. Circulation. Cardiovascular interventions 2011;**4**(2):195-205.
50. Wilson GJ, Huibregtse BA, Pennington DE, Dawkins KD. Comparison of the SYNERGY with the PROMUS (XIENCE V) and bare metal and polymer-only Element control stents in porcine coronary arteries. EuroIntervention 2012;**8**(2):250-7.
51. Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrié D, Walsh S, Oldroyd KG, Varenne O, El-Jack S, Moreno R, Joshi AA, Allocco DJ, Dawkins KD. Primary Endpoint Results of the EVOLVE TrialA Randomized Evaluation of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent. Journal of the American College of Cardiology 2012;**59**(15):1362-1370.
52. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of Incomplete Revascularization and its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score * Clinical Perspective. Circulation 2013;**128**(2):141-51.
53. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012;**59**(24):2165-74.

54. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;**24**(9):881-2.
55. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;**16**(1):9-13.
56. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;**15**(6):816-22; discussion 822-3.
57. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. Eur J Cardiothorac Surg 2012;**41**(4):734-44; discussion 744-5.
58. Takkenberg JJ, Kappetein AP, Steyerberg EW. The role of EuroSCORE II in 21st century cardiac surgery practice. Eur J Cardiothorac Surg 2013;**43**(1):32-3.
59. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. EuroIntervention 2012;**8**(4):511-9.
60. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;**58**(19):1989-97.
61. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;**308**(12):1237-45.
62. Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX Score. Heart 2013.
63. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;**16**(1):31-41.
64. Samady H, Lepper W, Powers ER, Wei K, Ragosta M, Bishop GG, Sarembock IJ, Gimple L, Watson DD, Beller GA, Barringhaus KG. Fractional flow reserve of infarct-related arteries identifies reversible defects on noninvasive myocardial perfusion imaging early after myocardial infarction. J Am Coll Cardiol 2006;**47**(11):2187-93.
65. Leesar MA, Abdul-Baki T, Akkus NI, Sharma A, Kannan T, Bolli R. Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. J Am Coll Cardiol 2003;**41**(7):1115-21.
66. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. JACC Cardiovasc Interv 2010;**3**(12):1274-81.
67. Petraco R, Park JJ, Sen S, Nijjer SS, Malik IS, Echavarria-Pinto M, Asrress KN, Nam CW, Macias E, Foale RA, Sethi A, Mikhail GW, Kaprielian R, Baker CS, Lefroy D, Bellamy M, Al-Bustami M, Khan MA, Gonzalo N, Hughes AD, Francis DP, Mayet J, Di Mario C, Redwood

S, Escaned J, Koo BK, Davies JE. Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. EuroIntervention 2013;**8**(10):1157-65.
68. Rao SV, Cohen MG, Kandzari DE, Bertrand OF, Gilchrist IC. The transradial approach to percutaneous coronary intervention: historical perspective, current concepts, and future directions. J Am Coll Cardiol 2010;**55**(20):2187-95.
69. Hildick-Smith D, Lassen JF, Albiero R, Lefevre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y. Consensus from the 5th European Bifurcation Club meeting. EuroIntervention 2010;**6**(1):34-8.
70. Stankovic G, Lefevre T, Chieffo A, Hildick-Smith D, Lassen JF, Pan M, Darremont O, Albiero R, Ferenc M, Finet G, Adriaenssens T, Koo BK, Burzotta F, Louvard Y. Consensus from the 7th European Bifurcation Club meeting. EuroIntervention 2013;**9**(1):36-45.
71. Werner GS, Schofer J, Sievert H, Kugler C, Reifart NJ. Multicentre experience with the BridgePoint devices to facilitate recanalisation of chronic total coronary occlusions through controlled subintimal re-entry. EuroIntervention 2011;**7**(2):192-200.
72. Baks T, van Geuns RJ, Duncker DJ, Cademartiri F, Mollet NR, Krestin GP, Serruys PW, de Feyter PJ. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. Journal of the American College of Cardiology 2006;**47**(4):721-5.
73. Kwon DH, Hachamovitch R, Popovic ZB, Starling RC, Desai MY, Flamm SD, Lytle BW, Marwick TH. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: association with end-systolic volume and viability. Circulation 2012;**126**(11 Suppl 1):S3-8.
74. Gerber BL, Rousseau MF, Ahn SA, le Polain de Waroux JB, Pouleur AC, Phlips T, Vancraeynest D, Pasquet A, Vanoverschelde JL. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. J Am Coll Cardiol 2012;**59**(9):825-35.
75. Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, Lammertsma AA, Liedtke AJ, Paternostro G, Vatner SF. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). Circulation 1997;**96**(9):3205-14.
76. Fiocchi F, Sgura F, Di Girolamo A, Ligabue G, Ferraresi S, Rossi R, D'Amico R, Modena MG, Torricelli P. Chronic total coronary occlusion in patients with intermediate viability: value of low-dose dobutamine and contrast-enhanced 3-T MRI in predicting functional recovery in patients undergoing percutaneous revascularisation with drug-eluting stent. Radiol Med 2009;**114**(5):692-704.
77. Kirschbaum SW, Baks T, van den Ent M, Sianos G, Krestin GP, Serruys PW, de Feyter PJ, van Geuns RJ. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. Am J Cardiol 2008;**101**(2):179-85.
78. Galassi AR, Tomasello SD, Crea F, Costanzo L, Campisano MB, Marza F, Tamburino C. Transient impairment of vasomotion function after successful chronic total occlusion recanalization. J Am Coll Cardiol 2012;**59**(8):711-8.
79. Mosseri M, Satler LF, Pichard AD, Waksman R. Impact of vessel calcification on outcomes after coronary stenting. Cardiovasc Revasc Med 2005;**6**(4):147-53.

80. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;**361**(11):1045-57.
81. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;**120**(25):2577-85.
82. Farooq V, Serruys PW, Holmes DR, Kappetein AP, Mack M, Feldman T, Dawkins KD, Mohr FW, James S, Ståhle E. Abstract: The long term (4-year) prognostic significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous revascularisation: a substudy from the SYNTAX Trial. Presented at: Congress of the European-Society-of-Cardiology (ESC), AUG 25-29, 2012, Munchen, GERMANY. European Heart Journal 2012;**33**(suppl 1):500.
83. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. Circulation 2004;**110**(6):674-8.
84. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, Di Sciascio G. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. J Am Coll Cardiol 2007;**49**(12):1272-8.
85. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. J Am Coll Cardiol 2009;**54**(6):558-65.
86. Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, Mussardo M, Montorfano M, Ricciardelli B, Colombo A. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. J Am Coll Cardiol 2009;**54**(23):2157-63.
87. Briguori C, Colombo A, Airoldi F, Violante A, Focaccio A, Balestrieri P, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Librera M, Bonizzoni E, Ricciardelli B. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. Eur Heart J 2004;**25**(20):1822-8.
88. Ribichini I, Romano M, Rosiello R, Vecchia LL, Cabianca E, Caramanno G, Milazzo D, Loschiavo P, Rigattieri S, Musarò S, Pironi B, Fiscella A, Amico F, Indolfi C, Spaccarotella C, Bartorelli A, Trabattoni D, Rovere FD, Rolandi A, Beqaraj F, Belli R, Sangiorgio P, Villani R, Berni A, Sheiban I, Quijada MJL, Cappi B, Ribaldi L, Vassanelli C. A Clinical and Angiographic Study of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with Multi-Vessel Coronary Artery Disease. The EXECUTIVE Trial. JACC Interventions (In Press) 2013.
89. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-

artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;**344**(15):1117-24.
90. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, Colombo A, Hamm C, Bartorelli A, Rothman M, Nobuyoshi M, Yamaguchi T, Voudris V, DiMario C, Makovski S, Hausmann D, Rowe S, Rabinovich S, Sunamura M, van Es GA. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). Eur Heart J 1998;**19**(8):1214-23.

17 APPENDIX I: SCHEDULE OF EVENTS

Event	**Screen**	**Procedure**	**Post - Procedure to Hospital D/c**	**1 Mo** ±7 days	**6 Mo** ±14 days	**1 Yrs** ±30 days	**2-5Yrs** ±30 days
Type of contact				***Visit***	***Visit***	***Visit***	***Phone***
Local Heart Team conference - Inclusion/ exclusion Criteria - SYNTAX Score II - EuroSCORE - EuroSCORE II	X						
Informed consent	X						
Physical examination	X						
Medical and Cardiac history	X						
Anginal Status	X		X	X	X	X	X
[1]CBC, blood chemistry, lipids	X						
CK-MB	X[2]		X[3]				
Troponin	X[2]		X[3]				
12 lead ECG[7]	X[4]		X[5]	X	X	X	
Medication regimen	X	X	X	X	X	X	X
Angiography[6, 7]		X					
IVUS[7]		X					
FFR/(iFR)[7]		X					
MSCT[7]	X						
Serious Adverse Event monitoring		X	X	X	X	X	X

[1] within 7 days prior to procedure

[2] CK-MB/Troponin is drawn at least 24 hours prior to PCI.

[3] CK-MB/Troponin is determined pre-discharge or within 48 hours whatever comes first

[4] ECG at time of screening should be at least 24 hours prior to PCI

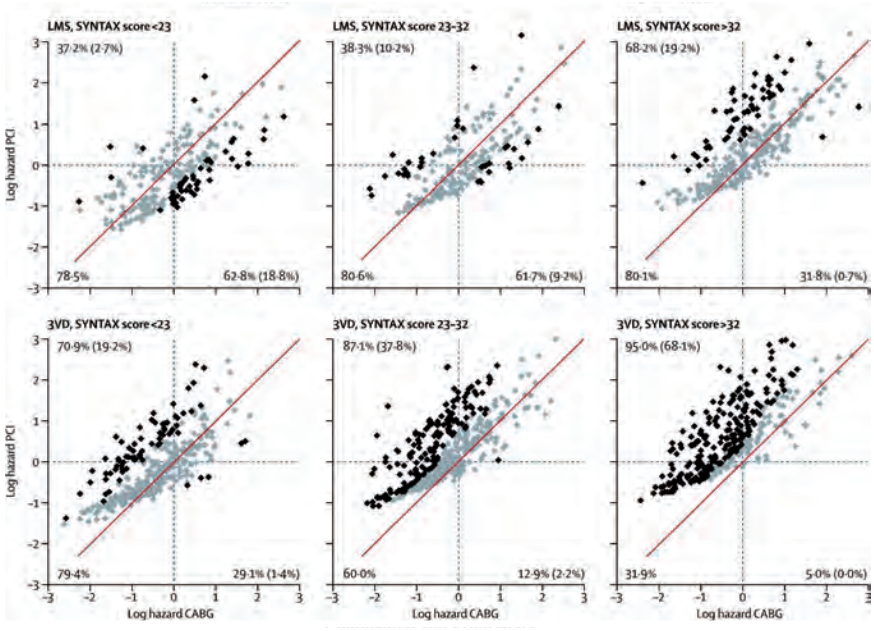
[5] within 24 hours post-procedure or at discharge, whichever comes first

[6] In index angiograms for anatomical SYNTAX Score assessment both the right coronary artery (RCA) and left coronary artery (LCA, incl. LAD and LCX) must be imaged.

[7] Collect and forward to central Core Lab (material collection only).

18 APPENDIX II: PROPORTION OF 3VD PATIENTS SUITABLE FOR PCI

Mortality predictions for CABG versus PCI for each individual patient in the randomised SYNTAX trial (n=1800). Scatter plots illustrating mortality predictions for the left main (upper panel) and 3VD (lower panel) cohorts separated by conventional tertiles of the SYNTAX Score. The diagonal line represents identical mortality predictions for CABG and PCI. Individual predictions plotted to the left of the diagonal line favour CABG (actual percentages shown in top left corner), and to the right favour PCI (actual percentages shown in bottom right corner). Individual mortality predictions for CABG or PCI that could be separated with 95% confidence ($p<0{\cdot}05$) are coloured black (actual percentage shown in parentheses in respective corners). Mortality predictions that could not be separated with 95% confidence ($p>0{\cdot}05$) are highlighted in grey, and identify patients with similar 4-year mortality. Percentages of patients in each category are shown. CABG=coronary artery bypass surgery. PCI=percutaneous coronary intervention. LMS=left main stem. 3VD=three-vessel disease. Adapted and reproduced from Farooq et al.[26]



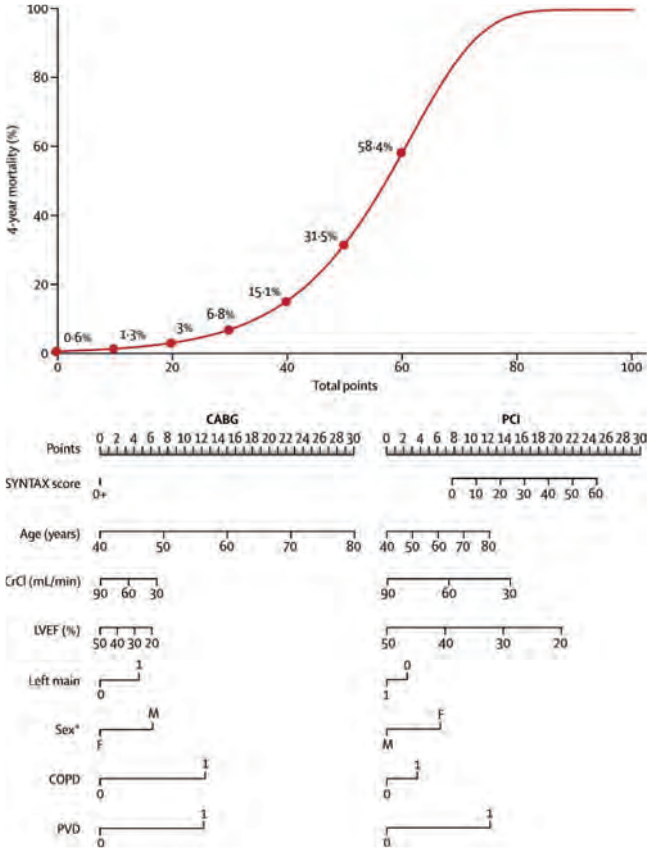
19 APPENDIX III: SYNTAX SCORE II

SYNTAX Score II nomogram for bedside application. An online version will be made available online at the original SYNTAX Score website (www.syntaxscore.com).[1]

Total number of points for 8 factors can be used to accurately predict 4-year mortality for the individual patient proposing to undergo for CABG or PCI. For example, a 60 year old man with an anatomical SYNTAX score of 30, unprotected left main coronary artery disease, creatinine clearance of 60 mL/min, an LVEF of 50%, and COPD, would have 41 points (predicted 4-year mortality 16·3%) to undergo CABG and 33 points (predicted 4-year mortality 8·7%) to undergo PCI respectively. The same example without COPD included would lead to identical points (29 points) and 4-year mortality predictions (6·3%) for CABG and PCI.

COPD defined with EuroSCORE definition,[54] long-term use of bronchodilators or steroids for lung disease. PVD defined according to ARTS I definition,[89] aorta and arteries other than coronaries, with exercise-related claudication, or revascularisation surgery, or reduced or absent pulsation, or angiographic stenosis of more than 50%, or combinations of these characteristics.

Adapted from Farooq et al.[26]



*Because of the rarity of complex coronary artery disease in premenopausal women, mortality predictions in younger women are predominantly based on the linear relation of age with mortality. The differences in mortality predictions in younger women between CABG and PCI will therefore be affected by larger 95% CIs than those in older women.

20 APPENDIX IV: IVUS CRITERIA

IVUS Criteria (**Modified MUSIC Criteria**[90]): for evaluation of appropriate stent apposition:

1). Complete apposition against the vessel wall of the entire stent *AND*

2). a) ≥90% of the average reference lumen area or ≥100% of lumen area of the reference segment with the lowest lumen area; *or*

b) MLA >between 5.5 mm^2; *or*

c) MLA ≥80% of the average reference lumen area or ≥90% of lumen area of the reference segment with the lowest lumen area. AND

3). Symmetric stent expansion.

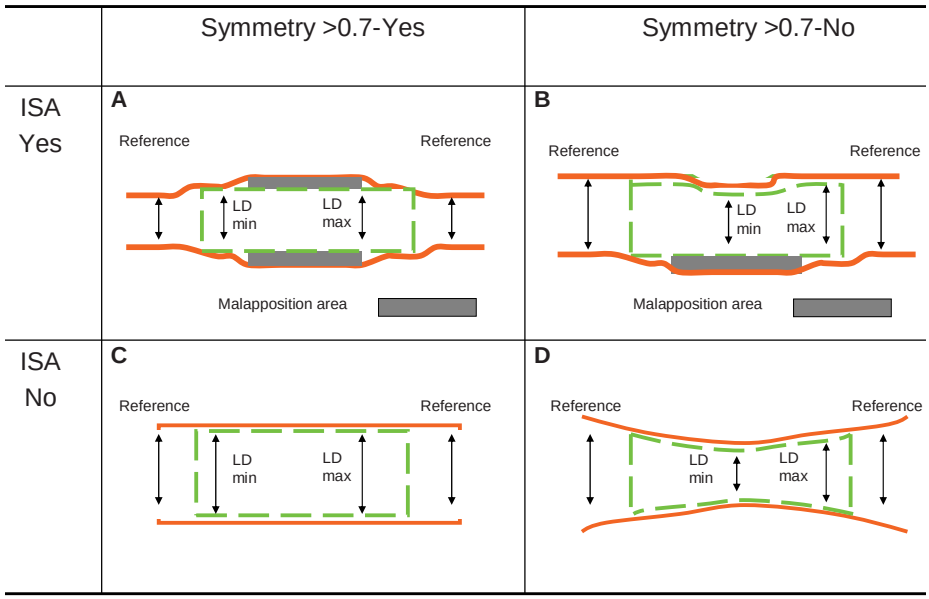


Figure: Stent Symmetry, Expansion and Apposition

ISA: Incomplete Stent Apposition

A. Symmetry check: LD min/LD max is close to 1, thus is symmetric; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is a space behind the struts, thus the stent is not lying on the vessel luminal wall and therefore is not well apposed. **We recommend postdilation, preferably with a non compliant balloon according the inflation chart.**

B. Symmetry check: LD min/LD max is far from 1, thus is asymmetric. **We recommend postdilation preferably with a non compliant balloon according the inflation chart**; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is a space behind the struts, thus the stent is not lying on the vessel luminal wall and therefore is not well apposed. **We recommend postdilation, preferably with a non compliant balloon according the inflation chart.**

C. Symmetry check: LD min/LD max is 1, thus is symmetric; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is NO space behind the struts, thus the stent is lying on the vessel luminal wall and therefore is well apposed and therefore no extra actions are needed.

D. Symmetry check: LD min/LD max is far from 1, thus is asymmetric. **We recommend postdilation, preferably with a non compliant balloon according the inflation chart.**; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is NO space behind the struts, thus the stent is lying on the vessel luminal wall and therefore is well apposed and therefore no extra actions are needed.

21 APPENDIX V: BIFURCATION MANAGEMENT CRITERIA

Principals - consistent with European Bifurcation club

1) Provisional T is preferred strategy
2) 2 wires from the outset are *recommended* when branch is of sufficient size for the lesion to be considered a bifurcation and it has some disease
3) Probable 2 stents (operators choice of technique) when disease is in a suitably sized side branch and branch disease extends >5mm
4) When 2 stents are used kissing balloon post dilatation is *mandatory* at completion
5) When 1 stent used- kissing balloon post dilatation is not mandatory at completion
6) Large side branch with proximal disease and very challenging access should be stented once accessed - (no iFR/FFR required of branch before treatment) - these are exceptional cases.

Performance/technique- pre stent

7) Plan to perform iFR/FFR to main vessel prior to PCI – *mandatory*
8) When performing elective 2 stents strategy- iFR/FFR to main vessel prior to PCI – *mandatory* and branch iFR/FFR *at operators discretion*
9) Plan to perform provisional approach and branch appears diseased and may require stenting – iFR/FFR of branch *recommended*
10) In 0,0,1 lesion iFR/FFR of main vessel *mandatory* and branch *recommended*

Performance/technique- post stent

11) Post stent deployment in main vessel iFR/FFR *recommended of main vessel*
12) Post stent deployment in main vessel – treatment of branch vessel
    a. Normal flow in branch with discrete pinched ostium – *operators discretion* either leave it or iFR/FFR prior to stenting – *mandatory*
    b. Reduced flow / dissection in significant branch - *bail out strategy at operators discretion- can do iFR/FFR at completion at operators discretion. If 2 stents placed final kissing is mandatory.*

Angiographically 1,1,0 LAD D1 bifurcation

iFR/FFR of the LAD confirms need for stent
stent placed, discrete ostial pinch of D1 but normal flow
iFR/FFR mandatory if further stent to D1 considered
iFR/FFR of LAD at completion

Angiographically 1,1,0 LAD D1 bifurcation

iFR/FFR of the LAD confirms need for stent
LAD stent placed , but TIMI II flow in D1
wire with any wire chosen by operator and proceed as per usual practice including additional stent if considered necessary
iFR/FFR of LAD at completion and D1 if possible

Angiographically 1,0,1 LAD D1 bifurcation
iFR/FFR of the LAD confirms need for stent
unable to comment on D1 ostium in presence of proximal stenosis using iFR/FFR
if disease >5mm in D1- 2 stent strategy of operators choice with kissing to complete procedure
if disease <5mm in D1- stent LAD and then iFR/FFR of D1 is further stent considered
iFR/FFR of LAD at completion

Angiographically 0,0,1 LAD D1 bifurcation
iFR/FFR of the LAD confirms no requirement for LAD stent
iFR/FFR of the D1 confirms requirement for stent (unusual)
stent strategy of operators choice
iFR/FFR of LAD and D1 at completion

Angiographically 0, 1, 0 LAD D1 bifurcation
iFR/FFR of the LAD confirms requirement for LAD stent
stent to LAD – will usually cover bifurcation
stent strategy of operators choice
discrete ostial pinch of D1 but normal flow iFR/FFR mandatory if further stent to D1 considered
iFR/FFR of LAD and ideally D1 at completion

22 APPENDIX VI: DEFINITIONS

I. According to SYNTAX I Trial, MACCE is defined as:

- All cause death
- Cerebrovascular event (stroke)
- Documented myocardial infarction
- Repeat revascularization (PCI and/or CABG).

DEATH

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.
Cardiac Death: any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death.
Vascular Cause death: death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
Non-Cardiovascular death: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

STROKE

A focal neurological deficit of central origin lasting more than 72 hours and results in irreversible brain damage or permanent body impairment. Type and severity of symptoms is dependent on the location and extent of brain tissue whose circulation has been involved. Strokes will be further classified as ischemic or hemorrhagic based on imaging studies. When blood flow to the brain is interrupted because of rupture of a vessel causing bleeding into or around the brain, it is considered hemorrhagic. When a vessel that supplies the brain is blocked, the event is considered ischemic.

MYOCARDIAL INFARCTION

A myocardial infarction will be considered whether it occurred spontaneously or in association with angioplasty or coronary bypass graft surgery procedures. A definite diagnosis of myocardial infarction is made:

Definition I: Within the first 7 days post intervention:
New Q-waves (*) and one plasma level of CKMB 5x upper limit for normal.

Definition II: At least 7 days after any intervention procedure:
Either a. New Q-waves (*)
Or one plasma level of CKMB 5x upper limit for normal

(*) development of new abnormal Q-waves not present on the patient's baseline (i.e. before allocation) ECG. The Minnesota Code for pathological Q-waves will be used.
(*) In cases of ECG diagnosis of MI in the presence of a complete left bundle branch block, peak CKMB levels should be obtained locally.

TLR
Target Lesion Revascularization is defined as any ischemia-driven repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel due to any of the following:
1. the patient had a positive functional study corresponding to the area served by the target lesion.
2. ischemic ECG changes at rest in a distribution consistent with the target vessel
3. ischemic symptoms referable to the target lesion.

TVR
Target Vessel Revascularization is defined as any ischemia-driven repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel due to any of the following:
1. the patient had a positive functional study corresponding to the area served by the target vessel
2. ischemic ECG changes at rest in a distribution consistent with the target vessel
3. ischemic symptoms referable to the target lesion.

II. Contemporary definitions

Death (Per ARC Circulation 2007; 115: 2344-2351)

The deaths will be adjudicated per the ARC definition. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

- **Cardiac death:**
  Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all study procedure related deaths including those related to concomitant treatment.

- **Vascular death:**
  Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

- **Non-cardiovascular death:**
  Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

Stroke

1. Duration of a focal/global neurological deficit ≥24 hours or<24 hours if any of the following conditions exist:
   i. at least one of the following therapeutic interventions:
      a. Pharmacologic (i.e., thrombolytic drug administration)
      b. Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)
   ii. Available brain imaging clearly documents a new hemorrhage or infarct
   iii. The neurological deficit results in death
2. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
3. Confirmation of the diagnosis by a neurology or neurosurgical specialist and at least one of the following:
   a. Brain imaging procedure (at least one of the following):
      i. CT scan
      ii. MRI scan
      iii. Cerebral vessel angiography
   b. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

A. If the acute focal signs represent a worsening of a previous deficit, these signs must have either
   1. Persisted for more than one week, or
   2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

B. Strokes may be sub-classified as follows:
   1. Ischemic (Non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology.
   2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,* and primary subarachnoid hemorrhage.
      *All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus nontraumatic.
   3. Unknown: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

C. Stroke Disability

All strokes with stroke disability of Modified Rankin Scale (mRS) ≥1 will be included in the primary endpoint. All diagnosed strokes (even with mRS 0) will also be tabulated. Stroke disability will be classified using an adaptation of the modified Rankin Scale.

Scale	Disability
0	No stroke symptoms at all. (May have other complaints)
1	No significant disability; symptoms present but no physical or other limitations.
2	Slight disability; limitations in participation in usual social roles, but independent for activities of daily living (ADL)
3	some need for assistance but able to walk without assistance
4	Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care
5	Severe disability requiring constant nursing care and attention.
Stroke: Modified Rankin score ≥1 and increase by ≥1 from baseline	

D. Transient Ischemic Attack (as compared to stroke) is defined as:

- New focal neurologic deficit with rapid symptom resolution, usually 1-2 hours, always within 24 hours
- Neuroimaging without tissue injury

Myocardial Infarction

New Universal Definition 2012

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values>5 x 99th percentile URL in patients with normal baseline values ($\leq 99^{th}$ percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Revascularization

The revascularizations will be adjudicated per the ARC definition.

- **Location of Revascularization:**

  - **Target Lesion Revascularization (TLR)**
    TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

  - **Target Vessel Revascularization (TVR)**
    TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself

  - **Non Target Lesion Revascularization (Non-TLR)**
    Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

  - **Non Target Vessel Revascularization (Non-TVR)**
    Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Stent Thrombosis (Per ARC Circulation 2007; 115: 2344-2351)

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject left the catheterization lab.

- **Timing:**
  - Acute stent thrombosis*: 0 - 24 hours post stent implantation
  - Subacute stent thrombosis*: >24 hours . 30 days post stent implantation
  - Late stent thrombosis†: 30 days - 1 year post stent implantation
  - Very late stent thrombosis†: >1 year post stent implantation

  * Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0 - 30 days) - this definition is currently used in the community.
  † Including “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosis after a target segment revascularization.

- **Categories:**
  - Definite
  - Probable
  - Possible

Definitions of each category are as follows.

- **Definite stent thrombosis**
  Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

  Angiographic confirmation of stent thrombosis*
  The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:
    - Acute onset of ischemic symptoms at rest
    - New ischemic ECG changes that suggest acute ischemia
    - Typical elevation or depression in cardiac biomarkers (refer to definition of spontaneous MI)
    - Nonocclusive thrombosis
      - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
    - Occlusive thrombus
      - TIMI 0 or TIMI 1 in-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

  * The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis.
  † Intracoronary thrombus.

  Pathological confirmation of stent thrombosis
  Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

- **Probable stent thrombosis**
  Either of the following occurred after stent implantation will be considered a probable stent thrombosis:
    - Any unexplained death within the first 30 days
    - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- **Possible stent thrombosis**
  Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

III. Other definitions

ACUTE SUCCESS DEFINITIONS

Clinical Device Success (Lesion Basis)
Successful delivery and deployment of the assigned device at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of < 30% by QCA (by visual estimation if QCA unavailable).

Clinical Procedure Success (Patient Basis)
Achievement of final in-stent residual stenosis of < 30% by QCA (by visual estimation if QCA unavailable) with successful delivery and deployment of the assigned device at the intended target lesion and successful withdrawal of the delivery system without the occurrence of MACCE during the hospital stay (maximum of 7 days), and with or without use of other therapeutic device.

In multiple target lesion setting all lesions must meet clinical procedure success criteria to have a patient level procedure success.

ADVERSE EVENT DEFINITIONS

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation when subject was treated with a study product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product whether or not related to the investigational device.

Serious Adverse Event (SAE)

If an adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE).

- Led to death;
- Led to serious deterioration in the health of a patient that:
  - Resulted in a life threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in patients hospitalisation or prolongation of existing hospitalisation;
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

Adverse Device Effect

Adverse device effects include issues related to its specifications, product experiences and device malfunctions, insufficient contents of instruction for use and adverse device effects. It also includes inevitable adverse events potentially occurs even if a device is properly used. This means that an adverse device effect is defined as any adverse event that is related to the study device, or whose relationship to the study device is unknown.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is an adverse device effect (including infection that is suspected to relate to use of the device) of which occurrence and the occurrence trend such as number and frequency of the occurrences, and conditions on the occurrence cannot be predicted from the Investigator's Brochure of the investigational device.

Angina Pectoris

- **Braunwald Classification of Unstable Angina:**
  - I. New onset of severe or accelerated angina. Patients with new onset (≤ 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.
  - II. Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.
  - III. Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

- **Canadian Cardiovascular Society [CCS] Classification of Stable Angina:**
  - I. Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.
  - II. Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
  - III. Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.
  - IV. Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

TIMI (Thrombosis in Myocardial Infarction) Flow Grades

0. No contrast flow through the stenosis.
1. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
2. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
3. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.

23 APPENDIX VI: MSCT ACQUISITION GUIDELINES

[Optimizing Imaging Quality for MSCT and FFR_{CT}]

Introduction

- Please utilize **64 Slice CT** Scanner.
- Imaging the **entire coronary tree** allows for the most accurate FFRCT computation.

Preparation

- Assess heart rate and rhythm. Heart rate control (below 60 beats per minute) reduces misregistration and motion artifacts.
- Heart rate modulation for heart rates >60/min during breath holding.
    - Oral: metoprolol tartrate 100 mg, one hour before the exam.
      atenolol 50 mg, one hour before the exam.
    - IV: metoprolol 5 mg, repeated up to 3 times.
    - Contraindications: conduction delays, hypotension, severe asthma, allergy to betablockers.
    - Consider ivabradin or calcium antagonist for patients with contra-indications to betablockers.
- Full explanation of exam, and practice breath hold. Ensure breath hold time will be sufficient for scan time. Evaluate impact of breath holds on heart rate.

Nitrates and FFR_{CT}.

- use NTG preferably 3 minutes prior to CT image acquisition;
- use 1-2 sprays (0.4mg-0.8mg)
- use beta-blocker with it to avoid reflex tachycardia/vasoconstriction
- ask patients not to take any nitrates 12-14 hours prior to CT acquisition
- additional Beta blockade may be given after nitroglycerin to counteract the reflex tachycardia

    - Confirm absence of allergy to contrast media (consider prophylaxis for patients with doubtful or mild reactions to contrast in the past).
    - No caffeine (coffee, tea, energy drinks, and most soda) products <12h pre-scan.
    - No smoking 5 minutes prior to scan.

Patient installation

- Attach ECG leads, avoid respiratory muscles, check signal stability during breath hold.
- Placement of an IV catheter that allows a flow of at least 4 ml/s.

Data acquisition

- Overview/scout of the entire chest.
- Contrast enhancement:
  - ≥300 g/L iodine contrast medium.
  - Injection rate: 4-6 ml/s.
  - Total amount depends on the patient size, the scan mode and the scan duration.
  - Contrast-scan timing:
  - Test bolus acquisition: 15-20 ml of contrast is injected, preferably followed by a bolus chaser. The time of (maximum) enhancement is used as the delay of the data acquisition after start of contrast injection.
  - Bolus tracking: arrival of the (entire) bolus is monitored in the ascending aorta. To avoid premature triggering of the scan the ROI should be sufficiently large and placed away form the superior vena cava.
  - A saline bolus of ≈50 ml is injected after the contrast medium at the same rate.
- Scan mode (depending on the available CT equipment and local experience):
  - ECG-gated spiral scan mode. ECG-triggered tube modulation: use and nominal output width depending on the heart rate and rate stability. Full-output window wider, to include both end-systolic and diastolic phase, for heart rates >70/min.
  - ECG-triggered sequential (step-and-shoot) scan mode can be used by experienced sites for patients with a modest heart rate (<70-75/min) without rhythm irregularities. Scan window preferably widened to allow reconstruction of more phases, wider for faster heart rates (>65/min).
  - High-pitch spiral scans (Definition Flash®) not recommended.
- Acquisition parameters:
  - Thinnest detector width.
  - Tube current (mA), depending on the size of the patient.
  - Tube voltage 120 kV, 100 kV can be considered for (very) small patients (<70 kg).
  - Scan range: from 1-2 cm below the carina until the caudal border of the heart.

Image reconstruction (appropriately labelled):

1) Standard reconstructions:

- Standard medium-sharp convolution kernel.
- ECG-editing, if necessary.
- Field-of-view enclosing the entire heart (cover inferior carina to lower heart border) (approx. 18 x 18 cm).
- Reconstructed slice thickness equal or slightly wider than the individual detector width. In case of noisy images (obesity), thicker-slice reconstructions may be added.
- Reconstructions of at least three different phases. Depending on the scan protocol both diastolic and systolic reconstructions should be performed.

- Reconstructions should be optimized for the segments of interest (ROI). In case of suboptimal image quality other phases should be explored.
- In case of slab artifacts at the level of the lesions/segments of interest, ECG editing may improve image quality.

2) Sharp-kernel reconstructions:

- Thinnest slice thickness
- One or two reconstructions at the best phase for each of the one or two stented segments, based on the standard reconstructions.

DVD recording:

- Topogram.
- ECG file.
- Scan protocol file containing: scan mode, mA, kV, DLP, etc.
- Standard kernel reconstructions, at least one (or the same) optimal phase for each diseased coronary segment, preferably three or more datasets including both systolic and diastolic phases.
- Sharp kernel reconstructions (dedicated stent reconstruction), at least one (or the same) optimal phase for each diseased segment.

Summary

• FFR_{CT} is derived from precise modelling of the coronary tree, not just areas of disease

• cCTA best practices = best practices for FFR_{CT} data

J Cardiovasc Comput Tomogr. 2009 May-Jun;3(3):190-204

• Scan optimization is essential in unlocking the potential of FFR_{CT}