Implementation of the best practice principle in contemporary percutaneous coronary intervention

Kogame, N.

Publication date
2022

Document Version
Final published version

Implementation of the best practice principle in contemporary percutaneous coronary intervention

Norihiro Kogame

Implementation of the best practice principle in contemporary percutaneous coronary intervention

Norihiro Kogame

Implementation of the best practice principle in contemporary percutaneous coronary intervention

Dissertation, University of Amsterdam, the Netherlands

ISBN: 978-4-600-01003-4
Author: Norihiro Kogame
Lay-out and printing by OHNISHI PRINTING, Tokyo, Japan

Implementation of the best practice principle in contemporary percutaneous coronary intervention

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op maandag 23 mei 2022, te 14.00 uur
door Norihiro Kogame
geboren te Hiroshima

Promotiecommissie:

Promotores:	prof. dr. J.J. Piek	AMC-UvA
	prof. dr. P.W.J.C. Serruys	National University of Ireland Galway
Copromotores:	dr. J.J. Wykrzykowska	AMC-UvA
	prof. dr. Y. Onuma	National University of Ireland Galway
Overige leden:	prof. dr. J. Kluin	AMC-UvA
	prof. mr. dr. B.A.J.M. de Mol	AMC-UvA
	prof. dr. J.P.S. Henriques	AMC-UvA
	prof. dr. N. van Royen	Radboud Universiteit Nijmegen
	prof. dr. R.J.M. van Geuns	Radboud Universiteit Nijmegen
	prof. dr. C. von Birgelen	Universiteit Twente

Faculteit der Geneeskunde

Table of contents

Part C: Assessment of optimal coronary artery stenting with intracoronary imaging

Part D: Coronary physiology for optimal revascularization strategy

Part E: Optimal antithrombotic therapy after stent implanation

1

General introduction and outline of the thesis

Norihiro Kogame

GENERAL INTRODUCTION

Coronary artery disease

Coronary artery disease (CAD) is the most common type of heart disease and the leading cause of death, responsible for 16% of the world's total deaths [1, 2]. Patients with CAD typically present with chest pain. CAD is caused by the blockage of blood flow to the myocardium due to build-up plaque (atherosclerosis) in the epicardial coronary arteries. CAD is the process of atherosclerotic plaque accumulation which is mainly caused by hypertension, diabetes, dyslipidemia, and smoking. CAD can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. Therefore, CAD is categorized into acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) according to its stability [3]. The purpose of the treatment for CAD is to modify the process of atherosclerotic plaque accumulation. The treatment of CAD includes lifestyle adjustment, pharmacological therapies, and invasive intervention for revascularization such as coronary bypass grafting (CABG) and percutaneous coronary intervention (PCI). ACS patients are mainly treated with early invasive revascularization [4]. While invasive revascularization plays an important role in the management of CCS on top of medical treatment whenever pharmacological therapy fails to alleviate the anginal complaints.

History of PCI and antithrombotic therapy

PCI with balloon angioplasty was introduced by Andreas Gruntzig in 1977 [5]. The limitation of balloon angioplasty such as abrupt vessel closure due to dissection and restenosis, prompted the development of bare metal stent (BMS) to maintain lumen integrity [6]. BMS improved procedural safety and efficacy and eliminated the need for surgical standby [7]. However, initial iterations were associated with elevated thrombosis rates [8]. Antithrombotic treatment following coronary stent implantation evolved significantly over the years and after a period of extensive use of intravenous and oral anticoagulation, dual antiplatelet therapy (DAPT) consisting of aspirin and ticlopidine became the mainstay strategy to reduce stent thrombosis together with technical refinements such as the use of routine high-pressure stent deployment [9-11]. Subsequently, the introduction of clopidogrel led to the popularization of the DAPT regimen that became a basic recommendation in the practice guidelines in early 2000 [12-15].

Although BMS and DAPT solved the acute vessel closure problem, it was still associated with high restenosis rate, prompted research toward the development of drug-eluting stent (DES). The introduction of the first generation DES such as Cypher (Cordis, Warren, New Jersey, USA) and Taxus (Boston Scientific, Natick, Massachusetts, USA) with certification mark (CE Mark) approval acquired in 2002 (Cypher) and 2003 (Taxus) heralded a major technological breakthrough, which resulted in a dramatic reduction of neointimal proliferation, binary restenosis rate and subsequently repeat revascularization rate [16]. However, the potent antiproliferative effect and consequent partial non-coverage of thick struts in the first-generation DES were responsible for the increased risk of late thrombotic events associated with these stents, especially if they were not fully apposed [17]. Therefore, the Food and Drug Administration (FDA) supported empirical treatment of 12 months of dual antiplatelet therapy (DAPT) on the basis of consensus opinion [18]. Second generation

DES was introduced to overcome this problem with thinner struts (80-90 µm), new drugs with better elution profiles and more biocompatible polymers. It showed better antirestenostic properties coupled with adequate strut coverage [19, 20], resulting in significant lower rate of thrombotic complications when compared to first generation DES and BMS [21].

The most challenging subset of patients for PCI

After the introduction of second generation DES, PCI has become the most frequently performed therapeutic procedure in medicine [22]. Despite the tremendous evolutions in PCI, three-vessel disease (3VD) remains the most challenging subset of patients for PCI [23]. Current data show that in non-diabetic patients with 3VD and low anatomical complexity (anatomical SYNTAX score ≤22) PCI and CABG achieve similar long-term outcomes in terms of death and the composite of death, stroke, and myocardial infarction (MI), and consequently current guidelines give PCI a Class I (evidence level A) recommendation for these patients [24]. In contrast, percutaneous revascularization is not recommended in those patients with 3VD at low surgical risk if the complexity of their coronary artery disease is intermediate to severe (anatomical SYNTAX score >22), or if they have diabetes mellitus regardless of anatomical complexity.

The results of a recent individual patient-level meta-analysis lead the ESC Guidelines to downgrade PCI in diabetic patients with 3VD and a low SYNTAX score to Class IIb, whilst reaffirming a Class I (evidence level A) recommendation for CABG [24, 25].

OUTLINE OF THESIS

In this thesis we aim to evaluate the impact of contemporary best practice PCI strategy for patients with 3VD and to explore further development of this strategy.

Part A: Best practice in coronary revascularization of three-vessel disease

In **chapter 2** we will investigate the impact of a contemporary best practice PCI strategy (SYNTAX-II strategy) on clinical outcomes in patients with de novo 3VD, compared to a prespecified and matched population of the SYNTAX-I trial, utilizing the SYNTAX score II to identify patients with equipoise for long term mortality between CABG and PCI [26-28].

Part B: Standardization of the assessment of the device success in the contemporary stent trials

The rate of device success has been recognized as an intraprocedural endpoint to evaluate the mechanical ability to complete a procedure with the specific device assigned by protocol in randomized comparative trials. Therefore, a consistent definition of device success is essential to allow scientific comparisons of technical performance endpoints between devices across different trials. In **chapter 3**, we will perform a systematic evaluation of definitions and reporting of device success in clinical trials. We will propose an extended definition as well as considerations for approaching the determination of the device success rates in future percutaneous coronary intervention trials. In **chapter 4** we will conduct an all-comers trial to investigate non-inferiority of clinical outcomes after implantation of the ultra-thin strut Supraflex DES compared with the Xience DES.

Part C: Assessment of optimal coronary artery stenting with intracoronary imaging

Intracoronary imaging modalities such as IVUS and optical coherence tomography (OCT) enables the assessment of artery lumen and wall geometry as well as distribution, and histological type of atherosclerotic plaque. Recently, IVUS and OCT have been used not only for diagnosis but also for treatment guidance during PCI [29-31]. In **chapter 5** we will investigate the impact of minimal stent area (MSA) evaluated by post-procedural IVUS on clinical outcomes after best practice PCI in patients with 3VD. In **chapter 6** we will investigate clinical implication of 3-dimensional optical frequency domain imaging (3D-OFDI)-guided stenting for bifurcation lesions in the randomized controlled trial.

Part D: Coronary physiology for optimal revascularization strategy

Physiological assessment of CAD has become one of the cornerstones of decision making for myocardial revascularization, with a large body of evidence supporting the benefits of using fractional flow reserve and other pressure-based indexes for functional assessment of coronary stenoses. However, the clinical impact of post-PCI physiological assessment is undetermined. In **chapter 7** we will investigate the impact of post-PCI quantitative flow ratio (QFR) on clinical outcomes in patients with de novo 3VD treated with best practice PCI. In **chapter 8**, we will review more than 10 modalities of functional coronary assessment according to their timing of use: outside the catheterization laboratory, in the catheterization laboratory prior to PCI, and in the catheterization laboratory during or after PCI.

Part E: Optimal antithrombotic therapy after stent implantation

Patients with CAD undergoing PCI are traditionally treated with aspirin and a P2Y12 inhibitor during first period post procedure, followed by withdrawal of the P2Y12 inhibitor and maintenance of aspirin as the single antiplatelet drug thereafter. However, the best antithrombotic approach after stenting is still an open matter, currently under intense clinical investigation. In this regard, several recent trials have shown promising results with a scheme comprising short DAPT duration followed by the administration of solely a P2Y12 antagonist, instead of aspirin[32]. In **chapter 9** we will investigate the clinical impact of ticagrelor monotherapy following 1-month DAPT after PCI for bifurcation lesions which are the one of the most challenging anatomical characteristics for PCI. In **chapter 10** we will evaluate the hypothesis that prasugrel monotherapy following successful everolimus-eluting stent implantation is feasible and safe in patients with stable CAD.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;**367**(9524):1747-57.
2. WHO methods and data sources for country‐level causes of death 2000‐2019 Department of Data and Analytics (DNA), Division of Data, Analytics and Delivery for Impact (DDI), WHO, Geneva, December 2020. Available at: https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_cod_methods.pdf?sfvrsn=37bcfacc_5 [Last accessed 10 January 2022].
3. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Group ESCSD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;**40**(2):87-165.
5. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;**1**(8058):263.
6. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;**316**(12):701-6.
7. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;**331**(8):489-95.
8. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, Meier B, Goy JJ, Vogt P, Kappenberger L, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med 1991;**324**(1):13-7.
9. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;**91**(6):1676-88.
10. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;**334**(17):1084-9.
11. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998;**339**(23):1665-71.
12. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators C. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;**102**(6):624-9.
13. 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, American College of Cardiology F, American Heart Association Task Force on Practice G, Society for Cardiovascular A, Interventions. 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.

14. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS 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)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;**35**(37):2541-619.
15. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA, Clopidogrel in Unstable angina to prevent Recurrent Events trial I. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;**358**(9281):527-33.
16. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R, Lesions RSGRSwtS-CBVB-ESitToPwdNNCA. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;**346**(23):1773-80.
17. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C, Investigators B-L. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006;**48**(12):2584-91.
18. Serruys PW. FDA panel, 7 and 8 December 2006 - The impact on our practice and research. EuroIntervention 2007;**2**(4):405-7.
19. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;**47**(1):175-81.
20. 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**(5):333-42.
21. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, Valgimigli M, Orlandi C, Petrou M, Rapezzi C, Stone GW. Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. J Am Coll Cardiol 2015;**65**(23):2496-507.
22. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 2012;**366**(1):54-63.
23. 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.
24. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;**40**(2):87-165.
25. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Makikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF, 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;**391**(10124):939-948.

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. Serruys PW, Chichareon P, Modolo R, Leaman DM, Reiber JHC, Emanuelsson H, Di Mario C, Pijls NHJ, Morel MA, Valgimigli M, Farooq V, van Klaveren D, Capodanno D, Andreini D, Bourantas CV, Davies J, Banning AP, Escaned J, Piek JJ, Echavarria-Pinto M, Taylor CA, Thomsen B, Collet C, Pompilio G, Bartorelli AL, Glocker B, Dressler O, Stone GW, Onuma Y. The SYNTAX score on its way out or ... towards artificial intelligence: part I. EuroIntervention 2020;**16**(1):44-59.
28. Serruys PW, Chichareon P, Modolo R, Leaman DM, Reiber JHC, Emanuelsson H, Di Mario C, Pijls NHJ, Morel MA, Valgimigli M, Farooq V, van Klaveren D, Capodanno D, Andreini D, Bourantas CV, Davies J, Banning AP, Escaned J, Piek JJ, Echavarria-Pinto M, Taylor CA, Thomsen B, Collet C, Pompilio G, Bartorelli AL, Glocker B, Dressler O, Stone GW, Onuma Y. The SYNTAX score on its way out or ... towards artificial intelligence: part II. EuroIntervention 2020;**16**(1):60-75.
29. Onuma Y, Katagiri Y, Burzotta F, Holm NR, Amabile N, Okamura T, Mintz GS, Darremont O, Lassen JF, Lefevre T, Louvard Y, Stankovic G, Serruys PW. Joint consensus on the use of OCT in coronary bifurcation lesions by the European and Japanese bifurcation clubs. EuroIntervention 2019;**14**(15):e1568-e1577.
30. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Kang WC, Her AY, Kim YH, Hur SH, Hong BK, Kwon H, Jang Y, Hong MK. Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation: The IVUS-XPL Randomized Clinical Trial. JAMA 2015;**314**(20):2155-63.
31. Kang SJ, Ahn JM, Song H, Kim WJ, Lee JY, Park DW, Yun SC, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW, Park SJ. Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. Circ Cardiovasc Interv 2011;**4**(6):562-9.
32. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J 2020.

2

Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study.

Patrick W. Serruys*, Norihiro Kogame*, Yuki Katagiri, Rodrigo Modolo, Pawel E. Buszman, Andres Iniguez, Javier Goicolea, David Hildick-Smith, Andrzej Ochala, Dariusz Dudek, Jan J. Piek, Joanna J. Wykrzykowska, Javier Escaned, Adrian P. Banning, Vasim Farooq, Yoshinobu Onuma. *Authors contributed equally

EuroIntervention. 2019 Jun 12;15(3):e244-e252.

Abstract

Aims

The purpose of the study was to investigate whether the favourable outcomes of state-of-the-art PCI in the SYNTAX II trial, demonstrated at one year, were maintained at two-year follow-up.

Methods and results

The SYNTAX II study was a multicentre, single-arm study that investigated the impact of a contemporary PCI strategy on clinical outcomes in 454 patients with de novo three-vessel coro- nary artery disease, without left main disease. Clinical outcomes in SYNTAX II were compared to the predefined PCI (SYNTAX-I PCI) and coronary artery bypass graft (SYNTAX-I CABG) cohorts from the landmark SYNTAX trial (SYNTAX-I), selected on the basis of equipoise for long-term (four-year) mortality utilising the SYNTAX score II. At two years, major adverse cardiac and cerebrovascular events (MACCE: a composite of all-cause death, any stroke, myocardial infarction, or revascularisation) in SYNTAX II were significantly lower compared to SYNTAX-I PCI (13.2% vs. 21.9%, p=0.001). Furthermore, similar two- year outcomes for MACCE were evident between SYNTAX II PCI and SYNTAX-I CABG (13.2% vs. 15.1%, p=0.42).

Conclusions

At two years, clinical outcomes with the SYNTAX II strategy remained superior to the pre-defined SYNTAX-I PCI cohort, and similar to the predefined SYNTAX-I CABG cohort.

Introduction

With the introduction of drug-eluting stents (DES), the efficacy of percutaneous coronary intervention (PCI) has improved compared to bare metal stents[1]. Despite this, five-year follow-up of the landmark SYNTAX-I (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial demonstrated that PCI with first-generation DES was inferior to coronary artery bypass graft (CABG) surgery, being associated with a higher incidence of a composite of all-cause death, any stroke, or myocardial infarction (MI) (PCI 20.8% vs. CABG 16.7%, p=0.03)[2].

In the *de novo* three-vessel disease (3VD) cohort of SYNTAX-I, patients with a low anatomical complexity (anatomic SYNTAX score ≤22) were shown to have similar outcomes between CABG and PCI at five years. Conversely, in patients with more anatomically complex coronary artery disease (anatomic SYNTAX score>22), CABG was demonstrated to have superior clinical outcomes. As a reflection of these findings, 3VD with low anatomic SYNTAX score (≤22) is now given a class Ia recommendation for PCI, with more complex coronary artery disease (>22) given a class III recommendation for PCI, and patients recommended to undergo CABG[3]. Furthermore, due to the results of a recent patient-level meta-analysis[3,4], guidelines downgrade patients with 3VD with a low SYNTAX score and diabetes mellitus to a class IIb recommendation for PCI, and class Ia for CABG.

Since the completion of the SYNTAX-I trial, major technical and procedural advances influencing PCI outcomes have taken place. The SYNTAX II trial investigated the impact of a contemporary PCI strategy (SYNTAX II strategy) on clinical outcomes in patients with *de novo* 3VD, compared to a pre-specified and matched population of the SYNTAX-I trial, utilising the SYNTAX score II to identify patients with equipoise for long-term mortality between CABG and PCI.

At one year, the SYNTAX II strategy was superior to predefined SYNTAX-I PCI with respect to major adverse cardiac and cerebrovascular events (MACCE: a composite of all-cause death, any stroke, MI, or revascularisation, 10.6% vs. 17.4%, p=0.006). Furthermore, the non-inferiority of the SYNTAX II strategy compared to SYNTAX-I CABG was demonstrated, with respect to one-year MACCE (10.6% vs. 11.2%, p for non-inferiority <0.001)[5]. In terms of a composite of all-cause death, any stroke, or MI, the SYNTAX II strategy was similar to predefined SYNTAX-I CABG (4.0% vs. 5.9%, p=0.20). The long-term clinical outcomes of contemporary PCI remain to be proven.

The purpose of this paper was to investigate whether the favourable outcomes of state-of-the-art PCI in the SYNTAX II trial at one year were maintained at two-year follow-up.

Methods

STUDY DESIGN

The design for this trial has been described previously[5,6]. The clinical outcomes in SYNTAX II were compared with predefined PCI (SYNTAX-I PCI) and CABG (SYNTAX-I CABG) cohorts from SYNTAX-I. These patients were selected on the basis of equipoise for long-term four-year mortality between CABG and PCI utilising the SYNTAX score II.

Following the selection of patients utilising the SYNTAX score II, consensus of the Heart Team (cardiac surgeons and interventional cardiologists) – that equivalent anatomical revascularisation was achievable – was mandated. Only then was the patient eligible for recruitment in SYNTAX II. Coronary lesions agreed by the Heart Team as requiring revascularisation were identified as "target lesions". Coronary lesions agreed by the Heart Team as not requiring revascularisation were identified as "non-target lesions".

Target lesions for revascularisation in SYNTAX II were assessed with a hybrid instantaneous wave-free ratio (iFR)/fractional flow reserve (FFR) approach. Physiologically significant lesions were treated with the SYNERGY™ DES (Boston Scientific, Marlborough, MA, USA). Post-PCI intravascular ultrasound assessment was mandatory to optimise stent expansion and apposition, with a recommendation to use the modified MUSIC criteria[7]. In addition, contemporary chronic total occlusion revascularisation techniques[8] by dedicated operators, and guideline-directed medical therapy, including antiplatelet therapy and high-intensity statin therapy[3,9], were recommended. The patient's clinical status was assessed at discharge, and at one- and two-year follow-up. Extended yearly follow-up is planned up to five years. The local ethics committee approved the study in all participating sites. All patients provided written informed consent before enrolment.

ENDPOINTS

MACCE was defined as a composite of all-cause death, any stroke, MI, or revascularisation.

The primary analysis was two-year MACCE in the SYNTAX II compared with the SYNTAX-I PCI cohort. Spontaneous MI was defined as new Q-waves or one plasma level of creatine kinase myocardial band (CK-MB) 5x ULN (or troponin ≥35 ULN if CK-MB not available)[10] in the context of clinical syndrome consistent with acute coronary syndrome[11]. Secondary endpoints included the individual components of MACCE and definite stent thrombosis (ST) according to Academic Research Consortium (ARC) definitions at two-year follow-up[12].

By the SYNTAX II trial design, non-target vessel revascularisation (non-TVR) at follow-up was classified as:

1. occurring in a non-target lesion, anatomically assessed by visual inspection at the time of screening by the Heart Team and agreed as not for revascularisation;
2. occurring in a deferred coronary lesion based on iFR/FFR at the index procedure.

As an additional exploratory analysis, two-year MACCE was compared with the predefined SYNTAX-I CABG cohort of the original SYNTAX-I trial. Adverse events were adjudicated by an independent clinical events committee.

STATISTICAL ANALYSIS

The statistical analysis for this trial has been described previously[5,6] and is summarised in **Supplementary Appendix 1.**

Results

BASELINE AND PROCEDURAL CHARACTERISTICS

Between February 2014 and November 2015, 454 patients out of 708 screened patients were enrolled in SYNTAX II[13]. In SYNTAX-I, 643 (58.8%) patients with 3VD without left main disease had an equipoise recommendation for CABG or PCI based on the SYNTAX score II

and were used as the comparator. Baseline and procedural characteristics and achievement of SYNTAX II strategy are shown in **Supplementary Table 1-Supplementary Table 3**. In SYNTAX II, the distribution of the anatomic SYNTAX score was as follows: low (≤22) 298 patients (65.6%); intermediate (23–32) 140 patients (30.8%), high (>32) 16 patients (3.5%).

In SYNTAX II, statins were used in 97.3% and 92.3% of patients at discharge and two-year follow-up, respectively. Dual antiplatelet therapy use involved 6.8% of patients at two-year follow-up.

TWO-YEAR MACCE AND COMPONENTS

At two years in SYNTAX II, five patients withdrew their consent and six patients were lost to follow-up, resulting in complete two-year follow-up in 97.6% (n=434). Comparatively, in SYNTAX-I PCI, six patients were lost to follow-up, resulting in complete two-year follow-up in 98.0% (n=309); in SYNTAX-I CABG, 25 patients were lost to follow-up, resulting in complete two-year follow-up in 92.5% (n=309).

Table 1 and **Figure 1** show MACCE and its components at two-year follow-up. The incidence of MACCE was significantly lower in SYNTAX II compared to SYNTAX-I PCI (13.2% vs. 21.9%; hazard ratio[HR]0.57,95%confidenceinterval[CI]:0.40-0.81],p=0.001). This difference was driven by a reduction of 66% in any MI and 38% in any revascularisation. We found a trend towards lower incidences of all-cause death and stroke in SYNTAX II compared to SYNTAX-I PCI (2.7% vs. 5.5%, p=0.055, 0.4% vs. 2.0%, p=0.07, respectively).

There was no difference in MACCE between SYNTAX II patients with low (≤22) vs. intermediate or high (>22) anatomical SYNTAX score (12.3% vs. 15.0%, p=0.439) **(Figure 2)**, patients with vs. without any diabetes mellitus (15.0% vs. 12.5%, p=0.50), or patients with diabetes mellitus treated with insulin vs. without insulin (18.4% vs. 13.4%, p=0.46) **(Supplementary Figure 1, Supplementary Figure 2)**.

In multivariate analysis, chronic obstructive pulmonary disease (HR 2.90, 95% CI: 1.30-6.44), peripheral vascular disease (HR 3.38, 95% CI: 1.32-8.62), and anatomical SYNTAX score per unit of score (HR 1.05, 95% CI: 1.002-1.101) were significant **(Supplementary Table 4)**.

REPEAT REVASCULARISATION BETWEEN ONE-YEAR AND TWO-YEAR FOLLOW-UP

The description of the revascularisation procedures in SYNTAX II is presented in **Supplementary Table 5**. Between one-year and two-year follow-up, 22 revascularisations occurred in 20 out of 1,559 lesions and two lesions were treated twice. Four lesions had already experienced a first event up to one year. The majority of revascularisations occurred in the initially stented lesions (77%, n=17 events), whereas there were few events in the initially deferred lesions (14%, n=3 events) **(Figure 3)**. No MI in the territory of the initially deferred lesions occurred.

STENT THROMBOSIS

The incidence of definite ST in SYNTAX II was significantly lower compared to SYNTAX-I PCI (0.9% vs. 2.9%; HR 0.30, 95% CI: 0.09-0.99, p=0.048] **(Table 1, Figure 1)**. No difference was found in the incidence of late (between 30 days and one year) and very late ST (after one year) between groups. Between one- and two-year follow-up, only one ST occurred as MI in SYNTAX II.

Table 1. Two-year clinical outcomes between SYNTAX II and SYNTAX-I PCI.

Outcome	SYNTAX-II (n = 454)	SYNTAX-I PCI (n = 315)	Hazard ratio (95% CI)	P-value
MACCE*, % (n)	13.2% (59)	21.9% (68)	0.57 (0.40-0.81)	0.001
All-cause death, stroke and any MI, % (n)	4.7% (21)	10.6% (33)	0.43 (0.25-0.74)	0.002
All-cause death, % (n)	2.7% (12)	5.5% (17)	0.48 (0.23-1.02)	0.055
Cardiac death, % (n)	1.4% (6)	3.9% (12)	-	0.025
Vascular death, % (n)	0.5% (2)	0.3% (1)	-	0.80
Non-cardiovascular death, % (n)	0.9% (4)	1.3% (4)	-	0.59
Stroke, % (n)	0.4% (2)	2.0% (6)	0.23 (0.05-1.13)	0.07
Ischemic, % (n)	0.4% (2)	1.4% (4)	-	0.19
Haemorrhagic, % (n)	0.2% (1)	0.7% (2)	-	0.36
Any MI, % (n)	2.1% (9) †	5.8% (18)	0.34 (0.15-0.76)	0.008
Periprocedural MI, % (n)	0.2% (1)	3.8% (12)	-	<0.001
Spontaneous MI, % (n)	1.6% (7)	2.0% (6)	-	0.66
Any revascularization, % (n)	10.2% (45)	15.7% (48)	0.62 (0.41-0.94)	0.022
CABG, % (n)	1.1% (5)	2.6% (8)	-	0.12
PCI, % (n)	9.3% (41)	14.1% (43)	-	0.036
Definite stent thrombosis, % (n)	0.9% (4)	2.9% (9)	0.30 (0.09-0.99)	0.048
Acute, % (n)	0.2% (1)	0.0% (0)	-	0.40
Sub-acute, % (n)	0.0% (0)	1.6% (5)	-	0.007
Late, % (n)	0.4% (2)	1.0% (3)	-	0.37
Very late, % (n)	0.2% (1)	0.3% (1)	-	0.78
Probable stent thrombosis, % (n)	0.2% (1)	NA	-	

* MACCE was defined as all-cause death, any stroke, MI, or revascularization. † One MI occurred after enrolment before index procedure. The event rates are based on Kaplan-Meier estimates. CABG = coronary artery bypass grafting, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, PCI = percutaneous coronary intervention.

EXPLORATORY COMPARISON WITH SYNTAX-I CABG

The exploratory comparison with the predefined SYNTAX-I CABG demonstrated a similar incidence of MACCE at two years (SYNTAX II 13.2% vs. SYNTAX-I CABG 15.1%; HR 0.85, 95% CI: 0.58-1.25, p=0.42) **(Table 2, Figure 4)**. The incidence of stroke was significantly lower in SYNTAX II compared to SYNTAX-I CABG (0.4% vs. 2.2%, p=0.045). The incidence of all-cause revascularisation was similar (10.2% vs. 8.4%, p=0.41). We found a trend towards a higher incidence of non-TVR in SYNTAX II compared with SYNTAX-I CABG (2.0% [9/454] vs. 0.6% [2/334], p=0.12).

Looking at the details of nine non-TVR in SYNTAX II, seven non-TVR occurred in initially deferred lesions based on iFR/FFR at the index procedure. One non-TVR occurred in an anatomically non-target lesion at the index procedure. The second patient developed unstable angina before a planned staged procedure at day 2.

At the time of revascularisation (day 544 and day 303, respectively), one lesion was justified with FFR of 0.76, and one lesion had become a total occlusion.

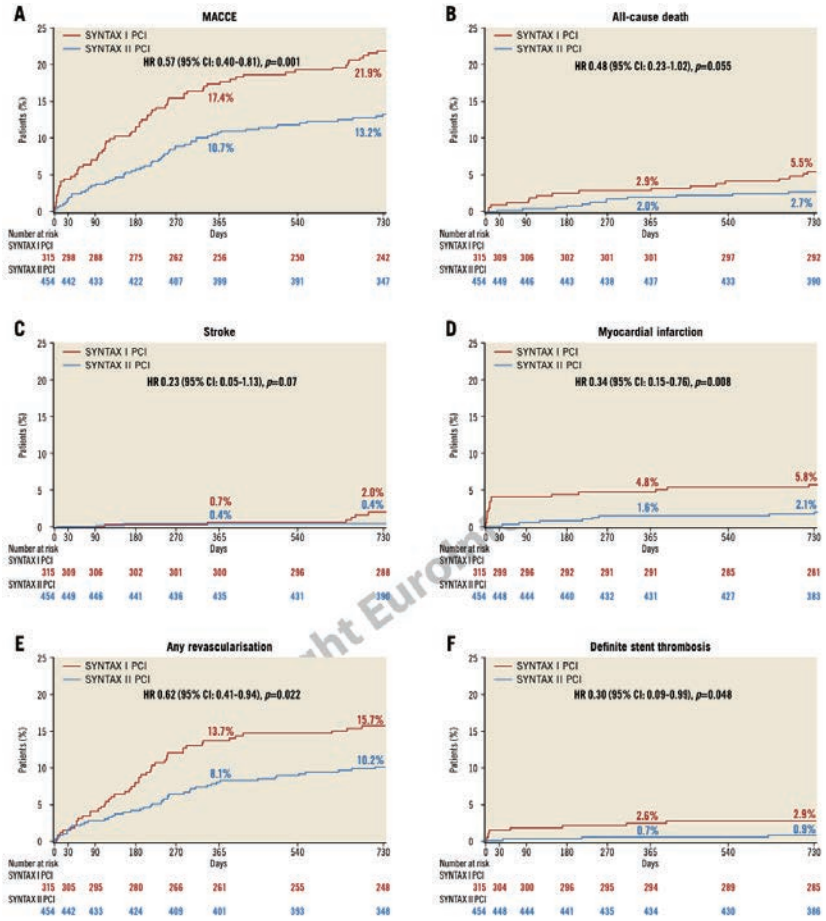


Figure 1. Two-year clinical outcomes among the study patients, compared with the SYNTAX-I PCI cohort. Kaplan-Meier curves are shown for SYNTAX II (blue) and SYNTAX-I PCI (red) for the composite endpoint of major adverse cardiac or cerebrovascular events (MACCE) (A), all-cause death (B), stroke (C), any myocardial infarction (D), any revascularisation (E), and definite stent thrombosis (F). MACCE was defined as all-cause death, any stroke, MI, or revascularisation.

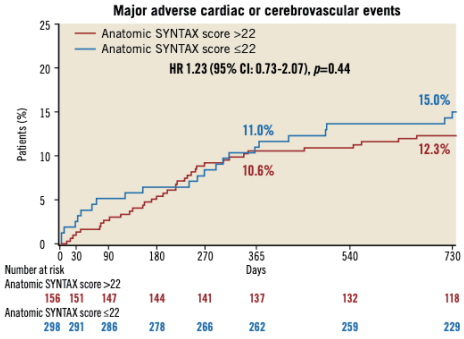


Figure 2. Kaplan-Meier cumulative incidence for major adverse cardiac or cerebrovascular events in SYNTAX II patients stratified by anatomic SYNTAX score ≤22 (blue) and >22 (red).

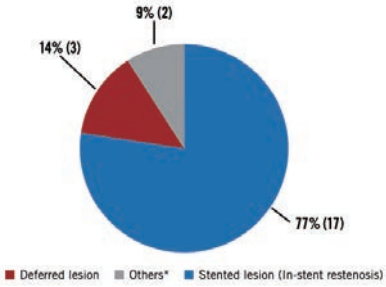


Figure 3. Distribution of baseline lesion type that caused revascularisation from one-year to two-year follow-up. In a total of 22 revascularisations, the majority of revascularisations occurred in the initially stented lesions (77%, n=17 events, blue), whereas there were few events in the initially deferred lesions (14%, n=3 events, red). *One revascularisation occurred in a distal lesion far from the initially stented lesion. In addition, one revascularisation of a CTO lesion was staged and not treated at the index procedure (9%, n=2 events, grey).

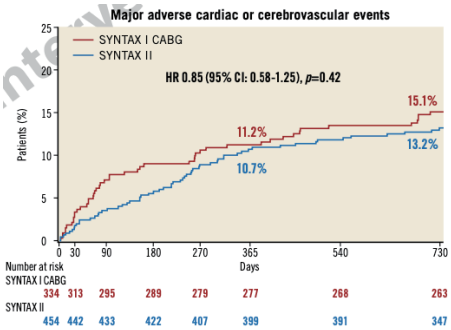


Figure 4. Two-year major adverse cardiac or cerebrovascular events among the study patients, compared with the SYNTAX-I CABG cohort. Kaplan-Meier curves are shown for SYNTAX II (blue) and SYNTAX-I CABG (red) for the exploratory composite endpoint of major adverse cardiac or cerebrovascular events (MACCE). MACCE was defined as all-cause death, any stroke, MI, or revascularisation.

Table 2. Two years clinical outcomes between SYNTAX-II and SYNTAX-I CABG

Outcome	SYNTAX-II (n = 454)	SYNTAX-I CABG (n = 334)	Hazard ratio (95% CI)	P-value
MACCE*, % (n)	13.2% (59)	15.1% (48)	0.85 (0.58-1.25)	0.42
All-cause death, stroke and any MI, % (n)	4.7% (21)	8.2% (26)		0.045
All-cause death, % (n)	2.7% (12)	5.1% (16)	0.52 (0.25-1.11)	0.09
Cardiac death, % (n)	1.4% (6)	2.8% (9)		0.14
Vascular death, % (n)	0.5% (2)	0.7% (2)		0.71
Non-cardiovascular death, % (n)	0.9% (4)	1.7% (5)		0.37
Stroke, % (n)	0.4% (2)	2.2% (7)	0.20 (0.04-0.96)	0.045
Ischemic, % (n)	0.4% (2)	1.9% (6)		0.052
Haemorrhagic, % (n)	0.2% (1)	0.3% (1)		0.79
Any MI, % (n)	2.1% (9)	2.2% (7)	0.91 (0.34-2.44)	0.85
Periprocedural MI, % (n)	0.2% (1)	1.5% (5)		0.04
Spontaneous MI, % (n)	1.6% (7)	0.7% (2)		0.25
Any revascularization, % (n)	10.2% (45)	8.4% (26)	1.23 (0.76-1.99)	0.41
CABG, % (n)	1.1% (5)	1.0% (3)		0.83
PCI, % (n)	9.3% (41)	7.8% (24)		0.46

* MACCE was defined as all-cause death, any stroke, MI, or revascularization. CABG = coronary artery bypass grafting, MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, PCI = percutaneous coronary intervention

Discussion

The main findings of the study are the following: 1) PCI undertaken with the SYNTAX II strategy was associated with superior outcomes compared with the predefined SYNTAX-I PCI cohort, with a lower incidence of MACCE predominantly driven by a reduction in MI, all-cause revascularisation, and definite ST at two-year follow-up; 2) the two-year outcomes of patients with intermediate or high anatomical SYNTAX score (>22), treated with PCI using the SYNTAX score II risk stratification algorithm, were similar to those observed in patients with the low anatomical SYNTAX score (≤22); 3) the two-year outcome of deferred lesions on the basis of a hybrid iFR/FFR approach was benign; 4) in an exploratory analysis at two years, PCI with the SYNTAX II strategy was similar to the predefined SYNTAX-I CABG cohort, with respect to the incidence of MACCE.

Even if some of the elements of the SYNTAX II strategy were not fully applied **(Supplementary Table 3)**, it is important for clinicians to realise that these results were not just the outcomes of contemporary PCI, but instead were only obtained by "best of PCI practice", which includes adoption of the SYNTAX II strategy in a high proportion if not all 3VD cases.

As shown in the FAME trial, physiology-guided revascularisation in patients with multivessel disease resulted in a significant reduction of a composite of death or MI at two-year follow-up after the index procedure compared with angiography-guided revascularisation[14]. In the present study, the proportion of the initially deferred lesions revascularised between one-year and two-year follow-up was quite low (14%, 3/22 lesions). Notably, no MI in the territory of the initially deferred lesions occurred. While recent trial data have revealed excellent outcomes of revascularisation deferral based on either iFR or FFR in low- and intermediate-risk populations[15], the findings in the SYNTAX II trial demonstrate that safe decision making can also be performed in the high-risk 3VD patients who have been selected on the basis of equipoise for long-term mortality between CABG and PCI utilising the SYNTAX score II. Furthermore, as the decision to perform or defer revascularisation was based on iFR in more than 75% of interrogated stenoses, the SYNTAX II study provides indirect support to the safety of resting pressure-derived indices to decide revascularisation in this complex patient subset.

In the exploratory comparison with the predefined SYNTAX-I CABG cohort, no significant differences were shown in the incidence of MACCE between groups. The similar outcomes were maintained from one-year to two-year follow-up. Comparatively, the BEST trial, in which second-generation everolimus-eluting stents were used to treat multivessel disease, demonstrated that CABG was associated with a lower incidence of MACCE at five years, driven by a reduction in the incidence of MI and repeat revascularisation[16]. In the present study, the incidence of MI and repeat revascularisation in the SYNTAX II group remained similar to the SYNTAX-I CABG cohort at two years.

In addition, the incidence of definite ST at two years in SYNTAX II (0.9%) was comparable with current all-comers trials with newer-generation DES (BIOSCIENCE: 0.8 to 1.1%, BIO-RESORT: 0.6 to 1.0%, DESSOLVE III: 0.6 to 1.0%)[17-19], and was lower than in the ARTS II trial (2.0%)[20].

The favourable outcomes of the SYNTAX II strategy are exemplified by the absence of convergence and crossing over of endpoints at two years **(Figure 4)** which was evident in ARTS I and II. The incidence of non-TVR in SYNTAX II was numerically higher compared to

SYNTAX-I CABG (2.0% [9/454] vs. 0.6% [2/334], p=0.12). In SYNTAX II, the majority of non-TVR occurred in initially deferred lesions at the index procedure with negative iFR/ FFR values (7/9, 77.8%). In addition, two patients (2/9, 22.2%) at follow-up were justified by either anatomical character (total occlusion) or reduced FFR.

Study limitations

Firstly, this is a single-arm study comparing a contemporary PCI strategy with an historical control group (SYNTAX-I). Secondly, because of the observed advantage of CABG in females and young patients in the landmark SYNTAX trial, the SYNTAX score II resulted in a low proportion of these subgroups of patients in the present study. Thirdly, there is a nine-year lapse of time between the enrolment periods of SYNTAX I and II; with recent improvements in surgical techniques and concomitant medication, it is possible that the clinical results of a randomised trial could be at variance with the results of this present observational study[21,22]. Fourthly, although the use of coronary physiology was mandatory in lesions intended to be treated, mild stenoses not included in the anatomic SYNTAX score (i.e., <50%) may potentially be associated with physiological significance and were not systematically assessed by iFR/FFR. Finally, these data cannot be extrapolated to patients with left main disease and to 3VD patients without SYNTAX score II equipoise.

Conclusions

At two years, the SYNTAX II strategy was associated with improved clinical outcomes compared with the PCI performed in patients with 3VD without left main disease matched by the SYNTAX score II from the original SYNTAX-I trial. At two years, clinical outcomes of the SYNTAX II strategy compared favourably with the SYNTAX-I CABG cohort. Later follow-up is warranted, in addition to a randomised trial (with five to 10 years of follow-up) which will be mandatory to shed light on the respective values of contemporary and future surgical or percutaneous revascularisation treatments.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.
2. 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.
3. NeumannFJ,Sousa-UvaM,AhlssonA,AlfonsoF,BanningAP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2018;40:87-165.
4. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Makikallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet.* 2018;391: 939-48.
5. EscanedJ,ColletC,RyanN,DeMariaGL,WalshS,SabateM, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Ej West N, Piek JJ, Zaman A, Fath-Ordoubadi F, Stables RH, Appleby C, van Mieghem N, van Geuns RJ, Uren N, Zueco J, Buszman P, Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Hanratty C, Cavalcante R, Kappetein AP, Taggart DP, van Es GA, Morel MA, de Vries T, Onuma Y, Farooq V, Serruys PW, Banning AP. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J.* 2017;38:3124-34.
6. Escaned J, Banning A, Farooq V, Echavarria-Pinto M, Onuma Y, Ryan N, Cavalcante R, Campos CM, Stanetic BM, Ishibashi Y, Suwannasom P, Kappetein AP, Taggart D, Morel MA, van Es GA, Serruys PW. Rationale and design of the SYNTAX II trial evaluating the short to long-term outcomes of state-of-the-art percutaneous coronary revascularisation in patients with de novo three-vessel disease. *EuroIntervention.* 2016;12:e224-34.
7. 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;19:1214-23.
8. Sianos G, Werner GS, Galassi AR, Papafaklis MI, Escaned J, Hildick-Smith D, Christiansen EH, Gershlick A, Carlino M, Karlas A, Konstantinidis NV, Tomasello SD, Di Mario C, Reifart N; EuroCTO Club. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. *EuroIntervention.* 2012;8:139-45.
9. Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP, Feldman T, Stahle E, Escaned J, Banning AP, Gunn JP, Colombo A, Steyerberg EW, Mohr FW, Serruys PW. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. *Circulation.* 2015;131:1269-77.

10. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW; Society for Cardiovascular Angiography and Interventions. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *Catheter Cardiovasc Interv.* 2014;83:27-36.
11. 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..
12. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, LanskyA,HamonM,KrucoffMW,SerruysPW;AcademicResearch Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.
13. Campos CM, Stanetic BM, Farooq V, Walsh S, Ishibashi Y, Onuma Y, Garcia-Garcia HM, Escaned J, Banning A, Serruys PW; SYNTAX II Study Group. Risk stratification in 3-vessel coronary artery disease: Applying the SYNTAX Score II in the Heart Team Discussion of the SYNTAX II trial. *Catheter Cardiovasc Interv.* 2015;86:E229-38.
14. 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; FAME Study Investigators. 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.
15. EscanedJ,RyanN,Mejia-RenteriaH,CookCM,DehbiHM, Alegria-Barrero E, Alghamdi A, Al-Lamee R, Altman J, AmbrosiaA,BaptistaSB,BertilssonM,BhindiR,BirganderM, Bojara W, Brugaletta S, Buller C, Calais F, Silva PC, Carlsson J, Christiansen EH, Danielewicz M, Di Mario C, Doh JH, Erglis A, Erlinge D, Gerber RT, Going O, Gudmundsdottir I, Harle T, Hauer D, Hellig F, Indolfi C, Jakobsen L, Janssens L, Jensen J, Jeremias A, Kåregren A, Karlsson AC, Kharbanda RK, Khashaba A, Kikuta Y, Krackhardt F, Koo BK, Koul S, Laine M, Lehman SJ, Lindroos P, Malik IS, Maeng M, Matsuo H, Meuwissen M, NamCW,NiccoliG,NijjerSS,OlssonH,OlssonSE,OmerovicE, Panayi G, Petraco R, Piek JJ, Ribichini F, Samady H, Samuels B, Sandhall L, Sapontis J, Sen S, Seto AH, Sezer M, Sharp ASP, Shin ES, Singh J, Takashima H, Talwar S, Tanaka N, Tang K, Van Belle E, van Royen N, Varenhorst C, Vinhas H, Vrints CJ, Walters D, Yokoi H, Fröbert O, Patel MR, Serruys P, Davies JE, Götberg M. Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease andAcuteCoronarySyndromes.*JACCCardiovascInterv.*2018; 11:1437-49.
16. Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Choo SJ, Chung CH, Lee JW, Cohen DJ, Yeung AC, Hur SH, Seung KB, Ahn TH, Kwon HM, Lim DS, Rha SW, Jeong MH, Lee BK, Tresukosol D, Fu GS, Ong TK; BEST Trial Investigators. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med.* 2015;372:1204-12.
17. Zbinden R, Piccolo R, Heg D, Roffi M, Kurz DJ, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Franzone A, Eberli F, Juni P, Windecker S, Pilgrim T. Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable-Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization: 2-Year Results of the BIOSCIENCE Trial. *J Am Heart Assoc.* 2016;5:e003255.
18. Kok MM, Zocca P, Buiten RA, Danse PW, Schotborgh CE, Scholte M, Hartmann M, Stoel MG, van Houwelingen G, Linssen GCM, Doggen CJM, von Birgelen C. Two-year clinical outcome of all-comers treated with three highly dissimilar contemporary coronary drug-eluting stents in the randomised BIO-RESORT trial. *EuroIntervention.* 2018;14:915-23.
19. Katagiri Y, Onuma Y, Lurz P, Buszman P, Piek JJ, Wykrzykowska JJ, Asano T, Kogame N, Takahashi K, Chang CC, de Winter RJ, Serruys PW, Wijns W; Collaborators. Two-year follow-up of the DESSOLVE

III trial: bioabsorbable polymer sirolimus-eluting stent vs. durable polymer everolimus-eluting stent. *EuroIntervention.* 2019 Feb 5. [Epub ahead of print].
20. 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;55:1093-101.
21. Gaudino M, Taggart DP. What is new in the armamentarium of coronary surgeons to compete with PCI? *EuroIntervention.* 2018;14:e387-9.
22. Banning AP, Serruys PW. The ball is now in our court. *EuroIntervention.* 2018;14:739-41.

Supplementary data

Supplementary Appendix 1. Statistical analysis

Continuous variables are presented as mean±standard deviation or median (interquartile range [IQR]) and compared with the Student's t-test or Mann-Whitney test as appropriate. Categorical variables are presented as counts and percentages and compared with the chi- squared test.

The outcome analyses were performed according to the intention-to-treat principle and are presented as Kaplan-Meier estimates and compared with Cox proportional hazards models. A separate multivariate analysis was performed to determine independent predictors of MACCE within the SYNTAX II population only. The following variables were tested on a per-patient univariate analysis to determine suitability for inclusion in the multivariate model: age, sex, diabetes mellitus, current smoking, previous MI, hypertension, hyperlipidaemia, creatinine clearance, ejection fraction, peripheral vascular disease, chronic obstructive pulmonary disease (COPD) and anatomic SYNTAX score. Finally, a multivariate Cox proportional hazards model was built using the univariate predictors with p-value <0.25. A p- value <0.05 was considered significant. The statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Supplementary Table 1. Baseline clinical characteristics.

	SYNTAX II (n=454)	**SYNTAX-I PCI (n=315)**	***p*-value**
Age (years)	66.7±9.7 (454)	66.7±9.1 (315)	0.99
Male	93.2% (423/454)	93.0% (293/315)	0.93
Body mass index (kg/m^2)	28.9±4.7 (449)	28.2±4.4 (315)	0.032
Diabetes mellitus type 1 or 2	30.3% (135/446)	29.2% (92/315)	0.75
Insulin-treated	8.5% (38/446)	10.5% (33/315)	0.36
Oral medication	19.5% (87/446)	16.8% (53/315)	0.35
Diet only	2.0% (9/446)	1.9% (6/315)	0.91
Current smoker	14.7% (64/435)	17.8% (56/315)	0.26
Previous MI	12.5% (56/44)	28.7% (89/310)	<0.001
Previous stroke	5.6% (25/449)	1.9% (6/315)	0.01
Hypertension	77.0% (344/447)	73.4% (229/312)	0.26
Hyperlipidaemia	77.3% (341/441)	74.4% (232/312)	0.35
Creatinine clearance (ml/min)	82.0±26.9 (454)	87.3±28.5 (315)	0.008
LVEF (%)	58.1±8.3 (454)	61.8±11.3 (315)	<0.001
Peripheral vascular disease	7.7% (35/454)	9.5% (30/315)	0.37
COPD	10.8% (49/454)	12.7% (40/315)	0.42
Clinical presentation			<0.001
Silent ischaemia	5.5% (30/449)	13.3% (42/315)	
Stable angina	68.8% (309/449)	61.6% (194/315)	
Unstable angina	25.6% (115/449)	25.1% (79/315)	
Anatomic SYNTAX score	20.3±6.4 (454)	22.8±8.7 (315)	<0.001
SYNTAX score II PCI	30.2±8.6 (454)	30.6±8.7 (315)	0.528
Predicted 4-year mortality PCI (%)	8.9±8.8 (454)	9.2±8.7 (315)	0.64
SYNTAX score II CABG	29.1±10.4 (454)	29.1±9.6 (315)	1
Predicted 4-year mortality CABG (%)	9.0±9.3 (454)	8.5±8.1 (315)	0.44

CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 2. Lesion and procedural characteristics and medication.

	SYNTAX II	SYNTAX-I PCI	*p*-value
Lesions anatomical SYNTAX score per patient	4.16±1.17 (454)	4.31±1.34 (315)	0.1
Lesions intended to be treated per patient	3.49±0.97 (447)	4.6±1.55 (311)	<0.001
Lesions treated per patient	2.64±1.11 (440)	4.02±1.34 (311)	<0.001
Stents per patient	3.78±1.92 (440)	5.19±2.04 (308)	<0.001
Stents per lesion	1.43±0.76 (1,165)	1.28±0.65 (1,251)	<0.001
Vessel assessed by physiology (iFR/FFR)			
Left main	0.9% (4/447)	N/A	
RCA	86.4% (386/447)	N/A	
LAD	98.9% (442/447)	N/A	
LCX	96% (429/447)	N/A	
Assessment in three vessels	82.8% (370/447)		
Vessel treated			
Left main	0.9% (4/441)	2.3% (7/311)	0.22
RCA	60.5% (267/441)	87.1% (271/311)	<0.001
LAD	92.5% (408/441)	99% (308/311)	<0.001
LCX	67.1% (296/441)	96.5% (300/311)	<0.001
Treatment in three vessels	37.2% (164/441)	83.3% (259/311)	<0.001
Mean stent length (per stent, mm)	24.43±9.18 (1,663)	18.82±7.04 (1,599)	<0.001
Total stent length (per patient, mm)	92.32±52.78 (440)	97.71±43.66 (308)	0.13
Bifurcation treated (%)	35% (159/454)	60.6% (191/315)	<0.001
Total occlusion treated (%)	27.8% (126/453)	28.3% (89/315)	0.88
Post-implantation IVUS MLA (mm^2)	6.17±2.31 (1,094)	N/A	
Medication			
Aspirin			
At discharge	99.8% (448/449)	96.2% (302/314)	<0.001
At 1 month	99.6% (443/445)	93.9% (292/311)	<0.001
At 1 year	95.6% (413/432)	92.1% (278/302)	0.046
At 2 years	91.9% (391/429)	N/A	
$P2Y_{12}$ inhibitor			
At discharge	99.3% (446/449)	98.4% (309/314)	0.234
Clopidogrel	66.8% (298/446)	N/A	
Prasugrel	4.5% (20/446)	N/A	
Ticagrelor	28.7% (128/446)	N/A	
At 1 month	99.6% (443/445)	97.1% (302/311)	0.004
Clopidogrel	66.8% (298/446)	N/A	
Prasugrel	4.5% (20/446)	N/A	
Ticagrelor	28.7% (128/446)	N/A	
DAPT at 1 year	61.8% (267/432)	72.2% (218/302)	0.0034
DAPT at 2 years	6.8% (29/429)	N/A	
Statin at discharge	97.3% (437/449)	85.4% (268/314)	<0.001
Statin at 2 years	92.3% (396/429)	N/A	

DAPT: dual antiplatelet therapy; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; LAD: left anterior descending artery; LCX: left circumflex; MLA: minimal lumenarea; PCI: percutaneous coronary intervention; RCA: right coronary artery

Supplementary Table 3. Achievement of SYNTAX II strategy.

	SYNTAX II	SYNTAX-I PCI	*p*-value
SYNTAX score II calculated	100% (454/454)	100% (315/315)	1.000
iFR/FFR per patient	96.4% (431/447)	NA	NA
iFR/FFR per lesion	75.5% (1,177/1,559)	NA	NA
Post-stenting IVUS per patient	84.1% (384/454)	4.8% (15/311)	<0.001
Post-stenting IVUS per lesion	76.4% (872/1,142)	NA	NA
Success rate of CTO PCI per lesion	87.0% (94/108)	57.4% (54/94)	<0.001
Current-generation DES used	98.4% (440/447)	0% (0/315)	<0.001
	SYNERGY EES (strut thickness: 74 µm)	TAXUS PES (strut thickness: 132 µm)	
Statin at discharge	97.3% (437/449)	85.4% (268/314)	<0.001

CTO: chronic total occlusion; DES: drug-eluting stent; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention

Supplementary Table 4. Univariate and multivariate independent predictors of two-year MACCE* in SYNTAX II.

	Univariable predictors at 2 years			**Multivariable predictors at 2 years**		
Variables	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
COPD	2.835	1.556-5.165	0.010	2.899	1.304-6.444	0.009
Female sex	2.508	1.190-5.285	0.016	3.192	1.196-8.518	0.200
Creatinine clearance (per ml/min)	0.983	0.969-0.998	0.022	0.987	0.972-1.002	0.096
Peripheral vascular disease	1.941	0.921-4.089	0.081	3.377	1.323-8.624	0.011
Previous MI	1.533	0.776-3.031	0.219	1.637	0.677-3.959	0.274
Anatomic SYNTAX score	1.024	0.985-1.064	0.226	1.051	1.002-1.101	0.040
Hypertension	1.330	0.690-2.564	0.395			
Diabetes mellitus	1.222	0.711-2.099	0.469			
Current smoking	1.152	0.564-2.354	0.697			
Age (years)	1.005	0.979-1.032	0.713			
Hyperlipidaemia	0.904	0.496-1.650	0.743			
LVEF (per %)	0.999	0.969-1.029	0.933			

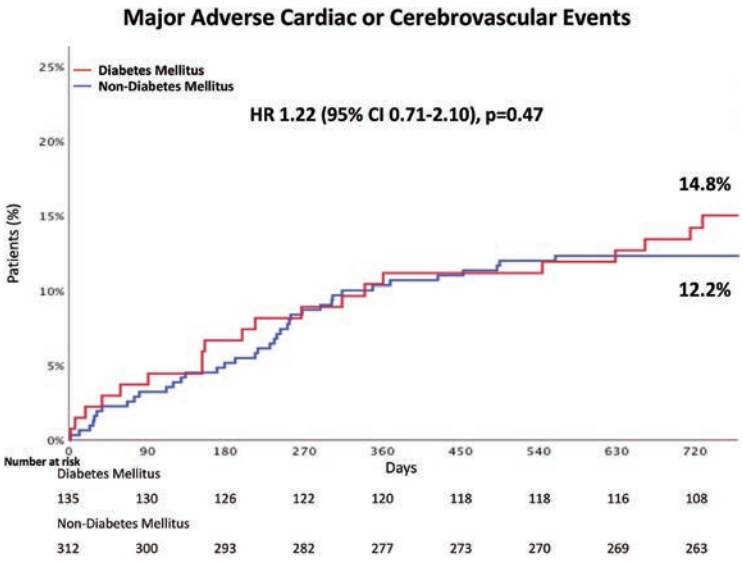
* MACCE was defined as all-cause death, any stroke, MI, or revascularisation.
COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; MACCE: major adversecardiac and cerebrovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 5. Revascularisation at two years[1] in the SYNTAX II study.

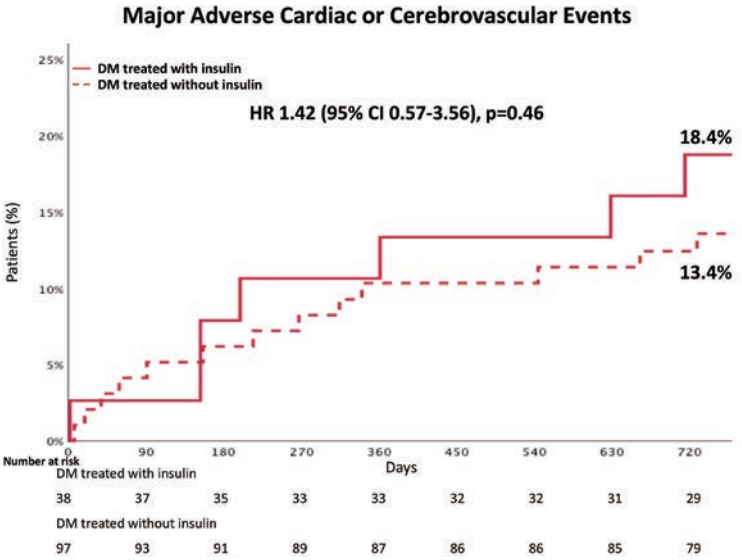
Outcome	SYNTAX II (n=454)[2]
Any revascularisation	10.2% (45)
Target vessel	8.6% (38)
Clinically driven	6.8% (30)
Non-clinically driven	2.0% (9)
Target lesion	8.1% (36)
Clinically driven	6.4% (28)
Non-clinically driven	1.8% (8)
Target vessel-non target lesion	1.6% (7)
Clinically driven	1.4% (6)
Non-clinically driven	0.2% (1)
Non-target vessel	2.0% (9)
CABG	1.1% (5)
Target vessel	1.1% (5)
Clinically driven	1.1% (5)
Non-clinically driven	0.2% (1)
Target lesion	1.1% (5)
Clinically driven	1.1% (5)
Non-clinically driven	0.0% (0)
Target vessel-non target lesion	0.7% (3)
Clinically driven	0.5% (2)
Non-clinically driven	0.2% (1)
Non-target vessel	0.5% (2)
Re-PCI	9.3% (41)
Target vessel	7.7% (34)
Clinically driven	5.9% (26)
Non-clinically driven	1.8% (8)
Target lesion	7.2% (32)
Clinically driven	5.4% (24)
Non-clinically driven	1.8% (8)
Target vessel-non target lesion	0.9% (4)
Clinically driven	0.9% (4)
Non-clinically driven	0.0% (0)
Non-target vessel	1.5% (7)

[1] two years: 730 days; [2] Kaplan-Meier estimates.

CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention



Supplementary Figure 1. Kaplan-Meier cumulative incidence for major adverse cardiac orcerebrovascular events in SYNTAX II patients stratified by diabetes mellitus (red) and non-diabetes mellitus (blue).



Supplementary Figure 2. Kaplan-Meier cumulative incidence for major adverse cardiac orcerebrovascular events in SYNTAX II patients with diabetes mellites stratified by insulin treated (red) and non-insulin treated (red broken).

3

Defining Device Success for Percutaneous Coronary Intervention Trials: A Position Statement from the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology.

Chun Chin Chang*, Norihiro Kogame*, Yoshinobu Onuma, Robert A. Byrne, Davide Capodanno, Stephan Windecker, Marie-Angèle Morel, Donald E. Cutlip, Mitchell W. Krucoff, Gregg W. Stone, Alexandra Lansky, Roxana Mehran, Ernest Spitzer, Alan G. Fraser, Andreas Baumbach, Patrick W. Serruys. *Authors contributed equally

EuroIntervention. 2020 Jan 17;15(13):1190-1198.

Abstract

Percutaneous coronary intervention with implantation of drug-eluting stents has become the most commonly performed revascularisation procedure in patients with symptomatic coronary artery disease. Continuous iterations of coronary devices incorporating changes in platform materials, geometry, strut thickness, drug release mechanisms and antiproliferative drugs have progressively reduced the rate of device-related adverse clinical events. Objective performance criteria have been proposed for clinical and angiographic outcomes of drug-eluting stents. The rate of device success has been recognised as an intraprocedural endpoint to evaluate the mechanical ability to complete a procedure with the specific device assigned by protocol in randomised comparative trials. The European Commission and the U.S. Food and Drug Administration both provide guidance documents, including the mechanistic evaluation of coronary stents, which recommend operational definitions of device success. While the majority of clinical trials investigating drug-eluting stents have adopted this endpoint definition, inconsistencies in application limit the reliability of comparisons across different trials reporting device success rates. In addition, it is not uncommon that device success rates are not reported by investigators. A consistent definition of device success is essential to allow scientific comparisons of this technical performance endpoint between devices across different trials. Therefore, we performed a systematic evaluation of definitions and reporting of device success in clinical trials. We propose an extended definition as well as considerations for approaching the determination of the device success rates in future percutaneous coronary intervention trials.

Introduction

Percutaneous coronary intervention (PCI) with implantation of drug-eluting stents (DES) has become the most commonly performed revascularisation procedure in patients with symptomatic coronary artery disease (CAD). Iterative developments of coronary devices that introduced changes in platform materials and geometry, strut thicknesses, drug release mechanisms, and antiproliferative drugs have progressively reduced the rate of clinical adverse events. Indeed, current stent technology is regarded as a mature field and it has been proposed that optimal performance criteria might be used to evaluate clinical and angiographic outcomes of new devices[1,2]. Most contemporary randomised PCI trials compare a novel DES to a current standard-of-care DES, in terms of a device-oriented or patient-oriented composite primary endpoint at one-year follow-up.

Device success rate is an important metric of acute stent performance in clinical trials. Device success is generally defined as the likelihood of completing the goal of the PCI procedure – to reduce a coronary obstruction to non-obstructive severity – using the specific stent allocated by the trial protocol. In addition to the stent design *per se*, device success may also be affected by the stent delivery system.

Device success is often reported in conjunction with a procedure success endpoint, which reflects that the lesion treatment result is achieved without doing harm to the patient. Assessment of device success is important in the evaluation of a new stent technology. Regulatory authorities, such as the European Commission and the U.S. Food and Drug Administration (FDA), provide guidance documents for the mechanistic evaluation of coronary stents which recommend an operational definition of device success as an acute device performance endpoint.

Although derivatives of this definition are frequently used in PCI trials, variable implementation and inconsistencies in adjudication limit the capability of meticulous comparisons across different trials reporting on device success rates. In addition, it is not uncommon that device success rates are not reported by investigators. A consistent definition is essential to allow scientific comparisons of this intraprocedural endpoint across different trials reporting on different devices or in different patient populations or coronary anatomy.

In contemporary trials, device failure rates range from <1% to 5%[3,4]. Whether observed variations in acute device success are in fact device design related or trial ascertainment dependent is uncertain and provides a rationale for the development of more consistent approaches and definitions. In the setting of low one-year clinical outcome event rates across contemporary stent platforms, more technical stent features such as deliverability reflected by device success may play a greater role for operators selecting stents for clinical practice.

We performed a systematic review to evaluate device success rates and definitions in clinical trials with broadly inclusive patient recruitment published in leading cardiology journals, based on critical appraisal of the literature, and summarised case examples of device failure. A summary of the literature search strategy and results is shown in **Supplementary Table 1** and **Supplementary Figure 1**. We propose a standardised extended definition of device success for future PCI trials.

DEFINITION OF DEVICE SUCCESS

In 2008, the European Commission and the U.S. FDA published guidance documents for non-clinical and clinical evaluations of DES to provide recommendations to manufacturers and notified bodies[5,6]. In the guidance document published by the European Commission, device success is defined as successful delivery and deployment of the device and attainment of <50% diameter stenosis using only the study device **(Table 1)**. Procedure success must meet the angiographic criterion of device success plus additional criteria related to the clinical outcome of the procedure regardless of whether the protocol-assigned device is used. In cases of multiple lesion treatment, all treated lesions must meet the clinical procedure success.

More specifically, procedure success requires the absence of ischaemia-driven adverse events during the hospital stay up to a maximum of the first seven days after the index procedure[5]. These adverse events include all-cause death, any myocardial infarction (including periprocedural), all coronary revascularisations (target lesion revascularisation, target vessel revascularisation or non-target vessel revascularisation), and coronary device thrombosis. The U.S. FDA Guidance for Industry on Coronary Drug-Eluting Stents does not refer specifically to device success, but rather to scenarios of device malfunction which correspond to device failure. A malfunction is defined when the device does not meet its performance specifications which include all claims made in the labelling for the device. This approach requires consistency throughout the labelling process for coronary stents.

In 2013, the European Society of Cardiology (ESC) was requested by the European Commission to make recommendations for a revision of the European Union medical device advisory document on the evaluation of coronary stents. This work was carried out by a Task Force established by the European Association of Percutaneous Cardiovascular Interventions (EAPCI)[1]. The document summarises the process required for regulatory and market approval for coronary stents in Europe. It offers the basis for establishing objective performance criteria for clinical and angiographic outcomes when evaluating new devices. A revision of the guidance document has not been published to date, though the recommendations of the Task Force are likely to be taken into account in preparing a new broadly similar type of document for coronary stents known as a Common Specification, which is at draft stage. Furthermore, the Task Force was not asked to propose a standardised methodology for the assessment of device success. In September 2018 the FDA announced a public consultation concerning their guidance document, which is being updated[7].

The Academic Research Consortium (ARC) consensus documents for clinical endpoint definitions in coronary stent trials[8,9] do not include definitions of device success as it is a mainly technical endpoint.

Table 1. Current and proposed definition of device success for PCI.

Current EU definition of acute device success (MEDDEV 2.7.1Appendix 1)
– Successful delivery and deployment of the investigational stent(s)at the intended target lesion. (This includes successful delivery and deployment of multipleoverlapping stents). – Attainment of a final residual in-stent stenosis of less than 50% as observed by QCA, or by visual estimation if QCA is not available, without use of a device outside the assigned treatmentstrategy. (Standard predilation catheters and post-dilatation catheters [ifapplicable] may be used).
Recommended new definition of acute device success
Device success (applying a lesion-level analysis) is defined by all of the following conditions: – Successful delivery, balloon expansion, and deployment of thefirst assigned device, at the intended target lesion. (Multiple attempts using the same instrument are allowed; for example, success at a second attempt with the same [first] investigational device after rewiring the vessel, use of a supportcatheter, or additional ballooning, vessel preparation, etc.). – Successful withdrawal of the device delivery system. – Attainment of a final in-stent or in-scaffold residual stenosis of <20% with final data reported by core laboratory QCA (preferredmethodology).
Additional notes for implementing the new definition
– All target lesions in which the assigned device is attempted areincluded as the denominator, e.g., a "per protocol" analysis. – The use of a second (or more) assigned device(s) or non-assigned devices, due to failure of the first assigned device, is classified asdevice failure for the target lesion. – When deployment of more than one assigned device is planned in advance, for a single target lesion (e.g., overlapping devices fora long lesion, or a two-stent strategy for a bifurcation lesion), all assigned devices are assessed and reported as one device. In thatcase, only when all assigned devices are successfully implanted at the intended target lesion is this classified as acute device success. – The use of bail-out devices (as allocated by randomisation) dueto edge dissections or geographic miss is not regarded as a device failure but rather as a clinical issue. – Successful deployment includes the expansion of the deliveryballoon to its appropriate diameter as indicated on the ballooncompliance chart. – Deployment failure is classified as device failure, independently from whether or not the device was safely removed; it needs to bedocumented. – Additional intravascular image may be useful to confirm the stentdeployment, particularly when interpretation of final angiographyis limited (e.g., tortuosity or angulation of the vessels, artery overlap, or no-reflow phenomenon) after stent implantation.

MEDDEV: Medical Device Guidance document; QCA: quantitative coronary angiography

Table 2. Comparison of analytic methods for device success.

Analytic method	Intention-to-treat	Per-protocol
Denominator	Number of all targetlesions to be stented (n)	Number of all target lesions in which the assigned device has beenattempted (n-X)
Pros	– Performed well – Simple to analyse	– Represents accurately the performance of thedevice
Cons	– Does not account forthe performance of the device, particularly when thenumber of lesions inwhich the assigned device is not attempted is large – May overestimate the device success rate	– Detailed explanation of the change in intention-to-treat needs to be captured (mandatory) inthe case report form – Selection bias might beintroduced if the operator does not even try to implant the assigned device (especially when treating extremely challenging lesions)

DEVICE SUCCESS IN ALL-COMERS TRIALS

Device success rate is usually reported in the first-in-human or pilot study results when testing new coronary devices. However, the results from such studies frequently lack generalisability due to the small sample size and the inclusion of highly selected patients with less complex lesions. A comprehensive evaluation of device success can be further substantiated in pivotal trial designs, which typically include a substantial number of patients and are powered to evaluate clinical endpoints. Moreover, trials with an "all-comers" design denoting inclusion of patients across the spectrum of clinical presentation and lesion complexity and more representative of those encountered in real-world practice have been introduced in the evaluation of coronary stents[10]. **Supplementary Table 2** summarises the definitions and success rates of devices used in all-comers trials.

Most PCI trials reporting on device success adopted the definition recommended by the European Commission, but it is noteworthy that device success rates are not reported in the same fashion and are not reported in all studies. The most common variation is the definition of final in-stent residual stenosis, which ranges from <20% to <50%. According to the principal angiographic endpoints recommended by the ESC/EAPCI Task Force on the evaluation of coronary stents[1], a post-procedural residual stenosis should be <20% as assessed by coronary angiography. It has been shown that in-stent stenosis ≥20% is associated with an increased risk of target lesion revascularisation[11]. Since visual estimation of coronary cineangiograms could have high interobserver and intraobserver variability[12,13], quantitative coronary angiography (QCA) is a preferred methodology for adjudication of device success.

In the SORT OUT (Scandinavian Organization for Randomized Trials with Clinical Outcome) trials (III, IV, V and VI), the term "device failure" was used instead of device success. The definition of device failure was stated, but the results were not provided[14-17]. In the BIOSCIENCE (Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization) trial, the first large randomised trial of a thin-strut cobalt-chromium sirolimus-eluting stent with a biodegradable polymer, compared to the XIENCE stent (Abbott Vascular, Santa Clara, CA, USA), the device success rate was also not reported[18]. In the SORT OUT VII trial, only the rate of device delivery failure was mentioned (Orsiro [Biotronik, Bülach, Switzerland] 1.6% vs Nobori® [Terumo Corp., Tokyo, Japan] 1.7%)[19]; the definition of device delivery failure was not provided.

Recently, the TARGET (Targeted therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent) all-comers trial was published. It compared a low-dose sirolimus-eluting stent, Firehawk® (MicroPort, Shanghai, China) to the XIENCE stent. The device success rate of Firehawk was significantly lower than that of XIENCE (Firehawk 92.4% vs XIENCE 94.8%, p=0.025)[20]. The device success rate in the XIENCE group in the TARGET trial was numerically lower than that reported in most previous all-comers trials. In the Firehawk group, 2.1% of lesions were treated by a non-assigned stent, 0.7% of lesions were crossover to the XIENCE stent, and 2.5% of lesions were not treated by stent implantation. These differences suggest a difference in the performance of the device during the index procedure. However, possible alternative explanations could be unbalanced differences in any of the following: protocol violation, assigned device not available, change of indication for stent implantation (e.g., patient was referred to surgery), PCI procedure failure (e.g., wire or balloon failed to cross target lesions), or failure to deliver

or deploy the assigned device. In fact, the reported unsuccessful study-stent implantation rate of Firehawk was only 0.9%.

Several factors affect the device success rate, including anatomical aspects, lesion characteristics, experience and blinding of operators, properties of both the stent and delivery system (balloon) design as well as the definition and reporting of device success. Theoretically, the influence of these factors would be minimised and balanced in a randomised trial. Thus, the device success rate of coronary devices could be attributed to the trackability, crossability, and pushability of the device. An increasing number of manufacturers are investing in and developing coronary stent/scaffold platforms worldwide. In this context, clinicians and trialists should maintain a high degree of attention to device success rates in PCI trials, as problems may first come to light after more widespread clinical use and investigation in post-marketing studies.

SPECIAL CONSIDERATIONS

LESION-BASED ANALYSIS ISSUES

In contemporary large-scale PCI trials, device success rate is usually reported by a lesion-based analysis, meaning that the numerator and denominator represent the number of lesions, instead of the number of devices. We propose to use the denominator for device success from “per-protocol” analysis, i.e., the denominator should consist of all target lesions where the assigned device is at least attempted once before any other non-protocol therapy. Therefore, target lesions for which PCI was not attempted, no device implantation was attempted (e.g., failure to cross the lesion with guidewires or lesions treated only with balloon angioplasty due to small vessel diameter or restenosis) and non-assigned device implantations without attempt to use assigned device (e.g., assigned device was transiently not available “on the shelf”) would be excluded from the denominator for device success. This per-protocol analysis could ascertain more accurately the technical performance of the device. However, it may be at variance with the conventional intention-to-treat analysis, particularly if the operator changes his intention-to-treat without testing the assigned device (e.g., when considering challenging lesions or for whatever reason). Therefore, detailed explanation of the changes of device selection need to be captured (mandatory). An intention-to-treat analysis for device success could be considered as a sensitivity analysis to assess whether all the intended devices have indeed been implanted. A comparison of analytic methods for device success is provided in **Table 2** and **Supplementary Figure 2**.

USE OF MULTIPLE DEVICES

Another scenario to be considered for more consistent reporting is the use of multiple devices in one target lesion. For instance, the first assigned device could not cross the target lesion due to inadequate lesion preparation or less deliverability of the device and subsequently the device (stent and its delivery system) was damaged or dislodged. Then, a second assigned stent was eventually implanted after more aggressive balloon predilatation. Normally this scenario would be considered as a device success. However, it might be informative to subclassify device success per protocol according to the number of assigned devices failing (replaced) before final deployment in the lesion. Another approach

was seen in the AIDA (Amsterdam Investigator-initiateD Absorb strategy all-comers) trial, where the investigators specified that the device success rate should be counted solely on the basis of the first assigned stent or scaffold[21]. Therefore, we suggest that the unplanned use of a second (or more) assigned device due to the failure of the first device should be considered as device failure irrespective of the mechanism (related to the device, the lesion or the operator). Health economic reasons (e.g., cost of the second device) could be put forward to rationalise and justify this recommendation. Careful consideration of additional scenarios is required if this approach is taken. For instance, on the basis of lesion-based analysis, when treating a long diffuse lesion or a bifurcation lesion, where implantation of two (or more) assigned devices is planned, the implanted devices should be assessed and reported as one, and all must be successfully implanted to meet the criteria of device success.

MULTIPLE LESIONS IN THE SAME VESSEL

Another scenario to be considered is when multiple target lesions exist in one target vessel, for instance, in the presence of a proximal and a distal lesion in the left anterior descending artery. Assume, for example, that the operator was intending to deliver an assigned device to a distal lesion first and had prepared both lesions for delivery. However, the operator failed to cross the proximal lesion with the assigned device, but then successfully implanted non-assigned devices in both the proximal and the distal lesions. Whether the treatment of the proximal lesion should be counted as device failure and the treatment of the distal lesion should be excluded from the denominator for device success analysis, or whether both lesions would be counted as device failures should have clear definition in the protocol or adjudication rules.

LESION SUCCESS VERSUS DEVICE SUCCESS

Lesion success rate, as opposed to device success rate, has been reported differently in several trials and requires a brief discussion. In the DUTCH PEERS (DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity) trial, lesion success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50% by any percutaneous method[22]. In the BIOFLOW V (Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation) trial, lesion success was also reported in a similar fashion with final diameter stenosis less than 30%[23]. In some scenarios, the treating physicians might change their mind during the procedure and decide not to implant the assigned device at the target lesion (e.g., small vessel diameter, in-stent restenosis, unsuccessful angioplasty, coronary slow-flow phenomenon). Thus, reporting lesion success rates provides complementary information on top of device success rates in PCI trials.

Nevertheless, one major limitation of the definition of lesion success is that it is based on the visual angiographic residual severity of the lesion after interventions, without any objective quantitative information such as the assessment of coronary blood flow. Since thresholds of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) pressure-derived parameters have been identified, and since the angiography-derived quantitative flow ratio (QFR) might become available for every treated vessel (lesion) by off-line analysis by a core laboratory, additional consideration should be given to an intraprocedural vessel-

oriented composite endpoint. Such a definition may require further consensus and is beyond the scope of this document.

RECOMMENDATIONS FOR FUTURE PCI TRIALS

The introduction of coronary stents for the treatment of CAD was accompanied by important developments in clinical research and trial conduct. Numerous clinical trials have been conducted to investigate new stent technologies in a protocolised and, as much as possible, standardised manner. Therefore, an extended definition of device success and a standardised methodology for assessing and reporting this acute performance endpoint in PCI trials are timely. The proposed extended definition is presented in **Table 1**.

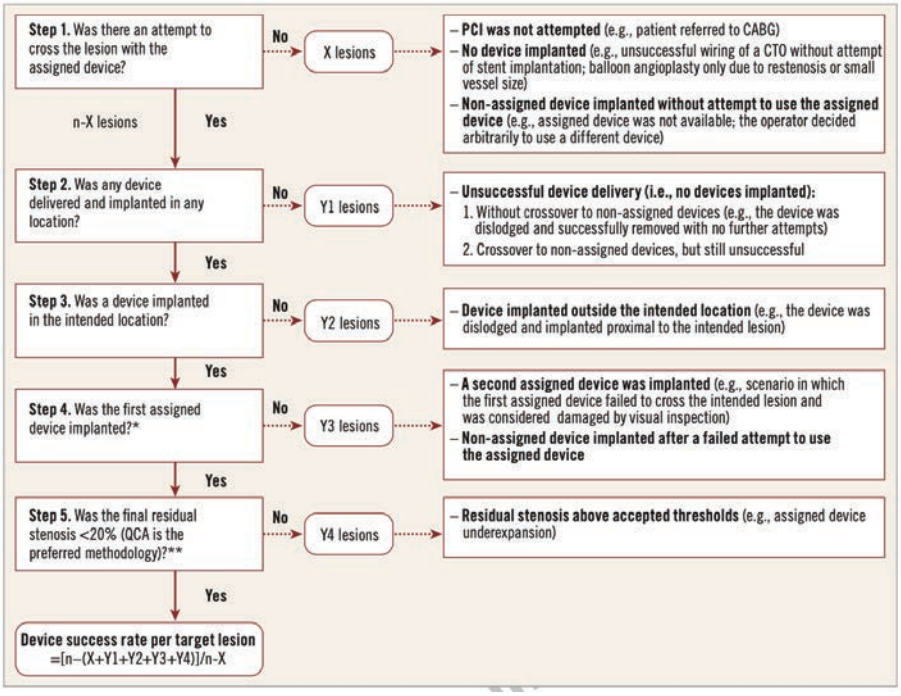


Figure 1: Algorithm for device success analysis. * Please refer to Table 1 if more than one assigned device is planned upfront for one target lesion and Supplementary Figure 3 for details on potential scenarios. ** Additional intravascular image may be useful to confirm the stent deployment, particularly when interpretation of final angiography is limited (e.g., tortuosity or angulation of the vessels, artery overlap, or no-reflow phenomenon) after stent implantation. CABG: coronary arterial bypass grafting; CTO: chronic total occlusion; n: total lesion number; PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography

Figure 1 illustrates a practical, mutually exclusive and chronological algorithm for analysing the device success rate. Step 1 establishes the denominator consistent with a "per protocol" analysis, and is the most crucial aspect of device success to decide upon for any given trial design. This denominator definition has a great influence on the device success rate. We suggest preferentially excluding target lesions where no implantation of the assigned device was attempted. The denominator of the device success rate would thus be

n-X, representing the number of lesions in which the operators did try to implant the assigned device. Step 2 identifies lesions for which no device (either the assigned or any non-assigned device) was implanted despite single or multiple attempts. Step 3 indicates lesions for which devices were implanted outside the intended location (e.g., device dislodgement with either deployment or crush of the device). Step 4 indicates lesions in which non-assigned devices or second (or more) assigned devices were implanted, because of the unsuccessful delivery or deployment or damage to the first assigned device (e.g., tortuosity/non-crossability of the lesion or defective delivery system/balloon). Lastly, step 5 excludes lesions with final in-stent/scaffold residual stenosis equal to or above 20% by QCA (preferred methodology) or by visual estimation if QCA is not available, along with the recommendation that final data reported for the trial ideally would rely on core laboratory QCA of the final residual stenosis.

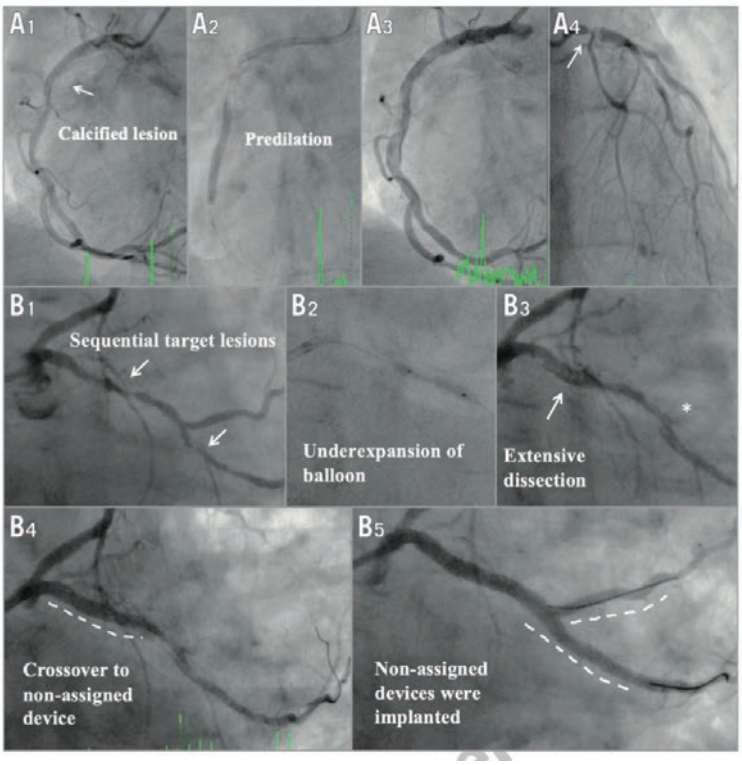


Figure 2: Examples of device failure in the device success analysis. A1. One calcified lesion in right coronary artery (segment 2). A2. Predilation. A3. Assigned device failed to cross the calcified lesion. No device was implanted. A4. Because the assigned device failed to cross the lesion in the right coronary artery, the operator decided to use a non-assigned device for treatment of left main stem (segment 5). Segment 5 should be excluded from the denominator in the analysis of device success rate. Changes in intention-to-treat should be specifically reported in the case report form. B1. Two sequential lesions in left circumflex artery (segments 11 & 13). B2. Predilation. B3. Extensive dissection with compromised blood flow of side branch (*segment 12b). B4. Assigned device failed to cross the proximal lesion, then crossover to a non-assigned device. B5. The operator decided to use non-assigned devices for treatment of the distal lesion and the side branch. Segment 13 should be excluded in the analysis of device success rate. Segment 12b should be reported as a procedural complication with bail-out stenting of assigned device group based on intention-to-treat. Coronary artery segments are defined according to the American Heart Association classification.

Figure 2 summarises two examples of device failure and demonstrates the importance of knowing whether the assigned stent was attempted or not, in order to assess the device success rate. Potential scenarios after unsuccessful delivery of a first assigned device to the intended lesion are summarised in **Supplementary Figure 3**.

Issues of potential operator bias in the assessment of device success must also be considered. In current stent trials investigating two different platforms or iterations, it is not possible to mask the operator who can recognise the commercial products. Behavioural differences based on the experience of the operator cannot be avoided. In the TALENT study[24], more crossover to non-assigned stents occurred in the investigational group. Interestingly, this phenomenon was also observed in the TARGET study. It suggests that operators might tend to crossover quickly to the device with which they are familiar when facing difficulties during the PCI procedure, especially in treating patients with multivessel disease. In the TALENT study, the crossover to non-assigned stents was clustered in seven out of 23 centres and was related to the lesion complexity, PCI volume and possibly to the expertise of the operators.

In addition, it is also possible that the assigned device per randomisation is not available "on-shelf" at the time of the procedure, or that the available sizes and lengths of the investigational platform offer fewer options than the comparator, increasing the chance of crossover to the comparator. Alternatively, the new device may be truly less effective in crossing lesions, requiring more frequent crossover. Differentiating between these possibilities is problematic without detailed questioning in the case report form. It is acknowledged that accurate determination of this more granular, consistent and informative approach to device success will challenge existing clinical trial processes to include site work documentation, monitoring visits to ensure accuracy, and a simple, flexible case report form for study use. We propose an example of a case report form that will capture important parameters for the adjudication of device success in PCI trials **(Supplementary Table 3)**.

FUTURE PERSPECTIVES OF DEFINING DEVICE SUCCESS

Stent underexpansion is usually defined according to the diameter stenosis after the procedure, measured by QCA. Coronary angiography only assesses residual stenosis which can be influenced by many factors (e.g., plaque prolapse). The discrepancy in QCA between metallic DES and polymeric bioresorbable scaffolds has been reported[25]. Intracoronary imaging, such as intravascular ultrasound or optical coherence tomography, provides more accurate ascertainment than angiography in optimising PCI procedures and improves clinical outcome[26,27]. The use of intracoronary imaging might be a preferred method rather than QCA to assess acute performance of devices for state-of-the-art trials.

Computational fluid dynamic models have shown that, even at the same diameter stenosis, anatomic differences such as stent eccentricity affect local haemodynamics which are related to stent restenosis[28]. On the other hand, post-PCI FFR has been shown to be a predictor of long-term outcome[29,30]. Suboptimal stent deployment is known to be associated with a trans-stent FFR gradient after PCI[31]. Local haemodynamics and functional assessment of stented vessels might become alternative approaches to evaluate the acute performance of devices. Nevertheless, the systematic use of intravascular imaging or FFR after PCI needs to be balanced with risks and costs. In this context, the use of angiography-derived functional assessment such as QFR that does not require the use of additional

catheters[32-34] will probably become widely available in catheterisation laboratories and play an increasing role in the assessment of device success, including the independent assessment by core laboratories. The additional value versus the cost of such data collection enhancements may vary across different study design applications.

Conclusions

Between devices with similar long-term clinical outcomes, device success rates may convey important information for operators choosing devices in clinical practice. Consistent approaches and definitions for device success may greatly enhance the value of such data. This document proposes a feasible approach summarised in a simple algorithm which, if embraced by international cardiovascular societies and clinical research organisations, will allow meaningful comparisons among future studies and advance regulatory science for informative device evaluation.

References

1. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, Joner M, Oktay S, Jüni P, Kastrati A, Sianos G, Stefanini GG, Wijns W, Windecker S. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur Heart J. 2015;36:2608-20.
2. Byrne RA, Stefanini GG, Capodanno D, Onuma Y, Baumbach A, Escaned J, Haude M, James S, Joner M, Jüni P, Kastrati A, Oktay S, Wijns W, Serruys PW, Windecker S. Report of an ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for percutaneous coronary intervention: executive summary. EuroIntervention. 2018;13:1574-86.
3. 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, Jüni 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.
4. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. J Am Coll Cardiol. 2013;62:181-90.
5. European Commission. Guidelines on Medical Devices. Evaluation of clinical data – a guide for manufacturers and notified bodies. Appendix 1: Clinical Evaluation of Coronary Stents. https://www.emergobyul.com/blog/2009/02/ new-european-meddev-guidance-clinical-evaluation. 2008.
6. U.S. Food and Drug Administration Coronary Drug-Eluting Stents— Nonclinical and Clinical Studies: guidance for industry. 2008. https://www.fda. gov/media/71521/download
7. Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies and Companion Guidance Document; Draft Guidance for Industry and Food and Drug Administration Staff; Availability; Reopening of the Comment Period. 2018.
https://www.federalregister.gov/documents/2018/09/27/2018-21041/ coronary-drug-eluting-stents-nonclinical-and-clinical-studies-and-companion- guidance-document-draft
8. 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;115:2344-51.
9. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Eur Heart J. 2018;39:2192-207.
10. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek 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;363:136-46.
11. Watanabe H, Morimoto T, Shiomi H, Natsuaki M, Kawai K, Kozuma K, Igarashi K, Kadota K, Tanabe K, Morino Y, Hibi K, Akasaka T, Abe M, Suwa S, Muramatsu T, Kobayashi M, Dai K, Nakao K, Tarutani Y, Fujii K, Kimura T; RESET and NEXT Investigators. Impact of Angiographic Residual Stenosis on Clinical Outcomes After New-Generation Drug-Eluting Stents Implantation: Insights From a Pooled Analysis of the RESET and NEXT Trials. J Am Heart Assoc. 2018 Jun 30;7(13).

12. DeRouen TA, Murray JA, Owen W. Variability in the analysis of coronary arteriograms. Circulation. 1977;55:324-8.
13. Girasis C, Onuma Y, Schuurbiers JC, Morel MA, van Es GA, van Geuns RJ, Wentzel JJ, Serruys PW; 5th meeting of the European Bifurcation Club. Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club. Catheter Cardiovasc Interv. 2012;79:361-8.
14. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, Abildgaard U, Christiansen EH, Engstrom T, Krusell LR, Ravkilde J, Hansen PR, Hansen KN, Abildstrom SZ, Aaroe J, Jensen JS, Kristensen SD, Botker HE, Madsen M, Johnsen SP, Jensen LO, Sorensen HT, Thuesen L, Lassen JF; SORT OUT III study group. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet. 2010;375:1090-9.
15. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, Villadsen AB, Junker A, Hansen KN, Kaltoft A, Maeng M, Pedersen KE, Kristensen SD, Botker HE, Ravkilde J, Sanchez R, Aaroe J, Madsen M, Sorensen HT, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV) Investigators. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation. 2012;125:1246-55.
16. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, Kaltoft A, Maeng M, Kristensen SD, Botker HE, Terkelsen CJ, Villadsen AB, Ravkilde J, Aaroe J, Madsen M, Thuesen L, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT) V investigators. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. Lancet. 2013;381:661-9.
17. Raungaard B, Jensen LO, Tilsted HH, Christiansen EH, Maeng M, Terkelsen CJ, Krusell LR, Kaltoft A, Kristensen SD, Botker HE, Thuesen L, Aaroe J, Jensen SE, Villadsen AB, Thayssen P, Veien KT, Hansen KN, Junker A, Madsen M, Ravkilde J, Lassen JF; Scandinavian Organization for Randomized Trials with Clinical Outcome (SORT OUT). Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. Lancet. 2015;385:1527-35.
18. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Jüni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet. 2014;384:2111-22.
19. Jensen LO, Thayssen P, Maeng M, Ravkilde J, Krusell LR, Raungaard B, Junker A, Terkelsen CJ, Veien KT, Villadsen AB, Kaltoft A, Tilsted HH, Hansen KN, Aaroe J, Kristensen SD, Hansen HS, Jensen SE, Madsen M, Botker HE, Berencsi K, Lassen JF, Christiansen EH. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent With a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated With Percutaneous Coronary Intervention: The SORT OUT VII Trial. Circ Cardiovasc Interv. 2016 Jul;9(7).
20. Lansky A, Wijns W, Xu B, Kelbaek H, van Royen N, Zheng M, Morel MA, Knaapen P, Slagboom T, Johnson TW, Vlachojannis G, Arkenbout KE, Holmvang L, Janssens L, Ochala A, Brugaletta S, Naber CK, Anderson R, Rittger H, Berti S, Barbato E, Toth GG, Maillard L, Valina C, Buszman P, Thiele H, Schächinger V, Baumbach A; TARGET All Comers Investigators. Targeted therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent (TARGET All Comers): a multicentre, open-label, randomised non-inferiority trial. Lancet. 2018;392:1117-26.
21. Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, IJsselmuiden AJ, Elias J, van Dongen IM, Tijssen RYG, Koch KT, Baan J Jr, Vis MM, de Winter RJ, Piek JJ, Tijssen JGP,

Henriques JPS; AIDA Investigators. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. N Engl J Med. 2017;376:2319-28.
22. von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, van Houwelingen GK, Schramm AR, Gin RM, Louwerenburg JW, de Man FH, Stoel MG, Lowik MM, Linssen GC, Said SA, Nienhuis MB, Verhorst PM, Basalus MW, Doggen CJ, Tandjung K. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet. 2014;383:413-23.
23. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia- Garcia HM, Bennett J, Roguin A, Gharib EG, Cutlip DE, Waksman R; BIOFLOW V Investigators. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet. 2017;390:1843-52.
24. Zaman A, de Winter RJ, Kogame N, Chang CC, Modolo R, Spitzer E, Tonino P, Hofma S, Zurakowski A, Smits PC, Prokopczuk J, Moreno R, Choudhury A, Petrov I, Cequier A, Kukreja N, Hoye A, Iniguez A, Ungi I, Serra A, Gil RJ, Walsh S, Tonev G, Mathur A, Merkely B, Colombo A, Ijsselmuiden S, Soliman O, Kaul U, Onuma Y, Serruys PW; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospec- tive multicentre randomised controlled trial. Lancet. 2019;393:987-97.
25. Sotomi Y, Onuma Y, Suwannasom P, Tateishi H, Tenekecioglu E, Zeng Y, Cavalcante R, Jonker H, Dijkstra J, Foin N, Koon JN, Collet C, de Winter RJ, Wykrzykowska JJ, Stone GW, Popma JJ, Kozuma K, Tanabe K, Serruys PW, Kimura T. Is quantitative coronary angiography reliable in assessing the lumen gain after treatment with the everolimus-eluting bioresorbable polylactide scaffold? EuroIntervention. 2016;12:e998-1008.
26. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, Radu MD, Joner M, Yu B, Jia H, Meneveau N, de la Torre Hernandez JM, Escaned J, Hill J, Prati F, Colombo A, Di Mario C, Regar E, Capodanno D, Wijns W, Byrne RA, Guagliumi G. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention. 2018;14:656-77.
27. Jones DA, Rathod KS, Koganti S, Hamshere S, Astroulakis Z, Lim P, Sirker A, O'Mahony C, Jain AK, Knight CJ, Dalby MC, Malik IS, Mathur A, Rakhit R, Lockie T, Redwood S, MacCarthy PA, Desilva R, Weerackody R, Wragg A, Smith EJ, Bourantas CV. Angiography Alone Versus Angiography Plus Optical Coherence Tomography to Guide Percutaneous Coronary Intervention: Outcomes From the Pan-London PCI Cohort. JACC Cardiovasc Interv. 2018;11:1313-21.
28. Ng J, Bourantas CV, Torii R, Ang HY, Tenekecioglu E, Serruys PW, Foin N. Local Hemodynamic Forces After Stenting: Implications on Restenosis and Thrombosis. Arterioscler Thromb Vasc Biol. 2017;37:2231-242.
29. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, Frohlich GM, Banning AP. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;16:177.
30. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N, Rioufol G, Pijls NHJ, Fearon WF, Jüni P, De Bruyne B. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. Circ Cardiovasc Interv. 2017 Oct;10(10).
31. Tonino PA, Johnson NP. Why Is Fractional Flow Reserve After Percutaneous Coronary Intervention Not Always 1.0? JACC Cardiovasc Interv. 2016;9:1032-5.
32. Asano T, Katagiri Y, Collet C, Tenekecioglu E, Miyazaki Y, Sotomi Y, Amoroso G, Aminian A, Brugaletta S, Vrolix M, Hernandez-Antolin R, van de Harst P, Iniguez-Romo A, Janssens L, Smits PC, Wykrzykowska JJ, Ribeiro VG, Pereira H, da Silva PC, Piek JJ, Reiber JHC, von Birgelen C, Sabaté M, Onuma Y, Serruys PW. Functional comparison between the BuMA Supreme biodegradable polymer sirolimus-eluting stent and a durable polymer zotarolimus-eluting coronary stent using quantitative flow ratio: PIONEER QFR substudy. EuroIntervention. 2018;14:e570-9.

33. Collet C, Onuma Y, Sonck J, Asano T, Vandeloo B, Kornowski R, Tu S, Westra J, Holm NR, Xu B, de Winter RJ, Tijssen JG, Miyazaki Y, Katagiri Y, Tenekecioglu E, Modolo R, Chichareon P, Cosyns B, Schoors D, Roosens B, Lochy S, Argacha JF, van Rosendael A, Bax J, Reiber JHC, Escaned J, De Bruyne B, Wijns W, Serruys PW. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018;39:3314-21.
34. Asano T, Katagiri Y, Chang CC, Kogame N, Chichareon P, Takahashi K, Modolo R, Tenekecioglu E, Collet C, Jonker H, Appleby C, Zaman A, van Mieghem N, Uren N, Zueco J, Piek JJ, Reiber JHC, Farooq V, Escaned J, Banning AP, Serruys PW, Onuma Y. Angiography-Derived Fractional Flow Reserve in the SYNTAX II Trial: Feasibility, Diagnostic Performance of Quantitative Flow Ratio and Clinical Prognostic Value of Functional SYNTAX Score Derived From Quantitative Flow Ratio in Patients With Three-Vessel Disease. JACC Cardiovasc Interv. 2019;12:259-70.

Supplementary data

Supplementary Table 1. Eligibility criteria for the literature search.

Inclusion criteria
Coronary intervention randomised trials between 01/01/2007 and 12/04/2019
All-comers design
Published in NEJM, Lancet, EHJ, JACC or Circulation
Exclusion criteria
Extended follow-up report
Sub-analysis or post hoc analysis (e.g., imaging, gender)
Primarily imaging study
Non-coronary research
Not a randomised trial (meta-analysis, review, retrospective, etc.)Drug trial
Thrombolysis
Treatment modification trial (e.g., logistics, timing)
Magnetic navigation system
Regenerative therapy (cell, gene, drugs)
Thrombus aspiration and others (e.g., interventions targeting reperfusion)Pre-conditioning/post-conditioning/cooling
Circulatory support (e.g., intra-aortic balloon pump)
Medical arm as control
Genetic study

Supplementary Table 2. Lesion and procedural characteristics and medication.

Study	Year	Journal	Definition of acute device success or device failure	Device success rate		*p*-value
TALENT	2019	Lancet	Successful delivery, deployment, and withdrawal of the assigneddevice at the intended target lesion with a final in-stent residual stenosis of less than 30% by visual estimation.	Supraflex 720 patients 1,046 lesions 97.6%	XIENCE 715 patients 1,030 lesions 99.5%	0.0003
ReCre8	2019	Circulation	Not reported in the main paper.	Resolute 744 patients 1,024 lesions Not reported	Cre8 747 patients 1,087 lesions Not reported	NA
TARGET	2018	Lancet	Successful delivery, deployment, and withdrawal of the assigneddevice at the intended target lesion with a final in-stent residual stenosis of less than 30% by visual estimation.	Firehawk 823 patients 1,221 lesions 92.4%	XIENCE 830 patients 1,179 lesions 94.8%	0.025
BIONYX	2018	Lancet	Less than 50% residual stenosis after percutaneous coronaryintervention with assigned stents only.	Onyx 1,243 patients 1,646 lesions 98.4%	Orsiro 1,245 patients 1,593 lesions 97.8%	NA
DESSOLVE III	2018	Lancet	Successful delivery and deployment of (only) the assigned device atthe intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of <30% (by visual estimation).	MiStent 703 patients 1,037 lesions Not reported	XIENCE 695 patients 993 lesions Not reported	NA
AIDA	2017	NEJM	Successful delivery and deployment of the first study scaffold/stentin the intended target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold/stent residual stenosis of less than 20% by visual estimate and TIMI 3 flow grade of the treated vessel.	Absorb 924 patients 1,237 lesions 92%	XIENCE 921 patients 1,209 lesions 98%	<0.001

PANDA III	2016	JACC	The attainment at the target site of a final residual diameter stenosis of less than 50 percent using only the assigned study device.	BuMA 1,174 patients 1,605 lesions 99.8%		Excel 1,174 patients 1,572 lesions 99.95%	0.22
BIO-RESORT	2016	Lancet	A final residual diameter stenosis of less than 50% if achieved withassigned study stents only.	SYNERGY 1,172 patients 1,594 lesions 98.5%	Resolute 1,173 patients 1,876 lesions 97.5%	Orsiro 1,169 patients 1,594 lesions 99.7%	NA
EVERBIO II	2015	JACC	Not reported in study protocol and main paper.	Absorb 78 patients 96 lesions Not reported	PROMUS 80 patients 112 lesions Not reported	BioMatrix 80 patients 117 lesions Not reported	NA
SORT OUT VI	2015	Lancet	The inability to implant the assigned study stent and cover the targetlesion.	Resolute 1,502 patients 1,883 lesions Not reported		BioMatrix 1,497 patients 1,791 lesions Not reported	NA
BIOSCIENCE	2014	Lancet	Achievement of a final residual diameter stenosis of less than 30%(by visual estimation), using the assigned device only.	Orsiro 1,063 patients 1,594 lesions Not reported		XIENCE 1,056 patients 1,545 lesions Not reported	NA
DUTCH PEERS	2014	Lancet	A final residual diameter stenosis of less than 50% if achieved withassigned study stents only.	Resolute 697 patients 1,080 lesions 98%		XIENCE 694 patients 1,036 lesions 98.4%	0.17
HOST-ASSURE	2014	JACC	Not reported in the main paper and Appendix.	PROMUS 2,503 patients 3,426 lesions 99.4%		Resolute 1,252 patients 1,661 lesions 99.8%	0.054

NEXT	2013	JACC	All the study stents attempted were successfully deployed in a given lesion with residual diameter stenosis <50%.	Nobori 1,617 patients 2,059 lesions 99.6%	XIENCE/Promus 1,618 patients 2,010 lesions 99.6%	0.97
COMPARE II	2013	Lancet	Not reported in the main paper and Appendix.	Nobori 1,795 patients 2,638 lesions Not reported	XIENCE 912 patients 1,387 lesions Not reported	NA
SORT OUT V	2013	Lancet	Inability to implant the assigned study stent in a target lesion.	Nobori 1,229 patients 1,532 lesions Not reported	CYPHER 1,239 patients 1,555 lesions Not reported	NA
SORT OUT IV	2012	Circulation	Inability to implant the assigned study stent in >1 target lesion.	EES 1,390 patients 1,805 lesions Not reported	CYPHER 1,384 patients 1,779 lesions Not reported	NA
RESET	2012	Circulation	All the study stents attempted were successfully deployed in a given lesion with residual diameter stenosis <50%.	XIENCE 1,597 patients 1,967 lesions 99.8%	CYPHER 1,600 patients 1,960 lesions 99.5%	0.07
COMPARE	2010	Lancet	Not reported in the main paper.	XIENCE 897 patients 1,286 lesions Not reported	TAXUS 903 patients 1,294 lesions Not reported	NA
SORT OUT III	2010	Lancet	Inability to implant the assigned study stent in one or more of the target lesions.	Endeavor 1,162 patients 1,619 lesions Not reported	CYPHER 1,170 patients 1,611 lesions Not reported	NA

RESOLUTE	2010	NEJM	Achievement of a final residual diameter stenosis of less than 50% during the initial procedure, with use of the study stent only.	Resolute 1,140 patients 1,876 lesions 97%	XIENCE 1,152 atients 1,954 lesions 97%	0.52
LEADERS	2008	Lancet	Achievement of a final residual diameter stenosis of less than 50% during the initial procedure, with use of the study stent only.	BioMatrix 857 patients 1,256 lesions 95.8%	CYPHER 850 patients 1,213 lesions 94.2%	0.11

Supplementary Table 3. An example of a case report form.

Target lesion information

1. Specify which segments are diseased for this lesion

2. Did the operator make an attempt to delivery and deploy the assigned device?

□ **Yes**

2-1 Were any devices implanted at this target lesion?

□ Yes; how many devices were implanted? _____

Which type of device was implanted?

□ Assigned device;_____number _____

□ Non-assigned device;_____number_____;

Please specify reason(s) why it occurred.

□ Assigned device failed to cross the lesion

□ Assigned device dislodgement

□ Others_____

□ No; please specify reason(s) why it occurred. _____

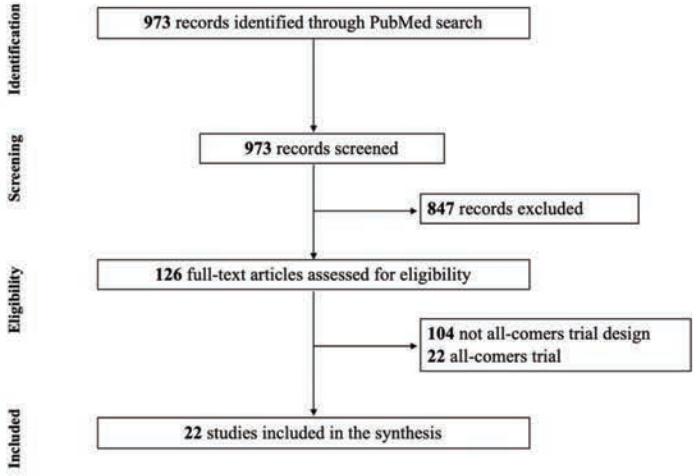
□ **No;** please specify reason(s) why it occurred. _____

2-2 Were non-assigned devices implanted at this target lesion?

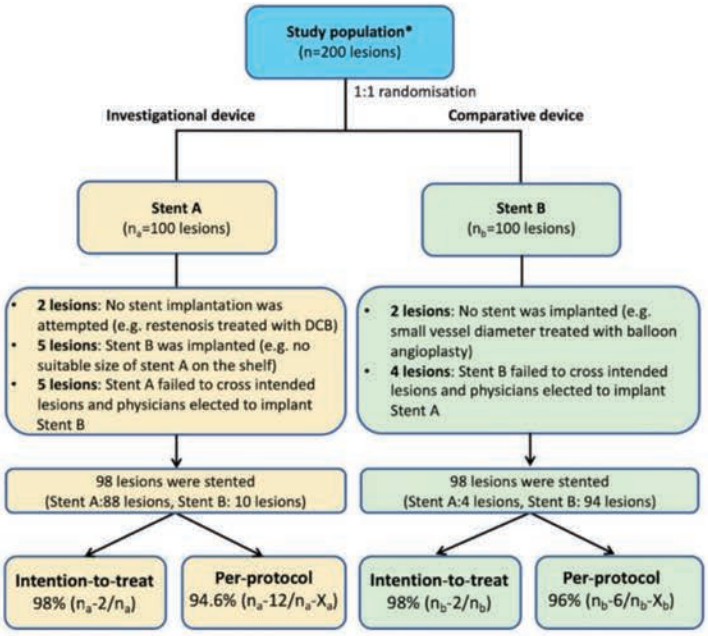
□ Yes; how many non-assigned devices were implanted? _____

Please specify reason(s) why it occurred. ___

□ No; please specify reason(s) why it occurred.



Supplementary Figure 1. Flow chart of the literature search and selection of studies.



Supplementary Figure 2. An example of a trial comparing stent A versus stent B.

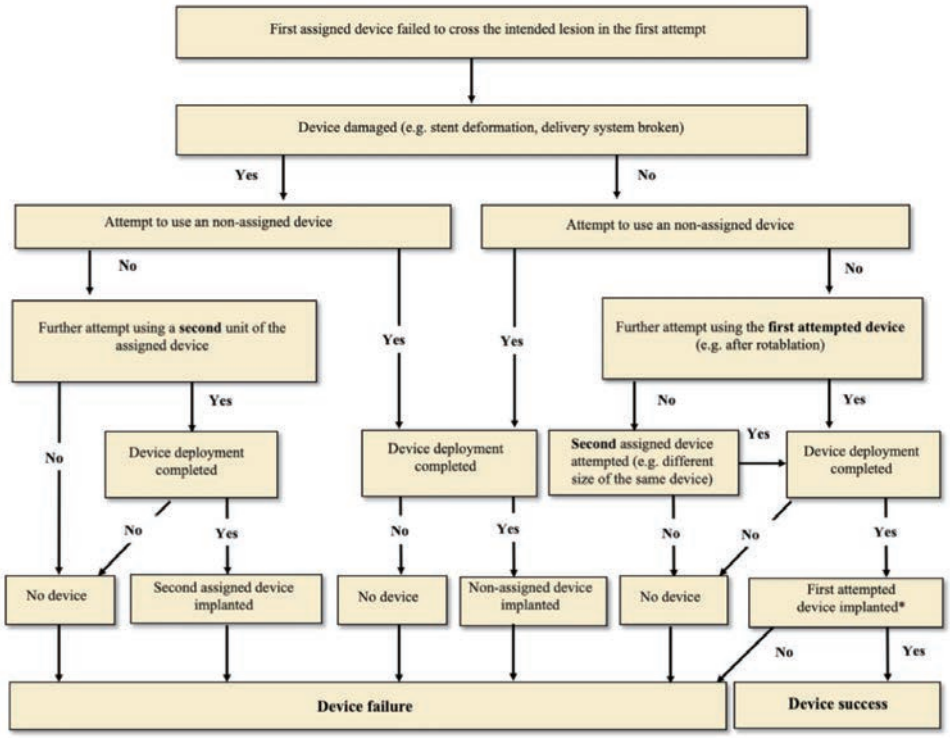
n_a: number of lesions to be treated with stent A;

n_b: number of lesions to be treated with stent B;

X_a: number of lesions in which the stent implantation (A) was not attempted;

X_b: number of lesions in which the stent implantation (B) was not attempted.

*e.g., single lesion trial, including restenosis



Supplementary Figure 3. Scenarios describing attempts with the assigned or non-assigned devices and relationship to device success.

* Per consensus the use of a second device is considered as device failure independent of the mechanism (related to the device, the lesion or the operator).

4

Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial.

Azfar Zaman, Robbert J de Winter, Norihiro Kogame, Chun Chin Chang, Rodrigo Modolo, Ernest Spitzer, Pim Tonino, Sjoerd Hofma, Aleksander Zurakowski, Pieter C Smits, Janusz Prokopczuk, Raul Moreno, Anirban Choudhury, Ivo Petrov, Angel Cequier, Neville Kukreja, Angela Hoye, Andrés Iniguez, Imre Ungi, Antonio Serra, Robert J Gil, Simon Walsh, Gincho Tonev, Anthony Mathur, Bela Merkely, Antonio Colombo, Sander Ijsselmuiden, Osama Soliman, Upendra Kaul, Yoshinobu Onuma, Patrick W Serruys; TALENT trial investigators.

Lancet. 2019 Mar 9;393(10175):987-997.

Summary

Background

Supraflex is a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts. We aimed to compare Supraflex with the standard of care, Xience, an everolimus-eluting stent with a durable polymer coating, regarding clinical outcomes with a randomised trial in an all-comer population.

Methods

We did a prospective, randomised, single-blind, multicentre study (TALENT) across 23 centres in Europe (the Netherlands, Poland, the UK, Spain, Bulgaria, Hungary, and Italy). Eligible participants were aged 18 years or older, had one or more coronary artery stenosis of 50% or greater in a native coronary artery, saphenous venous graft, or arterial bypass conduit, and had a reference vessel diameter of 2.25–4.50 mm. Patients underwent percutaneous coronary intervention in an all-comer manner. We randomly assigned patients (1:1) to implantation of either a sirolimus-eluting stent with a biodegradable polymer coating and ultra-thin struts (Supraflex) or an everolimus-eluting stent with a durable polymer coating (Xience). Randomisation was done by local investigators by use of a web-based software with random blocks according to centre. The primary endpoint was a non-inferiority comparison of a device-oriented composite endpoint—cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation—between groups at 12 months after the procedure, assessed in an intention-to-treat population. On assumption of 1-year composite endpoint prevalence of 8.3%, a margin of 4.0% was defined for non-inferiority of the Supraflex group compared with the Xience group. This trial is registered with ClinicalTrials.gov, number NCT 02870140.

Findings

Between Oct 21, 2016, and July 3, 2017, 1435 patients with 1046 lesions were randomly assigned to Supraflex, of whom 720 received the index procedure, and 715 patients with 1030 lesions were assigned to Xience, all receiving the index procedure. At 12 months, the primary endpoint had occurred in 35 patients (4.9 %) in the Supraflex group and in 37 patients (5.3%) in the Xience group (absolute difference –0.3% [one-sided 95% upper confidence bound 1.6%], $p_{non\text{-}inferiority} < 0.0001$). Definite or probable stent thrombosis prevalence, a safety indicator, was low in both groups and did not differ between them.

Interpretaion

The Supraflex stent was non-inferior to the Xience stent for a device-oriented composite clinical endpoint at 12 months in an all-comer population. Supraflex seems a safe and effective alternative drug-eluting stent to other stents in clinical practice.

Introduction

The evolution of coronary stent technologies has led to reduced adverse outcomes in patients who undergo percutaneous coronary intervention. These technological developments stem from reductions in strut and polymer thickness, improvements in metal alloys and biocompatibility of coating, and optimisation of the kinetics of drug release. The second generation of drug-eluting stents was introduced with thin struts (80–90 μm), new antiproliferative drugs with better elution profiles, and biocompatible polymers. These new stents had lower rates of restenosis coupled with adequate strut coverage,[1,2] resulting in significantly lower rates of thrombotic complications compared with those of first-generation, drug-eluting stents and bare metal stents.[3,4] Subsequently, biodegradable polymers were developed to disappear after drug release, thereby leaving a bare metal stent-like platform. The efficacy of drug-eluting stents with biodegradable polymer coating was shown to be non-inferior to that of stents with durable polymer coating in several studies.[5–7] A study[8] published in 2017 showed that a drug-eluting stent with a biodegradable polymer coating and ultra-thin struts was superior to a stent with durable polymer coating, achieving a lower rate of target lesion failure at 12 months than that of the stent with durable coating. Additionally, a metaanalysis[9] published in 2018 showed that drug-eluting stents with ultra-thin struts (strut thickness <70 μm) reduced the incidence of target lesion failure compared with that of contemporary stents with thicker struts. Because clinical outcomes of contemporary stents are reaching a safety plateau, it is probable that cost-effectiveness might influence the decision on which stent to use.

The Supraflex is a sirolimus-eluting coronary stent made with a cobalt chromium alloy that has a biodegradable polymer technology and an ultra-thin strut thickness of 60 μm. With this stent, the drug is released over a short period of 48 days. Provided that clinical outcomes are comparable with market-leading stents, the introduction of Supraflex in the European market will increase competition and might drive down healthcare costs.[10] In the FLEX-Registry,[11] Supraflex showed a low incidence of major adverse cardiac events at 12 months of follow-up (3.7%) and excellent strut coverage at 6 months of follow-up in 995 unselected realworld patients. Although the ultra-thin strut stent with biodegradable polymer might have an important role in patients' outcomes,[7] the Supraflex has not yet been tested in the context of a randomised clinical trial.

We therefore did a trial to investigate non-inferiority of clinical outcomes after implantation of the Supraflex stent compared with the standard of care for atherosclerotic lesions (Xience, an everolimus-eluting stent with durable polymer coating) in broad patient and lesion scenarios from an all-comer European population.

Methods

Study design and participants

The TALENT trial was a prospective, randomised, controlled, single-blind, multicentre study in an all-comers population across 23 hospitals or specialised centres in Europe (the Netherlands, Poland, the UK, Spain, Bulgaria, Hungary, and Italy). There were few inclusion and exclusion criteria (appendix).[12] Briefly, patients aged at least 18 years, with one or more coronary artery stenosis of 50% or greater in a native coronary artery, saphenous venous

graft, or arterial bypass conduit with a reference vessel diameter of 2.25–4.50 mm, who were suitable for coronary stent implantation were eligible for inclusion. Any type of coronary artery lesions and anatomical locations were included. The number of stents, treated lesions, and vessels and the length of lesions was unrestricted. All patients signed informed consent, which was approved by the ethics committee of each enrolling centre.

Randomisation and masking

Patients who met the enrolment criteria were randomly assigned (1:1) to implantation of either the Supraflex or the Xience stent. Randomisation was done by local investigators by use of a web-based software with random blocks according to centre. Clinical data were adjudicated by an independent clinical event committee, which was masked to the type of stent allocated to the patient.

Procedures

The Supraflex is a new generation metallic stent (Sahajanand Medical Technologies, Surat, India) consisting of an L605 cobalt–chromium alloy platform with ultra-thin struts (60 µm) across all stent diameters, highly flexible S-link connectors, and a biodegradable polymeric matrix coating (poly L-lactide, 50:50 mixture poly D, L-lactide-co-glycolide and polyvinyl pyrrolidone). Sirolimus, at a concentration of 1·4 µg/mm² and together with the polymeric matrix, is coated on the conformal surface of the stent. The average thickness of coating ranged from 4 µm to 5 µm. The drug is 70% released within 7 days, and the remainder is released over a period of 48 days.[11] The polymer gradually degrades over 9–12 months. Available stent diameters for this trial were between 2·25 mm and 4·0 mm, and available stent lengths were 8–48 mm. The crossing profile of Supraflex is 0·99 mm, whereas the crossing profile of the newest Xience Alpine is 1·10 mm and of Xience Sierra is 0·99 mm.

The control stent with durable polymer coating, Xience (Abbot Vascular, Santa Clara, CA, USA), is a cobalt–chromium alloy device with a strut thickness of 81 µm and an 8 µm-thick durable polymer coating. This polymer is made of polyvinylidene fluoride–hexafluoropropylene loaded with everolimus.[13] We used only Xience stents with similar diameter and length to those of Supraflex, thus Xience stents up to 48 mm in length and with diameters between 2·25 mm and 4·0 mm were allowed for implantation.

Investigators determined lesion parameters by visual estimation with angiography or online quantitative coronary angiography. Patients with stable coronary artery disease received dual antiplatelet therapy for at least 6 months after percutaneous coronary intervention, followed by aspirin monotherapy indefinitely. Patients with acute coronary syndrome received dual antiplatelet therapy for at least 12 months after percutaneous coronary intervention, followed by aspirin monotherapy indefinitely. For patients with acute coronary syndrome, the order of preference for P2Y12 (P2Y purinoceptor 12) inhibitors was ticagrelor, followed by prasugrel (or clopidogrel), according to local practice and drug availability.

Cardiac biomarkers (creatine kinase, creatine kinase-myocardial band, and troponin I or T) were measured within 24 h before percutaneous coronary intervention and 3–8 h after the procedure (appendix). Patients were followed up by hospital visit at 1 month and 12 months and by phone contact at 6 months to assess clinical status and adverse events. All information was recorded for data collection at each visit.

Outcomes

The primary endpoint of the study was a non-inferiority comparison at 12 months between the Supraflex group and the Xience group regarding a device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation. The composite secondary endpoints were a patient-oriented composite endpoint of all-cause death, any myocardial infarction, and any revascularisation, a target vessel failure of cardiac death, target vessel myocardial infarction, and clinically indicated target vessel revascularisation. Other secondary endpoints of the study included individual components of composite endpoints and stent thrombosis (appendix).

Definite and probable stent thrombosis, which are safety indicators, were adjudicated according to the definition of the Academic Research Consortium (ARC).[14] Myocardial infarction was defined according to the Society for Cardiovascular Angiography and Interventions consensus for periprocedural myocardial infarction (when occurring 48 h or earlier after the index procedure) or according to the Third Universal Definition for myocardial infarction (when occurring later than 48 h after the index procedure).[15,16] Device success was defined as successful delivery and deployment of (only) the assigned device at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of less than 30% (preferably by online quantitative coronary angiography).

Statistical analysis

The trial was powered for testing of non-inferiority for the primary endpoint at 12 months after the procedure. After reviewing event rates from published data, we expected the composite endpoint prevalences at 12 months for both treatment groups to be 8·3%.[17] A margin of 4% (50% of the expected event rate) was defined for the non-inferiority margin of the Supraflex group compared with the Xience group. On the basis of this margin and a one-sided type I error of 0·05, a total of 1386 patients (693 patients in each group) would have at least 85% power to detect non-inferiority. Accounting for approximately 3% of patients lost to follow-up, we randomly assigned a total of 1435 patients.

The primary analyses were based on an intention-to-treat population. For the primary endpoint analysis, we used a standard normal distribution to create a one-sided 95% upper confidence bound for the difference in Kaplan-Meier rates for the device-oriented composite endpoints of the Supraflex group and the Xience group. If the one-sided 95% upper confidence bound was less than or equal to the non-inferiority margin of 4·0%, Supraflex was declared to be non-inferior to Xience. This testing implied a 5·0% one-sided significance level. A secondary analysis of the primary endpoint and all secondary clinical endpoints was done in the per- protocol population, which consisted of patients who had received only the assigned study stent. Continuous variables were presented as mean (SD) and compared with the use of t test. Categorical variables were reported as n (%). Categorical variables with more than two categories were assessed by Mantel-Haenszel rank score test, and dichotomous variables were assessed by Fisher's exact test. Composite endpoints were calculated by use of time-to-first of any of the composite events per patient. Patients started being at risk on the day of index percutaneous coronary intervention or, if no procedure was done, on the day of randomisation. Survival curves were constructed with use of Kaplan-Meier estimates and the log-rank test was used to compare between-group differences. We pre-specified stratified analyses of the primary endpoint at 12 months for subgroups of patients with diabetes, ST-segment elevation myocardial infarction, small

vessels (≤2·75 mm), multivessel treatment, long lesions (>18 mm), in-stent restenosis, bypass graft, left main treatment, bifurcation treatment, or overl- apping stents. We calculated the interaction p value for the subgroup analysis. Unless otherwise specified, a two-sided p value of less than 0·05 was considered to indicate statistical significance. All statistical analyses were done using SAS software version 9.3. An independent data safety and monitoring board monitored the individual and collective safety of the patients in the study during the enrolment phase. This trial is registered with ClinicalTrials.gov, number NCT 02870140.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, and did not participate in the decision to submit the manuscript for publication. The executive committee (AZa, RJdW, UK, and PWS) had full access to all the data in the study, and the corresponding authors (YO and PWS) had full responsibility for the decision to submit for publication.

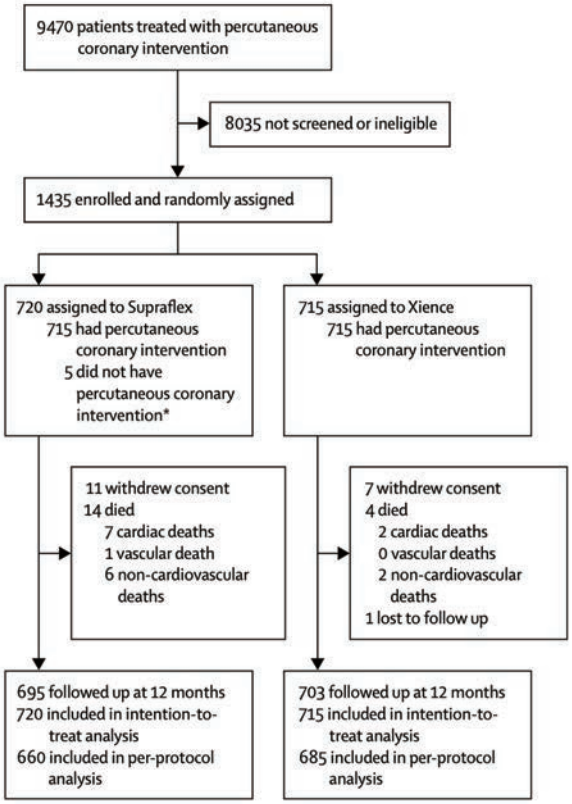


Figure 1. Study profile

*Percutaneous intervention was cancelled in two patients on the basis of intravascular ultrasound finding. In one patient, vasospastic stenosis observed during diagnostic angiography was not confirmed at the time of planned coronary intervention; therefore the procedure was not done. One patient was referred after randomisation to surgery because of concomitant mitral regurgitation. One patient did not receive percutaneous intervention because of a randomisation error.

Results

Between Oct 21, 2016 and July 3, 2017, we randomly assigned 1435 patients with a total of 2076 lesions to either the Supraflex group (720 patients with 1046 lesions) or the Xience group (715 patients with 1030 lesions; **figure 1**). Five patients in the Supraflex group did not undergo percutaneous coronary intervention. 11 patients (1·5%) in the Supraflex group and seven patients (1·0%) in the Xience group withdrew consent within 12 months of the procedure. Baseline clinical characteristics were similar in the two study groups (**table 1**). 429 patients (59·6%) in the Supraflex group and 405 (56·6%) in the Xience group presented with acute coronary syndrome. To enable a timely report of the primary endpoint, the steering committee decided to encourage patients who were randomly assigned between June 3 and July 3, 2017 (last month of enrolment) to undergo the 1-year follow-up visit before 360 days had passed, with a minimum of 330 days after the index procedure. 720 patients from the Supraflex group and 715 from the Xience group were included in the intention-to-treat population.

Table 1. Patient baseline characteristics

Characteristic	Supraflex (n=720)	Xience (n=715)
Age (years)	65·0±10·3 (n=720)	64·7±10·1 (n=715)
Male	546/720 (75·8%)	547/715 (76·5%)
Body mass index (kg/m^2)	28·3±4·8 (n=719)	28·3±4·6 (n=715)
Smoking status		
Current	176/719 (24·5%)	172/715 (24·1%)
Previous	286/719 (39·8%)	311/715 (43·5%)
Never	257/719 (35·7%)	232/715 (32·4%)
Diabetes mellitus	157/720 (21·8%)	178/715 (24·9%)
Insulin-dependent	48/720 (6·7%)	67/715 (9·4%)
Non-insulin-dependent	109/720 (15·1%)	111/715 (15·5%)
No diabetes mellitus	563/720 (78·2%)	537/715 (75·1%)
Hypertension	470/720 (65·3%)	472/714 (66·1%)
Hypercholesterolemia	444/718 (61·8%)	428/711 (60·2%)
Family history of coronary artery disease	311/671 (46·3%)	303/671 (45·2%)
Previous MI	136/720 (18·9%)	128/715 (17·9%)
Established Peripheral Vascular Disease	51/720 (7·1%)	64/715 (9·0%)
Previous PCI	175/720 (24·3%)	153/715 (21·4%)
Previous CABG	33/720 (4·6%)	55/715 (7·7%)
Heart Failure	34/720 (4·7%)	49/715 (6·9%)
Renal Insufficiency*	20/720 (2·8%)	14/715 (2·0%)
Indication		
Stable angina	291/720 (40·4%)	310/715 (43·4%)
ACS	429/720 (59·6%)	405/715 (56·6%)
Unstable angina	116/720 (16·1%)	99/715 (13·8%)
Non-ST elevation MI	194/720 (26·9%)	189/715 (26·4%)
ST-elevation MI	119/720 (16·5%)	117/715 (16·4%)

Data are mean (SD) or n (%). PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft.
*Defined as serum creatinine concentration>2·5 mg/dL or creatinine clearance ≤30 mL/min.

Table 2. Angiographic and procedural characteristics.

	Supraflex n=1046 lesions	Xience n=1030 lesions	p value
Vessel location:			0·070
LAD	468 (44·7%)	432 (41·9%)	
LCX	220 (21·0%)	237 (23·0%)	
RCA	338 (32·3%)	328 (31·8%)	
Left main	15 (1·4%)	16 (1·6%)	
Bypass graft	5 (0·5%)	17 (1·7%)	
Number of lesions treated	1·45±0·77 (n=720)	1·44±0·74 (715)	0·760
Total stented length per patients (mm)	37·2±27·4 (n=709)	37·2±27·0 (710)	0·961
Index PCI performed	715 (99·3%)	715 (100%)	0·062
Reason PCI not performed			
Medical treatment only	3 (0·4%)	0 (0·0%)	
Other reason	2 (0·3%)	0 (0·0%)	
TIMI flow pre-procedure			0·122
Flow 0	143 (13·7%)	112 (10·9%)	
Flow 1	40 (3·8%)	42 (4·1%)	
Flow 2	66 (6·3%)	84 (8·2%)	
Flow 3	758 (72·5%)	744 (72·2%)	
Assessment not done	39 (3·7%)	48 (4·7%)	
Restenotic lesion	44 (4·2%)	42 (4·1%)	0·883
Small vessel (≤ 2·75 mm)	420 (40·2%)	414 (40·2%)	0·999
Long lesion (> 18 mm)	518 (49·7%)	511 (49·6%)	0·964
Bifurcation involved	167 (16·0%)	157 (15·2%)	0·650
Thrombus aspiration	40 (3·8%)	39 (3·8%)	0·961
Pre-dilatation	807 (77·2%)	782 (75·9%)	0·509
Maximum pressure (atm)	13·6±4·3 (n=801)	13·5±4·1 (n=777)	0·677
Maximum balloon length (mm)	15·75±4·77 (n=805)	15·40±4·50 (n=782)	0·130
Maximum balloon diameter (mm)	2·52±0·43 (805)	2·46±0·43 (782)	0·006
Stent characteristics			
Number of stents used per lesion	1·2±0·5 (1046)	1·2±0·5 (1030)	0·592
Total stent length per lesion (mm)	25·7±14·5 (1028)	26·0±14·5 (1015)	0·623
Overlapping stents per lesion	221/1046 (21·1%)	201/1030 (19·5%)	0·361
Stent length per stent (mm)	21·3±8·3 (1239)	21·8±8·8 (1208)	0·120
Stent diameter per stent (mm)	3·0±0·5 (1239)	3·0±0·5 (1208)	0·186
Post-stenting balloon dilatation	544 (52·0%)	538 (52·2%)	0·918
Maximum pressure (atm)	17·1±4·3 (n=543)	17·5±3·9 (n=532)	0·096
Maximum balloon length (mm)	13·79±4·83 (n=544)	14·39±4·88 (n=537)	0·041
Maximum balloon diameter (mm)	3·30±0·58 (n=544)	3·29±0·60 (n=538)	0·804
TIMI flow post-procedure			0·198
Flow 0	7 (0·7%)	1 (0·1%)	
Flow 1	2 (0·2%)	3 (0·3%)	
Flow 2	11 (1·1%)	9 (0·9%)	
Flow 3	995 (95·1%)	975 (94·7%)	
Assessment not done	31 (3·0%)	42 (4·1%)	

Data are counts (percentage) or mean ± SD (number).

LAD = Left anterior descending artery, LCX = Left circumflex artery, PCI = percutaneous coronary intervention

RCA = Right coronary artery, TIMI=thrombolysis in myocardial infarction.

Overall, lesion characteristics were similar between the two groups (**table 2**). Mean pre-dilatation balloon diameter was larger in the Supraflex group than in the Xience group. Mean stent length and diameter per stent were similar between groups. The number of stents used was not different between both groups. Mean post-dilatation balloon length was greater in the Xience group than in the Supraflex group. The device success proportion was analysed in 2000 lesions in which investigators attempted to implant the allocated

stent. The detailed reasons for not using the allocated stent are provided in the appendix. The device success proportion per lesion in both groups was high, but there was significant difference between the Supraflex and the Xience group (973 [97·6%] of 997 lesions vs 998 [99·5%] of 1003; difference –1·9%, 95% CI –3·0 to –0·9; p=0·0003; appendix). This difference was mainly driven by increased crossover to non-allocated stent in the Supraflex group compared with that in the Xience group. There were no differences in the residual in-stent stenosis of 30% or greater between groups. This difference in device success did not affect in-hospital patient outcomes (in-hospital device-oriented composite endpoint 11 [1·5%] of 720 patients vs 10 [1·4%] of 715; difference 0·1%, 95% CI –1·2 to 1·5; p=0·837).

The primary device-oriented composite endpoint occurred in 35 (4·9%) of 720 patients in the Supraflex group and in 37 (5·3%) of 715 in the Xience group (**table 3**, **figure 2A**). Non-inferiority of the Supraflex stent compared with the Xience stent was shown, with an absolute difference of –0·3% and one-sided 95% upper confidence bound of 1·6% ($P_{non\text{-}inferiority}$ <0·0001, $P_{superiority}$=0·801). The frequencies of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation were similar for both stent types (**table 3**, **figure 2**). The details of cardiac deaths are described in the appendix. Results of the device-oriented composite endpoint from the perprotocol analysis, including 1345 patients, also showed non-inferiority of Supraflex compared with Xience (23 [3·5%] of 660 patients in the Supraflex group vs 30 [4·4%] of 685 in the Xience group; difference –0·9%, 95% CI –3·0 to 1·2; $P_{non\text{-}inferiority}$ <0·0001, $P_{superiority}$=0·41), with a significantly lower clinically indicated target lesion revascularisation in the Supraflex group (8 [1·2%] patients in Supraflex vs 21 [3·1%] in Xience; difference –1·9%, –3·5 to –0·3; p=0·021; appendix).

At 12 months, definite or probable stent thrombosis did not differ between groups (**table 3**). In the Supraflex group, there were two unexplained and unwitnessed deaths attributed to possible stent thrombosis according to ARC-1 definition. Frequency of any stent thrombosis (definite, probable, or possible) also did not differ between groups (**table 3**).

The patient-oriented composite endpoint was similar between the Supraflex group and the Xience group (**table 3**). There were 18 all-cause deaths in the trial and, as described previously, cardiac death was not statistically different between groups (**table 3**). Seven deaths in the Supraflex group were related to non-cardiac conditions (eg, cancer, sepsis, and pneumonia), compared with two deaths in the Xience group. The treatment effect of Supraflex against Xience was consistent across subgroups, except for patients with small vessels (≤2·75 mm; **figure 3**). In the per-protocol analysis of our study (appendix), Supraflex showed a 20% relative risk reduction in device-oriented composite endpoint at 1 year, mainly driven by a 61% reduction in clinically indicated target lesion revascularisation.

The proportion of patients on dual antiplatelet therapy did not differ between the two groups at 6 and 12 months (626 [89·9%] of 696 patients in the Supraflex group vs 642 [91·3%] of 703 in the Xience group, p=0·376 at 6 months, and 552 [80·2%] of 688 in the Supraflex group vs 575 [81·8%] of 703 in the Xience group, p=0·458 at 12 months).

Table 3. Clinical outcomes at 12 months after stent implantation (intention-to-treat basis).

	Supraflex n=720	Xience n=715	Percentage difference (95% CI)	p value
Primary outcome				
Device-oriented composite endpoint*	4·9% (35)	5·3% (37)	-0·3% (-2·6 to 2·0%)	0·801**
Separate endpoints for the primary outcomes				
Cardiac death	1·0% (7)	0·3% (2)	0·7% (-0·1 to 1·5%)	0·097
Target-vessel myocardial infarction†	2·5% (18)	2·8% (20)	-0·3% (-2·0 to 1·4%)	0·734
Clinically indicated target-lesion revascularization	2·7% (19)	4·0% (28)	-1·3% (-3·2 to 0·6%)	0·183
Secondary outcomes				
Patient-oriented composite endpoint‡	9·9% (70)	8·7% (61)	1·2% (-1·8 to 4·3%)	0·434
Target vessel failure§	5·4% (38)	6·1% (43)	-0·8% (-3·2 to 1·7%)	0·565
Any death	2·0% (14)	0·6% (4)	1·4% (0·3 to 2·6%)	0·019
Cardiac death	1·0% (7)	0·3% (2)	0·7% (-0·1 to 1·5%)	0·097
Any myocardial infarction†	3·1% (22)	3·7% (26)	-0·6% (-2·5 to 1·3%)	0·551
Q wave	0·4% (3)	0·4% (3)	0·0% (-0·7 to 0·7%)	0·996
Non-Q wave	2·7% (19)	3·4% (24)	-0·7% (-2·5 to 1·1%)	0·435
Target-vessel myocardial infarction†	2·5% (18)	2·8% (20)	-0·3% (-2·0 to 1·4%)	0·734
Q wave	0·3% (2)	0·4% (3)	-0·1% (-0·8 to 0·5%)	0·651
Non-Q wave	2·3% (16)	2·6% (18)	-0·3% (-1·9 to 1·3%)	0·721
Non-target-vessel myocardial infarction†	0·6% (4)	0·9% (6)	-0·3% (-1·2 to 0·6%)	0·523
Q wave	0·1% (1)	0·0% (0)	0·1% (-0·1 to 0·4%)	0·317
Non-Q wave	0·4% (3)	0·9% (6)	-0·4% (-1·3 to 0·4%)	0·314
Peri-procedural myocardial infarction†	0·7% (5)	0·8% (6)	-0·1% (-1·0 to 0·8%)	0·755
Any revascularisation	7·3% (51)	7·4% (52)	-0·2% (-2·9 to 2·6%)	0·914
Target-lesion revascularisation	3·5% (25)	4·3% (30)	-0·7% (-2·8 to 1·3%)	0·494
Clinically indicated	2·7% (19)	4·0% (28)	-1·3% (-3·2 to 0·6%)	0·183
Non-clinically indicated	1·0% (7)	0·8% (6)	0·1% (-0·9 to 1·1%)	0·788
Target-vessel revascularisation	4·1% (29)	5·4% (38)	-1·3% (-3·6 to 0·9%)	0·263
Clinically indicated	3·3% (23)	5·0% (35)	-1·7% (-3·8 to 0·3%)	0·109
Non-clinically indicated	1·0% (7)	1·4% (10)	-0·4% (-1·6 to 0·7%)	0·459
Non-Target Vessel revascularization	4·7% (33)	3·0% (21)	1·7% (-0·3 to 3·7%)	0·098
Thrombosis endpoints				
Definite stent thrombosis	0·7% (5)	0·7% (5)	-0·0% (-0·9 to 0·9%)	0·996
Acute (0-1 days)	0·1% (1)	0·0% (0)	0·1% (-0·1 to 0·4%)	0·319
Sub-Acute (2-30 days)	0·1% (1)	0·3% (2)	-0·1% (-0·6 to 0·3%)	0·562
Late (31-360 days)	0·4% (3)	0·4% (3)	-0·0% (-0·7 to 0·7%)	0·997
Definite or probable stent thrombosis	0·8% (6)	0·9% (6)	-0·0% (-1·0 to 1·0%)	0·996
Acute (0-1 days)	0·1% (1)	0·0% (0)	0·1% (-0·1 to 0·4%)	0·319
Sub-Acute (2-30 days)	0·3% (2)	0·3% (2)	-0·0% (-0·6 to 0·5%)	0·998
Late (31-360 days)	0·4% (3)	0·6% (4)	-0·1% (-0·9 to 0·6%)	0·701
Possible stent thrombosis	0·3% (2)	0·0% (0)	0·3% (-0·1 to 0·7%)	0·159
Any stent thrombosis	1·1% (8)	0·9% (6)	0·3% (-0·8 to 1·3%)	0·597

Data are percentage (counts).

* Cardiac death, target-vessel myocardial infarction, or clinically-indicated target-lesion revascularisation.

** p value for non-inferiority was <0.001. One-sided 95% upper confidence bound was 1·6%.

† Determined on the basis of the SCAI 2013 definition within 48 hours post procedure or the third universal definition after 48 hours post procedure.

‡ All-cause death, any myocardial infarction, or any revascularisation.

§ Cardiac death, target-vessel myocardial infarction, or clinically-indicated target-vessel revascularisation.

CI = confidence interval.

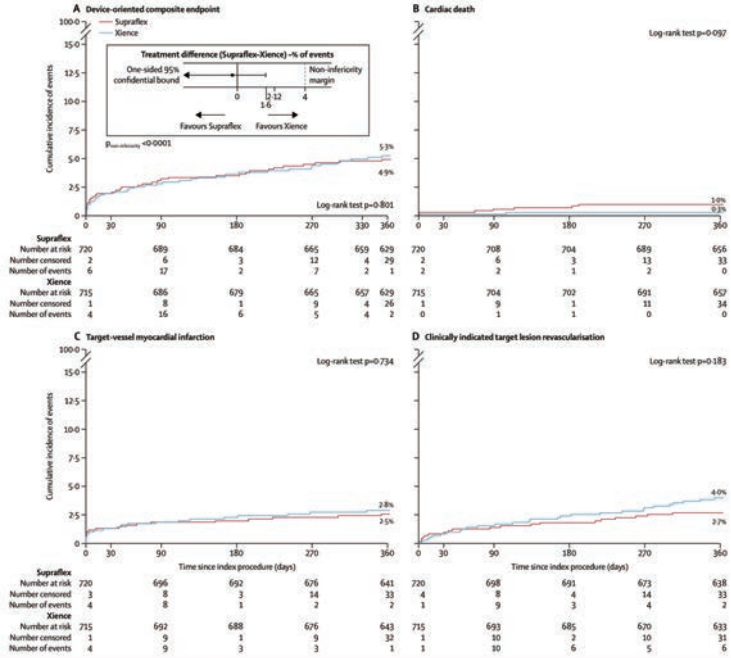


Figure 2. Kaplan-Meier plot for primary endpoint and its components over 360 days of follow-up
Kaplan-Meier curves show the cumulative incidence of device-oriented composite endpoint (primary endpoint; A) and of its components: cardiac death (B), target-vessel myocardial infarction (C), and clinically indicated target lesion revascularisation (D).

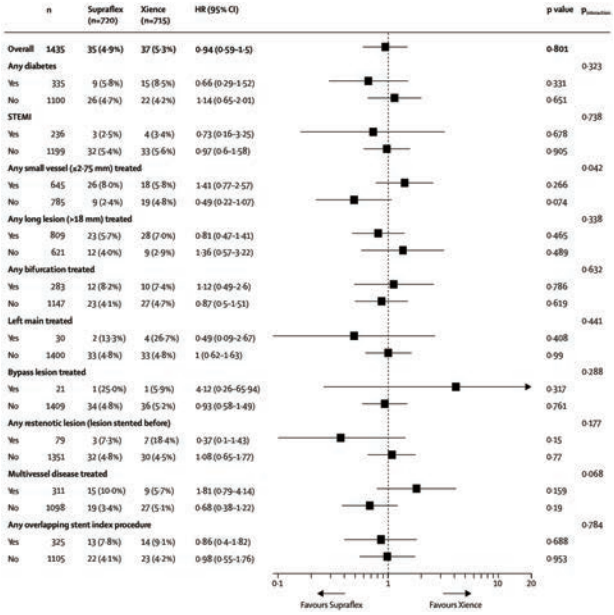


Figure 3. Stratified analyses of the device-oriented composite endpoint at 12 months across subgroups
Hazard ratio (HR) with 95% CI and p value results were from Cox proportional hazards analysis. STEMI=ST-segment elevation myocardial infarction.

Discussion

In the TALENT study, we showed that Supraflex, a sirolimus-eluting coronary stent with biodegradable polymer coating and ultra-thin struts, was non-inferior to the standard of care, an everolimus-eluting stent with durable polymer coating, for a device-oriented composite endpoint of cardiac death, target-vessel myocardial infarction, or clinically indicated target lesion revascularisation at 12 months, in an all-comer European population.

Although device success was high in our study, we found a significant difference that favoured Xience over Supraflex (appendix). This difference was mainly due to a crossover to the comparator that has been on the market for over a decade and with which the investigators are very familiar. When resistance in crossing a lesion was found, some investigators (in seven of 23 centres) tended to quickly crossover to a familiar stent technology. Despite the slight difference in device success proportions between the groups, the success proportions of Supraflex are similar or even superior to other drug-eluting stents in all-comer trials (appendix).[17–19] For instance, device success proportion in the TARGET all-comer trial[18] was 92·4% in the FIREHAWK group and 94·8% in the Xience group, whereas in the BIOFLOW V trial,[8] a non-all-comer trial, it was 98% in the Orsiro group and 97% in the Xience group.

Supraflex, in line with current generation drug- eluting stents with a biodegradable polymer coating and an ultra-thin strut thickness (60 µm), was designed to overcome the limitations of the second-generation drug-eluting stents with durable polymer coating, which have been reported with 2–3% annual increased rate for the device-oriented composite endpoint 1 year after the procedure.[20] By contrast with the Orsiro stent, all Supraflex stents have the same strut thickness, irrespective of their diameter (from 2·00 mm to 4·50 mm). In our study, visual assessment or quantitative coronary angiography online by the operator showed absence of recoil, supporting findings already documented in a previous study.[21] Regarding the MiStent stent, there is a fundamental difference between the drug release kinetics of MiStent and Supraflex. Drug release is completed in 48 days, with a burst elution of 70% within the first 7 days, with the Supraflex stent, whereas MiStent has no drug release within the first 3 days and its polymer is fully biodegraded and resorbed within 3 months after implantation, but microcrystalline sirolimus is impacted and embedded in the vessel wall, acting as a tissue reservoir for 270 days. The arterial sirolimus concentrations still reach more than 2 ng/mg at 270 days. Additionally, the clinical outcome of Supraflex in our study is similar to Orsiro and MiStent in their pivotal trials (appendix).[5,6,8,22]

A meta-analysis[9] published in 2018, of ten randomised trials including 11658 patients, compared the performance of three drug-eluting stents with ultra-thin struts (Orsiro, MiStent, and BioMime) with that of three second-generation drug-eluting stents with thicker struts (Xience, Resolute, and Nobori). The results showed that newer generation stents with ultra-thin struts were associated with a 16% relative risk reduction in device-oriented composite endpoint at 1 year. Additionally, in that meta-analysis, ultra-thin strut stents had numerically, but not significantly, lower prevalences of stent thrombosis.[9] One theoretical disadvantage of thicker struts compared with ultra-thin struts is that thick, protruding struts disrupt the laminar flow and induce flow disturbance, which could further activate a platelet-signalling procoagulation pathway.[23,24] Whether the benefit of drug-eluting stents with thin struts could improve clinical outcomes remains to be assessed by studies with longer follow-up periods.

Supraflex has both thinner total thickness (strut plus coating is 68–70 μm) and shorter duration of drug release (48 days) than those of Xience. In an optical coherence tomography subanalysis in the FLEX registry,[11] Supraflex showed excellent strut coverage of 98·1% at 6 months, whereas strut coverage of Xience was 94·1% in a previous study.[25] Moreover, Supraflex had a favourable healing score in the FLEX registry, which might be attributed to its ultra-thin strut thickness and shorter duration of drug release. The early healing process of Supraflex might allow shorter duration of dual antiplatelet therapy, although further study is needed to assess this.

Our study had some limitations. The observed device-oriented composite endpoint in the control group was lower than the estimated event rate in the sample size calculation. This was mainly due to lower prevalence of target vessel myocardial infarction in the Xience group than in the referenced trial, RESOLUTE.[17] This difference might be caused by different definitions of periprocedural myocardial infarction. In the TALENT study, the Society for Cardiovascular Angiography and Interventions consensus, which is more clinically relevant in terms of prognosis, was adopted for defining periprocedural myocardial infarction.[15]

The predefined non-inferiority margin might be considered, in retrospect, to be too wide. The original non-inferiority margin of 4·0% was determined as half of the device-oriented clinical endpoint prevalence of 8·3% in the Xience group of the RESOLUTE trial.[17] However, with a post-hoc non-inferiority margin of 2·1%, which corresponds to a hazard ratio of 1·4 based on the observed device-oriented composite endpoint prevalence in the Xience group, non-inferiority would still be met (post-hoc $P_{non\text{-}inferiority}$=0·019).

Although the trial was not powered for all-cause mortality, we found a significant difference in all-cause death between the two groups. The all-cause mortality (0·6%) of the TALENT trial was lower than that observed in the other all-comer trials, such as TARGET,[18] BIOSCIENCE,[6] TWENTE,[26] and RESOLUTE[17] (2·2–2·8%), suggesting the play of chance (appendix).

This trial was single-blinded, although the effect of this approach on event reporting is minimal because of the adjudication by an independent blinded clinical event committee.

1-year follow-up visits were done up to 30 days earlier than 360 days in 55 patients, although the effect of this early follow-up on primary endpoint measurement would be minimal with the Kaplan-Meier method. Finally, our report was limited to a short follow-up of 12 months. The protocol specifies that the follow-up of patients will continue for up to 3 years to assess the long-term benefits of biodegradable polymer coating (NCT02870140).

In conclusion, the Supraflex sirolimus-eluting stent with biodegradable polymer coating and ultra-thin strut was non-inferior to the Xience everolimus-eluting stent with durable polymer coating for a device oriented composite clinical endpoint at 12 months in an all-comer population.

References

1 Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008; 52: 333–42.
2 Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006; 47: 175–81.
3 Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015; 65: 2496–507.
4 Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2018; 40: 87–165.
5 de Winter RJ, Katagiri Y, Asano T, et al. A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III): a randomised, single-blind, multicentre, non-inferiority, phase 3 trial. Lancet 2018; 391: 431–40.
6 Pilgrim T, Heg D, Roffi M, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet 2014; 384: 2111–22.
7 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. JACC Cardiovasc Interv 2013; 6: 777–89.
8 Kandzari DE, Mauri L, Koolen JJ, et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet 2017; 390: 1843–52.
9 Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer generation ultra-thin strut drug-eluting stents versus older second-generation thicker strut drug-eluting stents for coronary artery disease: a meta-analysis of randomized trials. Circulation 2018; 138: 2216–26.
10 Kaul U. The new pricing policy for coronary stents in India: a boon or a bane? EuroIntervention 2017; 13: 267–68.
11 Lemos PA, Chandwani P, Saxena S, et al. Clinical outcomes in 995 unselected real-world patients treated with an ultrathin biodegradable polymer-coated sirolimus-eluting stent: 12-month results from the FLEX Registry. BMJ Open 2016; 6: e010028.
12 Modolo R, Chichareon P, Kogame N, et al. A prospective multicenter randomized all-comers trial to assess the safety and effectiveness of the thin-strut sirolimus-eluting coronary stent SUPRAFLEX: rationale and design of the TALENT trial. EuroIntervention 2018; published online July 31. DOI:10.4244/EIJ-D-18–00499.
13 Saez A, Moreno R. Everolimus-eluting coronary stents. Med Devices 2010; 3: 51–56.
14 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.
15 Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013; 62: 1563–70.
16 Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012; 33: 2551–67.
17 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.

18 Lansky A, Wijns W, Xu B, et al. Targeted therapy with a localised abluminal groove, low-dose sirolimus-eluting, biodegradable polymer coronary stent (TARGET All Comers): a multicentre, open-label, randomised non-inferiority trial. Lancet 2018; 392: 1117–26.
19 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.
20 Dangas GD, Serruys PW, Kereiakes DJ, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv 2013; 6: 914–22.
21 Abhyankar AD, Thakkar AS. In vivo assessment of stent recoil of biodegradable polymer-coated cobalt-chromium sirolimus-eluting coronary stent system. Indian Heart J 2012; 64: 541–46.
22 Jensen LO, Thayssen P, Maeng M, et al. Randomized comparison of a biodegradable polymer ultrathin strut sirolimus-eluting stent with a biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: the SORT OUT VII trial. Circ Cardiovasc Interv 2016; 9: e003610.
23 Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011; 123: 1400–09.
24 Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. J Am Coll Cardiol 2012; 59: 1337–49.
25 Guagliumi G, Capodanno D, Ikejima H, et al. Impact of different stent alloys on human vascular response to everolimus-eluting stent: an optical coherence tomography study: the OCTEVEREST. Catheter Cardiovasc Interv 2013; 8: 510–18.
26 von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012; 59: 1350–61.

Supplementary data

Inclusion and exclusion criteria

Subject selection

Subjects participating in the study met all the inclusion criteria. Subjects who met any of the exclusion criteria could not be registered in the study.

Inclusion Criteria

1. Male or female patients ≥18 years;
2. Presence of one or more coronary artery stenosis of ≥50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation.
3. The vessel should have a reference vessel diameter ranging from ≥2·25 mm to ≤4·5 mm (no limitation on the number of treated lesions, vessels, or lesion length). All lesions of the patient must comply with the angiographic inclusion criteria.
4. The patient (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed. Patient is willing to comply with all protocol-required evaluations.

Exclusion Criteria

1. Known pregnancy or breastfeeding at time of randomization.
2. Known contraindication or hypersensitivity to sirolimus, everolimus, cobalt-chromium, or to medications such as aspirin, heparin, bivalirudin, and all of the following four medications: clopidogrel bisulfate, ticlopidine, prasugrel, ticagrelor.
3. Any PCI treatment within 6 months prior to the index procedure.
4. Concurrent medical condition with a life expectancy of less than 12 months.
5. Unwilling/ not able to return for outpatient clinic at 1 month and 12 months follow-up.
6. Currently participating in another trial and not yet at its primary endpoint.

Secondary Endpoints (evaluated at each follow-up visit/contact)

1. Composite Endpoints

- Patient-oriented composite endpoint defined as all-cause death, any myocardial infarction, or any revascularization
- Target vessel failure defined as cardiac death, target vessel myocardial infarction, or clinically-indicated target vessel revascularization
- Device-oriented composite endpoint defined as cardiac death, target vessel myocardial infarction or clinically indicated target lesion revascularization (for all follow-up/visits other than 12 months)

2. Mortality

- All death
- Cardiac death
- Non-cardiac death (vascular and non-cardiovascular)

3. Myocardial Infarction

- All myocardial infarction
- Target vessel myocardial infarction
- Non-TV-MI

4. Revascularization

- Target Lesion revascularization (TLR) (any, clinically-indicated TLR, non-clinically indicated TLR)
- Target Vessel revascularization (TVR) (any, clinically-indicated TVR, non-clinically indicated TVR)
- Non-TV revascularization
- Any revascularization

5. Stent thrombosis rates according to the Academic Research Consortium classification

- Early (Acute, Sub-acute), Late, Very Late.
- Definite, Probable, Possible
- Definite/Probable

Online Table 1. Number of patients randomized per site (Total number of patients: 1435)

Site ID	Site Name	Principal Investigator	City	Country	Patients enrolled	Date first patient enrolled	Date last patient enrolled
NL007	Amsterdam University Medical Center	Prof. R-J. de Winter	Amsterdam	The Netherlands	224	2016-10-21	2017-06-30
NL009	Catharina hospital	Dr. P. Tonino	Eindhoven	The Netherlands	217	2016-12-13	2017-06-30
NL002	Medisch Centrum Leeuwarden	Dr. S. Hofma	Leeuwarden	The Netherlands	154	2016-10-28	2017-06-26
PL002	PAKS Chrzanów (Maloposkie Centrum Sercowo-Naczyniowe)	Dr. A. Zurakowski	Chrzanow	Poland	116	2017-02-14	2017-07-01
NL003	Maasstad ziekenhuis	Dr. P. Smits	Rotterdam	The Netherlands	100	2017-02-28	2017-06-29
PL005	PAKS Kędzierzyn- Koźle	Dr. J. Prokopczuk	Kędzierzyn- Koźle	Poland	94	2017-02-10	2017-06-26
ES012	Hospital La Paz	Dr. R. Moreno	Madrid	Spain	69	2017-04-20	2017-06-29
GB002	University Hospital of Wales	Dr. A. Choudhury	Cardiff	UK	65	2017-02-06	2017-06-23
GB013	Freeman Hospital	Prof. A. Zaman	Newcastle-Upon-Tyne	UK	63	2017-04-04	2017-06-29
BG001	City Clinic Heart and Vascular Institute	Prof. I. Petrov	Sofia	Bulgaria	61	2017-04-11	2017-06-30
ES003	Bellvitge University Hospital	Dr. A. Cequier	Barcelona	Spain	53	2017-04-04	2017-06-29
GB012	Lister Hospital	Dr. N. Kukreja	Stevenage	UK	36	2017-03-17	2017-06-30
GB010	Castle Hill Hospital	Dr. A. Hoye	Cottingham	UK	33	2017-01-31	2017-06-27
ES018	Hospital alvaro Cunqueiro University Hospital of Vigo	Dr. Andres Iniguez	Vigo	Spain	29	2017-03-13	2017-06-23
HU001	Invasive Cardiology Unit, Cardiology Center	Dr. I. Ungi	Szeged	Hungary	27	2017-04-18	2017-06-23
ES005	Hospital de Sant Pau	Dr. A. Serra	Barcelona	Spain	23	2017-03-13	2017-06-27
PL009	Central Hospital of the Internal and Administration Ministry	Prof. R. Gil	Warsaw	Poland	13	2017-03-17	2017-06-12
GB021	Royal Victoria Hospital	Dr. S. Walsh	Belfast	UK	12	2017-04-25	2017-06-27
BG004	St. George's University Multi-profile Hospital for Active Treatment	Dr. Gincho Tonev	Plovdiv	Bulgaria	11	2017-06-08	2017-06-28
IT001	Ospedale San Raffaele	Prof. A. Colombo	Milan	Italy	10	2017-05-05	2017-06-19
HU002	Semmelweis University Heart and Vascular Center	Prof. B. Merkely	Budapest	Hungary	10	2017-04-20	2017-06-20
GB022	St Bartholomew's Hospital	Prof. A. Mathur	London	UK	10	2017-05-10	2017-06-22
NL008	Amphia Ziekenhuis	Dr. Sander IJsselmuiden	Breda	The Netherlands	5	2017-06-30	2017-07-03

Online Table 2. Comparison of device success between Supraflex and Xience

	Supraflex n=720 patients n=1046 lesions	**Xience** n=715 patients n=1030 lesions	Difference (95% CI)	p value
Operators did not attempt to implant the allocated stent	49 lesions (4·7%)	27 lesions (2·6%)	2·1% (0·5 to 3·7%)	0.014
No stent was implanted	17 (1·6%)	11 (1·1%)	0·6% (-0·4 to 1·5%)	0·342
• Procedure failure (Failure of wire/balloon crossing)	9 (0·8%)	2 (0·2%)	0·7% (0·0 to 1·3%)	0·065
• *Only balloon angioplasty (Small vessel size*/in-stent stenosis)	8 (0·8%)	9 (0·9%)	-0·1% (-0·9 to 0·7%)	0·812
Operator implanted another stent without attempt to use allocated stent	32 (3·0%)	16 (1·6%)	1·5% (0·2 to 2·8%)	0·028
• Allocated stent not available	12 (1·1%)	8 (0·8%)	0·4% (-0·5 to 1·2%)	0·502
• In patients with multiple target lesions, allocated stent failed to cross in 1st lesion, then operator didn't attempt to use allocated stent in 2nd or 3rd lesion	7 (0·7%)	0 (0·0%)	0·7% (0·2 to 1·2%)	0·016
• Protocol violation	13 (1·2%)	8 (0·8%)	0·5% (-0·4 to 1·3%)	0·381
○ Physician's decision	6 (0·5%)	5 (0·5%)	0·1% (-0·5 to 0·7%)	1·000
○ Human mistakes	7 (0·7%)	3 (0·3%)	0·4% (-0·2 to 1·0%)	0·343
Operators attempted to implant the allocated stent	997 lesions	1003 lesions	-2·1% (-3·7 to -0·5%)	0·014
No stent was able to cross the lesion	1 (0·1%)	3 (0·3%)	- 0·2% (-0·6 to 0·2%)	0·371
Stent dislodgement and failure to retrieve	1 (0·1%)	0 (0·0%)	0·1% (-0·1 to 0·3%)	1·000
Allocated stent did not cross the lesion	21 (2·0%)	1 (0·1%)	1·9% (1·0 to 2·8%)	0·000
In-stent residual stenosis ≥30%	1 (0·1%)	1 (0·1%)	-0·0% (-0·3 to 0·3%)	1·000
Device success rate (per lesion)	97·6% (973/997)	99·5% (998/1003)	-1·9% (-3·0 to -0·9%)	0·0003
Procedure success rate (per patient)	95·6% (673/704)	98·3% (695/707)	-2·7% (-4·5 to -0·9%)	0·003

Online Table 3. Device success rate in clinical trials

TALENT All-comers	Supraflex n=720 patients n=1046 lesions	Xience n=715 patients n=1030 lesions	Struct thickness of study stent (µm)	p value
	97·6%	99·5%	60 µm	0·0003
TARGET All-comers	Firehawk n=823 patients n=1221 lesions	Xience n=830 patients n=1179 lesions		p value
	92·4%	94·8%	86 µm	0·025
BIOSCIENCE All-comers	Orsiro n=1063 patients n=1594 lesions	Xience n=1056 patients n=1545 lesions		p value
	Not reported	Not reported	60 µm (2·25 to 3·0 mm) 80 µm (3·5 to 4·0 mm)	NA
TWENTE All-comers	Resolute n=697 patients n=1080 lesions	Xience n=694 patients n=1036 lesions		p value
	98%	98·4%	91 µm	0·17
RESOLUTE All-comers	Resolute n= 1140 patients n= 1876 lesions	Xience n= 1152 patients n= 1954 lesions		
	97%	97%	91 µm	0·52
LEADERS All-comers	BioMatrix n= 857 patients n= 1256 lesions	Cypher n= 850 patients n= 1213 lesions		p value
	95·8%	94·2%	120 µm	0·11
BIOFLOW V (not all-comers)	Orsiro n=884 patients n=1111 lesions	Xience n=450 patients n=589 lesions	60 µm (2·25 to 3·0 mm) 80 µm (3·5 to 4·0 mm)	p value
	98%	97%		0·415

Online Table 4. Peri-procedural complications

	Supraflex SES (N=720)	**Xience EES (N=715)**	**Difference (95% CI)**	**p-Value**
Any peri-procedural complication	6·7% (48/715)	5·6% (40/715)	1·1% [-1·4%, 3·6%]	0·379
Dissection	2·8% (20/715)	2·2% (16/715)	0·6% [-1·1%, 2·2%]	0·500
Occlusion	1·0% (7/715)	1·3% (9/715)	-0·3% [-1·4%, 0·8%]	0·615
Coronary spasm	0·0% (0/715)	0·0% (0/715)		NA
Coronary embolism	0·4% (3/715)	0·3% (2/715)	0·1% [-0·5%, 0·8%]	1·000
Coronary perforation	0·4% (3/715)	0·3% (2/715)	0·1% [-0·5%, 0·8%]	1·000
Thrombi at stented site	0·1% (1/715)	0·1% (1/715)	0·0% [-0·4%, 0·4%]	1·000
Other	2·4% (17/715)	2·0% (14/715)	0·4% [-1·1%, 1·9%]	0·586

Online Table 5. List of cardiac deaths depicted

Patient ID and allocation	Days after index procedure	Type of death	Comments
NL007-1116 Supraflex	0 days	• Explained • Witnessed	• Heavily calcified LAD in the angiography. • Residual significant lesion at the proximal part of the stent (untreated) and dissection in the middle part of the vessel caused by cutting balloon dilatation (untreated). • Chronic total occlusion of the RCA, with grade 3 collateral from the left coronary system. • No stent thrombosis seen in the angiography • Patient died 15 minutes after the procedure, outside of the table but still in the Catheterization Laboratory • No stent thrombosis
PL005-1047 Supraflex	0 days	• Explained • Witnessed	• Patient underwent PCI with a stent in the proximal LAD. • Left the catheterization laboratory with chest pain and presented with an anterior STEMI in the Intensive care Unit. • New coronary angiography 2 hours later showed patency of the arteries, absence of thrombus, but with a translucent image in the proximal edge of the stent characterized as a linear dissection without limiting the distal flow. No treatment was performed. Patient presented with continuous deterioration of clinical status during the procedure and cardiogenic shock. • Transferred to the ICU, 20 minutes had a cardiac arrest, successfully resuscitated with CPR. Later, presented a new cardiac arrest in asystole, without success in the CPR. • No stent thrombosis
GB001-1054 Supraflex	67 days	• Unexplained • Witnessed	• The site investigator, after consulting the patient's daughter confirmed that the patient died at home, before the ambulance arrived. No autopsy was performed. • Therefore – unexplained death more than 30 days after PCI → possible stent thrombosis.
HU001-1026 Supraflex	89 days	• Explained • Witnessed	• Patient was hospitalized due to decompensated Chronic heart failure with severe ventricular dysfunction. • Was clinically treated and did not recover with the use of levosimendan, ultrafiltration. • Presented decrease of general clinical status requiring mechanical ventilation. • Died due to decompensation of HF. • No stent thrombosis
PL005-1020 Supraflex	114 days	• Unexplained • Witnessed	• Patient was hospitalized in the Neurology Department one month before death without discharge letter. • Patient died in another hospital. Data obtained from a family member who informed that the patient had a circulatory and respiratory failure.

			• No angiographies • No letter from the hospital • Unexplained death beyond 30 days of the procedure → Possible stent thrombosis.
GB013-1058 Supraflex	183 days	• Explained • Unwitnessed	• Found dead in his car. • Paramedics confirmed his death when getting in site. • Autopsy confirmed complete occlusion of the stent vessel. • Thrombosis of the stented segment of the vessel confirmed by autopsy → Definite stent thrombosis.
NL007-1227 Supraflex	191 days	• Explained • Witnessed	• Patient hospitalized due to heart failure decompensation in the setting of acute pancreatitis. • Cause of death by the physician's reports is cardiomyopathy caused by three-vessel chronic coronary artery disease. • No stent thrombosis
PL002-1093 Xience	1 day	• Explained • Witnessed	• Patient presented with an anterior STEMI with an occluded LAD to perform the index procedure. • After stenting patient had a final TIMI 1 flow (no-reflow phenomenon) • Presented progressive symptoms of cardiogenic shock • Had a cardiac arrest in the next morning. • No stent thrombosis
GB002-1002 Xience	104 days	• Explained • Unwitnessed	• Patient collapsed at home – had a ventricular fibrillation that degenerated to asystole → declared dead after CPR attempts. • Autopsy was performed • Cause of death was thrombus on the stented vessel. • Definite stent thrombosis.

LAD: left anterior descending coronary artery; RCA: right coronary artery; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; ICU: intensive care unit; CPR: cardio-pulmonary resuscitation; HF: heart failure.

Online Table 6. 1-year all-cause mortality rate in clinical trials

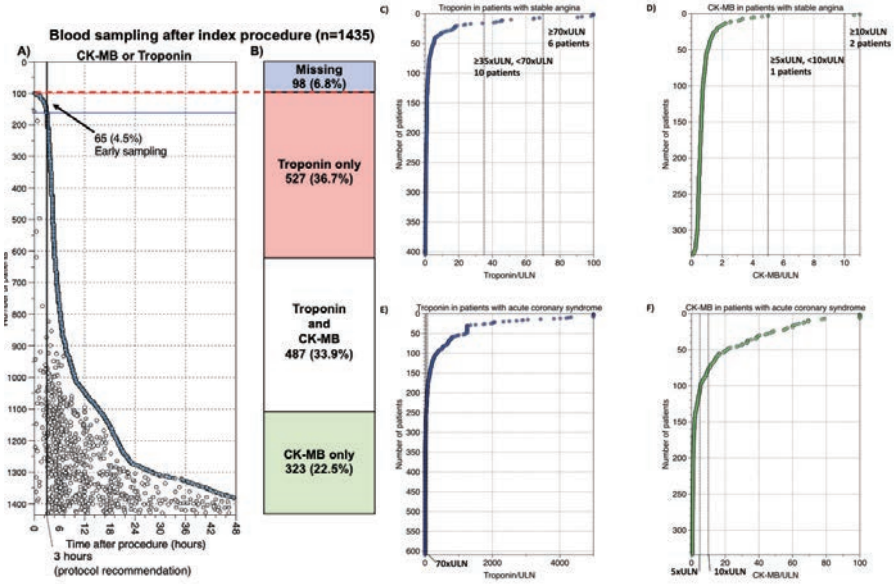
TALENT All-comers	**Supraflex n=720 patients n=1046 lesions**	**Xience n=715 patients n=1030 lesions**	**p value**
	2·0%	**0·6%**	**0·019**
TARGET All-comers	**Firehawk n=823 patients n=1221 lesions**	**Xience n=830 patients n=1179 lesions**	**p value**
	2·2%	**2·2%**	**0·98**
BIOSCIENCE All-comers	**Orsiro n=1063 patients n=1594 lesions**	**Xience n=1056 patients n=1545 lesions**	**p value**
	3·3%	**2·6%**	**0·360**
TWENTE All-comers	**Resolute n=697 patients n=1080 lesions**	**Xience n=694 patients n=1036 lesions**	**p value**
	2·1%	**2·2%**	**0·86**
RESOLUTE All-comers	**Resolute n= 1140 patients n= 1876 lesions**	**Xience n= 1152 patients n= 1954 lesions**	**P value**
	1·6%	**2·8%**	**0·08**
BIOFIOW V (not all comers)	**Orsiro n=884 patients n= 1111 lesions**	**Xience n=450 patients n= 589 lesions**	**p value**
	1·0%	**1·0%**	**0·382**

Online Table 7. 1-year device-oriented composite endpoint and components in pivotal clinical trials of Orsiro and MiStent.

	TALENT	**DESSOLVE III**	**BIOSCIENCE**	**SORT OUT VII**	**BIOFLOW V**
	All-comers	**All-comers**	**All-comers**	**All-comers**	**Non-all-comers**
Study device	Supraflex	MiStent	Orsiro	Orsiro	Orsiro
Device-oriented composite endpoint	4·9%	5·8%	6·7%	3·8%	6·0%
Cardiac death	1·0%	2·0%	1·9%	1·3%	<1·0%
Target-vessel myocardial infarction	2·5%	1·9%	2·9%	1·0%	5·0%
Clinically-indicated target lesion revascularisation	2·7%	1·9%	3·4%	2·0%	2·0%

Online figure 1. Time points and availability for the assessment of post-procedural cardiac enzyme at index procedure.

A) X axis indicates blood sampling time after procedure. Y axis indicates each patient ordered by the last sampling time. Each dot represents one sample. Either CK-MB or troponin was available in 1,337 (93·2%) patients.
B) Number and proportion of subjects having either missing enzyme, troponin only, CK-MB only, or both.
C) Cumulative distribution curve for maximum ratio of troponin to upper limit of normal in patients with stable angina.
D) Cumulative distribution curve for maximum ratio of CK-MB to upper limit of normal in patients with stable angina.
E) Cumulative distribution curve for maximum ratio of troponin to upper limit of normal in patients with acute coronary syndrome.
F) Cumulative distribution curve for maximum ratio of CK-MB to upper limit of normal in patients with acute coronary syndrome.



5

Impact of post-procedural minimal stent area on 2-year clinical outcomes in the SYNTAX II trial.

Yuki Katagiri, Giovanni Luigi De Maria, Norihiro Kogame, Ply Chichareon, Kuniaki Takahashi, Chun Chin Chang, Rodrigo Modolo, Simon Walsh, Manel Sabate, Justin Davies, Maciej Lesiak, Raul Moreno, Ignacio Cruz-Gonzalez, Nick E J West, Jan J Piek, Joanna J Wykrzykowska, Vasim Farooq, Javier Escaned, Adrian P Banning, Yoshinobu Onuma, Patrick W Serruys.

Catheter Cardiovasc Interv. 2019 Mar 1;93(4):E225-E234.

Abstract

Objectives:
To investigate the impact of minimal stent area (MSA) evaluated by post-procedural intravascular ultrasound (IVUS) on clinical outcomes after contemporary PCI in patients with three-vessel disease (TVD).

Background:
The impact of post-procedural MSA on clinical outcomes has not yet been extensively studied in patients with TVD.

Methods:
The SYNTAX II study is a multicenter, all-comers, open-label, single arm study that investigated the impact of a state-of-the-art PCI strategy on clinical outcomes in patients with TVD (454 patients with 1,559 lesions). The relationships between post-procedural MSA and lesion-level outcomes at 2 years were investigated. Clinical events adjudicated per patient by clinical event committee were assessed per lesion. Lesion-oriented composite endpoint (LOCE) was defined as the composite of cardiac death, target-vessel myocardial infarction, and ischemia-driven target lesion revascularization.

Results:
Eight hundred and nineteen lesions with post-procedural MSA available in 367 patients were included in the analysis. The post-procedural MSA per lesion was divided into terciles (smallest tercile: ≤5.0 mm^2, intermediate tercile: 5.0–6.7 mm^2, and largest tercile: >6.7 mm^2). LOCE was observed in 16/288 (5.6%), 15/265 (5.7%), and 8/266 (3.0%) (P = 0.266). Target lesion revascularization (TLR) was observed in 16/288(5.6%), 12/265 (4.5%), and 4/266 (1.5%) (P = 0.042). The multivariate analysis demonstrated that smaller post-procedural MSA, as well as creatinine clearance, history of previous stroke, chronic total occlusion, and lesion SYNTAX Score was an independent predictor of TLR.

Conclusions:
In the SYNTAX II trial, larger post-procedural MSA was independently associated with the lower rate of TLR at 2 years.

Introduction

The SYNTAX II trial has shown that, in patients with three-vessel disease, contemporary PCI strategy, in which target lesions were assessed with coronary physiology approach and treated with the use of thin-strut drug-eluting stent (DES), was associated with improved clinical results compared with patients from the SYNTAX I PCI cohort.[1,2] In the SYNTAX II trial, protocol-mandated post-procedural intravascular ultrasound (IVUS) assessment was used to optimize stent expansion and apposition based on MUSIC criteria.[3]

IVUS has an advantage of measuring luminal dimensions more precisely than angiography especially when the lesion is eccentric.[4] A growing body of evidence suggests that DES implantation with IVUS guidance in complex anatomical subsets may contribute to better patient outcomes. Specifically, a meta-analysis of IVUS-guidance of DES implantation in almost 20,000 subjects has reported significant reductions in stent thrombosis and mortality.[5,6]

There have been several reports showing the predictive value of post-procedural minimum stent area (MSA) measured by IVUS on the incidence of restenosis.[7,8] However, these studies were conducted in patients with simple lesion characteristics excluding chronic total occlusion (CTO) or long lesions. Although there has been an attempt to elucidate the impact of post-procedural MSA in more complex anatomy,[9] to the best of our knowledge, the impact of post-procedural MSA on clinical outcomes has not yet been extensively studied in patients with three-vessel disease. It is also unclear whether MSA still has a predictive value of clinical events in lesions treated with the contemporary PCI strategy. The aim of this report is to evaluate the IVUS parameters (MSA, expansion index, and stent symmetry) that best predicted clinical events at 2-year follow-up after PCI in patients with three-vessel disease, eventually focusing on MSA.

Materials and Methods

Patient population and protocol

SYNTAX II is a multicenter, all-comers, open label, single-arm study which included patients with de novo three-vessel disease. Patients were enrolled in 22 interventional cardiology centers from four European countries between February 2014 and November 2015. The study design has been described previously.[10] Briefly, patients with de novo three-vessel disease with no left main involvement were screened by the local heart team (interventional cardiologist and cardiac surgeon). All site-reported, anatomical SYNTAX scores were eligible for initial screening.[11] Eligible patients had a SYNTAX score II (site-reported) with an equipoise recommendation between CABG and PCI based on 4-year mortality.[12] SYNTAX II was an investigator-initiated study, sponsored by the European Cardiovascular Research Institute (ECRI, Rotterdam, the Netherlands) with unrestricted research grants from Volcano and Boston Scientific. The grant givers were not involved in data collection, data interpretation or writing of the manuscript. The local ethics committee approved the study in all participating sites. All the enrolled patients signed written informed consent. This IVUS sub study is a post-hoc analysis of the SYNTAX II trial.

Procedural characteristics

Target lesions were assessed using a hybrid coronary physiology approach [Instantaneous wave-free ratio (Volcano Corporation) and fractional flow reserve (iFR/FFR)] to define the appropriateness of revascularization based on the presence of ischemia. An iFR <0.86 indicated need for revascularization, an iFR between 0.86 and 0.93 required decision making based on FFR, and an iFR >0.93 indicated deferral of PCI.[10] The thin-strut (≤81 μm) bioabsorbable abluminal polymer-coated SYNERGY DES (Boston Scientific, Natick, MA, USA) eluting everolimus was implanted according to routine local clinical practice. The use of SYNERGY DES was supported by the favorable results of the EVOLVE II pivotal and the BIO-RESORT all-comer trials.[13,14]

IVUS protocol and analysis

Pre-procedural IVUS was used at the discretion of the operator. Post-procedural IVUS assessment was mandatory to optimize stent apposition, expansion and symmetry based on MUSIC criteria.[3] Mechanical IVUS catheters (45 MHz Revolution® Rotational Imaging Catheter / Volcano Therapeutics or 40 MHz Atlantis™ SR Pro or SR Pro2 Imaging Catheter or Opticross™ / Boston Scientific Corp) or phased array IVUS catheters (20 MHz EagleEye® Platinum Digital IVUS Catheter / Volcano Therapeutics) was used to guide SYNERGY implantation. Use of either motorized or manual IVUS pullback was allowed, although motorized pullback was recommended. The results of final IVUS pullback: presence of malapposition; numerical values of MSA; minimum and maximum lumen diameter within the stent; proximal and distal reference maximum lumen area (within 5 mm of the stent edge) were reported by the sites in the electronic case report form (eCRF). Reference lumen area was defined as an average of proximal and distal reference maximum lumen area. Expansion index was calculated as MSA divided by reference lumen area. Stent symmetry was defined as minimum divided by maximum lumen diameter throughout the pullback within the stented segment.[3]

Endpoint definition

The study population of the present study is non-left main (non-LM) lesions with post-procedural MSA measurement. Lesion-oriented composite endpoint (LOCE) was defined as a composite of cardiac death, target-vessel myocardial infarction (TVMI), and ischemia-driven target lesion revascularization (ID-TLR). Cardiac death was defined as any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause were classified as cardiac death. The definition of MI was reported previously.[2] TLR was defined as any repeat percutaneous intervention of the target lesion (a segment from 5 mm proximal to the stent and to 5 mm distal to the stent) or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. Target lesion revascularization (TLR) was considered as ischemia-driven when repeat percutaneous intervention or bypass surgery was 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 lesion.; 3. ischemic symptoms referable to the target lesion. Definite or probable stent thrombosis (ST) was adjudicated according to the Academic Research Consortium definitions.[15] All clinical outcomes were adjudicated by an independent clinical event committee (CEC) at patient level for the original SYNTAX II trial. For the present analysis, all the available information including angiogram at event and the site reports in eCRF were reviewed and evaluated independently by 2 interventional cardiologists (Y.K. and N.K.), blinded to

baseline clinical and procedural characteristics, as well as to post-PCI MSA value. Clinical events per patient were adjudicated per lesion as lesion-related or not lesion-related. In case the patient was adjudicated as cardiac death at follow-up, this was judged as an event related to each lesion initially treated. In case of disagreement, angiogram at event and the site reports in eCRF were reviewed by a third assessor and a 2:1 agreement was achieved.

Statistical methods

Categorical variables were summarized as frequencies and percentages and were compared between groups using chi-square statistics or Fisher's exact test, as appropriate. Continuous variables were presented as mean ± SD and compared between groups using 2-tailed, unpaired *t* tests. Differences were considered to be statistically significant when the p value was <0.05.

Clinical endpoints at 2 years were analyzed by log-rank test according to terciles of post-procedural MSA, expansion index, and stent symmetry.

Multivariate Cox regression analysis was used to determine predictors of TLR. All patient, lesion, and IVUS covariates listed in **Table 1** and **2** were modeled first univariately and multivariately using variables with univariate p value <0.05. Independency among lesions were assumed throughout the analyses.[16] However, as a sensitivity analysis, robust sandwich variance estimator was used in the multivariate model,[17] and the results were compared with the former results of conventional Cox regression.

Receiver-operator characteristic (ROC) analysis was used to measure the ability of post-procedural MSA to discriminate between those subjects with and without TLR. The ROC curves plot the probability of detecting true positive fraction (sensitivity) against false positive fraction (1-specificity) of 2-year clinical events over the entire range of observed MSAs. In general: 1) ROC = 0.5 suggests no discrimination; 2) 0.7 ≤ ROC < 0.8 is considered acceptable discrimination; 3) 0.8 ≤ ROC < 0.9 is considered excellent discrimination; and 4) ROC ≥ 0.9 is considered outstanding discrimination. In order to determine the IVUS MSA cut-off point value for each treatment group that best predicted TLR, the cross point of sensitivity and specificity curves was used. Statistical tests were performed using SPSS version 24.0.0.2 and R version 3.4.3.

Results

Patient baseline characteristics

Out of 454 patients included in the SYNTAX II trial, 819 non-LM lesions with post-procedural MSA measurement in 367 patients with at least one post-procedural MSA available were included in the analysis. (**Figure 1**). Patient characteristics comparing patients with post-procedural MSA measurement with those with no post-procedural MSA measurements at all are shown in **Table 1**. Baselines demographics are comparable except for current smoking status and unstable angina being more frequent in patients who had at least one lesion with post-procedural MSA measurement; history of previous MI and hyperlipidemia being more frequent in patients without any post-procedural MSA measurement.

Table 1. Baseline clinical characteristics in patients with post-procedural IVUS MSA measurement and those without IVUS MSA measurement.

	Patients with MSA measurement n=367	Patients without any MSA measurement n=87	P value
Age (years)	66.5±9.9 (367)	67.5±8.7 (87)	0.404
Male	93.2% (342/367)	93.1% (81/87)	1.000
Body mass index (kg/m^2)	28.8±4.7 (367)	29.5±4.3 (82)	0.251
Diabetes mellitus type I or II	29.7% (108/364)	32.9% (27/82)	0.595
Insulin treated	8.5% (31/364)	8.5% (7/82)	1.000
Oral medication	19.0% (69/364)	22.0% (18/82)	0.539
Diet only	1.9% (7/364)	2.4% (2/82)	0.673
Current smoker	16.7% (59/354)	6.2% (5/81)	0.015
Previous MI	10.9% (40/366)	19.8% (16/81)	0.040
Previous stroke	5.4% (20/367)	6.1% (5/82)	0.791
Hypertension	75.1% (275/366)	85.2% (69/81)	0.058
Hyperlipidemia	75.3% (271/360)	86.4% (70/81)	0.039
Creatinine clearance (ml/min)	83.2±27.2 (367)	76.9±25.5 (87)	0.050
Ejection fraction (%)	58.5±8.2 (367)	56.6±8.5 (87)	0.053
Peripheral vascular disease	8.2% (30/367)	5.7% (5/87)	0.654
COPD	10.9% (40/367)	10.3% (9/87)	1.000
Clinical presentation			
Silent ischemia	5.7% (21/367)	10.3% (9/87)	0.041
Stable angina	66.8% (245/367)	73.6% (64/87)	
Unstable angina	27.5% (101/367)	16.1% (14/87)	
Anatomic SYNTAX Score	20.4±6.4 (367)	20.0±5.8 (87)	0.580
SYNTAX Score II PCI	29.9±8.6 (367)	31.3±8.5 (87)	0.199
Predicted 4-year mortality PCI (%)	8.8±8.8 (367)	9.6±8.5 (87)	0.434
SYNTAX Score II CABG	28.9±10.5 (367)	29.9±9.9 (87)	0.421
Predicted 4-year mortality CABG (%)	8.9±9.1 (367)	9.4±9.9 (87)	0.623

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; IVUS = intravascular ultrasound; MI = myocardial infarction; MSA = minimum stent area; PCI = percutaneous coronary intervention.

Table 2. Lesion characteristics and post-procedural IVUS findings.

	% (n) or mean±SD (n)
Lesion characteristics	
Vessel Treated	
RCA	25.5 % (209/819)
LAD	44.7 % (366/819)
LCx	29.7 % (243/819)
Bifurcation	15.4 % (126/819)
Total Occlusion	26.0 % (213/819)
Post-dilatation done based on IVUS findings	39.8 % (326/819)
Post-procedural IVUS findings	
Minimum Stent Area (mm^2)	6.15±2.24 (819)
Reference Lumen Area (mm^2)	7.30±2.95 (810)
Expansion Index	0.92±0.37 (810)
Area Stenosis (%)	8.9±36.8 (810)
Minimum Lumen Diameter (mm)	2.65±0.70 (814)
Maximum Lumen Diameter (mm)	3.48±1.18 (816)
Stent Symmetry	0.79±0.15 (814)
Total Stent Length (mm)	32.45±19.65 (819)
Any Malapposition	6.8 % (56/819)

IVUS = intravascular ultrasound; LAD = left anterior descending artery; LCx = left circumflex; MLA = minimum lumen area; RCA = right coronary artery; SD = standard deviation.

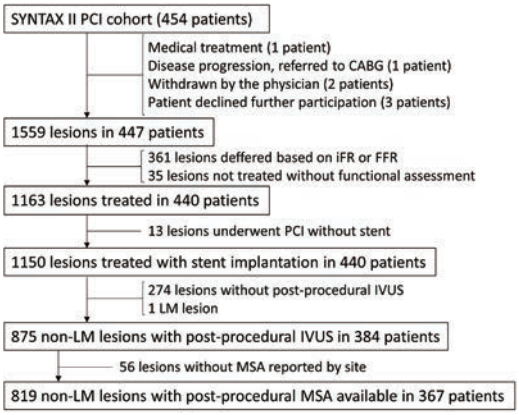


Figure 1. Flowchart of the IVUS MSA sub-study.
CABG = coronary-artery bypass grafting, IVUS = intravascular ultrasound, LM = left main; MSA = minimum stent area, PCI = percutaneous coronary intervention.

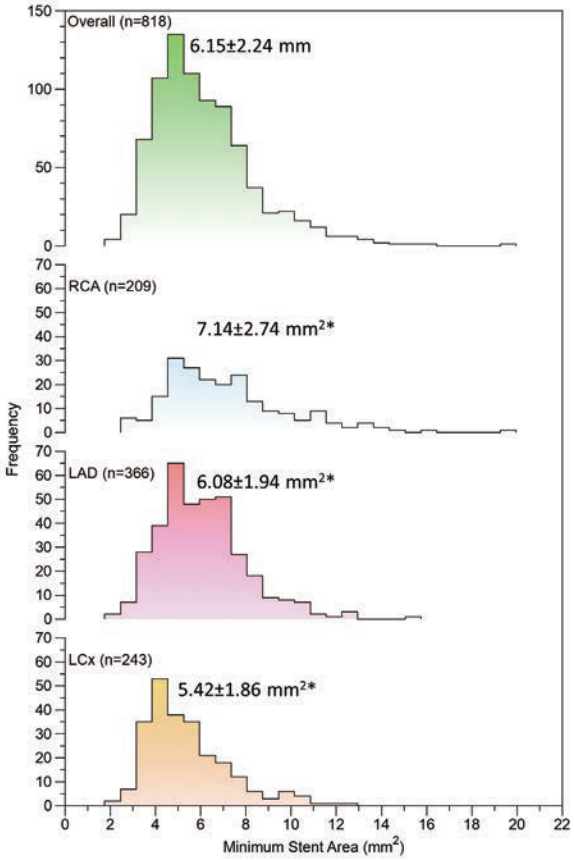


Figure 2. Frequency of minimum stent area post-procedure according to vessel location.
*Overall P value was <0.001. P values for any combinations of comparison (i.e., RCA vs. LAD, RCA vs. LCx, and LAD vs. LCx) were <0.001.

Post-procedural IVUS results

Lesion characteristics and post-procedural IVUS findings are tabulated in **Table 2**. Of note, IVUS findings led to post-dilatation in 39.8% (326/819) of lesions. As a result, post-procedural final MSA was 6.15±2.24 mm^2 with good expansion (expansion index 0.92±0.37) and stent symmetry (0.79±0.15). Any malapposition was found in 6.8% (56/819). Histograms of post-procedural MSA according to vessel location are shown in **Figure 2**. Post-procedural MSA of lesions in RCA was larger than those in LAD; and post-procedural MSA of lesions in LAD was larger than those in LCx.

Table 3. Frequency of clinical events per lesion up to 2 years according to terciles of IVUS metrics.

	Smallest MSA tercile (≤5.0 mm^2)	Intermediate MSA tercile (5.0-6.7 mm^2)	Largest MSA tercile (>6.7 mm^2)	P value
LOCE	16 / 288 (5.6 %)	15 / 265 (5.7 %)	8 / 266 (3.0 %)	0.266
Cardiac death	3 / 288 (1.0 %)	4 / 265 (1.5 %)	4 / 266 (1.5 %)	0.858
TVMI	4 / 288 (1.4 %)	5 / 265 (1.9 %)	1 / 266 (0.4 %)	0.269
TLR	16 / 288 (5.6 %)	12 / 265 (4.5 %)	4 / 266 (1.5 %)	0.042
ID-TLR	13 / 288 (4.5 %)	11 / 265 (4.2 %)	4 / 266 (1.5 %)	0.112
Definite/Probable ST	1 / 288 (0.3 %)	4 / 265 (1.5 %)	2 / 266 (0.8 %)	0.322

	Smallest Expansion Index tercile (≤0.76)	Intermediate Expansion Index tercile (0.76-0.96)	Largest Expansion Index tercile (>0.96)	P value
LOCE	11 / 271 (4.1 %)	14 / 270 (5.2 %)	14 / 269 (5.2 %)	0.798
Cardiac death	3 / 271 (1.1 %)	3 / 270 (1.1 %)	5 / 269 (1.9 %)	0.692
TVMI	4 / 271 (1.5 %)	6 / 270 (2.2 %)	0 / 269 (0.0 %)	0.061
TLR	9 / 271 (3.3 %)	12 / 270 (4.4 %)	11 / 269 (4.1 %)	0.803
ID-TLR	8 / 271 (3.0 %)	11 / 270 (4.1 %)	9 / 269 (3.3 %)	0.780
Definite/Probable ST	1 / 271 (0.4 %)	4 / 270 (1.5 %)	2 / 269 (0.7 %)	0.365

	Smallest Stent Symmetry tercile (≤0.74)	Intermediate Stent Symmetry tercile (0.74-0.86)	Largest Stent Symmetry tercile (>0.86)	P value
LOCE	17 / 278 (6.1 %)	15 / 276 (5.4 %)	7 / 260 (2.7 %)	0.148
Cardiac death	5 / 278 (1.8 %)	4 / 276 (1.4 %)	2 / 260 (0.8 %)	0.577
TVMI	7 / 278 (2.5 %)	3 / 276 (1.1 %)	0 / 260 (0.0 %)	0.028
TLR	13 / 278 (4.7 %)	12 / 276 (4.3 %)	7 / 260 (2.7 %)	0.448
ID-TLR	12 / 278 (4.3 %)	11 / 276 (4.0 %)	5 / 260 (1.9 %)	0.256
Definite/Probable ST	3 / 278 (1.1 %)	3 / 276 (1.1 %)	1 / 260 (0.4 %)	0.601

ID-TLR = ischemia-driven target lesion revascularization, LOCE = lesion-oriented composite endpoint, MSA = minimum stent area, ST = stent thrombosis, TLR = (all) target lesion revascularization, TVMI = target-vessel myocardial infarction.

Clinical outcomes stratified by terciles of IVUS measurements.

Table 3 shows clinical endpoints at 2 years according to terciles of post-procedural MSA, expansion index, and stent symmetry.

A graded relationship that a lower tercile of MSA has more events was present between MSA and the 2-year TLR and ID-TLR. However, statistical significance among MSA terciles was only retained in the relationships between MSA terciles and TLR (p=0.042). **Figure 3** shows Kaplan-Meier cumulative incidence of TLR according to MSA terciles.

When lesions were divided into terciles of expansion index, there was no difference for clinical endpoints amongst the terciles.

When lesions were divided into terciles of stent symmetry, a graded relationship that a lower tercile of stent symmetry has more events was present in LOCE, cardiac death, TVMI, TLR, ID-TLR. However, statistical significance was only retained in the relationships between stent symmetry terciles and TV-MI (p=0.028).

The details of four non-ID-TLR cases were shown in **Supplementary Table 1**. Interestingly, three of them were categorized in the smallest MSA tercile.

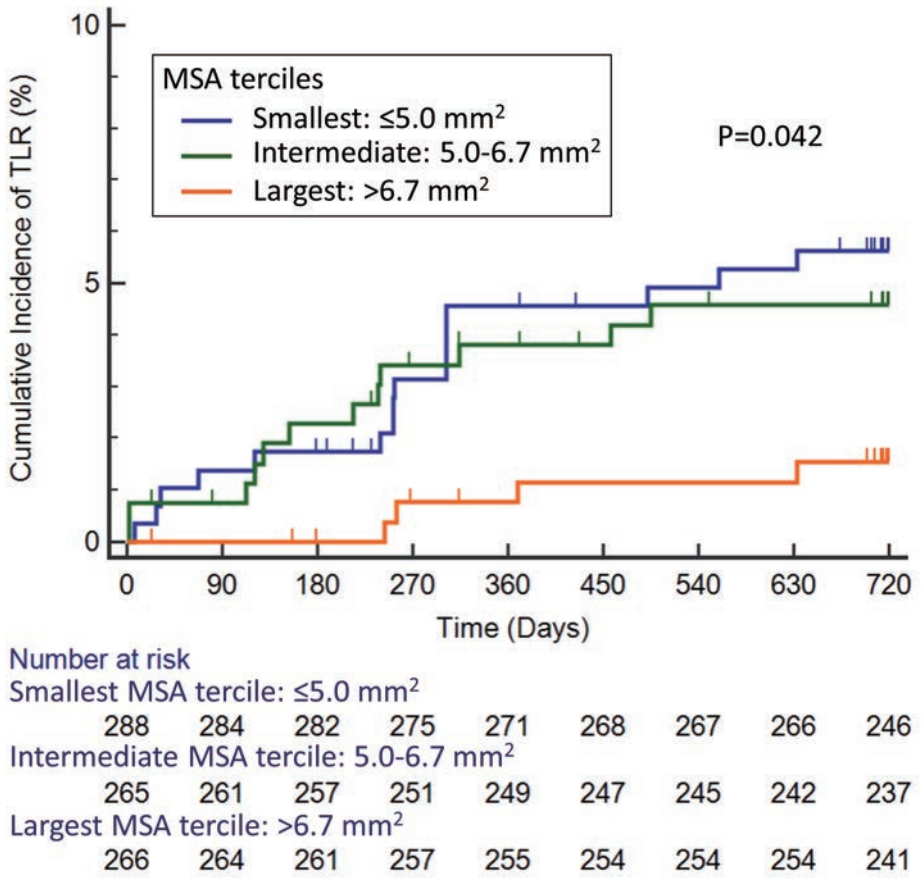


Figure 3. Kaplan-Meier cumulative incidence of TLR according to post-procedural MSA terciles.
MSA = minimum stent area, TLR = target lesion revascularization.

Independent predictors of target lesion revascularization

The result of univariate Cox regression analysis predicting TLR up to 2 years is tabulated in **Table 4**. Although gender showed significance in univariate analysis, it was not entered into

Table 4. Univariate Cox regression analysis per lesion predicting target lesion revascularization up to 2 years.

	HR	95% CI				P value
Patient characteristics						
Age (per year)	1.04	(	1.00	,	1.08	) 0.064
Male	0.31	(	0.13	,	0.71	) 0.006
Body mass index (per kg/m^2)	1.06	(	0.99	,	1.13	) 0.114
Diabetes mellitus type I or II	0.55	(	0.23	,	1.33	) 0.184
Current smoker	0.57	(	0.17	,	1.87	) 0.350
Previous MI	0.56	(	0.13	,	2.34	) 0.425
Previous stroke	3.23	(	1.13	,	9.22	) 0.028
Hypertension	1.22	(	0.53	,	2.82	) 0.641
Hyperlipidemia	1.50	(	0.62	,	3.65	) 0.370
Creatinine clearance (per 10 ml/min decrease)	1.23	(	1.08	,	1.43	) 0.003
Ejection fraction (per %)	0.99	(	0.95	,	1.04	) 0.790
Peripheral vascular disease	1.25	(	0.38	,	4.09	) 0.717
COPD	2.18	(	0.90	,	5.28	) 0.086
Clinical presentation (Reference: silent ischemia)						
Stable Angina	2.25	(	0.30	,	16.70	) 0.427
Unstable Angina	2.13	(	0.27	,	16.83	) 0.473
Lesion characteristics						
Vessel location						
RCA	0.66	(	0.27	,	1.61	) 0.363
LAD	1.43	(	0.71	,	2.87	) 0.311
LCx	0.92	(	0.43	,	1.99	) 0.832
Bifurcation	2.23	(	1.03	,	4.81	) 0.042
Total Occlusion	2.27	(	1.13	,	4.56	) 0.022
Lesion SYNTAX Score (per 1 increase)	1.15	(	1.05	,	1.25	) 0.001
Pre-dilatation performed	1.43	(	0.44	,	4.71	) 0.553
Post-dilatation done based on IVUS findings	1.18	(	0.59	,	2.38	) 0.637
Post-procedural IVUS findings						
Minimum Stent Area (per mm^2 decrease)	1.27	(	1.03	,	1.54	) 0.023
Reference Lumen Area (per mm^2)	0.89	(	0.78	,	1.03	) 0.108
Expansion Index (per 0.1)	1.00	(	0.90	,	1.10	) 0.937
Minimum Lumen Diameter (per mm)	1.36	(	0.93	,	1.98	) 0.113
Maximum Lumen Diameter (per mm)	1.17	(	0.97	,	1.41	) 0.107
Stent Symmetry (per 0.1)	0.90	(	0.71	,	1.14	) 0.370
Total Stent Length (per mm)	1.01	(	0.99	,	1.02	) 0.358
Any Malapposition	1.50	(	0.46	,	4.93	) 0.502

CABG = coronary artery bypass graft, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IVUS = intravascular ultrasound, LAD = left anterior descending artery, LCX = left circumflex, MI = myocardial infarction, PCI = percutaneous coronary intervention, and RCA = right coronary artery.

the subsequent multivariate model considering the fact that female sex only accounts for 6.8% of the study population. Two separate multivariate models (**Model A** and **B** in **Table 5**) were constructed as lesion SYNTAX Score includes CTO and bifurcation in its components. Both models demonstrated that smaller MSA, as well as creatinine clearance was an independent predictor of TLR up to 2 years, while CTO and history of previous stroke in

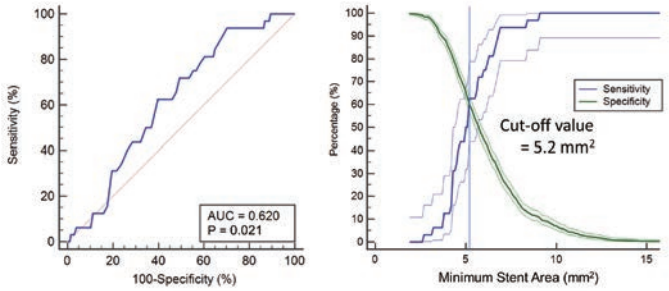


Figure 4. Optimal MSA to predict TLR.
(Left) Receiver-operator characteristic (ROC) analysis of the minimum stent area (MSA) for target lesion revascularization (TLR). The c-statistic was 0.620 (95% confidence interval: 0.537-0.703, p=0.021). (Right) Sensitivity and specificity curves for MSA predicting TLR. Thin lines represent 95% confidence interval. The single post-procedural MSA value that best separated patients with TLR from those with no TLR was 5.2 mm2.

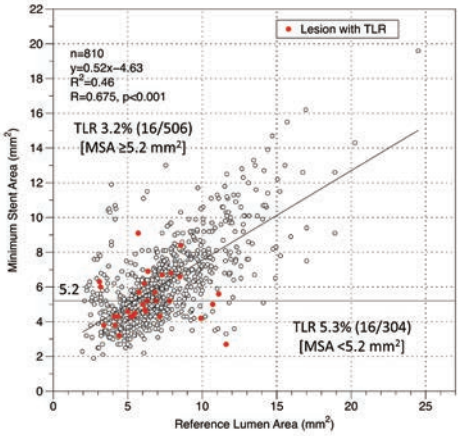


Figure 5. Distribution of TLR as a function of post-procedural MSA and reference lumen area.
The cut point of MSA: 5.2 mm2 was derived from ROC analysis in Figure 4. MSA = minimum stent area, TLR = target lesion revascularization.

Table 5. Multivariate Cox regression analysis per lesion predicting target lesion revascularization up to 2 years.

Model A

	HR	95% CI				P value
Minimum Stent Area (per 1 mm2 decrease)	1.24	(	1.01	,	1.53	) 0.044
Creatinine clearance (per 10 ml/min decrease)	1.23	(	1.06	,	1.43	) 0.006
Previous Stroke	3.01	(	1.05	,	8.59	) 0.040
Chronic Total Occlusion	2.07	(	1.02	,	4.20	) 0.043
Bifurcation	1.95	(	0.89	,	4.27	) 0.095

Model B

	HR	95% CI				P value
Minimum Stent Area (per 1 mm² decrease)	1.28	(	1.01	,	1.61	) 0.041
Creatinine clearance (per 10 ml/min decrease)	1.28	(	1.08	,	1.51	) 0.005
Previous Stroke	2.48	(	0.74	,	8.28	) 0.141
Lesion SYNTAX Score (per 1 increase)	1.19	(	1.09	,	1.30	) <0.001

CI = confidence interval, HR = hazard ratio.

Model A and lesion SYNTAX Score in Model B were additional independent predictors. The analysis with robust sandwich estimator similarly confirmed that smaller MSA was an independent predictor of TLR. (**Model A'** and **B'** in **Supplementary Table 2**).

Optimal MSA threshold to predict target lesion revascularization

The single post-procedural MSA value that best separated lesions with TLR from those with no TLR was 5.2 mm^2 (**Figure 4**). Using this cut-point revealed that the rate of 2-year TLR was 5.2% for lesions with an IVUS MSA <5.2 mm^2 compared with 3.1% in lesions with an IVUS MSA ≥5.2 mm^2 (p=0.132); and the sensitivity and specificity were 50.0% and 63.2%, respectively. **Figure 5** shows distribution of TLR as a function of post-procedural MSA and reference lumen area. The reference lumen area was 5.64±1.82, 6.73±2.08, and 9.66±3.17 mm^2 in lowest, intermediate, and largest MSA terciles, respectively (p<0.001). Although there was a linear relationship between post-procedural MSA and reference lumen area, only post-procedural MSA was retained in the multivariate model.

Discussion

The current analysis explores the IVUS predictors of 2-year clinical events after thin-strut biodegradable polymer drug-eluting stent implantation in three-vessel disease and, in particular, the relationship between post-procedural IVUS MSA and TLR in more than 800 lesions. The main findings are as follows: 1) Among post-procedural IVUS predictors including MSA, expansion index, and stent symmetry, MSA was the most predictive for TLR at 2 years. 2) Multivariate analysis revealed that smaller MSA, creatinine clearance, history of previous stroke, CTO and lesion SYNTAX Score were independent predictors of TLR up to 2 years. 3) A MSA threshold of 5.2 mm^2 or less predicted TLR at 2 years by ROC analysis.

Although expansion index, the relativity of MSA to the reference area, is another parameter of interest, the present analysis showed absolute value of MSA had more predictive value for TLR than expansion index. However, post-intervention IVUS may also help to achieve optimal stent expansion after thin-strut DES implantation by reducing underexpansion-related complications such as early/late thrombosis and restenosis.[18]

The importance of post-procedural MSA after implantation of DES

Compared with first generation DES, newer generation DES reduce stent thrombosis and improve clinical outcomes.[19] This is largely attributed to improvement in the design of more biocompatible polymers, biodegradable polymers, -limus based drugs, thinner stent struts through the incorporation of metallic alloys with greater radial strength.[20-22]

Doi et al. reported the optimal thresholds of post-intervention IVUS MSA that best predicted restenosis at 9 months were 5.7 mm^2 for Taxus paclitaxel-eluting stent.[7] Another study by Song et al. suggested 5.5 mm^2 for Cypher sirolimus-eluting stent, 5.3 mm^2 for Endeavor Resolute zotarolimus-eluting stent, and 5.4 mm^2 for Promus everolimus-eluting stent as thresholds to predict in-stent restenosis at 9 months.[23] Our finding that smaller post-procedural MSA predicts clinical outcomes is in line with their findings. However, we find that the threshold to predict TLR from the present study, is somewhat lower than previously-described thresholds, at 5.2 mm^2. There are multiple factors which potentially could explain the difference in threshold: difference in endpoint (angiographic in-stent

restenosis (≥50%) at 9 months vs. TLR at 2 years), newer generation of DES in the present study, and the difference in population included for analysis.

Is a MSA of 5.2 mm^2 large enough in all situations?

The Kaplan-Meier curves of the smallest (<5.0 mm^2) and intermediate (5.0-6.7 mm^2) MSA terciles overlap while the largest MSA tercile (>6.7 mm^2) had a lower rate of TLR (**Figure 3**). On the other hand, Sensitivity/specificity curve analysis of TLR identified 5.2 mm^2 as a threshold of MSA that best separates the subsequent presence of TLR from no TLR. The Kaplan-Meier analysis according to MSA ≤ 5.2 mm^2; MSA >5.2 mm^2 in intermediate MSA tercile (i.e., 5.2-6.7 mm^2); and the largest MSA tercile (>6.7 mm^2) showed a good separation of all the three curves (**Supplementary Figure 1**). For treatment guidance, a post-procedural MSA threshold of 5.2 mm^2 would be better than the cut-offs based on MSA terciles. However, this cut-off was selected from the pooled MSA values observed in the current trial and, therefore, cannot be generalized. There was a significant difference of MSA according to vessel location (**Figure 2**). Indeed, a report from EXCEL trial suggested that final MSA may impact long-term clinical outcomes after PCI of left main coronary artery disease,[9] with a proposed cut-off of 9.8 mm^2. The large difference in cut-off value can be explained by lesion location (left main [LM] or non-LM). However, studies have consistently showed a relationship between smaller post-procedural MSA and restenosis or clinical event at follow-up.[7,23-26]

Comparison of patient and lesion characteristics among MSA terciles

Supplementary Table 3 shows comparison of patient and lesion characteristics among MSA terciles. Regarding patient characteristics, previous history of MI was significantly less frequent in patients in the largest MSA tercile. Regarding lesion characteristics, the lesions in the smallest MSA tercile had significantly smaller reference lumen area, expansion index, and stent symmetry; higher area stenosis post-procedure; and longer stent length. Although the significant impact of these variables on TLR was not demonstrated in the regression analysis, more aggressive post-dilatation especially in small vessels may be encouraged to achieve better stent expansion, symmetry, and less area stenosis post-procedure.

Other predictors of TLR

Creatinine clearance has been shown to be predictive of clinical outcomes in logistic clinical SYNTAX,[27] and SYNTAX score II.[12] History of previous stroke was also identified as an independent predictor of TLR, which is in line with the previous report.[28] Identification of these patients in a daily practice may provide an opportunity to reduce their excess risk by intensive secondary prevention efforts.

Pre-procedural CTO in the lesion was identified as another independent predictor of TLR in the present study. This is in line with a study by Farooq et al. showing patients with total occlusion were associated with higher residual SYNTAX score, suggesting worse outcome.[29] A meta-analysis of 4394 patients suggests that the risk of restenosis following DES for CTO was 10.7%.[30] Over the last 10 years, the practice of CTO recanalization has been largely modified by the systematization in the approach to CTO recanalization and the development of new devices, however, the current study suggests that it still remains the major determinants of patient prognosis.

While worse clinical outcomes in patients with higher SYNTAX Score was previously shown,[1] the present analysis showed that SYNTAX Score per lesion was an independent

predictor of TLR in addition to post-procedural MSA. The risk stratification by pre-procedural anatomical assessment is still of importance in the contemporary PCI as well as post-procedural MSA assessment.

Study limitations

First, the results obtained are limited to vessel diameters and stents (SYNERGY DES) used in the SYNTAX II trial. Second, pre-procedural IVUS was not mandatory and the results were not collected. Third, there were 23.8% (274/1150) of lesions in which post-procedural IVUS was not performed, which may cause potential bias. The reason for this was not available in eCRF. Fourth, the post-procedural IVUS measurements were site-reported and not analyzed by the core lab, which may result in bias. Fifth, limited number of patients did not allow us to analyze relationship between MSA and clinical outcomes at the patient level (i.e., minimum MSA per patient and clinical outcomes). Sixth, female only accounts for 6.8% presumably due to screening by SYNTAX Score II,[12] which limits generalizability. Seventh, the low number of events per predictor may cause overfitting of the multivariate model, although 5 events per predictor could be acceptable.[31] Eighth, although post-procedural MSA was an independent predictor of TLR in the present analysis, the c-statistic in the ROC analysis was relatively low. Ninth, the use of iFR/FFR and IVUS in most patients is not yet a routine approach for most operators and may have lowered the incidence of TLR. Finally, this was a post-hoc analysis and the results are therefore hypothesis-generating.

Conclusion

In the IVUS sub-study of the SYNTAX II trial, post-intervention MSA measured by IVUS could predict TLR at 2 years.

References

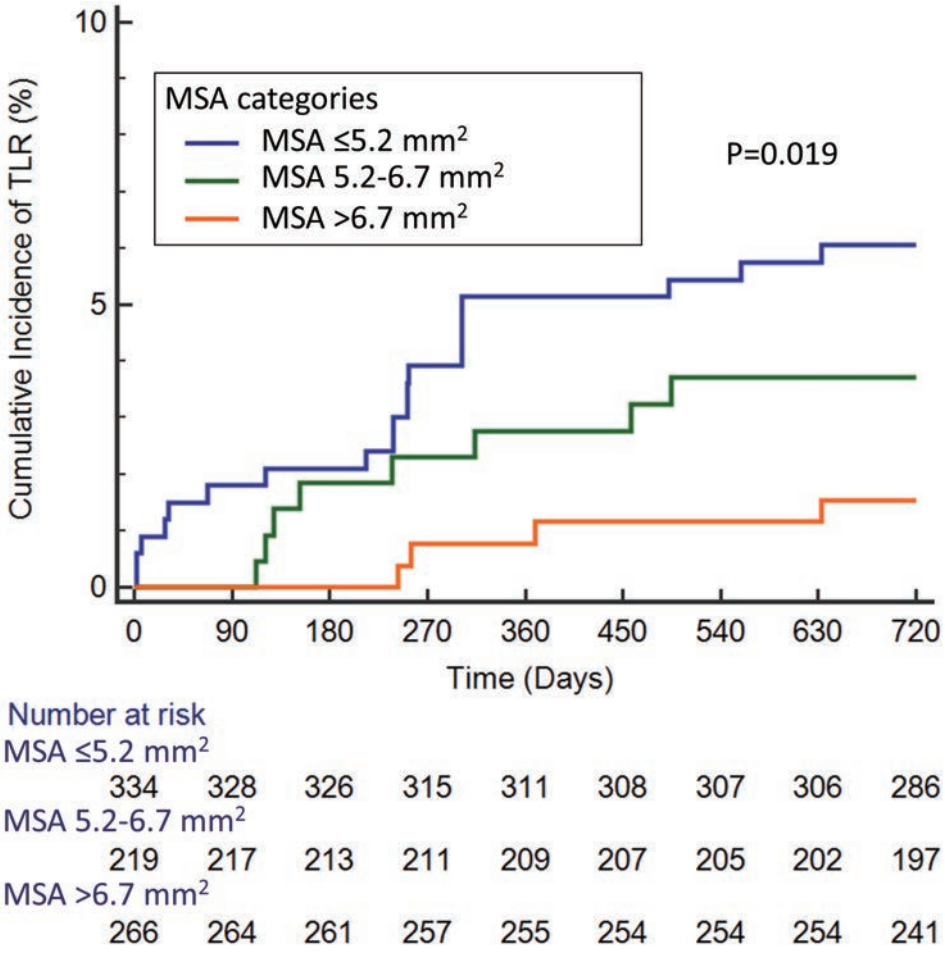
1. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ and others. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360(10):961-72.
2. Escaned J, Collet C, Ryan N, De Maria GL, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I and others. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. Eur Heart J 2017;38(42):3124-3134.
3. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, Colombo A, Hamm C, Bartorelli A, Rothman M and others. 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.
4. von Birgelen C, Kutryk MJ, Gil R, Ozaki Y, Di Mario C, Roelandt JR, de Feyter PJ, Serruys PW. Quantification of the minimal luminal cross-sectional area after coronary stenting by two- and three-dimensional intravascular ultrasound versus edge detection and videodensitometry. Am J Cardiol 1996;78(5):520-5.
5. 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.
6. 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;9(7):891-2.
7. Doi H, Maehara A, Mintz GS, Yu A, Wang H, Mandinov L, Popma JJ, Ellis SG, Grube E, Dawkins KD and others. 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(12):1269-75.
8. Choi SY, Maehara A, Cristea E, Witzenbichler B, Guagliumi G, Brodie B, Kellett MA, Jr., Dressler O, Lansky AJ, Parise H and others. Usefulness of minimum stent cross sectional area as a predictor of angiographic restenosis after primary percutaneous coronary intervention in acute myocardial infarction (from the HORIZONS-AMI Trial IVUS substudy). Am J Cardiol 2012;109(4):455-60.
9. Maehara A, Mintz G, Serruys P, Kappetein A, Kandzari D, Schampaert E, Van Boven A, Horkay F, Ungi I, Mansour S and others. IMPACT OF FINAL MINIMAL STENT AREA BY IVUS ON 3-YEAR OUTCOME AFTER PCI OF LEFT MAIN CORONARY ARTERY DISEASE: THE EXCEL TRIAL. Journal of the American College of Cardiology 2017;69(11 Supplement):963.
10. Escaned J, Banning A, Farooq V, Echavarria-Pinto M, Onuma Y, Ryan N, Cavalcante R, Campos CM, Stanetic BM, Ishibashi Y and others. Rationale and design of the SYNTAX II trial evaluating the short to long-term outcomes of state-of-the-art percutaneous coronary revascularisation in patients with de novo three-vessel disease. EuroIntervention 2016;12(2):e224-34.
11. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T and others. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5(1):50-6.
12. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr., Mack M and others. 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.

13. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, Gin R, Somi S, van Houwelingen KG, Stoel MG and others. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. Lancet 2016;388(10060):2607-2617.
14. Kereiakes DJ, Meredith IT, Windecker S, Lee Jobe R, Mehta SR, Sarembock IJ, Feldman RL, Stein B, Dubois C, Grady T and others. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. Circ Cardiovasc Interv 2015;8(4).
15. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P and others. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.
16. Gibson CM, Kuntz RE, Nobuyoshi M, Rosner B, Baim DS. Lesion-to-lesion independence of restenosis after treatment by conventional angioplasty, stenting, or directional atherectomy. Validation of lesion-based restenosis analysis. Circulation 1993;87(4):1123-9.
17. Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. Journal of the American Statistical Association 1989;84(408):1074-1078.
18. Witzenbichler B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR and others. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. Circulation 2014;129(4):463-70.
19. Navarese EP, Kowalewski M, Kandzari D, Lansky A, Gorny B, Koltowski L, Waksman R, Berti S, Musumeci G, Limbruno U and others. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. Open Heart 2014;1(1):e000064.
20. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368(3):254-65.
21. Kandzari DE, Mauri L, Koolen JJ, Massaro JM, Doros G, Garcia-Garcia HM, Bennett J, Roguin A, Gharib EG, Cutlip DE and others. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet 2017;390(10105):1843-1852.
22. de Winter RJ, Katagiri Y, Asano T, Milewski KP, Lurz P, Buszman P, Jessurun GAJ, Koch KT, Troquay RPT, Hamer BJB and others. A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III): a randomised, single-blind, multicentre, non-inferiority, phase 3 trial. Lancet 2018;391(10119):431-440.
23. Song HG, Kang SJ, Ahn JM, Kim WJ, Lee JY, Park DW, Lee SW, Kim YH, Lee CW, Park SW and others. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. Catheter Cardiovasc Interv 2014;83(6):873-8.
24. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y and others. 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(11):1959-63.
25. Hong MK, Mintz GS, Lee CW, Park DW, Choi BR, Park KH, Kim YH, Cheong SS, Song JK, Kim JJ and others. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. Eur Heart J 2006;27(11):1305-10.
26. Morino Y, Honda Y, Okura H, Oshima A, Hayase M, Bonneau HN, Kuntz RE, Yock PG, Fitzgerald PJ. An optimal diagnostic threshold for minimal stent area to predict target lesion revascularization following stent implantation in native coronary lesions. Am J Cardiol 2001;88(3):301-3.

27. Farooq V, Vergouwe Y, Raber L, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M and others. 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.
28. Dhamoon MS, Tai W, Boden-Albala B, Rundek T, Paik MC, Sacco RL, Elkind MS. Risk of myocardial infarction or vascular death after first ischemic stroke: the Northern Manhattan Study. Stroke 2007;38(6):1752-8.
29. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E and others. 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(2):141-51.
30. Colmenarez HJ, Escaned J, Fernandez C, Lobo L, Cano S, del Angel JG, Alfonso F, Jimenez P, Banuelos C, Gonzalo N and others. Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55(17):1854-66.
31. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165(6):710-8.

Supplementary Material

Supplementary Figure 1. Kaplan-Meier cumulative incidence of TLR in post-procedural MSA ≤ 5.2; 5.2-6.7; and >6.7 mm^2.
MSA = minimum stent area, TLR = target lesion revascularization.



Supplementary Table 1. Details of non-ischemia-driven target lesion revascularization.

Patient ID	Lesion Location	MSA after index procedure (mm^2)	Angina pectoris	Positive functional diagnostic test	Diameter Stenosis of the lesion	Comment
ES001-1007	#7	4.5	No	No	<50%	It appears that the operators considered the stent was crumpled distally at the end of the procedure. A further PCI was performed the next day with the new stent implantation at the distal edge.
ES001-1023	#7	6.3	Yes	No	<50%	Recurrent angina pectoris presumably related to target vessel. QCA on site showed DS 41%.
GB014-1020	#12b	4.2	No	No	<50%	POBA was performed in 12b in the index procedure. Now OM was stented.
GB014-1054	#6, #7	3.8	No	No	<50%	Malapposition seen on IVUS.

DS = diameter stenosis, IVUS = intravascular ultrasound, MSA = minimum stent area, OM = obtuse marginal, PCI = percutaneous coronary intervention, POBA = plain old balloon angioplasty, and QCA = quantitative coronary angiography.

Supplementary Table 2. Multivariate Cox regression analysis predicting target lesion revascularization up to 2 years with robust sandwich variance estimator to take into account clustering within patient.

Model A'

	HR	95% CI				P value
Minimum Stent Area (per mm^2 decrease)	1.24	(	1.03	,	1.49	) 0.023
Creatinine clearance (per 10 ml/min decrease)	1.23	(	1.00	,	1.52	) 0.055
Previous Stroke	3.01	(	0.78	,	11.58	) 0.109
Chronic Total Occlusion	2.07	(	0.81	,	5.30	) 0.126
Bifurcation	1.95	(	0.90	,	4.22	) 0.088

Model B'

	HR	95% CI				P value
Minimum Stent Area (per mm^2 decrease)	1.28	(	1.02	,	1.59	) 0.033
Creatinine clearance (per 10 ml/min decrease)	1.28	(	1.03	,	1.59	) 0.028
Previous Stroke	2.48	(	0.49	,	12.64	) 0.273
Lesion SYNTAX Score (per 1 increase)	1.19	(	1.08	,	1.31	) 0.001

CI = confidence interval, and HR = hazard ratio.

Supplementary Table 3. Comparison of patient and lesion characteristics among MSA terciles.

	Smallest MSA tercile	Intermediate MSA tercile	Largest MSA tercile	P value*
Patient characteristics	n=125	n=122	n=120	
Age (years)	67.0±9.7	66.3±10.5	66.2±9.5	0.781
Male	93.6% (117/125)	91.0% (111/122)	95.0% (114/120)	0.452
Body mass index (kg/m2)	28.6±4.6	28.9±5.2	29.0±4.3	0.770
Diabetes mellitus type I or II	29.6% (37/125)	30.8% (37/120)	28.6% (34/119)	0.929
Insulin treated	10.4% (13/125)	6.7% (8/120)	8.4% (10/119)	0.577
Oral medication	18.4% (23/125)	21.7% (26/120)	16.8% (20/119)	0.620
Diet only	0.8% (1/125)	2.5% (3/120)	2.5% (3/119)	0.529
Current smoker	12.5% (15/120)	15.3% (18/118)	22.4% (26/116)	0.109
Previous MI	15.2% (19/125)	14.9% (18/121)	2.5% (3/120)	0.001
Previous stroke	4.8% (6/125)	5.7% (7/122)	5.8% (7/120)	0.925
Hypertension	76.0% (95/125)	77.7% (94/121)	71.7% (86/120)	0.537
Hyperlipidaemia	68.5% (85/124)	81.4% (96/118)	76.3% (90/118)	0.066
Creatinine clearance (ml/min)	80.2±27.1	83.9±29.9	85.7±24.2	0.282
Ejection fraction (%)	59.1±7.3	57.7±9.2	58.6±8.0	0.374
Peripheral vascular disease	6.4% (8/125)	6.6% (8/122)	11.7% (14/120)	0.235
COPD	6.4% (8/125)	14.8% (18/122)	11.7% (14/120)	0.103
Clinical presentation				
Silent ischemia	4.8% (6/125)	5.7% (7/122)	6.7% (8/120)	0.916
Stable angina	67.2% (84/125)	64.8% (79/122)	68.3% (82/120)	
Unstable angina	28.0% (35/125)	29.5% (36/122)	25.0% (30/120)	
Anatomic SYNTAX Score	20.4±5.6	21.0±7.2	19.8±6.4	0.350
SYNTAX Score II PCI	29.8±7.9	30.6±9.5	29.4±8.5	0.528
Predicted 4-year mortality PCI (%)	8.3±7.8	9.7±9.9	8.4±8.6	0.406
SYNTAX Score II CABG	28.6±9.5	29.1±11.1	29.0±11.0	0.923
Predicted 4-year mortality CABG (%)	8.2±8.2	9.2±9.9	9.2±9.2	0.587
Lesion characteristics	n=288	n=265	n=266	
Bifurcation	16.7% (48/288)	16.2% (43/265)	13.2% (35/266)	0.467
Total Occlusion	23.6% (68/288)	30.2% (80/265)	24.4% (65/266)	0.165
Post-procedural IVUS findings				
Minimum Stent Area (mm^2)	4.11±0.66	5.83±0.50	8.69±1.93	<0.001
Reference Lumen Area (mm^2)	5.64±1.82	6.73±2.08	9.66±3.17	<0.001
Expansion Index	0.80±0.24	0.97±0.38	0.99±0.43	<0.001
Area Stenosis (%)	21.18±23.96	3.85±37.99	0.62±43.18	<0.001
Stent Symmetry	0.76±0.18	0.80±0.12	0.80±0.13	0.001
Total Stent Length (mm)	34.75±21.72	31.81±19.41	30.60±17.20	0.037
Any Malapposition	5.2% (15/288)	6.8% (18/265)	8.6% (23/266)	0.277

* By ANOVA or chi-square test.
Data are mean ± standard deviation or percentage (n/N).

6

A Randomized Trial Evaluating Online 3-Dimensional Optical Frequency Domain Imaging-Guided Percutaneous Coronary Intervention in Bifurcation Lesions.

Yoshinobu Onuma*, Norihiro Kogame*, Yohei Sotomi, Yosuke Miyazaki, Taku Asano, Kuniaki Takahashi, Hideyuki Kawashima, Masafumi Ono, Yuki Katagiri, Hiroyuki Kyono, Shimpei Nakatani, Takashi Muramatsu, Faisal Sharif, Yukio Ozaki, Patrick W Serruys, Takayuki Okamura, OPTIMUM Investigators. *Authors contributed equally

Circ Cardiovasc Interv. 2020 Dec;13(12):e009183.

Abstract

BACKGROUND:

Clinical implications of online three-dimensional optical frequency domain imaging (3D-OFDI) guided stenting for bifurcation lesions have not been investigated in the randomized controlled trials. To determine whether online 3D-OFDI guided stenting is superior to angiography-guided percutaneous coronary intervention (PCI) in terms of incomplete stent apposition (ISA) at the bifurcation segment.

METHODS:

The OPTIMUM trial was a randomized multi-center clinical trial. Eligible patients had an angiographically significant stenosis in the bifurcation lesion treated with a provisional single stent strategy using the Ultimaster sirolimus eluting stent. Patients were randomly allocated to either online 3D-OFDI guided or angiography guided PCI. Patients randomized to 3D-OFDI guidance underwent online 3D-OFDI assessment after rewiring into the jailed side branch after stenting and proximal optimization technique, while in the angiography guidance arm, rewiring was performed using conventional fluoroscopic/angiographic guidance. The primary endpoint of this trial was the post-procedural average percentage of malapposed struts per lesion assessed by OFDI in the confluence zone of the main and side branches.

RESULTS:

Between June 8, 2017, and Sep 26, 2018, 110 patients with 111 bifurcation lesions were randomized at four Japanese centers. Of these, 56 patients with 57 lesions were treated with 3D-OFDI guided PCI, whereas 54 patients with 54 lesions were treated with angiography guided PCI. In the 3D-OFDI guidance arm, the feasibility of online 3D-OFDI was 98.2%. The average percentage of incomplete stent apposition per lesion at bifurcation was lower in the 3D-OFDI guidance arm than that in the angiography guidance arm (19.5 ± 15.8% vs 27.5 ± 14.2%, p=0.008). The superiority of the 3D-OFDI guidance arm was also confirmed in the strut level analysis (odds ratio: 0.54 [95% confidence interval: 0.36-0.81], p=0.003).

CONCLUSIONS:

Online 3D-OFDI guided bifurcation PCI was superior to angiography guided bifurcation PCI in terms of acute incomplete stent apposition at bifurcation.

Registration:

URL: https://www.clinicaltrials.gov. Unique identifier: NCT02972489.

Introduction

Percutaneous coronary intervention (PCI) with drug eluting stent (DES) implantation is a common revascularization method for coronary artery disease with appropriate complexity of disease. By nature, coronary arteries taper at bifurcations with a flow conservation from main vessel (MV) and side branch (SB). Currently, coronary bifurcation lesions account for 15% to 20% of all patients undergoing PCI [1]. Due to the uneven distribution of shear stress at the bifurcation lesions, early plaque progression occurs in the lateral aspect of the bifurcation with low shear stress, often resulting in continuous atherosclerotic plaque extending from the proximal MV towards the daughter branches [2]. Stenting of the coronary bifurcation is complex, and requires modification of the coronary stents shape from their cylindrical geometry to fit the natural tapering anatomy of the bifurcation. This modification of stent shape is achieved through balloon dilatation following stent deployment through proximal optimization technique (POT), standard post dilatation, and kissing balloon dilatation (KBD) technique.

The current guidelines for myocardial revascularization of coronary bifurcations, recommend a provisional one stent strategy as a default stenting technique [3]. After placing a DES in the MV across SB ostium, POT with larger balloon is performed. This is followed by recrossing the wire to the SB and the KBD is recommended [4]. Ideally to reconstruct natural shape and restore rheology at the bifurcation, any presence of metallic strut in front of the SB should be avoided. Technically, this could be achieved by re-crossing through the optimal distal cell of the MV stent before the KBD (**Supplemental figure 1**) [5].

Angiography is inherently limited in the visualization of both bifurcation carina and the stent structure. Recently, optical frequency domain imaging (OFDI: LUNAWAVE, Terumo Corporation, Tokyo, Japan) with its high-speed pullback has enabled three-dimensional (3D) reconstruction of complex bifurcation anatomies and its relationship with the metallic structure. This novel imaging functionality is available in consoles and ready to use in the catheterization laboratory as an online software tool. Previous retrospective data and published case reports have suggested that it is feasible to perform online visualization of the bifurcation re-wiring position and that this approach can improve acute outcomes such as incomplete stent apposition (ISA). However, additional OFDI pullback step in the catheterization laboratories will increase the amount of total contrast volume as well as procedural time for the patients [6, 7]. The efficacy of online 3D-OFDI guided PCI in reduction of ISA has not yet been investigated prospectively in the context of a randomized controlled trial.

The main objective of this trial was to determine the superiority of the online 3D-OFDI guided PCI to angiography-guided PCI in terms of ISA at the coronary bifurcation segment.

Methods

The authors declare that all supporting data are available within the article and its online supplementary file.

Study design and patients

The design of the OPTIMUM (On-line 3-dimensional OPTical frequency domain Imaging to optimize bifurcation stenting using UltiMaster stent) trial (NCT 02972489) has been described elsewhere [8]. The OPTIMUM trial was a randomized (1:1; 3D-OFDI guidance arm vs. angiography guidance arm), active control, multicenter clinical trial across 4 Japanese canters (**Supplemental table 1**). Major eligibility criteria were the presence of de novo, native, previously unstented bifurcation lesion(s) with a SB diameter of ≥ 2.0 mm (by visual estimation) to be treated by PCI with a single stent strategy. Detailed inclusion and exclusion criteria are shown in **Supplemental table 2**. All patients signed the informed consent. The study was approved by the central and local ethics committees.

Randomization

Patients who met the eligibility criteria were randomly assigned (1:1) to either 3D-OFDI guided PCI or angiography guided PCI. Randomization was performed by local investigators using a web-based software with random blocks stratified by center [8].

Procedures

Detailed information on the study procedure has been provided elsewhere [8]. For all bifurcation lesions, the intention was to treat them with a provisional single stent strategy with the Ultimaster sirolimus eluting stent(s) (Terumo Corporation, Tokyo, Japan). The Ultimaster DES is available in diameters from 2.25 to 4.0 mm, and in lengths from 12 to 38 mm. Stent size was determined by the distal reference MV diameter. After stenting the MV, POT was mandatory with 0.25 – 0.5 mm larger balloon than the device size following the recommendations by the European Bifurcation Club [9]. In both arms, the proximal reference measured by OFDI before stent implantation could be used for the selection of the balloon size for POT. Patients randomized to 3D-OFDI guidance arm underwent online 3D-OFDI assessment of the MV after rewiring into the jailed SB following stent implantation. The OFDI image was acquired from approximately >10 mm distal to the distal edge of the MV stent with blood removal by contrast media at a pullback-speed of 20 mm/sec. The recrossing point was assessed with online 3D-OFDI image reconstruction on the console. The TERUMO OFDI console incorporates online software of 3D imaging with a possibility of stent enhancement, which enables the online reconstruction within one minute. If the wire was not positioned in the optimal cell (as defined in **Supplemental figure 2** [8]), further attempts to redirect the wire through the right cell were performed, with subsequent OFDI imaging to confirm the position in 2D and online 3D reconstructions. The final recrossing position was recorded based on the online 3D OFDI image.

In the angiography guidance arm, wire recrossing into the SB was performed using conventional fluoroscopic/angiographic guidance. Both groups received final kissing balloon dilatation (FKBD) using balloons matching the size of the SB and of the distal MV. After performing FKBD, final OFDI imaging was performed to document the primary endpoint for both treatment arms.

OFDI recordings were assessed by an independent core laboratory (Cardialysis B.V., Rotterdam, The Netherlands). The OFDI analysts were blinded to the patient's allocations. Quantitative analysis was performed using a dedicated semi-automated contour- detection system (QCU-CMS; Medis medical imaging systems bv, Leiden, The Netherlands) according to standard methods [6, 10]. Detailed methodology of the quantitative analysis of OFDI is shown in **Supplemental material**. All angiography recordings were also analyzed by the core lab with a bifurcation dedicated quantitative coronary angiography (QCA) software

(Coronary Angiography Analysis System [CAAS], version 5.9, Pie Medical Imaging, Maastricht, the Netherlands).

If a case a second stent at the SB was needed due to e.g. dissection, slow-flow, or high residual stenosis, the additional stenting was performed at operator's discretion.

Dual antiplatelet therapy (DAPT) was continued at least 6 months in accordance with the European Society of Cardiology (ESC) guidelines [3].

End points

The primary endpoint was superiority of 3D-OFDI guidance on the average post-procedural (FKBD) percentage of malapposed struts (or incomplete stent apposition) per lesion assessed by OFDI in the main branch of the bifurcation, which was calculated for each treated lesion as the ratio of the malapposed struts to the total number of struts in the bifurcation region (**Supplemental figure 3**) [11]. The primary endpoint was also analyzed on a strut-by-strut basis considering each strut as a binary outcome (malapposed or apposed). Malapposed struts included non-apposed struts at the SB orifice. Struts located at the ostium of side branches, with no vessel wall behind, were defined as non-apposed struts at the SB orifice [11]. Secondary OFDI endpoints are listed in **Supplemental material** [12]. The amount of contrast media, radiation time, and the procedure time at the index procedure were evaluated as a secondary safety endpoint. Of note, this trial was designed as a proof-of-concept, feasibility study of 3D-OFDI-guided, coronary bifurcation PCI with an imaging primary endpoint (malapposition); the study is underpowered for clinical endpoints. The clinical follow-up at 6- and 12-months post-procedure was performed to ensure the safety of the patients by either hospital visit or telephone contact. All cause death, myocardial infarction, revascularization, and stent thrombosis according to ARC definition were reported [13].

Statistical methods

Based on the data from past registries, angio-guidance would result in a 26% average malapposition rate per lesion (20% standard deviation) in bifurcation segment (confluence zone of main branch and side branch) and a 5% attrition rate due to insufficient quality of the OFDI image could be expected[7, 14]. Assuming that 3D-OFDI guidance reduces average malapposition rate per lesions by 50% (a 13% for the 3D-OFDI-guidance with a 20% standard deviation), a sample size of 106 patients would be needed to demonstrate superiority of 3D-OFDI guidance with a 5% two-sided level of significance (alpha) and a statistical power of 90%. The primary analyses were based on the intentiontotreat population. The averaging percentage method for the primary endpoint has to face the two following statistical issues: i) the imposed limits on the distribution; ii) unequal weight for each strut. To address these issues, as a post-hoc sensitivity analysis, the primary endpoint of the incidence of malapposed struts at bifurcation was also analyzed considering each strut as a binary outcome (malapposed or apposed) with a mixed-effects logistic regression model, accounting for the correlation of multiple struts within the same patient/lesion by including patient/lesion as a random effect. There were no formal interim analyses and stopping guidelines.

Categorical variables are summarized as frequencies and percentages and were compared between groups using Pearson chi-square or Fisher's exact test, as appropriate. Continuous variables are presented as mean ± SD or median (interquartile), and compared between groups using 2-tailed, unpaired *t* tests or Mann-Whitney test, as appropriate.

Stratified analysis of lesions with three different patterns of configurations of overhanging struts at the carina was performed on the average percentage of ISA per lesion at bifurcation using one-way ANOVA. A Tukey test was performed to identify the group with the greatest effect on the responsible variable.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS (version 27.0.0, IBM, New York).

Results

Between June 8, 2017, and Sep 26, 2018, 110 patients with 111 bifurcation lesions were randomized to 3D-OFDI guided PCI (56 patients with 57 lesions) and angiography guided PCI (54 patients with 54 lesions) (**Figure 1**). Representative cases in each arm are shown in **Figure 2**.

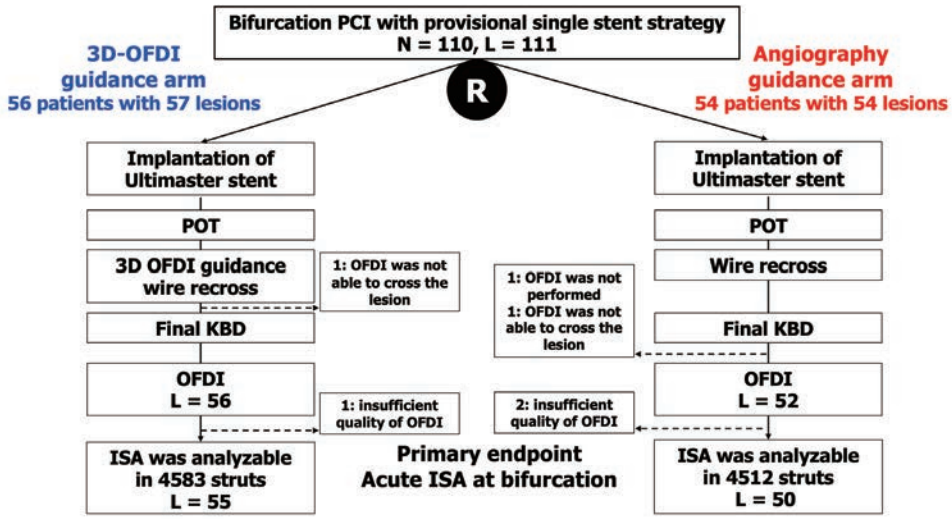


Figure 1. Study flow chart

ISA = incomplete stent apposition, KBD = kissing balloon dilatation, L = lesion, OFDI = optical frequency domain imaging, PCI = percutaneous coronary intervention, POT = proximal optimization technique, 3D = three dimensional.

Baseline characteristics did not differ between the two arms (**Table 1**). A majority of patients presented with stable angina or silent ischemia (91% in the 3D-OFDI guidance arm, 94% in the angiography guidance arm). Lesion and procedural characteristics are shown in **Table 2**. In the 3D-OFDI guided treatment group, there were fewer left main (LM) bifurcation lesions (1.8% vs 14.8% in the angiography guidance arm, p=0.013), but more left anterior descending artery-diagonal branch (LAD-Dx) bifurcation lesions (73.7% in the 3D-OFDI arm vs 51.9% in the angiography arm, p=0.017). The parameters derived from QCA did not differ between the treatment arms (**Table 3**). The mean angle between distal MV and SB was relatively small in both arms (53.3 ± 18.4° in the 3D-OFDI guidance arm vs 54.0 ± 23.3° in the angiography guidance arm, p=0.853).

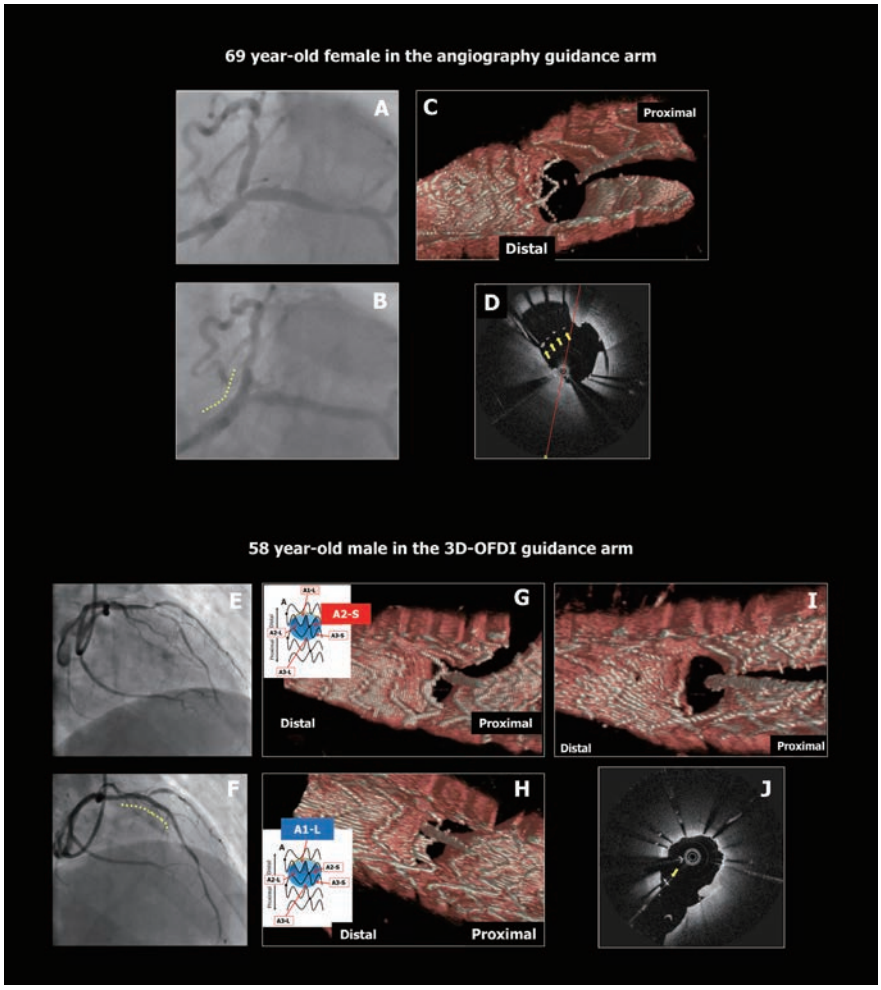


Figure 2. Representative cases of angiography guided and on-line 3D-OFDI guided PCI
Sixty-nine-year-old female with Medina 0, 1, 0 left main (LM) bifurcation lesion (diameter stenosis by quantitative coronary angiography: 58% in left anterior descending artery (LAD)) was randomized to the angiography arm (**panel A**). A 3.0 x 15 mm Ultimaster stent (**panel B: yellow dotted line**) was implanted in the LM toward proximal LAD, followed by proximal optimization technique (POT) with a 4.0 mm balloon and subsequent wire re-crossing to the left circumflex artery. After final kissing balloon dilatation (KBD), 3D-OFDI was performed for documentation purpose which revealed presence of metallic struts in front of the side branch ostium (**panel C**). The frequency of malapposed struts (**panel D: yellow arrow**) was 33.9% by cross-sectional OFDI image. Fifty-eight-year-old male with Medina 1, 1, 1, LAD bifurcation lesion was randomized to the 3D-OFDI arm (**panel E**). A 3.0 x 28 mm Ultimaster stent (**panel F: yellow dotted line**) was implanted in the LAD followed by POT. After the first attempt of re-wiring to the diagonal branch, 3D-OFDI revealed suboptimal position of the wire (A2-S) according to the specific classification (**panel G**). According to the protocol, crossing of the wire to the diagonal branch was repeated to achieve optimal wiring through the distal cell. A subsequent OFDI pullback confirmed the optimal position of the re-crossing wire (**panel H: A1-L**). After KBD, the final OFDI image demonstrated wide opening of the sidebranch ostium without overhanging metallic structure (**panel I** and **panel J: yellow arrow indicates malapposed strut**).
KDB: kissing balloon dilatation, LM: left main, LAD: left anterior descending, OFDI = optical frequency domain imaging, POT: proximal optimization technique, 3D = three dimensional.

Table 1. Baseline characteristics

	3D-OFDI guidance arm N=56	Angiography guidance arm N=54
Age	68.9 ± 10.2 (56)	69.4 ± 11.6 (54)
Male	44/56 (79)	40/54 (74)
BMI, kg/m2	25.3 ± 4.2 (56)	24.1 ± 4.1 (54)
Medical history		
Diabetes mellitus	29/56 (51.8)	25/54 (46.3)
Insulin-dependent diabetes mellitus	5/56 (8.9)	9/54 (16.7)
Hypertension	43/56 (76.8)	40/54 (74.1)
Hypercholesterolemia	48/56 (85.7)	46/54 (85.2)
Current smoker	13/56 (23.2)	10/54 (18.5)
Chronic obstructive pulmonary disease	23/56 (41.1)	32/54 (59.3)
Previous stroke	6/56 (10.7)	9/54 (16.7)
Previous myocardial infarction	9/56 (16.1)	8/54 (14.8)
Previous percutaneous coronary intervention	2/56 (3.6)	0/54 (0.0)
Previous coronary artery bypass grafting	12/56 (21.4)	19/54 (35.2)
Serum creatinine, mg/dL	0.79 (0.70-0.95)	0.81 (0.70-0.99)
Ejection fraction, %	60.8 ± 14.3 (53)	59.7 ± 11.8 (53)
Clinical presentation		
NSTEMI	1/56 (1.8)	1/54 (1.9)
UAP	4/56 (7.1)	2/54 (3.7)
Stable angina/Silent ischemia	51/56 (91.1)	49/54 (90.7)

Data are mean ± SD (N), median (interquartile 1-3), or n/N(%).
BMI = body mass index, NSTEMI = non ST-segment elevation myocardial infarction, OFDI = optical frequency domain imaging, PCI = percutaneous coronary intervention, UAP = unstable angina pectoris, 3D = three dimensional.

Procedures

All lesions were treated with the Ultimaster DES, and POT was performed in 98.2% of the lesions (98.2% in the 3D-OFDI guidance arm vs 98.1% in the angiography guidance arm).

The final OFDI assessment after FKBD was successfully performed in 56 lesions (98.2%) and 52 lesions (96.3%) in the 3D-OFDI guidance arm and the angiography guidance arm, respectively (**Figure 1**). In a patient randomized to the angiography arm, a second Ultimaster stent was implanted after the final OFDI assessment, using the T-stent technique due to the dissection in the side branch. After the final OFDI assessment, additional POT was performed in 7 lesions (12.7%) in the 3D-OFDI arm and 8 lesions (16.0%) in the angiography arm (p=0.842) and additional KBD was performed in 6 lesions (10.9%) in the 3D-OFDI arm and 4 lesions (8.0%) in the angiography arm (p=0.862).

3D-OFDI assessment of wire recrossing position

Identification of the wire recrossing point with 3D-OFDI imaging during the procedure was feasible in 98.2% of lesions (56/57 lesions). The frequency of optimal cell rewiring identified by the first 3D-OFDI was 55.4% (31/56); the success rate increased to 68% at the second attempt and eventually increased to 100% after >3 attempts. The median number of 3D-OFDI runs to achieve optimal cell rewiring was 1 (interquartile range: 1 – 3). Regarding configurations of overhanging struts at carina, pattern A (no ring at carina) was observed in 19% of vessels, pattern B (ring at carina) was in 39%, and pattern C (ring at carina with multiple second distal compartments) was in 40% (**Supplemental figure 4**).

Table 2. Lesion and procedural characteristics at lesion level

	3D-OFDI guidance arm 57 lesions	Angiography guidance arm 54 lesions	p value
Vascular access site			
Radial	31/57 (54.4)	35/54 (64.8)	0.263
Femoral	24/57 (42.1)	17/54 (31.5)	0.246
Brachial	2/57 (3.5)	2/54 (3.7)	0.670
Guide catheter size			
6F	30/57 (52.6)	28/54 (51.9)	0.934
7F	25/57 (43.9)	26/54 (48.1)	0.650
8F	2/57 (3.5)	0/54 (0.0)	0.261
Target bifurcation			
LMT	1/57 (1.8)	8/54 (14.8)	0.013
LMT or LAD proximal	27/57 (47.4)	25/54 (46.3)	0.910
LAD-Dx	42/57 (73.7)	28/54 (51.9)	0.017
LAD proximal-Dx	26/57 (45.6)	17/54 (31.5)	0.127
LCx-OM or PL	9/57 (15.8)	8/54 (14.8)	0.887
RCA PD-PL	5/57 (8.8)	10/54 (18.5)	0.133
Medina classification			
(1, 1, 1)	6/57 (10.5)	3/54 (5.6)	0.272
(1, 1, 0)	28/57 (49.1)	35/54 (64.8)	0.095
(1, 0, 1)	3/57 (5.3)	1/54 (1.9)	0.330
(1, 0, 0)	5/57 (8.8)	4/54 (7.4)	0.534
(0, 1, 1)	2/57 (3.5)	0/54 (0.0)	0.261
(0, 1, 0)	13/57 (22.8)	10/54 (18.5)	0.577
(0, 0, 1)	0/57 (0.0)	1/54 (1.9)	0.486
True bifurcation*	11/57 (19.3)	4/54 (7.4)	0.067
Calcified lesion	19/57 (33.3)	20/54 (37.0)	0.683
Thrombotic lesion	1/57 (1.8)	1/54 (1.9)	0.739
Rotablator	6/57 (10.5)	8/54 (14.8)	0.496
Directional coronary atherectomy	2/57 (3.5)	0/54 (0.0)	0.261
Pre-procedural OFDI assessment			
for main branch	56/57 (98.2)	52/54 (96.3)	0.480
for side branch	3/57 (5.3)	6/54 (11.1)	0.218
Ultimaster stent	57/57 (100)	54/54 (100)	NA
Size, mm	2.8 ± 0.4 (57)	2.7 ± 0.3 (54)	0.505
Length, mm	30.0 ± 7.3 (57)	28.8 ± 7.3 (54)	0.364
POT	56/57 (98.2)	53/54 (98.1)	0.739
Balloon size, mm	3.3 ± 0.5 (56)	3.3 ± 0.5 (53)	0.940
Pressure, atm	13.6 ± 3.2 (56)	13.9 ± 3.8 (53)	0.581
KBD			
Main branch balloon size, mm	3.0 ± 0.4 (57)	3.0 ± 0.4 (53)	0.961
Side branch balloon size, mm	2.1 ± 0.3 (57)	2.2 ± 0.3 (53)	0.507
Pressure, atm	9.0 ± 3.3 (57)	8.3 ± 2.4 (53)	0.214
Contrast volume, ml †	182.9 ± 56.0 (56)	185.1 ± 73.6 (54)	0.863
Radiation time, min †	42.3 ± 18.7 (56)	42.1 ± 20.0 (54)	0.949
Procedure time, min †	118.9 ± 43.4 (56)	118.1 ± 43.7 (54)	0.923

Data are mean ± SD (n) or n/N (%). Dx = diagonal branch, KBD = kissing balloon dilatation, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LM = left main, OFDI = optical frequency domain imaging, OM = obtuse marginal, PCI = percutaneous coronary intervention, PD = posterior descending branch, PL = posterolateral branch, POT = proximal optimization technique, RCA = right coronary artery, 3D = three dimensional.

* True bifurcation was defined as Medina (1.1.1), (1.0.1), or (0.1.1) lesions.

† At patient level.

Table 3. Dedicated bifurcation QCA results

	3D-OFDI guidance arm	Angiography guidance arm	p value
QCA pre-procedure			
PMV DS, %	34.2 ± 17.8 (57)	35.1 ± 19.6 (53*)	0.809
DMV DS, %	46.9 ± 18.7 (57)	44.5 ± 19.7 (53*)	0.497
SB DS, %	30.5 ± 19.3 (57)	27.3 ± 20.5 (53*)	0.406
PMV RD, mm	2.73 ± 0.59 (57)	2.94 ± 0.55 (53*)	0.059
DMV RD, mm	2.18 ± 0.46 (57)	2.24 ± 0.43 (53*)	0.468
SB RD, mm	1.96 ± 0.45 (57)	2.13 ± 0.48 (53*)	0.072
PMV-SB angle, °	153.2 ± 19.6 (57)	150.0 ± 18.4 (53*)	0.370
DMV-SB angle, °	53.3 ± 18.4 (57)	54.0 ± 23.3 (53*)	0.853
QCA post-procedure			
PMV DS, %	12.1 ± 6.9 (57)	10.3 ± 7.1 (54)	0.183
DMV DS, %	11.1 ± 6.6 (57)	11.2 ± 5.5 (54)	0.896
SB DS, %	23.1 ± 13.8 (57)	25.2 ± 15.9 (54)	0.459

Data are mean ± SD (n). DMV = distal main vessel, DS = diameter stenosis, OFDI = optical frequency domain imaging, PCI = percutaneous coronary intervention, PMV = proximal main vessel, QCA = quantitative coronary angiography, RD = reference diameter, SB = side branch, 3D = three dimensional.
* One lesion in the angiography arm was chronic total occlusion.

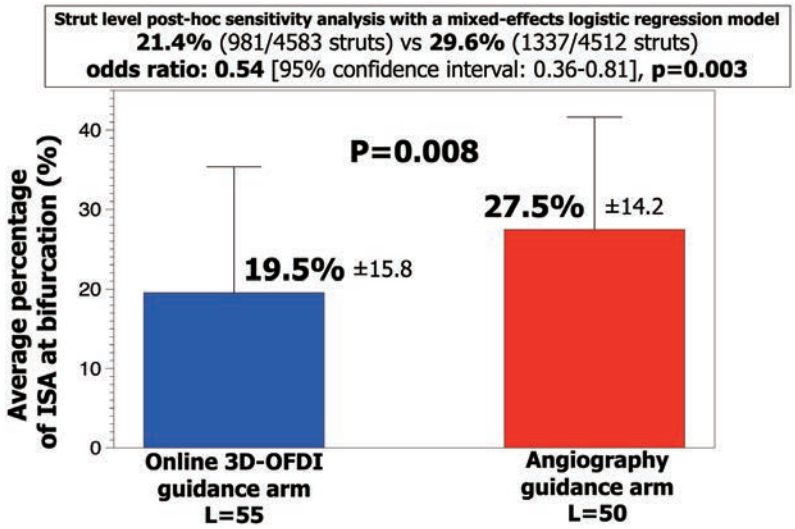


Figure 3. Average percentage of acute incomplete stent apposition per lesion at bifurcation.
ISA = incomplete stent apposition, L = lesion, OFDI = optical frequency domain imaging, PCI = percutaneous coronary intervention, 3D = three dimensional.

Acute incomplete stent apposition at bifurcation

OFDI assessment after the FKBD was successfully performed in 56 lesions (98.2%) in the 3D-OFDI guidance arm and 52 lesions (96.3%) of the angiography guidance arm (**Figure 1**). Due to insufficient imaging quality, the final assessment of ISA was not feasible in 3 cases (one in the 3D-OFDI guidance arm and 2 in the angiography guidance arm). Final OFDI images after the FKBD were analyzable and available in 55 lesions and 50 lesions in the 3D-OFDI guidance arm and the angiography guidance arm, respectively.

The primary endpoint of superiority of online 3D-OFDI guided PCI to the angiography guided PCI was reached: the average percentage of malapposed struts at bifurcation in the 3D-OFDI guidance arm was significantly lower than in the angiography guidance arm (19.5 ± 15.8% vs 27.5 ± 14.2%, p=0.008, **Figure 3**). In the strut level post-hoc sensitivity analysis with a mixed-effects logistic regression model, the incidence of malapposition in the 3D-OFDI guidance arm was also significantly lower than in the angiography guidance arm (21.4% [981/4583 struts] vs 29.6% [1337/4512 struts], odds ratio: 0.54 [95% confidence interval: 0.36-0.81], p=0.003, **Figure 3**). In the 3D-OFDI guidance arm, the risk of malapposed struts was influenced by the complexity of configurations of overhanging struts at carina (12.0 ± 10.1% in pattern A, 26.3 ± 18.8% in pattern B, and 16.4 ±12.4 in pattern C, p for overall p= 0.024, **Supplemental figure 4**).

The quantitative OFDI results in the entire stented segment of the main branch did not differ between the two arms: the percentage of malapposed struts was 11.6 ± 9.6% vs 11.7% ± 8.6% (p = 0.973), minimum lumen area was 4.82 ± 1.37 mm^2 vs 4.73 ± 1.25 mm^2 (p = 0.721), and mean lumen area was 6.96 ± 1.64 mm^2 vs 6.78 ± 1.78 mm^2 (p = 0.592) in the 3D-OFDI guidance arm and the angiography guidance arm, respectively (**Table 4**). The frequencies of incomplete stent apposition in proximal and distal main branch also did not differ between the two arms. Quantitative OFDI results of the stented segment at bifurcation, proximal and distal to bifurcation are tabulated in **Supplemental table 3**.

The amount of contrast media, radiation time and procedure time did not differ between arms (**Table 2**).

Table 4. Secondary OFDI endpoints after final kissing balloon dilatation in the entire main branch including proximal, bifurcation, and distal segment.

	3D-OFDI guidance arm L=55	Angiography guidance arm L=50	p value
Frequency of malapposed struts, %	11.6 ± 9.6	11.7 ± 8.6	0.973
Mean ISA area, mm^2	0.23 ± 0.20	0.27 ± 0.27	0.387
Minimum lumen area, mm^2	4.82 ± 1.37	4.73 ± 1.25	0.721
Mean lumen area, mm^2	6.96 ± 1.64	6.78 ± 1.78	0.592
Minimum stent area, mm^2	4.68 ± 1.42	4.51 ± 1.24	0.513
Mean stent area, mm^2	6.48 ± 1.61	6.20 ± 1.65	0.383
Mean protrusion area, mm^2	0.11 ± 0.09	0.08 ± 0.06	0.153
Maximum protrusion area, mm^2	0.45 ± 0.27	0.36 ± 0.24	0.070
Mean intrastent defect attached to/free from the vessel wall, mm^2	0.11 ± 0.09	0.09 ± 0.06	0.147
Maximum intrastent defect attached to/free from the vessel wall, mm^2	0.45 ± 0.28	0.36 ± 0.24	0.069
Minimum flow area, mm^2	4.72 ± 1.36	4.63 ± 1.24	0.704
Maximum flow area, mm^2	6.85 ± 1.63	6.67 ± 1.78	0.596

ISA = incomplete stent apposition, L = lesion, OFDI = optical frequency domain imaging, 3D = three dimensional.

Clinical outcomes up to 1-year follow-up

Target lesion related event was not observed in the participants over 1-year follow-up. Non-target lesion revascularization occurred in 7 and 3 patients in the 3D-OFDI and angiography arm, respectively. One patient in the 3D-OFDI arm died due to infectious myocarditis after transcatheter aortic valve implantation.

Discussion

To the best of our knowledge, the present study is the first randomized controlled trial to evaluate feasibility and efficacy of online 3D-OFDI guided PCI for bifurcation. The main findings are the followings:

1. Online 3D-OFDI for identification of the wire re-crossing point was feasible in all but one case (56/57 lesions, 98.2%). Optimal wire re-crossing was achieved in all lesions guided by the online 3D-OFDI (56/56 lesions, 100%).
2. Online 3D-OFDI guided PCI was superior to the angiography guided PCI in terms of percentage of acute ISA at the bifurcation.
3. Optimal rewiring remained unachievable after POT in 45% of lesions.
4. The configurations of overhanging struts at carina might influence the risk of acute ISA at bifurcation in patients treated with the online 3D-OFDI guided PCI.

In the present study, a superiority of the 3D-OFDI guided PCI over the angiography guided PCI was demonstrated in relation to acute ISA in the confluence zone of bifurcation. The feasibility of on-line 3D-OFDI in the present trial was as high as 98.2%, which was higher than previous registries using off-line OCT assessment. In a study of Okamura et al, the feasibility of the offline 3D-OCT assessment of the guidewire re-crossing point after MV stenting was 89.9% [11]. With the improvement of the console software, online assessment likely contributed to excellent feasibility through timely feedback to operators regarding the imaging acquisition.

In the OFDI-guidance arm, the rate of optimal cell rewiring at the first attempt was 55.4%, indicating that even after POT, in about half of the cases the wiring position was not optimal. This underlines the importance of 3D-OFDI guidance to reduce the overhanging struts in front of the side-branch ostium. Overhanging metallic struts in the bifurcation could alter micro-circulation around the stent struts, reduce the coverage of struts with an area of high shear rate (metallic carina), increase the neointimal growth within the area of low shear stress causing neointimal bridge between the rim of the ostium and metallic structure [15], and finally may hinder the access to the side-branch in case of repeat revascularization in the distal side-branch at later stage. Foin et al reported that ISA not only affects blood flow patterns assessed by shear rate calculated in computational fluid dynamic (CFD) simulation but also delays the process of strut coverage in the clinical OCT study [16]. The pathological study also demonstrated that a higher prevalence of late stent thrombosis in DES in bare metal stent was associated with higher rate of uncovered struts at flow divider sites such as the carina region, which is likely due to flow disturbances [17]. In a case report from a serial 3D-OCT follow-up of a natural course of jailed SB after MV stenting without the FKBD [18], Diletti et al reported that neointimal tissue attached on jailed struts in front of the SB ostium which resulted in reduced blood flow areas of the SB ostium at 6 months.

By implementing the OFDI-guidance, optimal wiring was achieved in 13% of lesions at the second attempt and in 32% of lesions at >3attempts. Eventually, the frequency increased to 100% with median numbers of attempts of 1 (interquartile range: 1 – 3). These findings show that utilization of this technology can result in optimal rewiring and subsequently superior stent apposition. To achieve the optimal wiring, pulling back of the MB wire (or a third wire in the same direction) is recommended using angiographic projection with best visualization of the ostia of two daughter branches[4]. When this technique fails, the use of angiographic projection perpendicular to side-branch ostial plane

may be useful; Although the distal main branch and side branch are overlapped in this projection, this specific angiographic view corresponds to the 3D-OFDI image of the side branch ostium, viewed from the main branch towards the distal side branch. The second wire could be manipulated and advanced into the optimal crossing point using the first recrossing wire (through the proximal cell) as landmark.

Despite a greater number of attempts to cross the optimal cell with OFDI imaging, there were no significant differences between the 3D-OFDI guidance arm and the angiography guidance arm in terms of amount of contrast media, radiation time, and procedure time. This may be attributed to shorter length of the OFDI pullback with a small amount of contrast media at the second or later attempts, since approximately 10 mm visualization around polygon of confluence suffices for recognition of the wire recrossing point.

In the current study, the optimal recrossing point was identified differently according to configurations of overhanging rings and links, to avoid extreme deformation of the stent. Previous registry data have demonstrated that a link-free configuration is favorable for SB dilatation [11], however, the location of the link at the bifurcation is not controllable during implantation by operators. In the current study, therefore, whenever the distal ring and/or link were in contact with the carina, the second distal cell was defined as optimal recrossing point instead of the most distal cell. This classification was incorporated into the electronic case report form, and helped the operator to achieve the optimal recrossing point when the 3D-OFDI guidance was used. In addition, ring-free configuration (type A) was associated with a lower incidence of ISA at bifurcation in the 3D-OFDI arm. However, it should be acknowledged that ring-free configuration (type A) was observed only in 19.0% of lesions in the 3D-OFDI arm and the high prevalence of non-ring-free configuration (type B: 39.0%) with the worst incidence of ISA at bifurcation (26.3±18.8%) might result in moderate incidence of ISA at bifurcation in the overall 3D-OFDI arm (19.5±15.8%). Even though, 61% of lesions had type A and C configurations which potentially have derived benefit from the 3D-OFDI guided bifurcation PCI and might be worth the effort of achieving favorable mechanical finding such as less incomplete stent apposition at bifurcation. However, this stratified analysis by the configurations was post-hoc and underpowered for comparison of three configurations. Furthermore, the distribution of the configurations in the angiography arm could not be evaluated, since OFDI had not been performed before wire re-crossing in the angiography arm according to the protocol. Further study is needed to evaluate this specific question.

Finally, ISA in bifurcation is strictly dependent on a) the type of stent used, b) size of SB, c) severity of the SB lesion and d) angle between MV and SB: a) DES with closed cell and more-link design can be associated with more malapposition. However, most of the currently available DESs have open cell and 2 or 3-link design. Therefore, the generalizability of the present study is acceptable with regard to type of DESs; b) In our cohort, the reference SB diameter was relatively small (1.96 mm in the 3D-OFDI arm and 2.13 mm in the angiography arm) and large SB has theoretically advantage from distal crossing. In particular in the 3D-OFDI arm, only one LM bifurcation was included despite randomization (8 in the angiography arm); c) In the present study, the severity of the SB lesions was mild to moderate (30.5% in the 3D-OFDI arm and 27,3% in the angiography arm) and resulted in a few inclusions of the true bifurcation (19.3% in the 3D-OFDI arm and 7.4% in the angiography arm). The bifurcation lesions with severe SB stenosis can further benefit from distal crossing and the achievement of distal crossing in these lesions seems difficult even under the 3D-OFDI guidance due to limited workspace for the wire; d) Theoretically, the

narrow angle between MB and SB may advantageously allow distal crossing and the bifurcation angle in the present trial was indeed relatively narrow (53.3° in the 3D-OFDI arm and 54.0° in the angiography arm). Overall, it is impossible to discriminate the effect of these four factors on acute ISA in the present trial due to limited sample size and unbalanced bifurcation lesion characteristics. Further trial with more complex and higher risk bifurcation lesion is needed to address this issue.

Limitations

The present study has several limitations. First, the clinical relevance of the overhanging struts in the bifurcation cannot be proven due the limited sample size and the lack of clinical follow-up. The study was not designed to evaluate clinical outcomes and the impact of difference in ISA at bifurcation on clinical outcomes remains to be elucidated. Furthermore, in the primary endpoint of the present trial the malapposition was strictly limited to few struts across the origin of the SB appropriately quantified in this mechanistic evaluation of the two strategies of implantation. However, this limited difference in malapposition may be insufficient to influence the clinical outcome. Secondly, the allocation of guidance strategy was not blinded for the operator, therefore there may be an inborn risk of bias towards the technology. Thirdly, the generalizability of the LM bifurcation results is limited due to a low prevalence and uneven distribution of LM bifurcation (1.8% in the 3D-OFDI arm vs. 14.8% in the angiography arm). Along the same line, a low prevalence of true bifurcation and relatively small mean SB diameter may limit the generalizability of the 3D-OFDI guided bifurcation PCI, although these lesions theoretically might benefit from OCT guidance. Fourthly, KBD was mandatory in the present trial, although a clinical advantage of KBD after crossover stenting is controversial [19, 20]. A main concern with KBD is the stent deformation in the proximal MV, therefore POT after KBD is recommended by the European Bifurcation Club [9] to avoid the elliptical shape of stent dilation in proximal MV. However, in the present trial, POT after KBD was not mandatory according to the protocol and performed in minority of lesions (12.7% in the 3D-OFDI arm and 16.0% in the angiography arm). Fifthly, pre-procedural OFDI assessment was performed in 96.3% of lesions in the angiography guidance arm, which may result in similar minimum and mean stent area between both arms (**Table 4**). Furthermore, the incomplete stent apposition in proximal and distal main branch did not differ between the two arms probably due to mandated POT and high adoption rate of pre-procedural OFDI assessment in the angiography arm (**Supplemental table 3**). Finally, in the angiography guidance arm, final OFDI was mandatory for documentation which may affect the amount of contrast media, radiation time, and procedure time among patients in this arm. Furthermore, in the 3D-OFDI arm, the operator may have intended to save angiographic contrast medium and shorten the radiation and procedure time in the context of an open-label design.

Conclusion

In a series of predominantly non-LM bifurcation lesions, online 3D-OFDI guided PCI demonstrated excellent feasibility and was superior to angiography guidance in reducing acute incomplete stent apposition at bifurcation. 3D-OFDI imaging guidance may therefore be preferable in bifurcation PCI. Further trials are warranted to confirm the long-term clinical benefit of these favorable mechanical findings.

References

1. Lassen JF, Holm NR, Stankovic G, Lefevre T, Chieffo A, Hildick-Smith D, Pan M, Darremont O, Albiero R, Ferenc M, et al. Percutaneous coronary intervention for coronary bifurcation disease: consensus from the first 10 years of the European Bifurcation Club meetings. EuroIntervention. 2014;10:545-60.
2. Asakura T and Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. Circulation research. 1990;66:1045-66.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165.
4. Banning AP, Lassen JF, Burzotta F, Lefevre T, Darremont O, Hildick-Smith D, Louvard Y and Stankovic G. Percutaneous coronary intervention for obstructive bifurcation lesions: the 14th consensus document from the European Bifurcation Club. EuroIntervention. 2019;15:90-98.
5. Onuma Y, Katagiri Y, Burzotta F, Holm NR, Amabile N, Okamura T, Mintz GS, Darremont O, Lassen JF, Lefevre T, et al. Joint consensus on the use of OCT in coronary bifurcation lesions by the European and Japanese bifurcation clubs. EuroIntervention. 2019;14:e1568-e1577.
6. Okamura T, Onuma Y, Garcia-Garcia HM, Bruining N and Serruys PW. High-speed intracoronary optical frequency domain imaging: implications for three-dimensional reconstruction and quantitative analysis. EuroIntervention. 2012;7:1216-26.
7. Okamura T, Onuma Y, Yamada J, Iqbal J, Tateishi H, Nao T, Oda T, Maeda T, Nakamura T, Miura T, et al. 3D optical coherence tomography: new insights into the process of optimal rewiring of side branches during bifurcational stenting. EuroIntervention. 2014;10:907-15.
8. Miyazaki Y, Muramatsu T, Asano T, Katagiri Y, Sotomi Y, Nakatani S, Takahashi K, Kogame N, Higuchi Y, Ishikawa M, et al. On-line three-dimensional OFDI guided PCI vs. angiography guided in bifurcation lesions: design and rationale of the randomized OPTIMUM trial. EuroIntervention. 2019; EIJ-D-18-00902. doi: 10.4244/EIJ-D-18-00902. Online ahead of print.
9. Lassen JF, Burzotta F, Banning AP, Lefevre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y, et al. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. EuroIntervention. 2018;13:1540-1553.
10. Nakatani S, Sotomi Y, Ishibashi Y, Grundeken MJ, Tateishi H, Tenekecioglu E, Zeng Y, Suwannasom P, Regar E, Radu MD, et al. Comparative analysis method of permanent metallic stents (XIENCE) and bioresorbable poly-L-lactic (PLLA) scaffolds (Absorb) on optical coherence tomography at baseline and follow-up. EuroIntervention. 2016;12:1498-1509.
11. Okamura T, Nagoshi R, Fujimura T, Murasato Y, Yamawaki M, Ono S, Serikawa T, Hikichi Y, Norita H, Nakao F, et al. Impact of guidewire recrossing point into stent jailed side branch for optimal kissing balloon dilatation: core lab 3D optical coherence tomography analysis. EuroIntervention. 2018;13:e1785-e1793.
12. Onuma Y, Thuesen L, van Geuns RJ, van der Ent M, Desch S, Fajadet J, Christiansen E, Smits P, Holm NR, Regar E, et al. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study--TROFI trial. Eur Heart J. 2013;34:1050-60.
13. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Circulation. 2018;137:2635-2650.
14. Alegria-Barrero E, Foin N, Chan PH, Syrseloudis D, Lindsay AC, Dimopolous K, Alonso-Gonzalez R, Viceconte N, De Silva R and Di Mario C. Optical coherence tomography for guidance of distal cell recrossing in bifurcation stenting: choosing the right cell matters. EuroIntervention. 2012;8:205-13.

15. Onuma Y, Grundeken MJ, Nakatani S, Asano T, Sotomi Y, Foin N, Ng J, Okamura T, Wykrzykowska JJ, de Winter RJ, et al. Serial 5-Year Evaluation of Side Branches Jailed by Bioresorbable Vascular Scaffolds Using 3-Dimensional Optical Coherence Tomography: Insights From the ABSORB Cohort B Trial (A Clinical Evaluation of the Bioabsorbable Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). Circ Cardiovasc Interv. 2017;10(9):e004393.
16. Foin N, Gutierrez-Chico JL, Nakatani S, Torii R, Bourantas CV, Sen S, Nijjer S, Petraco R, Kousera C, Ghione M, et al. Incomplete stent apposition causes high shear flow disturbances and delay in neointimal coverage as a function of strut to wall detachment distance: implications for the management of incomplete stent apposition. Circ Cardiovasc Interv. 2014;7:180-9.
17. Nakazawa G, Yazdani SK, Finn AV, Vorpahl M, Kolodgie FD and 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.
18. Diletti R, Farooq V, Muramatsu T, Gogas BD, Garcia-Garcia HM, van Geuns RJ and Serruys PW. Serial 2- and 3-dimensional visualization of side branch jailing after metallic stent implantation: to kiss or not to kiss...? JACC Cardiovasc Interv. 2012;5:1089-90.
19. Niemela M, Kervinen K, Erglis A, Holm NR, Maeng M, Christiansen EH, Kumsars I, Jegere S, Dombrovskis A, Gunnes P, et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. Circulation. 2011;123:79-86.
20. Kim YH, Lee JH, Roh JH, Ahn JM, Yoon SH, Park DW, Lee JY, Yun SC, Kang SJ, Lee SW, et al. Randomized Comparisons Between Different Stenting Approaches for Bifurcation Coronary Lesions With or Without Side Branch Stenosis. JACC Cardiovasc Interv. 2015;8:550-60.

Supplementary Material

Supplemental methods OFDI Core Lab analysis

OFDI recordings were sent to an independent core laboratory (Cardialysis B.V., Rotterdam, The Netherlands) for the assessment. Core laboratory was blinded the patients allocation. Quantitative analysis was performed using a dedicated semi-automated contour- detection system (QCU-CMS; Medis medical imaging systems bv, Leiden, The Netherlands) with the standard method [1, 2]. The region of interest (ROI) was the stented segment, defined as the region between the first and the last frame in which struts were visible over 360 degree vessel circumference, and 5 mm proximal and distal persistent site. Lumen contour was traced automatically for all frames of ROI with minimal manual corrections if needed. Strut malapposition was defined as a separation of luminal boundary of one or more of the stent struts from the vessel wall with a distance of more than the strut thickness (80 μm for Ultimaster stent) plus the axial resolution of the OCT (14 μm) [3]. Post-procedural percentage of malapposed struts (primary endpoint) was assessed in the main branch bifurcation region (Supplemental figure 2). Any struts without contact with vessel wall in 2-dimensional cross sections, taking into consideration strut thickness, were considered as malapposed struts. Frame-by-frame cross-sectional images were analyzed for the primary endpoint, while secondary endpoints were assessed with cross-sectional analysis at 1 mm longitudinal intervals.

Secondary OFDI endpoints

Secondary OFDI endpoints at post procedure are as follows: In the entire main branch,
1) frequency of malapposed struts, 2) incomplete stent apposition (ISA) area, 3) minimum/mean lumen area, 4) minimum/mean stent area, 5) mean/ maximum protrusion area,
6) mean/ maximum intra-stent defect attached to/ free from the vessel wall and 7) minimum/mean flow area. In the bifurcation region: 1) incidence of fulfilling optimal recrossing criteria on 3D-OFDI, 2) ISA area, 3) minimum/mean lumen area, 4) minimum/mean stent area, 5) mean/ maximum protrusion area, 6) mean/ maximum intra-stent defect attached to/ free from the vessel wall and 7) minimum/mean flow area. Intra-stent defect attached to the wall is defined as an irregular-shaped tissue attached to the luminal surface and Intra-stent defect free from the wall defined as an isolated structure in the lumen distant from the vessel wall. [4]

Supplemental table 1. Number of patients randomized per site in Japan (Total number of patients: 110)

Site Name	Principal Investigator	City	Patients enrolled	Date first patient enrolled	Date last patient enrolled
Osaka Police Hospital	Dr. Sotomi	Osaka	77	2017-07-31	2018-09-04
Fujita Health University Hospital	Dr. Muramatsu	Toyoake	17	2017-06-08	2018-08-09
Yamaguchi University Graduate School of Medicine	Dr. Okamura	Ube	14	2017-08-02	2018-09-26
Teikyo University School of Medicine	Dr. Kyono	Tokyo	2	2018-07-18	2018-08-16

Supplemental table 2. Inclusion and exclusion criteria

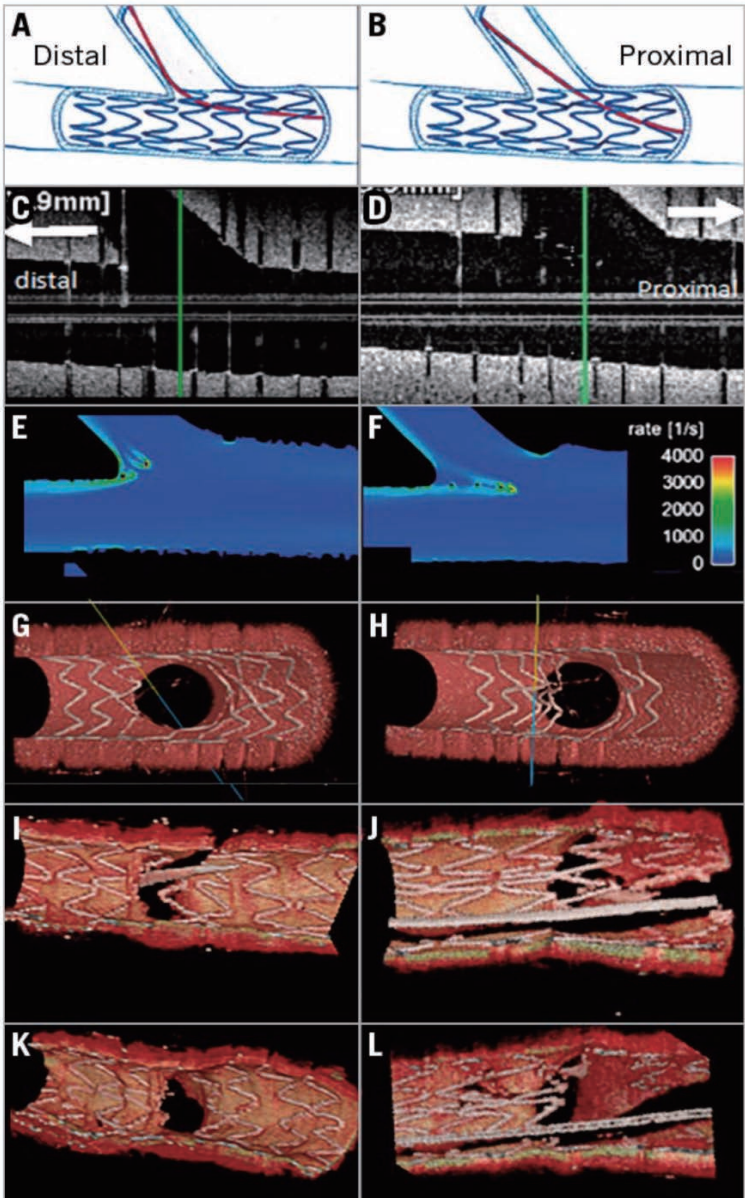
Clinical inclusion criteria
1. Subject has coronary artery disease involving a bifurcation with objective evidence of ischemia including patients with chronic stable angina, silent ischemia and NSTE-ACS
2. Subject is appropriate to be treated by PCI according to the local practice (operator's judgment or heart team decision)
3. Patient is at least 18 years of age.
4. Signed Informed Consent
5. The patient understands and accepts clinical follow-up and OFDI controls.
6. Patients residence is in the area covered by the hospital
Angiographic inclusion criteria
1. Patients with angiographically significant stenosis (>50 % by visual assessment) in de novo, native, previously unstented bifurcation lesion(s) including left main lesion, which is in operator's opinion appropriate to be treated by PCI with a single stent strategy
2. The size of main vessel matches available Ultimaster stent sizes (<4.0 mm, and >2.0 mm by visual assessment).
3. The size of side branch is >2.0mm in diameter by visual assessment.
4. The sidebranch is treatable with a sidebranch fenestration and/or kissing balloon
Exclusion criteria
1. Pregnancy.
2. Known intolerance to aspirin, clopidogrel, heparin, cobalt chromium, sirolimus, contrast material
3. Known thrombocytopaenia (platelet count< 100,000/mm^3)
4. Contraindications to PCI, stenting, ASA, clopidogrel, prasugrel or ticagrelor
5. Cardiogenic Shock
6. Significant comorbidities precluding clinical follow-up (as judged by investigators)
7. Major planned surgery that requires discontinuation of dual antiplatelet therapy
8. History of stenting in the target bifurcation lesion
9. Renal insufficiency (GFR/MDRD <45 ml/min), which precludes in operator's opinion contrast injection during repeat OFDI pullback
10. Severely tortuous or angulated coronary anatomy of the study vessel that in the opinion of the investigator would result in sub-optimal optical frequency domain imaging (OFDI) or excessive risk of complication to place an OFDI catheter.
11. Target lesion reference vessel diameter (RVD) < 2.25 and > 4 mm
12. Target bifurcation lesion has a previously implanted stent

Supplemental table 3. Secondary OFDI endpoints after final kissing balloon dilatation in each division of target region.

	Distal main branch			Bifurcation region			Proximal main branch		
	OFDI guidance arm L=55	Angiography guidance arm L=50	p value	OFDI Guidance arm L=55	Angiography guidance arm L=50	p value	OFDI guidance arm L=55	Angiography guidance arm L=50	p value
Frequency of malapposed struts, %	8.7 ± 9.5	7.4 ± 8.9	0.465	19.5 ± 15.8*	27.5 ± 14.2*	0.008*	17.2 ± 16.5	15.5 ± 13.9	0.582
Mean ISA area, mm^2	0.12 ± 0.15	0.11 ± 0.18	0.717	0.79 ± 0.98	1.10 ± 1.05	0.123	0.29 ± 0.33	0.31 ± 0.42	0.854
Minimum lumen area, mm^2	4.84 ± 1.36	4.74 ± 1.25	0.693	7.88 ± 1.82	7.97 ± 2.22	0.813	6.95 ± 1.84	6.76 ± 1.78	0.594
Mean lumen area, mm^2	5.91 ± 1.50	5.65 ± 1.34	0.356	8.69 ± 1.87	8.82 ± 2.40	0.758	8.25 ± 2.27	7.88 ± 2.17	0.406
Minimum stent area, mm^2	4.74 ± 1.47	4.54 ± 1.23	0.469	5.94 ± 1.67	5.86 ± 1.79	0.800	6.60 ± 1.77	6.43 ± 1.81	0.646
Mean stent area, mm^2	5.65 ± 1.50	5.37 ± 1.28	0.305	6.68 ± 1.66	6.34 ± 1.87	0.326	7.75 ± 2.15	7.38 ± 2.06	0.362
Mean protrusion area, mm^2	0.10 ± 0.09	0.08 ± 0.06	0.115	0.14 ± 0.16	0.09 ± 0.10	0.073	0.10 ± 0.11	0.09 ± 0.08	0.416
Maximum protrusion area, mm^2	0.36 ± 0.26	0.28 ± 0.21	0.087	0.20 ± 0.22	0.15 ± 0.17	0.183	0.29 ± 0.26	0.25 ± 0.23	0.417
Mean intrastent defect attached to/free from the vessel wall, mm^2	0.10 ± 0.09	0.08 ± 0.07	0.109	0.14 ± 0.16	0.10 ± 0.10	0.120	0.10 ± 0.11	0.09 ± 0.08	0.398
Maximum intrastent defect attached to/free from the vessel wall, mm^2	0.36 ± 0.26	0.28 ± 0.21	0.084	0.21 ± 0.22	0.16 ± 0.17	0.248	0.29 ± 0.26	0.25 ± 0.23	0.417
Minimum flow area, mm^2	4.74 ± 1.35	4.64 ± 1.24	0.692	7.74 ± 1.76	7.86 ± 2.23	0.751	6.84 ± 1.83	6.66 ± 1.78	0.610
Maximum flow area, mm^2	5.79 ± 1.49	5.54 ± 1.34	0.359	8.58 ± 1.84	8.71 ± 2.40	0.761	8.12 ± 2.27	7.76 ± 2.17	0.412

ISA = incomplete stent apposition, L = lesion, OFDI = optical frequency domain imaging.
*Cross-sectional images were analyzed frame-by-frame.

Supplemental figure 1. Impact of the rewiring position and strut malapposition in bifurcation. Left column (A, C, E, G, I and K) and right column (B, D, F, H, J, L) show distal rewiring and proximal rewiring, respectively. Panels C and D are longitudinal OFDI images. The computational flow simulation of the shear rate is shown in panels E and F. Panels G and H show the 3D reconstruction of struts in phantom. Panels I and J indicate the wiring position in 3D OCT in human coronary bifurcation before kissing balloon dilatation (KBD), whereas panels K and L are 3D reconstruction images after KBD.
Reprinted with permission from Onuma Y. *et al*. Joint consensus on the use of OCT in coronary bifurcation lesions by the European and Japanese bifurcation clubs. EuroIntervention 2019; 14:e1568-e1577, with permission from Europa Digital & Publishing [5].



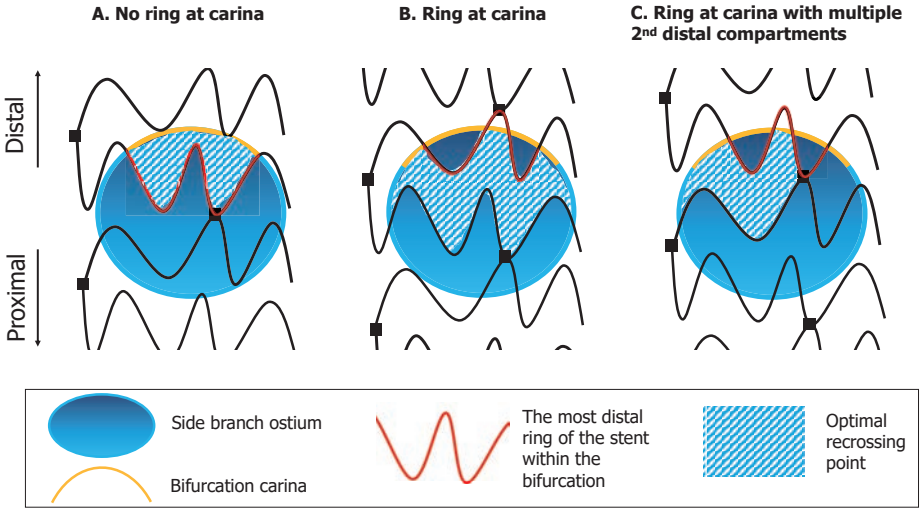
Supplemental figure 2. Definition of optimal cell

The optimal recrossing point is defined according to the configuration of overhanging strut in front of the side branch ostium. Three possible configurations are shown in panel A to C.

Panel A: When the most distal stent ring is not in contact with the rim of the carina, the most distal compartment is considered as optimal cell.

Panel B: When the most distal stent ring is in contact with the rim of the carina, a second distal compartment is considered as optimal cell.

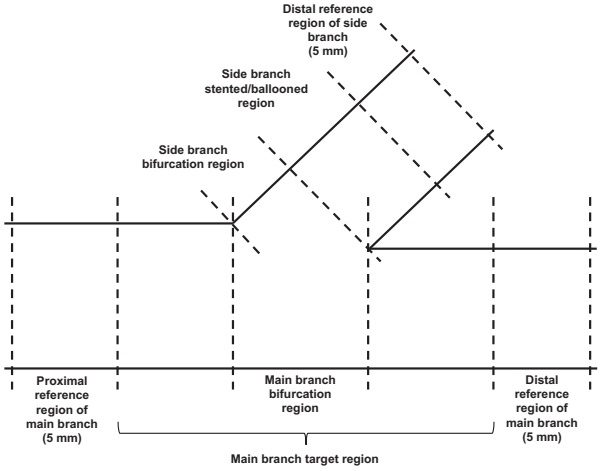
Panel C: When the most distal stent ring is in contact with the rim of the carina in presence of multiple second distal compartments, a larger compartment should be selected as optimal cell.



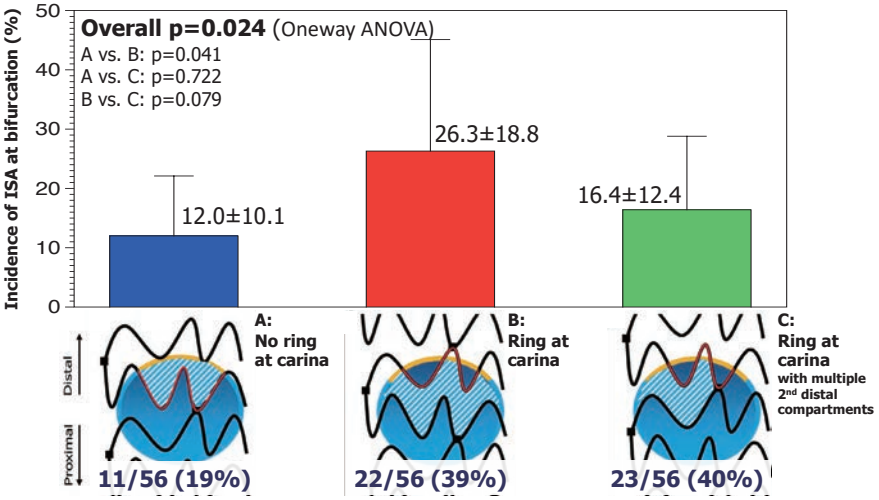
Supplemental figure 3. OFDI core lab analysis.

Post-procedural percentage of malapposed struts (primary endpoint) was assessed in the main branch bifurcation region.

OFDI = optical frequency domain imaging.



Supplemental figure 4. Average percentage of acute ISA per lesion at bifurcation stratified by the patterns of configurations of overhanging struts at carina in online 3D-OFDI guidance arm.
ISA = incomplete stent apposition, OFDI = optical frequency domain imaging, PCI = percutaneous coronary intervention, 3D = three dimensional.



Supplemental references

1. Okamura T, Onuma Y, Garcia-Garcia HM, Bruining N and Serruys PW. High-speed intracoronary optical frequency domain imaging: implications for three-dimensional reconstruction and quantitative analysis. *EuroIntervention*. 2012;7:1216-26.

2. Nakatani S, Sotomi Y, Ishibashi Y, Grundeken MJ, Tateishi H, Tenekecioglu E, Zeng Y, Suwannasom P, Regar E, Radu MD, Raber L, Bezerra H, Costa MA, Fitzgerald P, Prati F, Costa RA, Dijkstra J, Kimura T, Kozuma K, Tanabe K, Akasaka T, Di Mario C, Serruys PW and Onuma Y. Comparative analysis method of permanent metallic stents (XIENCE) and bioresorbable poly-L-lactic (PLLA) scaffolds (Absorb) on optical coherence tomography at baseline and follow-up. *EuroIntervention*. 2016;12:1498-1509.

3. Gutierrez-Chico JL, Regar E, Nuesch E, Okamura T, Wykrzykowska J, di Mario C, Windecker S, van Es GA, Gobbens P, Juni P and Serruys PW. Delayed coverage in malapposed and side-branch struts with respect to well-apposed struts in drug-eluting stents: in vivo assessment with optical coherence tomography. *Circulation*. 2011;124:612-23.

4. Onuma Y, Thuesen L, van Geuns RJ, van der Ent M, Desch S, Fajadet J, Christiansen E, Smits P, Holm NR, Regar E, van Mieghem N, Borovicanin V, Paunovic D, Senshu K, van Es GA, Muramatsu T, Lee IS, Schuler G, Zijlstra F, Garcia-Garcia HM, Serruys PW and Investigators T. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study--TROFI trial. *Eur Heart J*. 2013;34:1050-60.

5. Onuma Y, Katagiri Y, Burzotta F, Holm NR, Amabile N, Okamura T, Mintz GS, Darremont O, Lassen JF, Lefevre T, Louvard Y, Stankovic G and Serruys PW. Joint consensus on the use of OCT in coronary bifurcation lesions by the European and Japanese bifurcation clubs. *EuroIntervention*. 2019;14:e1568-e1577.

7

Clinical Implication of Quantitative Flow Ratio After Percutaneous Coronary Intervention for 3-Vessel Disease.

Norihiro Kogame, Kuniaki Takahashi, Mariusz Tomaniak, Ply Chichareon, Rodrigo Modolo, Chun Chin Chang, Hidenori Komiyama, Yuki Katagiri, Taku Asano, Rod Stables, Farzin Fath-Ordoubadi, Simon Walsh, Manel Sabaté, Justin E Davies, Jan J Piek, Robert-Jan van Geuns, Johan H C Reiber, Adrian P Banning, Javier Escaned, Vasim Farooq, Patrick W Serruys, Yoshinobu Onuma.

JACC Cardiovasc Interv. 2019 Oct 28;12(20):2064-2075.

Abstract

Objectives:
The aim of this study was to investigate the impact of post percutaneous coronary intervention (PCI) quantitative flow ratio (QFR) on clinical outcomes in patients with de novo three vessel disease (3VD) treated with contemporary PCI.

Background:
The clinical impact of post-PCI QFR in patients treated with state-of-art PCI for de novo 3VD is undetermined.

Methods:
All vessels treated in the SYNTAX II trial were retrospectively screened and analyzed for post-PCI QFR. The primary endpoint of this substudy was vessel-oriented composite endpoint (VOCE) at 2 years, defined as the composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization. Receiving-operating characteristic curve was used to calculate the optimal cut-off value of post-PCI QFR for predicting 2-year VOCE. All the analyzable vessels were stratified on the basis of the optimal cut-off value.

Results:
A total of 968 vessels treated with PCI were screened. Post-PCI QFR was analyzable in 771 vessels (79.6%). A total of 52 VOCE (6.7%) occurred at 2 years. The mean value of post-PCI QFR was 0.91±0.07. The diagnostic performance of post-PCI QFR to predict 2-year VOCE was moderate (area under the curve: 0.702 [95%CI: 0.633-0.772]), with the optimal cut-off value of post-PCI QFR for predicting 2-year VOCE 0.91 (sensitivity 0.652, specificity 0.635). The incidence of 2-year VOCE in the vessels with post-PCI QFR <0.91 (n=284) was significantly higher compared to vessels with post-PCI QFR ≥0.91 (n=487) (12.0% vs. 3.7%, HR 3.37 [95%CI: 1.91-5.97], p<0.001).

Conclusions:
A higher post-PCI QFR value is associated with improved vessel-related clinical outcomes in state of the art PCI practice for de novo 3VD. Achieving a post-PCI QFR value ≥0.91 in all treated vessels should be a target when treating de novo 3VD. These findings require confirmation in future prospective trials.

Introduction

Pre-procedural assessment of fractional flow reserve (FFR) is the established gold standard to evaluate the physiological severity of obstructive coronary stenoses in patients with coronary artery disease (1). Evidence from a multitude of clinical trials have shown that FFR guided percutaneous coronary intervention (PCI) reduces the number of stents implanted, with improved clinical outcomes compared to angiography guided PCI (2,3). Notably, two large randomized trials have shown instantaneous wave-free ratio (iFR) guided PCI to be non-inferior to FFR guided PCI in predicting long-term clinical outcomes (4,5). As a result, FFR and iFR guided PCI have been incorporated in to current European Society of Cardiology revascularization guidelines, with a Class I indication (level of evidence A) in stable patients with obstructive coronary stenosis without other objective evidence of ischemia (1).

Three-dimensional angiography-derived fractional flow reserve (QFR: quantitative flow ratio) results in virtual color coded pullbacks of FFR without the use of pressure wire or hyperemic agents (6). Several studies have reported substantial correlation between QFR and coronary wire-derived FFR in patients with non-complex coronary artery disease.(7-10) A recent Bayesian meta-analysis from 13 studies demonstrated the accuracy of angiography-derived FFR, including QFR, irrespective of the computational approaches and software packages used, to detect hemodynamically significant lesion, when pressure-wire measured FFR was used as the reference measure (11). A recent substudy of the SYNTAX II trial demonstrated substantial applicability of QFR in anatomically complex coronary artery disease patients, namely de novo three-vessel disease (3VD), when compared to the hybrid iFR/FFR approach (12).

With respect to post-PCI physiological assessments, several trials have demonstrated the post-PCI FFR value to independently predict long-term clinical outcomes (13). The clinical implication of a post-PCI QFR in patients with complex coronary artery disease has not yet been investigated.

The aim of this study was to investigate the impact of post-PCI QFR on clinical outcomes in patients with de novo 3VD without left main disease from the ongoing SYNTAX-II Trial.

Methods

Study design of the SYNTAX II trial

The design and main results of the SYNTAX II trial have been published previously. (14,15) Briefly, SYNTAX II was a multicenter, open-label, single arm study which investigated the impact of state-of-the-art PCI on clinical outcomes in 454 patients with de novo 3VD, without left main involvement.

The state-of-the-art PCI strategy included:
(i) patients selected on the basis of equipoise for long term (4-year) mortality between coronary artery bypass graft (CABG) surgery and PCI utilizing the SYNTAX Score II; (ii) target lesions for revascularization were assessed with hybrid iFR/FFR approach - the details of the specific physiological assessments are described in the **Online Appendix and Online figures 1 and 2**; physiologically significant lesions were treated with the SYNERGY DES (Boston Scientific, Natick, MA, USA); (iii) post-PCI intravascular ultrasound (IVUS) assessment was mandatory to optimize stent expansion and apposition, with the recommendation to use

the modified MUSIC criteria (16); (iv) contemporary chronic total occlusion revascularization techniques by dedicated operators were recommended; (v) guideline-directed medical therapy, including contemporary antiplatelet therapy and high-intensity statin therapy were recommended (1).

The patient's clinical status was assessed at discharge, and at one and two years follow up. Extended yearly follow-up is planned up to 5 years. The local Ethics committee approved the study in all participating sites. All patients provided written informed consent before enrolment. The trial is registered with ClinicalTrials.gov, number NCT02015832.

The present post-PCI QFR substudy is a post-hoc analysis of the SYNTAX II trial. In the SYNTAX II, all patients had angiographic de novo 3VD based on visual estimation of a diameter stenosis >50%. After wire-based physiological assessment, the majority of patients had ≥2 functionally significant disease and underwent PCI treatment in ≥2 vessels. The present subanalysis was therefore performed at vessel level. All available angiographic characteristics, including the anatomical SYNTAX score, pre-procedural QFR, and IVUS parameters have been analyzed and published previously. (12,17) Lesion characteristics were identified according to the anatomical SYNTAX score definition (18).

Post-PCI QFR computation

Procedural coronary angiography was recorded and collected after the PCI without specific acquisition guidelines for QFR analysis. Final angiography was preceded by an intra-coronary injection of isosorbide dinitrate or nitroglycerin.

All vessels with at least one lesion treated with PCI were eligible for analysis. The ramus vessel was included as LCX. Lesions were excluded from the analysis if they 1) were located less than 3 mm from the aorta (i.e. ostial lesion), 2) had a reference lumen diameter below 2.0 mm by visual assessment, 3) presented with no or slow coronary blood flow [TIMI 0-2], 4) were filmed with less than 2 projections with isocenter calibration information, 5) had severe vessel overlap at the stenotic segments or 6) had a poor angiographic image quality precluding precise contour delineation.

Off-line QFR analysis was performed by an independent academic corelab comprising certified analysts for usage of the software with the QAngio XA 3D V1.1 software package (Medis Medical Imaging System BV, The Netherlands). For the computation of QFR, contrast QFR without hyperemic setting beside frame counting method was applied. The analysts were blinded to clinical outcomes. Details regarding the QFR calculation have been reported previously.(6,7) Briefly, the QFR calculation is based on the 3D QCA reconstructed from 2 angiographic projections with angles ≥ 25˚apart and volumetric flow rate calculated by using contrast bolus frame count.(7) The volumetric flow from the proximal to the distal part of the quantified segment of the coronary artery was assessed by the product of area times flow velocity based on frame count.

Vessel QFR was analyzed from the ostium of the main vessels (right, left anterior descending, or left circumflex coronary artery) until the distal point defined in the present subanalysis as follows: the distal point was placed at the most distal anatomical landmark (e.g. side branch) in a vessel with diameter of ≥2.0 mm by visual estimation. If an anatomical landmark is not present, the distal point was set 10 mm distal to the stent edge.(19)

If a vessel had two or more daughter branches in the distal segment (e.g. right posterior descending artery or posterolateral branch from RCA, left posterolateral or posterior descending in LCX), the vessel with a greater diameter was analyzed as main vessel for the present analysis. The automatic reference interpolation function was used to

establish the reference for the calculation. Whenever a proper reference interpolated line could not be established, it was adjusted by using a selected non-diseased proximal/distal segment.

QFR within stent was measured using lesion QFR function and regarded as "in-stent QFR". If a vessel had two or more separate stented sites, an in-stent QFR per vessel was calculated as one minus the sum of two or more QFR gradients within stents.

Clinical endpoints per vessel

The primary endpoint of this substudy was the vessel-oriented composite endpoint (VOCE) at 2 years, defined as a composite of vessel-related cardiac death, vessel-related myocardial infarction (MI), and target vessel revascularization (TVR). Secondary endpoints were individual components of VOCE. All definitions of clinical endpoints were identical to the SYNTAX II study.(14) Cardiac death was defined as any death due to immediate cardiac causes (e.g. MI, heart failure, fatal arrhythmia). Unwitnessed death and death of unknown cause were classified as cardiac death. Periprocedural MI was defined according to the historical definition of SYNTAX I and SYNTAX II as following: CK-MB ≥5x ULN (or troponin ≥35x ULN if CK-MB not available) with new pathological Q-waves in the ECG within 7 days after PCI (14,20). Spontaneous MI was defined as new Q-waves or one plasma level of CK-MB 5x ULN (or Tn ≥35x ULN if CK-MB not available) in the context of acute coronary syndrome (ACS). TVR was defined as any repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel performed for restenosis or other complication of the target vessel. All clinical outcomes were adjudicated by an independent clinical event committee (CEC) from the SYNTAX II trial.

For the present analysis all the available information, including the coronary angiogram were independently reviewed and evaluated by 2 interventional cardiologists (N.K. and Y.K.), blinded to baseline clinical, procedural characteristics, and post-PCI QFR value. Clinical events were re-adjudicated per vessel as vessel-related or none vessel-related. In case the patient was adjudicated as cardiac death without clear relation to the specific treated vessel (e.g. heart failure, fatal arrhythmia) at follow-up, the death was adjudicated as a vessel-related cardiac death for all the vessels initially treated. Whenever an MI occurred without identifiable culprit vessel, it was adjudicated, as attributed to all the vessels initially treated. In case of disagreement, angiogram at event and the source documents were reviewed by a third assessor and a 2:1 agreement was achieved.

Statistical Analysis

Categorical variables are summarized as frequencies and percentages and compared between groups using Pearson chi-square or Fisher's exact test. Continuous variables are presented as mean ± SD or median (interquartile), and compared between groups using 2-tailed, unpaired *t* tests or Mann-Whitney test. The predictive value of clinical and angiographic characteristics on post-PCI QFR value was identified by a generalized linear mixed-effects regression model with patient identification as random effect to account for the non-independence of vessels within same patient.(21) The detailed methodology is described in the **online appendix**. The predictive value of post-PCI QFR for 2-year VOCE and TVR was analyzed using receiver-operating characteristic (ROC) curve, with cutoff value of QFR, sensitivity, specificity, area under the curve (AUC), 95% confidence interval (CI), and p value. As an exploratory analysis, the predictive value of in-stent QFR and MSA derived from IVUS was analyzed using ROC curve and compared by using the DeLong method.(22) Vessels

were stratified by post-PCI QFR cutoff value. Survival curves were constructed using Kaplan-Meier estimates and the log-rank test to compare between-group differences. A hazard ratio (HR) was reported with 95% confidence intervals (CI) based on the Cox regression model. The impact of a low post-PCI QFR versus a high post-PCI QFR among vessels treated with or without IVUS guidance was estimated with a Cox regression model. Multivariate Cox regression analysis was used to adjust for baseline imbalances between groups. The detailed methodology is described in the **online appendix**. Robust sandwich variance estimator was used together with cox regression to account for possible lesion correlation.(23) In addition, the patient level analysis was performed to confirm the consistency with the vessel level analysis (**Online appendix**).

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were undertaken in SPSS (version 25.0.0, IBM, New York) and R (version 3.4.3, R Foundation for statistical Computing, Vienna, Austria).

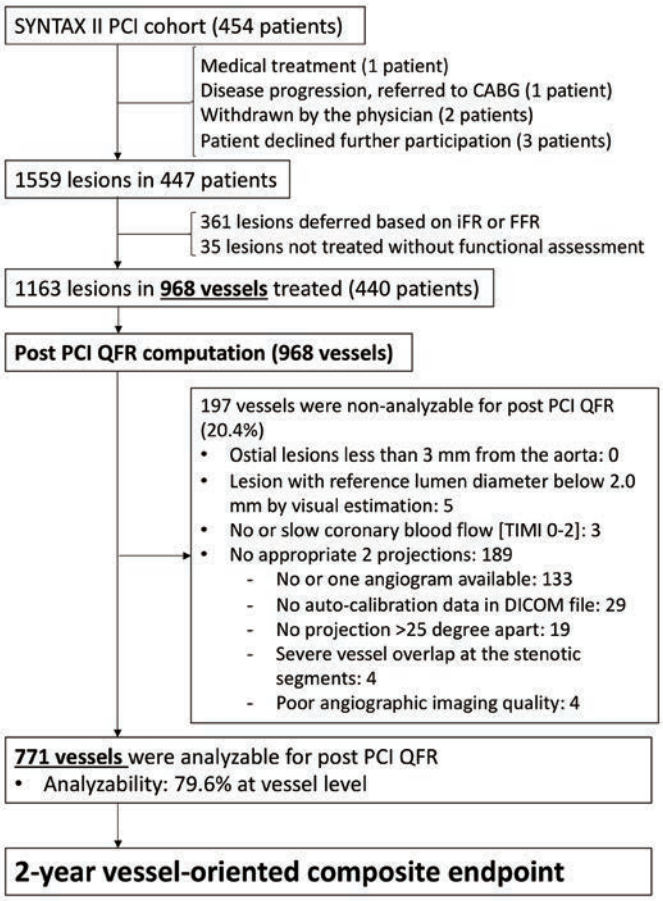


Figure 1. Study flow chart
CABG = coronary artery bypass graft, DICOM = Digital Imaging and Communications in Medicine, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TIMI = Thrombolysis In Myocardial Infarction.

Results

In the SYNTAX II trial, 1559 angiographically significant lesions (diameter stenosis ≥50% by visual estimation) in 454 patients were screened. After hybrid wire-based physiological assessment 1163 lesions in 968 vessels were treated with PCI and 361 lesions deferred. Out of 968 treated vessels treated, 771 vessels were analyzable for post-PCI QFR (79.6%) (**Figure 1**). The most frequent reasons of non-analyzability for post-PCI QFR was unavailability of 2 projections post procedure (133/968, 13.7%) and lack of auto-calibration data (29/968, 3.0%). One vessel was treated without any stent (1/968, 0.1%). Baseline clinical characteristics in patients with or without at least one post-PCI QFR measurement are shown in **Online table 1**.

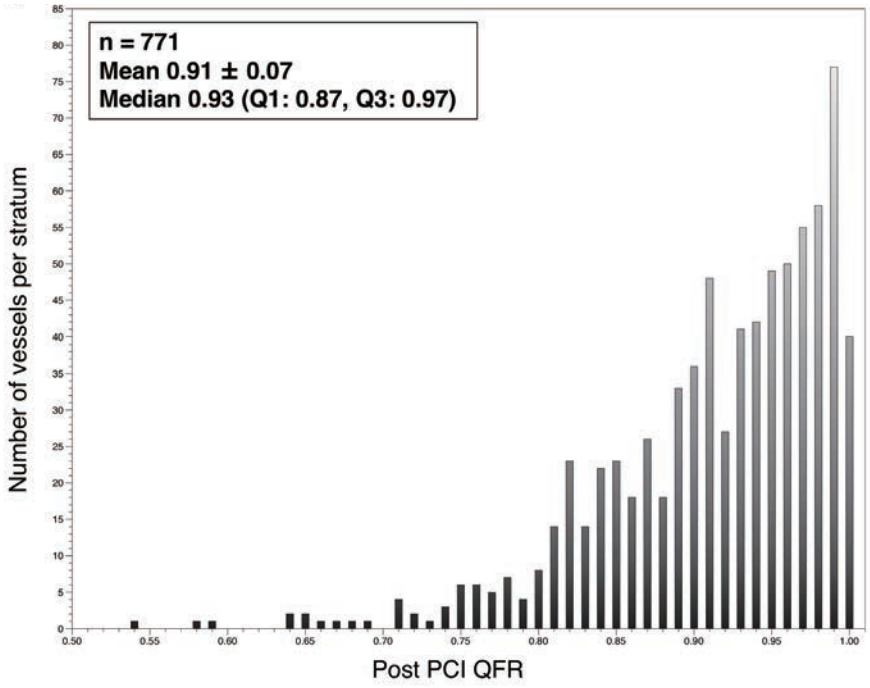


Figure 2. Distribution of post-PCI QFR values.
PCI = percutaneous coronary intervention, QFR = quantitative flow ratio.

Distribution and predictor of post-PCI QFR value

The mean value of post-PCI QFR was 0.91 ± 0.07. The distribution is shown in **Figure 2**. Baseline clinical and pre/post procedural characteristics are shown in **Table 1 and 2**. Left anterior descending (LAD) was the most frequently analyzed vessel (45.7%). Chronic total occlusion was treated in 10.5% of vessels. Pre-procedural QFR value was available in 68.6% of vessels. 103 vessels with TIMI flow <3 were excluded from denominator, resulting in analyzability of 79.2% (528/668). The mean value of pre-procedural QFR was 0.67 ± 0.18. 76.7% of vessels were assessed by iFR or FFR. IVUS for stent optimization was undertaken in 79.8% of patients (615/771).

Utilizing a generalized linear mixed-effect regression model, previous myocardial infarction, LAD stenosis, serial lesion, lower pre-procedural QFR value and lower MSA derived from IVUS were shown to be a significant predictors of lower post-PCI QFR value (**Table 3**).

Table 1. Baseline characteristics among the patients having at least one vessel with low post-PCI QFR (<0.91) or not (≥0.91)

	Total n=393	QFR<0.91 n=227	QFR≥0.91 n=166	p value
Age (years)	66.6 ± 9.8 (393)	66.7 ± 9.9 (227)	66.5 ± 9.6 (166)	0.872
Male	92.6 (364/393)	91.6 (208/227)	94.0 (156/166)	0.380
Body mass index (kg/m2)	29.0 ± 4.7 (393)	29.1 ± 4.6 (227)	28.9 ± 4.9 (166)	0.811
Diabetes mellitus type I or II	29.7 (116/391)	29.1 (66/227)	30.5 (50/164)	0.763
Insulin treated	8.7 (34/391)	9.3 (21/227)	7.9 (13/164)	0.647
Oral medication	18.7 (73/391)	17.6 (40/227)	20.1 (33/164)	0.531
Diet only	2.0 (8/391)	2.2 (5/227)	1.8 (3/164)	0.549
Current smoker	14.7 (56/381)	16.4 (36/220)	12.4 (20/161)	0.283
Previous myocardial infarction	12.3 (48/391)	12.9 (29/225)	11.4 (19/166)	0.667
Previous stroke	5.3 (21/393)	6.2 (14/227)	4.2 (7/166)	0.396
Hypertension	75.4 (295/391)	74.8 (169/226)	76.4 (126/165)	0.719
Hyperlipidemia	77.1 (297/385)	76.3 (171/224)	78.3 (126/161)	0.658
Creatinine clearance (ml/min)	81.8 ± 27.2 (393)	82.0 ± 27.2 (227)	81.4 ± 27.2 (166)	0.815
Ejection fraction (%)	58.3 ± 8.1 (393)	58.9 ± 7.0 (227)	57.5 ± 9.3 (166)	0.118
Peripheral vascular disease	7.6 (30/393)	8.4 (19/227)	6.6 (11/166)	0.520
Chronic obstructive pulmonary disease	11.5 (45/393)	11.0 (25/227)	12.0 (20/166)	0.750
Clinical presentation				
Silent ischemia	5.6 (22/392)	5.3 (12/227)	6.1 (10/165)	0.742
Stable angina	69.4 (272/392)	66.5 (151/227)	73.3 (121/165)	0.148
Unstable angina	25.0 (98/392)	28.2 (64/227)	20.6 (34/165)	0.087
SYNTAX score	20.6 ± 6.4 (393)	21.2 ± 6.7 (227)	19.8 ± 5.7 (166)	0.031
Residual SYNTAX score	3.7 ± 4.2 (393)	3.4 ± 4.2 (227)	4.0 ± 4.1 (166)	0.157

Data are mean ± SD or % (n/N).
PCI = percutaneous coronary intervention, QFR = quantitative flow ratio.

Optimal cutoff value of post-PCI QFR for predicting 2-year VOCE

At 2 years follow-up, 5 patients with 8 treated vessels were lost to follow-up, resulting in complete 2-year follow-up in 99.0% (763/771) at a vessel level. A total of 52 VOCE (6.7%) were recorded at 2 years. The distribution of VOCE stratified by post-PCI QFR value is shown in **Figure 3**. The incidence of VOCE in non-analyzable vessels was similar to analyzable vessels (11/197, 5.6%, Log rank p=0.529, in **Online figure 3**). When 2-year VOCE was used as a binary variable irrespective of the time to event, ROC curve demonstrated that the cut off value of post-PCI QFR for predicting 2-year VOCE was 0.91, with a sensitivity of 65% and specificity of 64% (AUC: 0.702, [95%CI: 0.633-0.772], p<0.001, **Figure 4**). After stratification into 2 groups according to this cutoff value, there were 284 (37%) vessels with a low post-PCI QFR (<0.91) and 487 (63%) vessels with a high post-PCI QFR (≥0.91).

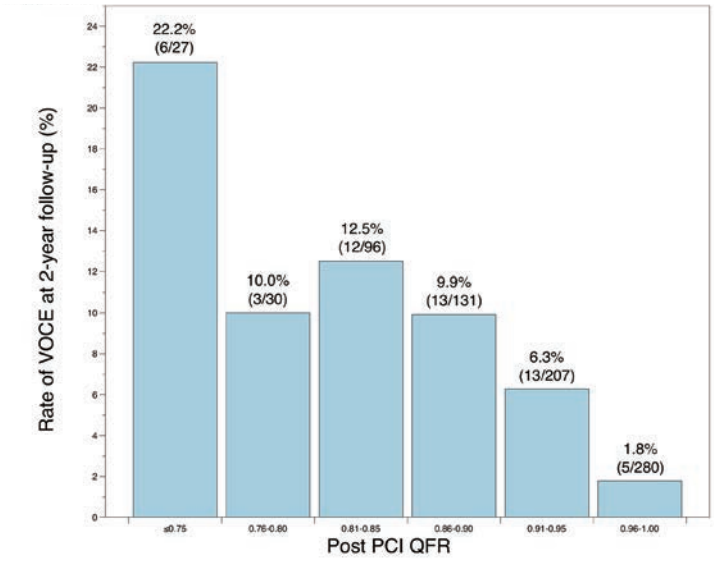


Figure 3. Rate of VOCE at 2-year follow-up in each 0.05 post-PCI QFR unit.
PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, VOCE = vessel-oriented composite endpoint – a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization.

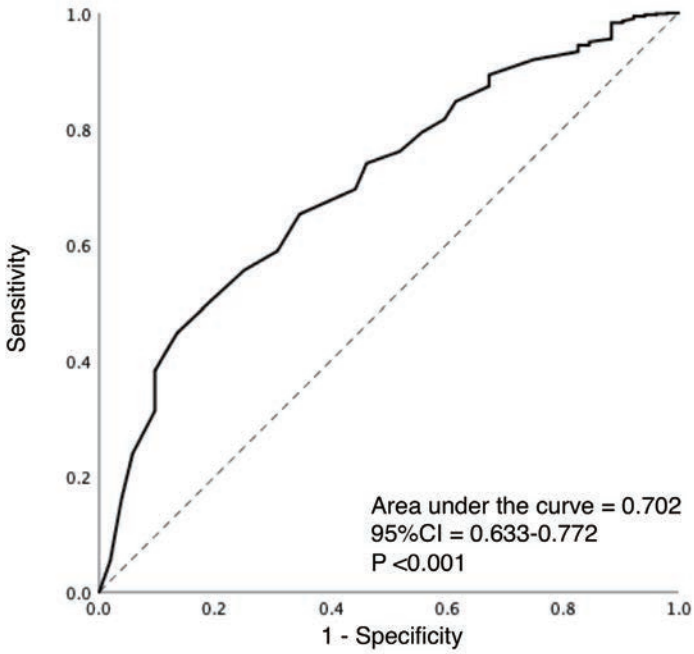


Figure 4. Receiver Operating Characteristic Curve of post-PCI QFR for 2-year VOCE
Post-PCI QFR <0.91 had a sensitivity of 65% and specificity of 78%.
PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, VOCE = vessel-oriented composite endpoint – a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization.

Table 2. Pre and post procedural characteristics of study vessels stratified by the cutoff value of post-PCI QFR at vessel level

	Total n=771	QFR<0.91 n=284	QFR≥0.91 n=487	p value
Vessel				
RCA	22.8 (176/771)	20.4 (58/284)	24.2 (118/487)	0.224
LAD	45.7 (352/771)	59.5 (169/284)	37.6 (183/487)	<0.001
LCX	31.5 (243/771)	20.1 (57/284)	38.2 (186/487)	<0.001
Number of lesions treated per vessel	1.44 ± 0.64 (771)	1.50 ± 0.64 (284)	1.40 ± 0.63 (487)	0.037
Serial lesion*	37.1 (286/771)	43.3 (123/284)	33.5 (163/487)	0.006
CTO	10.5 (81/771)	10.2 (29/284)	10.7 (52/487)	0.839
Bifurcation and trifurcation	33.3 (257/771)	37.7 (107/284)	30.8 (150/487)	0.051
Severe tortuosity	3.6 (28/771)	4.2 (12/284)	3.3 (16/487)	0.501
Length >20 mm	41.9 (323/771)	41.5 (118/284)	42.1 (205/487)	0.882
Heavy calcification	14.9 (115/771)	19.0 (54/284)	12.5 (61/487)	0.015
Diffuse disease	8.6 (66/771)	10.6 (30/284)	7.4 (36/487)	0.129
Pre procedural physiological and 3D-QCA assessment				
Pre procedural QFR	0.67 ± 0.18 (529)	0.64 ± 0.19 (195)	0.69 ± 0.17 (334)	0.007
Pre procedural iFR	0.69 ± 0.22 (578)	0.67 ± 0.22 (215)	0.70 ± 0.21 (363)	0.131
Pre procedural FFR	0.74 ± 0.09 (175)	0.74 ± 0.08 (65)	0.74 ± 0.09 (110)	0.599
Total lesion length per vessel (mm) †	24.0 ± 16.4 (538)	25.5 ± 18.6 (197)	23.2 ± 14.9 (341)	0.141
Reference luminal diameter (mm) †	2.41 ± 0.50 (538)	2.39 ± 0.47 (197)	2.43 ± 0.51 (341)	0.411
Diameter stenosis (%) †	60.9 ± 11.1 (535)	60.7 ± 11.0 (196)	61.1 ± 11.2 (339)	0.701
Procedural information				
Number of stents used per vessel	1.7 ± 0.9 (771)	1.7 ± 0.9 (284)	1.7 ± 0.9 (487)	0.782
Total stent length per vessel (mm)	42.6 ± 24.2 (771)	42.1 ± 24.8 (284)	42.9 ± 23.8 (487)	0.665
IVUS usage	79.8 (615/771)	80.6 (229/284)	79.3 (386/487)	0.647
Post dilatation based on IVUS finding	31.1 (240/771)	33.8 (96/284)	29.6 (144/487)	0.221
Minimum stent area (mm2)	6.03 ± 2.03 (492)	5.82 ± 1.92 (172)	6.15 ± 2.09 (320)	0.086
Post-PCI QFR	0.91 ± 0.07 (771)	0.84 ± 0.06 (284)	0.96 ± 0.03 (487)	<0.001
In-stent QFR	0.98 ± 0.03 (771)	0.97 ± 0.03 (284)	0.99 ± 0.01 (487)	<0.001
In-stent diameter stenosis (%) †	13.1 ± 10.0 (771)	12.8 ± 10.5 (284)	13.2 ± 9.7 (487)	0.523

Data are mean ± SD (n) or % (n/N). CTO = chronic total occlusion, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, IVUS = intravascular ultrasound, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, PCI = percutaneous coronary intervention, QCA = quantitative coronary angiography, QFR = quantitative flow ratio, RCA = right coronary artery.

* More or 2 vessels per vessel

† Value derived from 3-dimensional angiography in QFR analysis

Regarding baseline characteristics at a patient level, patients in the low post-PCI QFR group had a higher anatomical SYNTAX score compared to the high post-PCI QFR group (**Table 1**). In terms of procedural characteristics, vessels in the low post-PCI QFR group were more frequently located in LAD, and had lower pre-procedural and in-stent QFR values and a higher prevalence of serial lesion and heavy calcification, compared to the high post-PCI QFR group (**Table 2**).

The diagnostic performance of post-stent QFR to predict 2-year TVR was similar to 2-year VOCE (AUC: 0.707, [95%CI: 0.629-0.785], p<0.001). The diagnostic performances of in-stent QFR and MSA to predict 2-year VOCE and TVR were poor and worse than post-PCI QFR (**Online table 2**).

Clinical outcomes stratified by the best cutoff value of post-PCI QFR

The incidence of VOCE at 2 years was significantly higher in the low post-PCI QFR group (<0.91) compared to the high post-PCI QFR group (≥0.91) (12.0% in low group versus 3.7% in

high group; hazard ratio (HR), 3.37; 95% confidence interval (CI), 1.91 to 5.96; p<0.001) (**Central Illustration, Table 4**). This difference was driven by >x3 higher risk of 2-year TVR in the low group (10.6% versus 3.7%; HR, 3.83; 95% CI, 1.95 to 7.54; p<0.001), whereas the incidences of vessel-related cardiac death and MI did not significantly differ between groups. In vessels treated with or without IVUS guidance, the incidence of 2-year VOCE and TVR were higher in the low post-PCI QFR group compared to the high post-PCI QFR. The impact of low post-PCI QFR on 2-year VOCE was greater in vessels treated without IVUS guidance compared to vessels treated with IVUS guidance (p for interaction=0.063) (**Central Illustration, Online table 3**).

Two multivariate models demonstrated that the post-PCI QFR <0.91 remained as an independent predictor of 2-year VOCE (HR, 3.38; 95% CI, 1.85 to 6.20; p<0.001 in model 1, HR, 2.45; 95% CI, 1.07 to 5.64; p=0.035 in model 2) (**Table 5**). The result of univariate analysis is shown in **Online table 4**. These findings were confirmed in the patient level analysis (**Central Illustration, Online appendix, Online tables 5 and 6**).

Table 3. Predictive value of clinical and angiographic characteristics on the post-PCI QFR value

Model 1: pre-procedural variables

Variable	Standardized ß-coefficient	95% CI	p value
Previous myocardial infarction	-0.037	-0.055 to -0.020	<0.001
Left anterior descending stenosis	-0.026	-0.040 to -0.012	<0.001
Serial lesion *	-0.018	-0.031 to -0.006	0.004
Pre-procedural QFR (each 0.10 increase)	0.005	0.0005 to 0.009	0.030
Male sex	0.022	-0.004 to 0.048	0.094
Baseline diameter stenosis (each 10% increase) †	0.005	-0.002 to 0.012	0.157
Bifurcation or trifurcation lesion	0.007	-0.006 to 0.020	0.278
Heavy calcification	-0.007	-0.024 to 0.009	0.381
Any diabetes mellitus	-0.005	-0.018 to 0.008	0.447

Model 2: post-procedural variables

Variable	Standardized ß-coefficient	95% CI	p value
Minimal stent area (each 1.0 mm^2 increase) ‡	0.004	0.001 to 0.007	0.009
Number of stents per vessel	0.004	-0.004 to 0.011	0.364
In-stent diameter stenosis (each 10% increase) †	<0.001	-0.006 to 0.007	0.929

CI = confidence interval, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio.

* More or 2 lesions per vessel

† Value derived from 3-dimensional angiography in QFR analysis

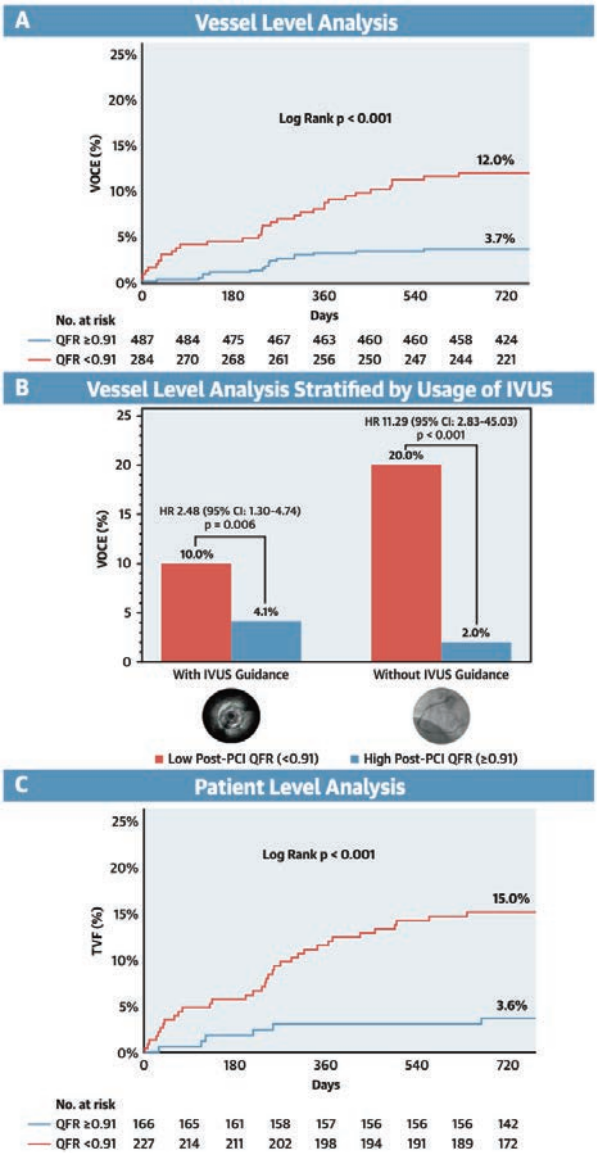
‡ Value derived from intravascular ultrasound

Table 4. Two-year clinical outcomes in vessels with low (<0.91) or high post-PCI QFR value (≥0.91).

	QFR<0.91 (n=284)	QFR≥0.91 (n=487)	HR (95%CI)	p value
Unadjusted				
VOCE*	34 (12.0%)	18 (3.7%)	3.37 (1.91-5.96)	<0.001
Cardiac death	4 (1.4%)	4 (0.8%)	1.72 (0.85-3.47)	0.133
MI	4 (1.4%)	4 (0.8%)	1.72 (0.32-9.36)	0.528
TVR	30 (10.6%)	14 (2.9)	3.83 (1.95-7.54)	<0.001

CI = confidence interval, HR = hazard ratio, MI = myocardial infarction, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TVR = target vessel revascularization, VOCE = vessel-oriented composite endpoint.

*VOCE: a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization



Central Illustration. Relationship between a low post-PCI QFR (<0.91) and 2-year composite clinical endpoints at the vessel and patient level.

Kaplan–Meier curves show the cumulative incidence of vessel-oriented composite endpoint (VOCE) -a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization (TVR) - over 730 days of follow-up among the vessels with low (<0.91) or high post-PCI QFR value (≥0.91) (Panel A). The impact of the low post-PCI QFR (<0.91) on 2-year VOCE among vessels with or without IVUS guidance is shown in Panel B (P for interaction 0.063). Kaplan–Meier curves show the cumulative incidence of target vessel failure (TVF) - a composite of cardiac death, target vessel myocardial infarction, and TVR - over 730 days of follow-up among the patients having at least one vessel with low post-PCI QFR (<0.91) or not (≥0.91) (Panel C).

CI = confidence interval, HR = hazard ratio, IVUS = intravascular ultrasound, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TVF = target vessel failure, TVR = target vessel revascularization, VOCE = vessel-oriented composite endpoint.

Table 5. Multivariate independent predictors of two-year VOCE* in the vessel level analysis.

Model 1			
Variables	**HR**	**95%CI**	**p value**
Post-PCI QFR<0.91	3.38	1.85-6.20	<0.001
Creatinine clearance (ml/min)	0.98	0.97-0.99	0.005
LAD stenosis	1.12	0.71-1.77	0.626
SYNTAX score	1.05	0.99-1.10	0.102

Model 2			
Variables	**HR**	**95%CI**	**p value**
Post-PCI QFR<0.91	2.45	1.07-5.64	0.035
Minimum stent area (mm2) **	0.92	0.73-1.15	0.453
Total stent length	1.00	0.98-1.01	0.621
In-stent diameter stenosis †	1.01	0.97-1.05	0.623
Residual SYNTAX score	1.00	0.88-1.15	0.948

CI = confidence interval, HR = hazard ratio, LAD = left anterior descending coronary artery, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, VOCE = vessel oriented composite endpoint.

* VOCE: a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization

** Value derived from intravascular ultrasound

† Value derived from 3-dimensional angiography in QFR analysis

Discussion

The main findings of this post hoc substudy of the SYNTAX II study are the followings:

1. Post-PCI QFR was analyzable in 79.6% of treated vessels without specific acquisition guideline in patients with de novo 3VD.
2. Previous myocardial infarction, serial lesions, LAD stenosis, lower pre-procedural QFR value and lower MSA derived from IVUS were associated with a lower post-PCI QFR value in patients with de novo 3VD.
3. The diagnostic performance of post-PCI QFR to predict 2-year VOCE was moderate with AUC of 0.702, and the low post-PCI QFR (<0.91) was associated with 2-year VOCE following adjustment for clinical, angiographic and procedural characteristics in patients with de novo 3VD.

Feasibility of post-PCI QFR in patients with three vessel disease

A recent nationwide Italian cross-sectional study reported a low adoption rate of post-PCI wire based physiological assessment (9%), even in patients who underwent wire based physiological assessment before PCI.(24)

In the present post hoc substudy, the analyzability of post-PCI QFR was acceptable. Notably, the majority of reasons for non-analyzability of post-PCI QFR can be avoided by using specific acquisition guideline. Although post-PCI QFR computation was performed offline in a blinded fashion to clinical outcomes, it is apparent that online computation of QFR is more pragmatic for daily practice. In the FAVOR II China trial utilizing invasive FFR as a reference measure, offline computation of pre-procedural QFR demonstrated a high diagnostic accuracy for hemodynamically significant coronary stenosis (93.3% in offline versus 92.7% in online). (8). These findings require confirmation in a prospective trial.

Clinical implication of post-PCI physiological assessment for predicting future clinical events

Multiple large observational studies and post hoc analyses of randomized controlled trials have established that the post-PCI FFR value to be an independent predictor of long-term clinical outcomes. Previous trials have consistently demonstrated that "higher is better" for post PCI FFR, although the optimal cut-off value of post-PCI FFR varied from 0.86 to 0.96 for the prediction of clinical events, utilizing differing definitions of the primary endpoint (19,25,26). Despite growing evidence, post-PCI FFR measurement has not yet become part of established clinical practice based on the lack of international guideline recommendations.(24)

To date little is known about the relationship between post-PCI QFR value and clinical outcomes. In the present study, a higher post-PCI QFR value in patients with de novo 3VD was associated with improved vessel-related clinical outcomes. This result is in line with previous trials of post-PCI FFR., The present study is unique for the following reasons:

Firstly, this study included relatively high-risk population, namely de novo 3VD (mean anatomical SYNTAX score 20.6). Post-PCI QFR computation for anatomically complex lesions is clinically relevant but challenging. Despite state-of-the-art PCI for de novo 3VD, the post-PCI QFR was the strongest independent predictor of VOCE at 2 years. Therefore, the operators should aim for a post-PCI QFR value ≥0.91 in all treated vessels for de novo 3VD.

Secondly, the usage of IVUS for stent optimization was relatively high in the present study (79.8% of vessels). The relatively low incidence of residual ischemia after PCI identified as post-PCI QFR ≤0.80 (7.4%) may be explained by the high usage of IVUS for stent optimization in the present study. According to the results of stratified analysis by vessels treated with or without IVUS guidance, post-PCI QFR may have a higher predictive value for 2-year VOCE in vessels treated without IVUS guidance compared to vessels treated with IVUS guidance. Notably in the IVUS substudy of the SYNTAX II trial, one third of the lesions had a suboptimal minimal stent area (≤5.2 mm^2).(17) This finding suggests that post-PCI physiological assessment, with FFR, iFR or QFR, may be feasible to guide further stent optimization, even after IVUS guidance stent optimization.

Thirdly, target lesions were exclusively treated with current generation thin-strut SYNERGY DES. This makes the impact of post-PCI QFR on clinical outcomes more likely.

In terms of a low adoption rate of post-PCI FFR in real world practice (24), the most likely causes are the need for pressure-wire and hyperemic agents, and prolonged procedural time. As compared to FFR, post-PCI QFR is a more user-friendly tool for interventional cardiologist due to the unnecessity of both pressure-wire and hyperemic agents, particularly for patients undergoing multivessel PCI. In addition, a previous trial has demonstrated online QFR computation to have significantly shorter measurement times compared to FFR.(10) Consequently, post-PCI QFR measurements may easily become part of established clinical practice than FFR. The relationship between post-PCI QFR and clinical outcomes, and its cost effectiveness, requires prospective validation in future trials with online computation according to specific acquisition guidelines.

Study limitations

This retrospective and non-pre-specified sub-analysis of the SYNTAX II study has several limitations.

Firstly, the angiography was not prospectively acquired according to a specific acquisition protocol to fulfill all the technical requirements of QFR analysis. Therefore, QFR was not analyzable in a significant proportion of vessels (20% in post-PCI and 30% in pre-PCI) in this highly selected SYNTAX II population, which may suggest that the post-hoc analyzability of QFR could possibly be worse in real world practice.

Secondly, the study was not able to evaluate the impact of further intervention in response to a suboptimal post-PCI QFR value on clinical outcomes. Functional optimization using virtual pullback curves of post-PCI QFR should be investigated in future trial.

Thirdly, the correlation between QFR and iFR or FFR after the procedure was not possible, since post-procedural iFR or FFR measurement was recommended but not mandatory in the protocol.

Last, we considered the QFR value of the entire vessel until its diameter became <2.0 mm similar to previously published pre-procedural QFR analysis in the SYNTAX II trial (12). However, there is no consistent definition of the most distal analysis point of QFR for predicting future clinical events.

Conclusion

A higher post-PCI QFR value is associated with improved vessel-related clinical outcomes in patients with de novo three vessel disease treated with state-of-the-art PCI. The operators should aim for post-PCI QFR value ≥0.91 in all treated vessels to improve clinical outcomes, when treating de novo 3VD. These findings require confirmation in future prospective trials with online computation according to the specific acquisition guidelines.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018.
2. 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.
3. van Nunen LX, Zimmermann FM, Tonino PA et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015;386:1853-60.
4. Davies JE, Sen S, Dehbi HM et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med 2017;376:1824-1834.
5. Gotberg M, Christiansen EH, Gudmundsdottir IJ et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med 2017;376:1813-1823.
6. Tu S, Barbato E, Koszegi Z et al. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. JACC Cardiovasc Interv 2014;7:768-77.
7. Tu S, Westra J, Yang J et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv 2016;9:2024-2035.
8. Xu B, Tu S, Qiao S et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol 2017;70:3077-3087.
9. Westra J, Tu S, Winther S et al. Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio During Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II). Circ Cardiovasc Imaging 2018;11:e007107.
10. Westra J, Andersen BK, Campo G et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc 2018;7.
11. Collet C, Onuma Y, Sonck J et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J 2018;39:3314-3321.
12. Asano T, Katagiri Y, Chang CC et al. Angiography-Derived Fractional Flow Reserve in the SYNTAX II Trial: Feasibility, Diagnostic Performance of Quantitative Flow Ratio, and Clinical Prognostic Value of Functional SYNTAX Score Derived From Quantitative Flow Ratio in Patients With 3-Vessel Disease. JACC Cardiovasc Interv 2019;12:259-270.
13. Hakeem A, Uretsky BF. Role of Postintervention Fractional Flow Reserve to Improve Procedural and Clinical Outcomes. Circulation 2019;139:694-706.
14. Escaned J, Collet C, Ryan N et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. Eur Heart J 2017;38:3124-3134.
15. Serruys PW, Kogame N, Katagiri Y et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019;15:e244-e252.
16. de Jaegere P, Mudra H, Figulla H et al. 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;19:1214-23.
17. Katagiri Y, De Maria GL, Kogame N et al. Impact of post-procedural minimal stent area on 2-year clinical outcomes in the SYNTAX II trial. Catheter Cardiovasc Interv 2019.
18. Serruys PW, Onuma Y, Garg S et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5:50-6.

19. Li SJ, Ge Z, Kan J et al. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. JACC Cardiovasc Interv 2017;10:986-995.
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. Kastrati A, Schomig A, Elezi S, Schuhlen H, Wilhelm M, Dirschinger J. Interlesion dependence of the risk for restenosis in patients with coronary stent placement in in multiple lesions. Circulation 1998;97:2396-401.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
23. Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. Journal of the American Statistical Association 1989;84:1074-1078.
24. Tebaldi M, Biscaglia S, Fineschi M et al. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. JACC Cardiovasc Interv 2018;11:1482-1491.
25. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv 2016;9:1022-31.
26. Piroth Z, Toth GG, Tonino PAL et al. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. Circ Cardiovasc Interv 2017;10.

Supplementary Material

Hybrid wire-based physiological assessment of the SYNTAX II trial

Lesions were firstly interrogated with iFR. If a lesion had an iFR value <0.86, the lesion was treated with PCI. If a lesion had an iFR >0.93, PCI for the lesion was deferred. When iFR of a lesion was between 0.86 and 0.93, the lesion was re-interrogated with FFR to confirm the significance of ischemia. In those lesions assessed with FFR, the lesions with FFR ≤0.80 were treated with PCI and the lesions with FFR >0.80 were not treated with PCI. (**Online figure 1**). In case of sequential lesions, the protocol of the SYNTAX II strongly recommended following physiological assessment strategy (**Online figure 2**) (1):

- Pressure measurements will be made distal to the most distal stenosis.
- If the iFR is <0.86 or FFR is ≤0.80, the most severe angiographic stenosis should be treated and physiological reassessment with the hybrid iFR/FFR approach carried out.

Detailed statistical methodology of the generalized linear mixed-effects regression model investigating the predictors of the post PCI QFR

Firstly, 6 variables were selected according to the previous publication regarding post-procedural FFR as follows: male sex, diabetes mellitus, LAD lesion, baseline diameter stenosis, pre-procedural QFR (instead of FFR), and number of stents per vessel. (2) Secondly, we added prior myocardial infarction, since angiographically severe stenoses in prior-MI-related coronary arteries are not necessary to induce myocardial ischemia due to reduction in the amount of viable myocardium.(3) Thirdly, we added variables derived from angiography before procedure such as bifurcation or trifurcation, heavy calcification, and serial lesion. Finally, we added in-stent diameter stenosis derived from 3-dimentional angiography and minimum stent area derived from IVUS. A total of 12 variables were stratified according to pre-procedural or post-procedural variables. Thereafter, the 9 pre-procedural variables were incorporated in the first generalized linear mixed model (GLMM), and the remaining 3 post-procedural variables were incorporated in the second GLMM.

Detailed statistical methodology of the multivariate Cox regression analysis with robust sandwich variance estimator

A total of 19 variables were selected according to the previous publications which investigated independent predictors including post PCI FFR of clinical events as follows: post PCI QFR <0.91, age, female sex, diabetes mellitus, previous MI, hypertension, hyperlipidemia, Creatine Clearance, left ventricular ejection fraction, unstable angina, SYNTAX score, residual SYNTAX score, LAD stenosis, serial lesion, diffuse disease, baseline diameter stenosis, total stent length, minimum stent area derived from IVUS, and in-stent diameter stenosis.(2,4-6) All selected variables were modeled first univariately and multivariately using variables with univariate P value <0.20. Consequently, the final model included post PCI QFR <0.91, Creatine clearance, LAD stenosis, and SYNTAX score. Furthermore, additional model including following procedure related variables was established: post PCI QFR <0.91, Minimum stent area, total stent length, in-stent diameter stenosis, and residual SYNTAX score.

Methods and results of the patient level analysis

The patient level analysis was performed to confirm the results of the vessel level analysis. A total of 393 patients who had at least one vessel with post PCI QFR measurement were included in the patient level analysis. Patients were stratified by either having at least one vessel with post PCI QFR <0.91 or not. Primary endpoint was target vessel failure (TVF) at 2 years defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization. Vessel-oriented composite endpoint (VOCE: a composite of a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization) which was used in the vessel level analysis, was derived from TVF with re-adjudication of certain cardiac death and target vessel myocardial infarction by 2 interventional cardiologists (N.K. and Y.K.). Therefore, TVF is reasonable endpoint for this sensitivity patient-level analysis. Individual components of TVF were analyzed as secondary endpoints. Survival curves were constructed using Kaplan-Meier estimates and the log-rank test was used to compare between-group differences. A hazard ratio (HR) was reported with 95% confidence intervals (CI) based on the Cox regression model. Multivariate Cox regression analysis was used to adjust for baseline imbalances between groups. Chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), and SYNTAX score were selected as independent variable for multivariate Cox regression analysis, since these three variables were independent predictors of a composite of all-cause death, any stroke, any myocardial infraction, and any revascularization in the SYNTAX II trial.(7)

Baseline characteristics are shown in Table 1. The SYNTAX score was slightly but significantly higher in patients with the low QFR (<0.91) when compared to ones with the high QFR (≥0.91) (21.2 vs. 19.8, p=0.031). The incidence of TVF at 2 years was significantly higher in the low post PCI QFR group (<0.91) when compared with the high post PCI QFR group (≥0.91) (15.0% in low group versus 3.6% in high group; hazard ratio (HR), 4.38; 95% confidence interval (CI), 1.84 to 10.42; p<0.001) (Central Illustration (C) and Online table 5). This difference was driven by more than 4 times higher risk of 2-year TVR in the low group (13.2% versus 3.0%; HR, 4.64; 95% CI, 1.80 to 11.95; p<0.001), whereas the incidences of cardiac death and MI did not differ between groups. After adjustment for COPD, PVD, and SYNTAX score, the post PCI QFR <0.91 still remained as an independent predictor of 2-year TVF (HR, 4.64; 95% CI, 1.80 to 11.95; p<0.001) (Online table 6).

Online Table 1. Baseline clinical characteristics in patients with at least one post PCI QFR measurement and those without any post PCI QFR measurement

	Patients with at least one post PCI QFR measurement (n=393)	Patients without any post PCI QFR measurement (n=61)	p value
Age (years)	66.6 ± 9.8 (393)	67.1 ± 8.9 (61)	0.722
Male	92.6 (364/393)	96.7 (59/61)	0.184
Body mass index (kg/m2)	29.0 ± 4.7 (393)	28.5 ± 4.2 (56)	0.452
Diabetes mellitus type I or II	29.7 (116/391)	34.5 (19/55)	0.461
Insulin treated	8.7 (34/391)	7.3 (4/55)	0.484
Oral medication	18.7 (73/391)	25.5 (14/55)	0.234
Diet only	2.0 (8/391)	1.8 (1/55)	0.693
Current smoker	14.7 (56/381)	14.8 (8/54)	0.982
Previous myocardial infarction	12.3 (48/391)	14.3 (8/56)	0.671
Previous stroke	5.3 (21/393)	7.1 (4/56)	0.381
Hypertension	75.4 (295/391)	87.5 (49/56)	0.045
Hyperlipidemia	77.1 (297/385)	78.6 (44/56)	0.811
Creatinine clearance (ml/min)	81.8 ± 27.2 (393)	83.7 ± 25.8 (61)	0.600
Ejection fraction (%)	58.3 ± 8.1 (393)	57.0 ± 9.5 (61)	0.269
Peripheral vascular disease	7.6 (30/393)	8.2 (5/61)	0.520
Chronic obstructive pulmonary disease	11.5 (45/393)	6.6 (4/61)	0.252
Clinical presentation			
Silent ischemia	5.6 (22/392)	3.6 (2/56)	0.402
Stable angina	69.4 (272/392)	66.1 (37/56)	0.616
Unstable angina	25.0 (98/392)	30.4 (17/56)	0.391
Anatomic SYNTAX score	20.6 ± 6.4 (393)	18.6 ± 5.8 (61)	0.026
SYNTAX Score II PCI	30.3 ± 8.6 (393)	29.7 ± 8.6 (61)	0.618
Predicted 4-year mortality with PCI (%)	9.0 ± 9.0 (393)	8.5 ± 7.2 (61)	0.671
SYNTAX score II CABG	29.1 ± 10.4 (393)	29.2 ± 10.3 (61)	0.951
Predicted 4-year mortality with CABG (%)	9.0 ± 9.3 (393)	9.0 ± 8.8 (61)	0.992

Data are mean ± SD or % (n/N). CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio.

Online Table 2. Comparison of the predictive value for 2-year VOCE* and TVR among Post PCI QFR, In-stent QFR, and minimal stent area derived from IVUS (MSA)

Predictive value for 2-year VOCE

	AUC	95%CI	p value	vs. Post PCI QFR	vs. In-stent QFR	vs. MSA
Post PCI QFR	0.702	0.633-0.772	<0.001	NA	<0.001	0.139
In-stent QFR	0.543	0.460-0.627	0.295	<0.001	NA	0.564
MSA**	0.569	0.470-0.669	0.217	0.139	0.564	NA

Predictive value for 2-year TVR

	AUC	95%CI	p value	vs. Post PCI QFR	vs. In-stent QFR	vs. MSA
Post PCI QFR	0.707	0.629-0.785	<0.001	NA	<0.001	0.263
In-stent QFR	0.522	0.430-0.615	0.622	<0.001	NA	0.960
MSA**	0.570	0.463-0.676	0.270	0.263	0.960	NA

CI = confidence interval, HR = hazard ratio, MSA = minimum stent area, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TVR = target vessel revascularization, VOCE = vessel-oriented composite endpoint.
* VOCE: a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization
** Value derived from intravascular ultrasound

Online Table 3. The impact of the low post-PCI QFR (<0.91) on 2-year VOCE* and individual components among vessels with or without IVUS guidance.

	With IVUS guidance (n=615)				Without IVUS guidance (n=156)				
	QFR<0.91	QFR≥0.91	HR (95%CI)	p value	QFR<0.91	QFR≥0.91	HR (95%CI)	p value	p for interaction
2 years									
VOCE*	23/229 (10.0)	16/386 (4.1)	2.48 (1.30-4.74)	0.006	11/55 (20.0)	2/101 (2.0)	11.29 (2.83-45.03)	<0.001	0.063
Cardiac death	4/229 (1.7)	3/386 (0.8)	2.24 (0.84-6.00)	0.109	0/55 (0.0)	1/101 (1.0)	NA	NA	NA
TV-MI	3/229 (1.3)	4/386 (1.0)	1.26 (0.21-7.54)	0.797	1/55 (1.8)	0/101 (0.0)	NA	NA	NA
TVR	19/229 (8.3)	13/386 (3.4)	2.53 (1.19-5.39)	0.016	11/55 (20.0)	1/101 (1.0)	22.45 (3.45-146.10)	0.001	0.036

CI = confidence interval, HR = hazard ratio, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TV-MI = target vessel myocardial infarction, TVR = target vessel revascularization, VOCE = vessel-oriented composite endpoint.
*VOCE: a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization

Online Table 4. Univariate independent predictors of two-year VOCE* in the vessel level analysis.

	Univariable predictors at 2 years		
Variables	**HR**	**95%CI**	**p value**
Post PCI QFR<0.91	3.37	1.91-5.96	<0.001
Creatinine clearance (ml/min)	0.98	0.97-0.99	0.002
LAD stenosis	1.42	0.94-2.16	0.099
SYNTAX score	1.03	0.99-1.08	0.159
Baseline diameter stenosis **	1.02	0.99-1.04	0.204
Hyperlipidemia	0.68	0.37-1.24	0.206
Diabetes mellitus	0.67	0.36-1.25	0.206
Hypertension	1.44	0.75-2.77	0.277
Minimum stent area (mm2) †	0.90	0.72-1.13	0.367
Female sex	1.47	0.59-3.65	0.409
In-stent diameter stenosis **	1.01	0.98-1.05	0.412
Diffuse disease	0.65	0.20-2.13	0.481
Total stent length	1.00	0.99-1.02	0.503
Residual SYNTAX score	1.02	0.94-1.11	0.610
Ejection fraction (%)	1.01	0.98-1.04	0.677
Serial lesion ‡	0.89	0.49-1.60	0.690
Unstable angina	1.15	0.55-2.44	0.709
Previous myocardial infarction	0.85	0.33-2.19	0.729
Age	1.00	0.98-1.02	0.873

CI = confidence interval, HR = hazard ratio, LAD = left anterior descending coronary artery, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, VOCE = vessel oriented composite endpoint.
* VOCE: a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization
** Value derived from 3-dimensional angiography in QFR analysis
† Value derived from intravascular ultrasound
‡ More or 2 lesions per vessel

Online Table 5. Two-year clinical outcomes among the patients having at least one vessel with low post PCI QFR (<0.91) or not (≥0.91).

	QFR<0.91 (n=227)	**QFR≥0.91** (n=166)	**HR (95%CI)**	**p value**
Unadjusted				
TVF*	34 (15.0%)	6 (3.6%)	4.38 (1.84-10.42)	<0.001
Cardiac death	4 (1.8%)	1 (0.6%)	2.92 (0.33-26.13)	0.315
TV-MI	6 (2.6%)	1 (0.6%)	4.43 (0.53-36.78)	0.132
TVR	30 (13.2%)	5 (3.0)	4.64 (1.80-11.95)	<0.001

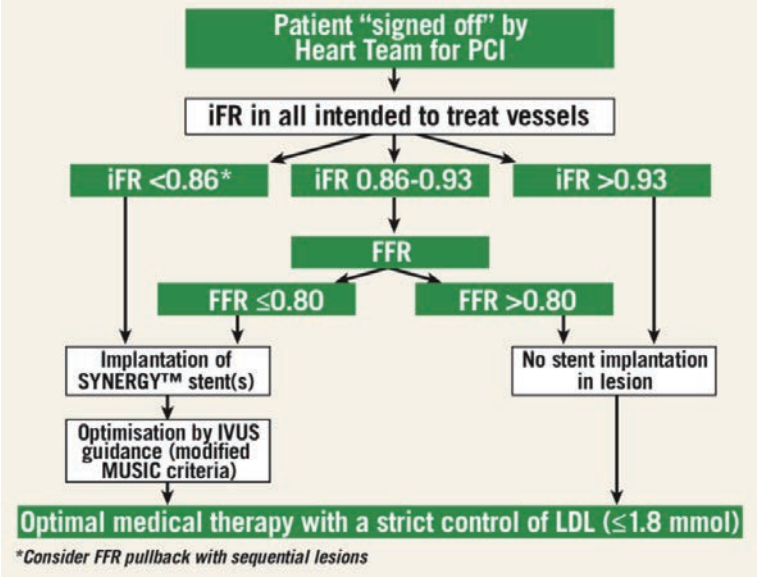
*TVF: a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization
CI = confidence interval, HR = hazard ratio, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TVF = target vessel failure, TVR = target vessel revascularization, TV-MI = target vessel myocardial infarction.

Online Table 6. Univariate and multivariate independent predictors of two-year TVF in the patient level analysis.

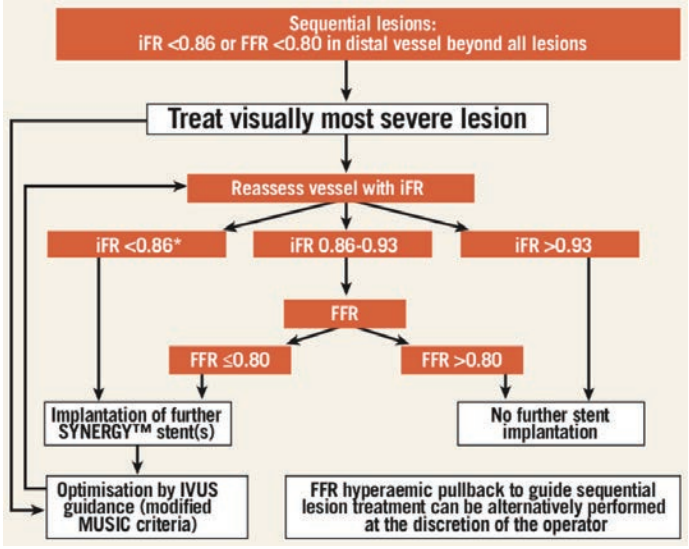
	Univariable predictors at 2 years			Multivariable predictors at 2 years		
Variables	**HR**	**95%CI**	**p value**	**HR**	**95%CI**	**p value**
Post PCI QFR<0.91	4.38	1.84-10.42	<0.001	4.59	1.92-10.98	<0.001
COPD	3.23	1.61-6.47	<0.001	3.45	1.72-6.95	<0.001
Peripheral vascular disease	0.65	0.16-2.67	0.546	0.58	0.14-2.41	0.452
SYNTAX score	1.02	0.97-1.07	0.526	1.00	0.96-1.05	0.996

*TVF: a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization
CI = confidence interval, COPD = Chronic obstructive pulmonary disease, HR = hazard ratio, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TVF = target vessel failure.

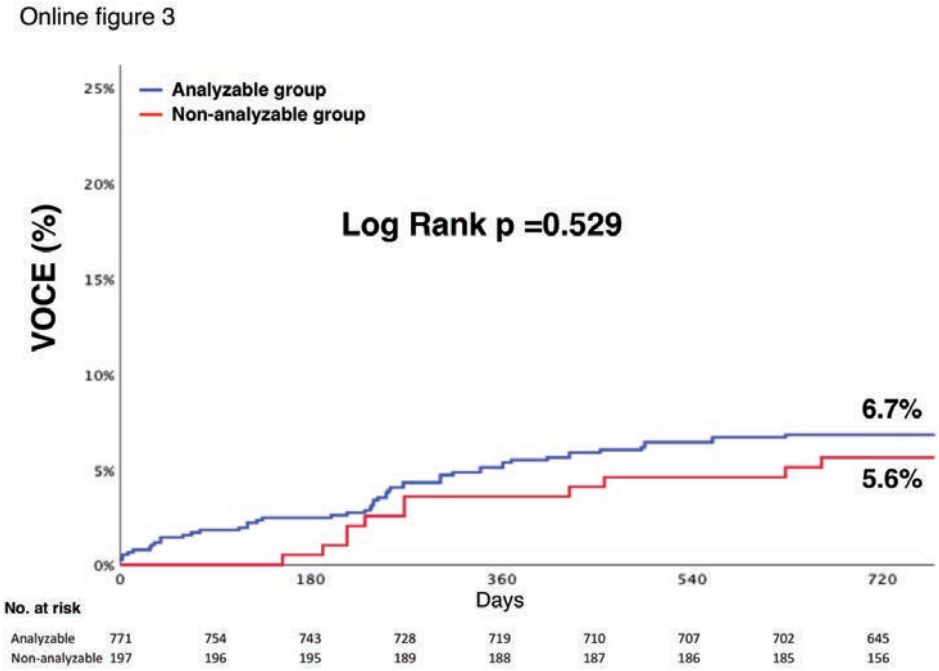
Online Figure 1. Algorithm for ischemia-driven revascularization in SYNTAX II.
Reprinted with permission from Escaned J. *et al*. Rationale and design of the SYNTAX II trial evaluating the short to long-term outcomes of state-of-the-art percutaneous coronary revascularisation in patients with de novo three-vessel disease. EuroIntervention 2016;12:e224-34.
FFR = fractional flow reserve, iFR = instantaneous wave free ratio, IVUS = intravascular ultrasound.



Online Figure 2. Flow chart depicting the physiological assessment and treatment in cases with sequential stenosis.
Reprinted with permission from Escaned J. *et al*. Rationale and design of the SYNTAX II trial evaluating the short to long-term outcomes of state-of-the-art percutaneous coronary revascularisation in patients with de novo three-vessel disease. EuroIntervention 2016;12:e224-34.
FFR = fractional flow reserve, iFR = instantaneous wave free ratio, IVUS = intravascular ultrasound.



Online Figure 3. Kaplan–Meier estimates for vessel-oriented composite endpoint over 730 days of follow-up among the vessels stratified by analyzability for post PCI QFR.
Kaplan–Meier curves show the cumulative incidence of vessel-oriented composite endpoint (VOCE) -a composite of vessel-related cardiac death, vessel-related myocardial infarction, and target vessel revascularization.
PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, VOCE = vessel-oriented composite endpoint.



Supplementary references

1. Escaned J, Banning A, Farooq V et al. Rationale and design of the SYNTAX II trial evaluating the short to long-term outcomes of state-of-the-art percutaneous coronary revascularisation in patients with de novo three-vessel disease. EuroIntervention 2016;12:e224-34.
2. Piroth Z, Toth GG, Tonino PAL et al. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. Circ Cardiovasc Interv 2017;10.
3. De Bruyne B, Pijls NH, Bartunek J et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation 2001;104:157-62.
4. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv 2016;9:1022-31.
5. Hwang D, Lee JM, Lee HJ et al. Influence of Target Vessel on Prognostic Relevance of Fractional Flow Reserve After Coronary Stenting. EuroIntervention 2018; pii: EIJ-D-18-00913.
6. Lee JM, Hwang D, Choi KH et al. Prognostic Implications of Relative Increase and Final Fractional Flow Reserve in Patients With Stent Implantation. JACC Cardiovasc Interv 2018;11:2099-2109.
7. Serruys PW, Kogame N, Katagiri Y et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with three-vessel disease: 2-year follow-up of the SYNTAX II study. EuroIntervention 2019.

8

The Impact of Coronary Physiology on Contemporary Clinical Decision Making.

Norihiro Kogame, Masafumi Ono, Hideyuki Kawashima, Mariusz Tomaniak, Hironori Hara, Jonathan Leipsic, Daniele Andreini, Carlos Collet, Manesh R Patel, Shengxian Tu, Bo Xu, Christos V Bourantas, Amir Lerman, Jan J Piek, Justin E Davies, Javier Escaned, William Wijns, Yoshinobu Onuma, Patrick W Serruys.

JACC Cardiovasc Interv. 2020 Jul 27;13(14):1617-1638.

Abstract

Physiological assessment of coronary artery disease (CAD) has become one of the cornerstones of decision-making for myocardial revascularization, with a large body of evidence supporting the benefits of using fractional flow reserve and other pressure-based indices for functional assessment of coronary stenoses. Furthermore, physiology allows the identification of specific vascular dysfunction mechanisms in patients without obstructive CAD. Currently more than 10 modalities of functional coronary assessment are available, although the overall adoption of these physiological tools, either of intracoronary or image-based nature, is still low. In this article we review these modalities of functional coronary assessment according to their timing of use: outside the catheterization laboratory (Cath Lab); in the Cath Lab prior to the percutaneous coronary intervention (PCI) and in the Cath Lab during or after PCI. We discuss how the obtained information can be used in setting the indication for PCI, in planning and guiding the procedure, and in documenting the final functional result of the intervention. The advantages and limitations of each modality in each setting are discussed. Furthermore, the key value of intracoronary physiology in diagnosing mechanisms of microcirculatory dysfunction, which account for the presence of ischemia in many patients without obstructive CAD, will be revisited. Based on the opportunities generated by the multiplicity of diagnostic tools described, we propose an algorithmic approach to physiological coronary investigations in clinical practice, with the key aims of 1) avoiding unneeded revascularization procedures, 2) improving procedural PCI and long-term outcomes in patients with obstructive CAD and 3) diagnosing vascular dysfunction mechanisms that can be effectively treated in patients with non-obstructive CAD. We believe that such structured approach may also contribute to a wider adoption of available technologies for functional assessment of patients with CAD.

Introduction

Physiological assessment of coronary artery disease(CAD) has become one of the cornerstones of decision-making for myocardial revascularization. To date we have more than 10 modalities for coronary physiological assessment(**Central illustration**), although the adoption of physiological assessment is still restricted and limited for multiple reasons. This review classifies these modalities according to their timing of use: outside the catheterization laboratory(Cath Lab) prior to the treatment decision; in the Cath Lab prior to percutaneous coronary intervention(PCI) and in the Cath Lab during or after PCI. We have elaborated on the advantages and limitations of each modality. Of note, the majority of these modalities used in daily practice only focus on the epicardial artery disease, however, a substantial number of patients suffer from combined epicardial and microvascular disease. Therefore, it is essential to always take into consideration the presence/absence of microvascular dysfunction and perform appropriate tests to identify that dominant endotype of coronary microvascular dysfunction(CMD).

Clinical Scenario 1: Pre-procedural physiological assessment of coronary stenoses outside the Cath Lab

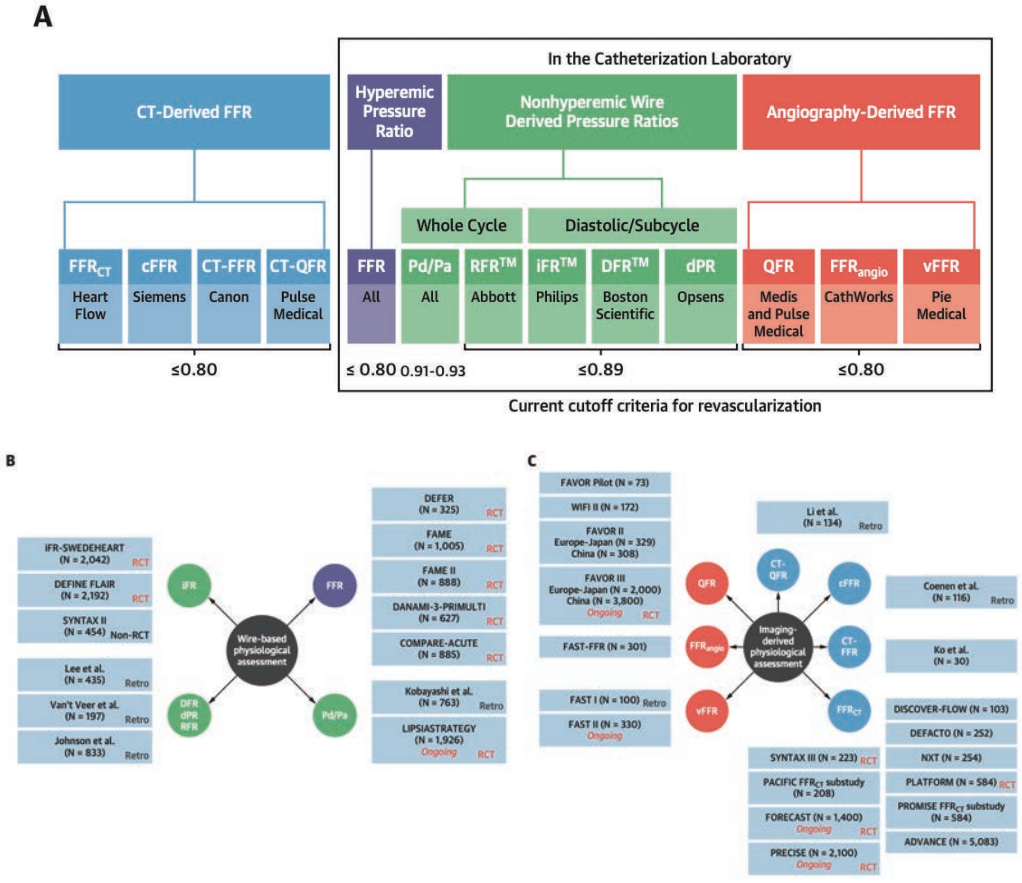
Interventional cardiologists are becoming familiar with physiological assessment in the Cath Lab such as fractional flow reserve(FFR) and instantaneous wave free ratio(iFR). Other non-invasive functional tests are recommended by current guidelines in patients with suspected CAD(1). In the MR-INFORM trial, the cardiac magnetic resonance(CMR)-guided PCI strategy demonstrated a non-inferiority to the FFR-guided PCI strategy in terms of a composite clinical outcome among patients with typical angina and cardiovascular risk factors(2). However, several reports have shown that non-invasive functional tests can be falsely negative or can underestimate the amount of ischemia, especially in patients with multivessel disease(MVD)(3). In this regard, computed tomography(CT) derived FFR has been introduced as a non-invasive physiological assessment to identify ischemia-generating stenoses before procedure.

Development of coronary computed tomography angiography(CCTA)

In the SCOT-HEART trial, among patients with suspected CAD, the additional CCTA on top of standard care did not improve symptom and quality of life at 6 months(4), but demonstrated a lower incidence of a composite hard endpoint at 5 years compared with standard care alone(5). The ongoing randomized DISCHARGE trial (NCT02400229) is designed to investigate the comparative effectiveness of CCTA and invasive coronary angiography(ICA) in 3546 patients with intermediate pretest probability of CAD(10-60%)(6).

In terms of recommendations from international guidelines, the CE-MARC2 trial randomized patients with suspected angina to three arms: CMR-guided, single-photon emission computed tomography(SPECT)-guided or National Institute for Health and Care Excellence(NICE)2010 guidelines-based management. NICE2010 guidelines recommended selecting the type of investigation according to CAD pretest likelihood(10-29%:CCTA, 30-60%:SPECT, 61-90%:ICA). At 12 months, CMR-guided management resulted in a lower probability of unnecessary angiography than NICE2010 guidelines-based management(7).

Thereafter, NICE guidelines was updated in November 2016(8). The updated NICE guidelines were notable for the use of CCTA as the first-line investigation in all patients with atypical or typical angina symptoms or those who were asymptomatic with suggested electrocardiogram(ECG) changes for ischemia. In current ESC guidelines for chronic coronary syndrome(CCS), non-invasive functional imaging for myocardial ischemia or CCTA is also recommended as the initial test for diagnosing CAD in symptomatic patients with Class I(Level B) recommendation(1). The same guidelines proposed CCTA as preferentially considered if the pretest likelihood of CAD is low and information on atherosclerosis desired.



Central illustration. Currently available physiological assessment
Overview is shown in **(A)**. Wire-based and imaging-derived physiological assessment with major trials are shown in **(B)** and **(C)**, respectively.
CT=computed tomography, DFR=diastolic hyperemia-free ratio, dPR=diastolic pressure ratio, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, QFR=quantitative flow ratio, RFR=resting full-cycle ratio, vFFR=vessel fractional flow reserve.

CT derived FFR(Table 1)

High sensitivity of CCTA is accompanied by a moderate specificity and may result in an increase of unnecessary ICA(9). In order to address the moderate specificity of CCTA, CT derived FFR was introduced in the field. FFR derived from CCTA(FFR_{CT}) was developed using 3-dimensional reconstruction of coronary arteries and computational fluid dynamics(10). Three major prospective trials demonstrated feasibility and diagnostic performance of FFR_{CT} using invasive FFR≤0.80 as reference(**Table 1**)(11-13). The NXT trial, in which best practice guidelines for the acquisition of CCTA and the updated Heart Flow FFR_{CT}(v.1.3) software were used, demonstrated the superiority of FFR_{CT} over CCTA with higher area under the curve (AUC) for FFR≤0.80(13). The specificity of FFR_{CT} for detecting invasive FFR≤0.80 was acceptable and higher than that of CCTA(79%vs.34%). In the PACIFIC study, FFR_{CT} demonstrated higher diagnostic performance for invasive FFR≤0.80 than CCTA, SPECT and positron emission tomography(PET) on a per vessel analysis, whereas PET had a favorable performance in per-patient and intention-to-diagnose analysis compared with CCTA, FFR_{CT}, and SPECT(14).

The PLATFORM trial, which randomized patients with new onset chest pain to either CCTA/FFR_{CT} arm or usual testing arm, demonstrated that CCTA/FFR_{CT} was a feasible and safe alternative to ICA and was associated with a significantly lower rate of ICA showing no obstructive CAD within 90 days(15). Furthermore, CTA/FFR_{CT} guided care was associated with equivalent clinical outcomes, QOL, and lower costs(33% reduction) compared with usual care over 1-year follow-up(16). The ongoing FORECAST trial(NCT03187639), which will randomize 1400 patients with new onset chest pain to either routine FFR_{CT} strategy or standard care according to updated NICE guidelines, is also investigating resource utilization.

In terms of clinical outcome, the 1-year results of the ADVANCE registry, which prospectively enrolled 5083 patients with suspected CAD, demonstrated that negative FFR_{CT} values(>0.80) was associated with favorable clinical outcomes compared with abnormal FFR_{CT} values(≤0.80)(17). Median 4.7 years follow-up of the NXT trial also showed an independent association of FFR_{CT} with MACE(18). However, more outcome data is needed especially from randomized controlled trials(RCT). The ongoing randomized PRECISE trial(NCT03702244) will compare 1-year outcomes between usual care versus CCTA/FFR_{CT}-guided therapy in 2100 patients with suspected CAD.

Recently the potential of CCTA/FFR_{CT} to help inform revascularization decision making was investigated. In the SYNTAX II trial, calculation of the non-invasive functional SYNTAX score with CCTA/FFR_{CT} was feasible and yielded similar results to those obtained with invasive pressure-wire assessment in patients with three-vessel disease(3VD)(19). Building on these findings, the hypothesis that combined non-invasive anatomy and physiology derived from CCTA plus FFR_{CT} may allow heart teams to plan complex coronary revascularization in patients with left main or 3VD was proven in the SYNTAX III trial(20). FFR_{CT} changed the treatment decision in 7% of the patients. These findings suggest that the SYNTAX score III has emerged as a potentially useful tool combining information from physical comorbidities, coronary anatomy and physiology derived from a single scan for decision making on the appropriate modality of revascularization(**Figure 1**).

The growing body of evidence suggests that the FFR_{CT} will be potentially a game-changer in the diagnosis of CCS patients. NICE(13 February 2017) issued guidance for the use of FFR_{CT}, which recommends FFR_{CT} as the most cost effective option when CCTA shows CAD with uncertain functional significance, or is non-diagnostic(21).

However, several limitations and pitfalls of FFR_{CT} should be noted before privileging it as initial test. Suboptimal imaging quality of CCTA is one of the major limitations of FFR_{CT}, which can be attributed to irregular heart rate, significant obesity, or inability to cooperate with breath-hold commands(1). The extra use of contrast media may also be one of consequence. Despite optimizing image quality, severe and extensive coronary calcification remains challenging for CCTA as well as FFR_{CT}; however, among patients with high Agatston score, FFR_{CT} provided high and superior diagnostic performance compared with CCTA alone using invasive FFR ≤0.80 as a reference(22). The rejection rate of FFR_{CT} ranged from 2.9% to 13% as determined in prospective trials and large clinical cohort(**Table 1**)(12,13,23). The main reason for the inability to perform FFR_{CT} was the presence of motion artifacts(23). Thinner CT slice thickness and lower patient heart rate may increase the analyzability of FFR_{CT}. Furthermore, a history of prior myocardial infarction or the presence of a chronic total occlusion may be a limitation of FFR_{CT}. Indeed a study comparing FFR_{CT} versus ICA using invasive FFR as reference for staged evaluation of non-culprit lesions in STEMI patients showed similar but moderate diagnostic accuracy of FFR_{CT} compared to conventional ICA(accuracy: 0.72 in both groups)(24). Of note, the use of FFR_{CT} is not validated in vessels previously revascularized. At the present time, the FFR_{CT} analysis is only feasible in a central core laboratory (HeartFlow, California, USA), limiting its real-time clinical use and necessitating telemedicine.

Thereafter, three CT derived FFR software have been developed in order to address longer computational time and inconvenience of off-site analysis. These modalities demonstrated acceptable diagnostic accuracy for FFR≤0.80 with shorter computational time, although none of them are commercially available(**Table 1**)(25-27).

According to current guidelines, CCTA is the first-line test in patients with suspected CAD especially with low clinical likelihood(1). Additional CT derived FFR will provide anatomic and lesion specific physiological information as “one-stop shop”, which may facilitate speed of diagnosis with a substantial impact on quality of life and cost-effectiveness, despite a somewhat lower specificity (around 80%) when compared to physiological assessment in the Cath Lab with pressure wire.

Table 1. Diagnostic performance of CT derived FFR using FFR ≤0.80 as reference.

	Trial or author name	Patient/vessel number	Rejection rate of CT derived FFR	AUC	Accuracy, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
FFR_{CT}	DISCOVER FLOW (11)	103 patients	NA	0.92	87	93	82	85	91
		159 vessels		0.90	84	88	82	74	92
	DeFACTO (12)	252 patients	13%	0.81	73	90	54	67	84
		407 vessels		NA	NA	80	61	NA	NA
	NXT (13)	254 patients	11%	0.90	81	86	79	65	93
		484 vessels		0.93	86	84	86	61	95
cFFR	Coenen et al. (25)	116 patients	5%	NA	NA	NA	NA	NA	NA
		203 lesions		NA	75	88	65	66	87
CT-FFR	Ko et al. (26)	30 patients	3%	0.88	NA	78	87	74	89
		58 vessels		0.77	84	79	74	60	88
CT-QFR	Li et al. (27)	134 patients	13%	NA	87	90	85	83	91
		156 vessels		NA	87	88	87	83	91

AUC = area under the curve, FFR = fractional flow reserve, NA = not available, NPV = negative predictive value, PPV = positive predictive value.

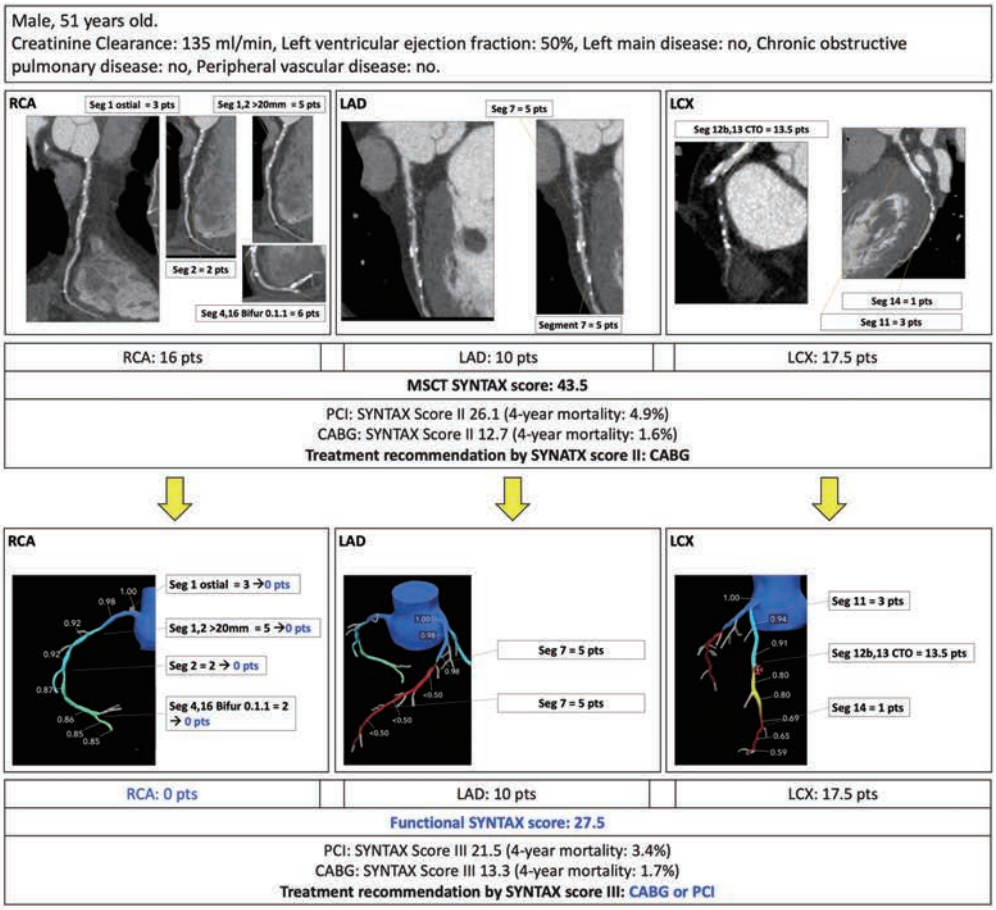


Figure 1. SYNTAX score III calculation by CCTA and FFR_{CT}

This figure shows representative case for the SYNTAX Score III calculation using CCTA and FFR_{CT}. After incorporation of FFR_{CT}, the treatment recommendation was changed from CABG to equipoise risk between CABG and PCI.

CABG=coronary artery bypass grafting, CCTA=coronary computed tomography angiography, CTO=chronic total occlusion, LCX=left circumflect artery, LAD=left anterior descending artery, PCI=percutaneous coronary intervention, RCA=right coronary artery.

Clinical Scenario 2: Physiological assessment before procedure in the Cath Lab

The second opportunity to perform physiological assessment is in the Cath Lab prior to revascularization when localized ischemia is not documented and stenosis severity between 50 to 90% diameter stenosis by visual estimation or MVD(1). Since less than half of all patients with stable CAD have documented ischemia by non-invasive testing within 90 days prior to elective PCI(28), a large number of patients are candidates to physiological assessment in the Cath Lab. Furthermore, even when proof of myocardial ischemia is

available, intracoronary interrogation may be required to identify which stenosis accounts for ischemia.

Fractional flow reserve

FFR is the best-known index for physiological assessment in the Cath Lab. FFR is the mean ratio of distal coronary pressure to aortic pressure at maximum hyperemia. Based on the linear coronary pressure-flow relationship during maximal hyperemia with a few assumptions incorporated into its theoretical framework, FFR expresses the percent contribution of a coronary stenosis to myocardial flow impairment. The clinical significance of FFR≤0.75 was first validated against non-invasive functional test(29). The 2005 ESC guidelines recommended, for the first time, considering the existence of a grey zone of FFR values(between 0.75 and 0.80) in which the decision to perform revascularization should be left to the operator(30). Since then, the cutoff threshold value of FFR≤0.80 has been used in most clinical studies.

Several studies and meta-analysis consistently demonstrated that FFR-guided PCI improves functional class and outcomes(31) , justifying the recommendation of performing FFR to assess functional coronary relevance, whenever prior evidence of ischemia is not available, laid out in the 2018 ESC guidelines(class I, evidence level A)(32). The first studies on FFR focused on setting the indication for PCI, thus avoiding unneeded revascularization of stenoses without functional relevance. DEFER study demonstrated the very long-term(15 years) safety and efficacy of deferral PCI in stenoses with FFR<0.75(**Table 2**)(33).

Table 2. Major randomized controlled trials using wire-based physiological assessment.

Study name	n	Follow-up	Population	Comparison	Primary endpoint	Result	p value
Defer	325	15 years	Patients with de novo stenosis (DS>50%)	Deferral with FFR≥0.75 vs Performed PCI with FFR≥0.75	MI	2.2% vs 10.0%	0.033
FAME	1005	5 years	Patients with multivessel disease	FFR guided vs angiography guided PCI	Composite of death, MI, or revascularization	28% vs 31%	0.31
FAME II	888	5 years	Patients with de novo stenosis with FFR≤0.80	FFR guided PCI plus OMT vs OMT alone	Composite of death, MI, or urgent revascularization	13.9% vs 27.0%	<0.001
DANAMI-3-PRIMULTI	627	1 year	STEMI patients with one or more clinically significant stenosis in the non-infract related vessel	FFR guided complete revascularization vs no further invasive treatment (culprit only)	Composite of death, non-fatal MI, or ischemia-driven revascularization	13% vs 22%	0.004
COMPARE-Acute	885	1 year	STEMI patients with one or more clinically significant stenosis in the non-infract related vessel	FFR guided complete revascularization vs no further invasive treatment (culprit only)	Composite of death, non-fatal MI, revascularization, and cerebrovascular events	7.8% vs 20.5%	<0.001
iFR-SWEDEHEART	2037	2 years	Patients with de novo stenosis (DS 40-70%)	FFR guided vs iFR guided PCI	Composite of death, non-fatal MI, or unplanned revascularization	8.4% vs 8.7%	0.93
DEFINE-FLAIRE	2492	2 years	Patients with de novo stenosis (DS 40-80%)	FFR guided vs iFR guided PCI	Composite of death, non-fatal MI, or unplanned revascularization	10.5% vs 11.8%	0.25

DS = diameter stenosis, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, MI = myocardial infarction, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, STEMI = ST segment elevated myocardial infarction.

The next large trial on FFR focused on its value in patients with MVD, a clinical scenario in which non-invasive functional test does not always provide accurate information to decide which stenoses should be considered for revascularization(3). FAME I demonstrated the

superiority of the FFR-guided PCI over angiography-guided PCI among patients with MVD in terms of a composite clinical endpoint at 1 year(34). Of note, the grounds of the recommendations of the 2005 ESC Guidelines(30), the FAME study applied for the first time an FFR≤0.80 cutoff for decision making. The favorable results of the study were achieved with lower cost and without prolongation of the procedure time(35). Even after 5 years, differences persisted, but lost statistical significance due to the smaller number of patients at risk(**Table 2**)(36).

Thereafter, FAME II demonstrated that the FFR-guided PCI with medical therapy is superior to medical therapy alone in clinical outcome in patients with at least one stenosis with FFR≤0.80(37). The 5-year follow-up clearly confirmed the initial results and extended these findings to a reduction in the composite of death and myocardial infarction(MI), driven mainly by a reduction in spontaneous MI with PCI compared to medical therapy(**Table 2**)(38).

Of note, the FAME II trial was launched in the aftermath of the COURAGE trial(39), which demonstrated a lack of benefit of PCI over optimal medical therapy(OMT) alone in terms of long-term death and MI rates. The results of COURAGE were criticized due to the inclusion of patients with mild myocardial ischemia. Recently, ISCHEMIA showed that in patients with moderate or severe myocardial ischemia assessed by non-invasive test an invasive strategy with OMT offers no clinical benefit compared to OMT alone strategy in terms of the composite primary endpoint at a median of 3.3 years(40). From the viewpoint of the physiological assessment, it is difficult to conclude that physiology-guided PCI plus OMT is not superior to OMT alone in term of hard endpoint among CCS patients with moderate or severe ischemia, since other important information such as the adoption rates of FFR or iFR has not yet been provided.

Another important subset of patients who might benefit from FFR interrogation are those presenting with ST-segment elevation myocardial infarction (STEMI) and MVD. Several studies in this subset of patients have used FFR to ascertain the functional relevance of non-culprit coronary stenoses(**Table 2**). In the COMPARE-acute and DANAMI-3-PRIMULTI trial, FFR-guided complete revascularization strategy significantly reduced the incidence of the composite clinical endpoint at 12 months when compared to the culprit only revascularization strategy in patients with STEMI and MVD(41,42). However, in the COMPLETE trial, angiography-guided complete revascularization of lesions with diameter stenosis>70% clearly demonstrated superiority to culprit only revascularization strategy among 4041 patients with STEMI and MVD in terms of the primary composite endpoint at 3 years(43). Further study is warranted to compare FFR-guided versus angiography-guided complete revascularization in patients with STEMI and MVD as far as outcomes and cost-effectiveness are concerned.

The growth of evidence supporting the clinical value of FFR was not mirrored by a substantial increase in its adoption in clinical practice(44). A number of potential causes for this(**Table 3**) include the following: i) Prolongation of procedural time; ii) Additional cost for pressure wire and adenosine or other drugs; iii) Discomfort or side effect from vasodilator drugs; iv) Submaximal hyperemia; v) Precise acquisition of coronary pressure measurement for avoiding pressure drift, aortic pressure ventricularization and aortic waveform distortion; vi) Suboptimal mechanical quality of pressure wire, which may result in difficult wire manipulation in complex anatomy and procedural complication.

Table 3. Advantages and limitations of physiological assessment in the Cath Lab.

	Wire-based physiological assessment				Imaging-based physiological assessment		
	Hyperemic index	Non-hyperemic pressure ratio (NHPR)			Angiography-derived		
	FFR	iFR	Novel NHPR (DFR, dPR, RFR)	Pd/Pa	QFR	FFRangio	vFFR
Advantage	○ Evidence for outcomes up to 15 years (vs angiography guided PCI, OMT alone) ○ Well validated with non-invasive functional tests in various clinical settings ○ Cost-effectiveness was demonstrated against angiography guided PCI ○ Available with all pressure wires	○ Evidence for outcomes up to 2 years (vs FFR guided PCI) ○ Validated with non-invasive functional tests in several clinical settings ○ Well validated with FFR in various clinical settings ○ Hyperemia independent ○ Quicker than FFR ○ Ability with potential to assess serial lesions ○ Co-registration with angiography available	○ Validated with FFR and iFR in limited clinical settings (retrospective) ○ Hyperemia independent ○ Quicker than FFR	○ Validated with FFR and iFR in limited clinical settings ○ Hyperemia independent ○ Quicker than FFR ○ Available with all pressure wires	○ Validated with FFR in limited clinical settings ○ Hyperemia independent ○ Pressure wire free ○ Flow information (TIMI frame count) incorporated ○ Quicker than FFR	○ Validated with FFR in limited clinical settings ○ Hyperemia independent ○ Pressure wire free	○ Validated with FFR in limited clinical settings (retrospective) ○ Hyperemia independent ○ Pressure information (Pa) incorporated ○ Pressure wire free
Limitation	• Hyperemia required (additional cost and hyperemic agent related side effect) • Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Prolonged procedure	• Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Proprietary and the software of specific vendor required	• No evidence for outcomes • Validation data with non-invasive functional tests are limited • Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Proprietary and the software of specific vendor required • No co-registration with angiography available	• No evidence for outcomes • Validation data with non-invasive functional tests are limited • Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Susceptible to miscalculation from pressure-wire drift • No co-registration with angiography available	• No evidence for outcomes (FAVOR III is ongoing) • Precise acquisition of angiography required • Specific software required • Manual correction required in some cases	• No evidence for outcomes • No validation data with non-invasive functional tests • Precise acquisition of angiography required • Specific software required • Manual correction required in some cases	• No evidence for outcomes • No validation data with non-invasive functional tests • Precise acquisition of angiography required • Specific software required • Manual correction required in some cases

DFR = diastolic hyperemia-free ratio, dPR = diastolic pressure ratio, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, IVUS = intravascular ultrasound, Pa = aortic pressure, Pd = distal coronary pressure, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, RFR = resting full-cycle ratio, vFFR = vessel fractional flow reserve.

Introduction of non-hyperemic pressure ratio (NHPR): iFR

To avoid adenosine administration NHPR has been recently introduced with iFR being the first index(45). iFR is measured as the mean ratio of instantaneous phasic distal coronary pressure to aortic pressure during a diastolic window free of newly generated wave activity called the "wave-free period". Interrogation of the coronary circulation over the wave-free period has the advantage that microcirculatory resistance is considered to be stable and the lowest value over the whole cardiac cycle(45). The wave-free period was calculated beginning 25% of the way into diastole (identified from the dicrotic notch of pressure waveform) and ending 5 ms before the end of diastole(**Figure 2**).

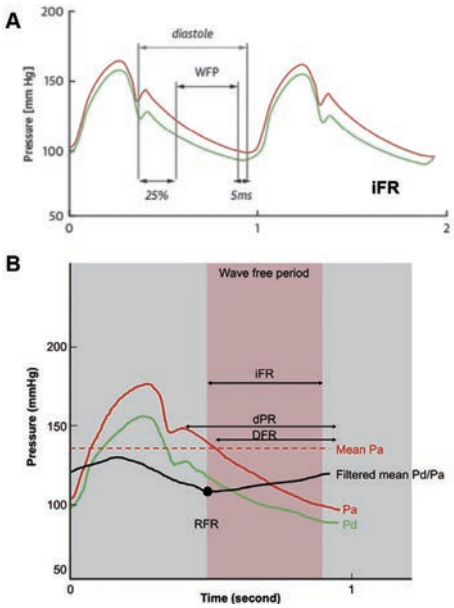


Figure 2. Commercially available non-hyperemic pressure ratio.
iFR is defined as average Pd/Pa during the wave-free period(the pink shaded area). The wave-free period was calculated beginning 25% of the way into diastole and ending 5 ms before the end of diastole(**A**). dPR is defined as average Pd/Pa during entire diastole(**B**). DFR is defined as average Pd/Pa during Pa<mean Pa with negative slope(**B**). RFR is defined as the lowest filtered mean Pd/Pa during entire cardiac cycle(**B**). Adopted with permission from Van't Veer *et al*(84).
Abbreviations as **Central illustration**.

The iFR concept has been tested in a number of validation studies with a direct comparison with FFR(45,46). An iFR value of 0.89 was determined as the best cut-off value to predict an FFR of 0.80(46), and has been widely used for decision-making.
Subsequent studies were performed focusing on head-to-head comparisons of iFR and FFR against other independent standards used for the detection of ischemia. These studies found no difference between iFR and FFR in terms of the diagnostic performance using as a reference PET(47,48) and SPECT(49).

Thereafter, two largest randomized trials in coronary physiology compared iFR to FFR with clinical outcomes as an endpoint (2042 patients in iFR-SWEDEHEART, 2492 patients in DEFINE FLAIR) and reached the same conclusion: iFR-guided PCI was noninferior to FFR-guided PCI in the selection of the vessels to be treated or deferred and in the resulting rates

of MACE at 12 months(50,51) (**Table 2**). The incidences of MACE in both arms did not differ up to 2 years in both trials(52). Nevertheless, limitations of iFR pertain to the lack of long-term prognostic data as opposed to FFR(38). However, it should be noted that the FFR long-term data is predominately in very significant lesions, and the first data to support the use of coronary physiology whether FFR or iFR in intermediate lesions was generated in the iFR outcomes studies.

Following iFR-SWEDEHEART and DEFINE-FLAIRE, the ESC guidelines were revised and gave class I (evidence level A) recommendation for guiding PCI in both iFR and FFR(32). Of note, iFR co-registration with angiography allows the physicians to identify the lesion and the length of the narrowing that has to be treated(**Figure 3**)(44). Some advantages of iFR over FFR include shorter procedure time, less patient discomfort, and easy pullback especially for evaluation of serial lesions(**Table 3**). iFR can separately assess the severity of each individual stenosis within the same tandem lesion but not FFR. Because in non-hyperemic conditions the coronary flow remains relatively constant and stable regardless of the severity of stenosis due to the autoregulation of microvascular circulation, whereas during hyperemia the coronary flow becomes unpredictable if it passes through stenosis with a dimeter stenosis ≥40%(53,54). In the iFR GRADIENT registry, iFR pullback predicted the physiological outcome of PCI with a difference of 0.011 ± 0.004 in tandem and diffuse coronary disease(55). Whereas Modi et al. reported that individual stenosis severity is significantly underestimated in the presence of serial disease, using both hyperemic and resting pressure-based indices(56). An important limitation of iFR is that it cannot be measured without the software of a specific vendor(Philips/Volcano, Amsterdam, the Netherlands)(**Table 3**).

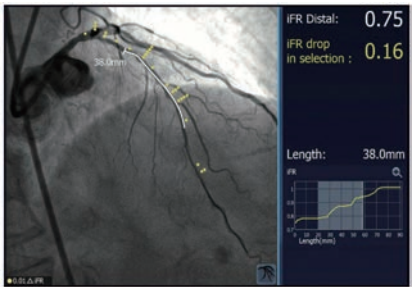


Figure 3. iFR co-registration
Figure shows the result of co-registering iFR pullback data with angiography in LAD with several irregularities. Each yellow dot represents a modification of 0.01 iFR units. Plot location of pressure loss on angiogram in its final interactive action allows the physicians to identify the lesion and the length of the narrowing that has to be treated. Adopted with permission from Gotberg et al(44).
iFR=instantaneous wave free ratio.

The discordance between FFR and iFR

Approximately 20% of cases show discrepancies between FFR with the threshold of 0.80 and iFR with the threshold of 0.89(57). The cause of the discordance may be attributable to different thresholds, effects of hyperemia (e.g. 2 to 3 times larger pressure gradient at maximum hyperemia than that at rest), and/or different responses to microvascular dysfunction. Interestingly, with regard to wire-based CFR, iFR was found to have a better diagnostic performance than FFR in three separate studies(58-60). This observation provided important clues on one of the main causes for discrepancy between FFR and iFR.

Yet, it has to be clarified that both FFR and iFR were unable to discriminate the impact of epicardial and microvascular disease.

The discordance between FFR and iFR would partially depend on the lesion location and type. Kobayashi, et al. reported that at a left main coronary artery (LMCA) or a proximal left anterior descending artery (LAD), iFR were less correlated with the reference of FFR compared to other lesion locations(61). In the sub-study of DEFINE-FLAIR trial, iFR-guided deferral for LAD lesion was associated with lower MACE rates at 1 year compared to FFR-guided deferral for LAD lesion(62). However, this result should be considered as a truly hypothesis generating due to post-hoc character of the analysis with insufficient statistical power. Thus, a further confirmatory randomized trial will be needed to conclude whether FFR or iFR is better, or comparable for LAD lesion.

Of note, the methodology of available studies investigating the discrepancy between FFR and iFR cannot rule out other important causes of FFR vs iFR discrepancy. As an example, none of the reported trials checked for patient intake of coffee over the last 24 hours prior to FFR interrogation, which has been demonstrated to blunt the effect of adenosine induced hyperemia and FFR values(63).

On the other hand, available evidence suggests that, overall, discordant FFR vs iFR results lack clinical relevance. Lee et al found that the presence of discordance between FFR and NHPRs including iFR was not an independent predictor of vessel-oriented composite outcomes(64). This lack of clinical translation of the discordance between indices is most likely related to its occurrence in borderline stenosis with a low risk of hard clinical events. Although further research might be needed to clarify clinical relevance of discordance between indices, it might be too challenging from a statistical standpoint. Based on some premises derived from iFR-SWEDEHEART and DEFINE-FLAIR, it is hypothesized the study would require the sample size of 290,000 patients to clarify the difference of predictive value for MACE between FFR and iFR(65). Therefore, we would have to discuss the appropriate clinical and lesional setting for the use of FFR or iFR, rather than to debate on whether one is superior to the other.

The difference of FFR and iFR in some specific clinical settings

- **Left main coronary artery disease**

The importance of physiological assessments has been suggested even in the field of LMCA diseases(66). The only dedicated study up to date is the DEFINE LM registry, which included patients in whom LM stenosis was deferred (51.9%) or revascularized (48.1%) according to the iFR cutoff of 0.89(67). The result suggests that decision making in the LMCA disease based on iFR is safe in terms of composite clinical endpoint at 30 months. Ongoing research includes the iLITRO study(NCT: 03767621) aims at demonstrating the actual feasibility and efficacy of iFR compared to FFR in patients with intermediate LMCA disease.

- **Diffuse and focal lesions**

Physiological pattern of lesions such as focal or diffuse obtained over iFR pullback curves has been reported as one of the factors of discordance between FFR and iFR. Warisawa et al demonstrated that a focal pattern was associated with the discordance of FFR≤0.80 and iFR>0.89, whereas diffuse pattern was associated with the discordance of FFR>0.80 and iFR≤0.89(68). These discordances may stem on one hand for the higher turbulence-generating potential of focal stenosis, which under hyperemia may cause lower FFR, and on the other from microvascular dysfunction, since diffuse disease is associated with presence of microvascular dysfunction(69) and response to microvascular dysfunction is different

between FFR and iFR as previously described(59). Physiological pattern, which can be derived from FFR(e.g. pullback pressure gradient(PPG) index)(70), may have the potential to determine the eligibility of revascularization for those lesions with discordance. The PPG index is a novel metric that is able to discriminate focal and diffuse functional coronary artery disease; further validation of this metric is still required. In the occasional cases in which the iFR/FFR discordance related to the focal and diffuse pattern is deemed to be clinically relevant, other non-invasive functional tests may be considered.

- **Multi-vessel disease**

The efficacy of FFR-guided PCI for patients with MVD has been demonstrated as previously described. From a practical perspective, the ease of performing multiple measurements and pressure pullbacks without inducing hyperemia makes of iFR a very attractive alternative to FFR in patients with MVD. iFR-SWEDEHEART and DEFINE-FLAIR trials included about 40% of patients with MVD(50,51), and the sub-study of iFR-SWEDEHEART demonstrated no significant difference between FFR- and iFR-guided revascularization in terms of MACE at 1 year in patients with MVD as well as single-vessel disease(71).

Recently, SYNTAX II that prospectively enrolled patients with 3VD, demonstrated less repeat revascularization in the deferred lesions based on iFR value than in the stented lesions between 1 and 2 years(72). The results support the safety of iFR-guided decision making for long-term results in patients with 3VD. iFR-guided PCI for MVD seems promising, but more prospective data is warranted to reinforce the evidence.

- **Non-infarct-related arteries at early phase of ACS**

The interest on using iFR in patients with ACS relates, on one hand, to circumventing the problem of blunted hyperemia associated to ACS and, on the other, to the reluctance of many operators to use of vasodilators during primary PCI. Several studies have fostered the interest of iFR as a faster and potentially safer alternative to FFR for interrogation of non-culprit stenoses of ACS. The pooled analysis of DEFINE-FLAIR and iFR SWEDEHEART showed the comparable clinical outcome between iFR- and FFR-guided PCI with more deferral in iFR arm in patients presenting with ACS but not including STEMI(73). In non-infarct-related lesions of STEMI, a substudy of REDUCE-MVI trial found lower iFR values in non-culprit vessels at the time of primary PCI than in the subacute STEMI phase with 11% of false positive classification of non-culprit stenosis(74). False positive measurements with iFR at the time of primary PCI might be a result of the documented increase in resting flow in non-culprit stenoses in patients with STEMI(75), potentially as a result of enhanced adrenergic drive during the acute STEMI phase.

On the other hand, Choi et al reported that FFR and iFR values were not significantly different between non-infarct-related vessels of acute MI and target vessels of stable CAD across all %DS groups, which contradicts the result of the previous report(76). Clarification of this will be provided by future research. The ongoing randomized trials such as iModern(NCT03298659) and SAFE-STEMI(NCT02939976) will provide key information on then reliability of iFR-guided intervention of non-culprit lesions during STEMI.

- **Severe aortic stenosis**

In patients with severe aortic stenosis(AS), simultaneous revascularization of severe coronary artery stenosis by visual estimation is recommended by the current guidelines(32). Some studies showed the feasibility and safety of wire-based physiological assessment including administration of adenosine in patients with severe AS(77), however, it is unclear whether wire-based physiological assessment has clinical implications as far as decision-making in patients with severe AS is concerned. The specific pathophysiological

characteristic of severe AS, including left ventricular hypertrophy, increased afterload and microvascular dysfunction, make the interpretation of wire-based physiological measurement difficult(78). The adjusted cutoff criteria of FFR and iFR for patients with severe AS has been reported but not yet been firmly established(79).

Ahmad et al reported changes of coronary physiological status in intermediate lesions before and after transcatheter aortic valve implantation(TAVI)(80). FFR was significantly reduced after TAVI(pre0.86 vs. post0.83), whereas iFR was unchanged(pre0.87 vs. post 0.87). This finding can be explained by the improvement of coronary microvascular circulation assessed by CFR after TAVI(pre1.56 vs. post1.74), suggesting that FFR may underestimate the severity of coronary stenosis in patients with severe AS. However, Pesarini et al. showed that the FFR was unchanged before and immediately after TAVR(pre0.89 vs. post0.89), although iFR was not measured in this study(77). These inconsistent findings indicate that the data remains uncertain and the robustness of previous analyses are debatable mainly due to small sample size. The ongoing FORTUNA(NCT: 03665389) and FAITAVI trial(NCT: 03360591) will provide new insights and evaluate the coronary physiology in severe AS.

Other NHPR

After the success of iFR, other NHPRs become commercially available such as: diastolic hyperemia-free ratio(DFR;Boston Scientific), diastolic pressure ratio(dPR;Opsens Medical), and resting full-cycle ratio(RFR;Abbott)(**Central illustration and Figure 2**). These novel NHPRs are also proprietary and can only be used with the software provided by the vendor. However, the fact that most of companies have their own pressure wires, wire-specific consoles, and their own NHPR, may ultimately result in wider adoption of physiology-guided PCI.

Pd/Pa is the oldest and straightforward NHPR. As early as in 1985, the first clinical application of Pd/Pa in humans was reported(81). High correlation and excellent agreement between Pd/Pa and iFR were reported(82). However, from a practical perspective, the use of Pd/Pa is limited by a lower signal-to-noise ratio and significantly lower data spread than iFR and other NHPRs, contributing to higher influence of pressure drift on measurements(47,83).

Other NHPRs are using phasic and beat-by-beat Pd/Pa during part or the entire diastolic phase except for RFR, since RFR is using the lowest filtered Pd/Pa over the entire cardiac cycle(**Figure 2**). van't Veer et al have evaluated 6 NHPRs and concluded that all diastolic resting indices tested were identical to iFR, both numerically and with respect to their agreement with FFR(84). Several studies also retrospectively demonstrated excellent correlation and agreement of RFR, dPR and DFR with iFR(85,86). However, previous validation studies were retrospective comparison using "cleaned" pressure database in the core lab and prospective in-vivo validation study using commercially available system has not yet been performed. Furthermore, we have to emphasize the fact that, until now, there are no RCT evaluating the impact of those new NHPR-guided PCI on clinical outcomes compared with established PCI strategies. The commonly shared opinion of experts in the field is that if RCTs do take place, there would be a great likelihood that they would lead to similar outcomes. Therefore, on top of in-vivo validation study, large-scale RCTs with clinical outcomes may not be necessarily required and single-arm prospective trials with objective performance criteria may be sufficient to demonstrate non-inferiority of non-iFR NHPR to FFR-, or iFR-guided PCI, which also may result in faster and wider adoption of physiological

assessment in daily practice. At this point, according to the latest appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease(87), it seems reasonable to suggest that NHPR may be considered as substitution for FFR in most clinical scenarios.

Angiography derived FFR

In the context of a growing interest on functional assessment of coronary stenoses, advances in computational power and three-dimensional coronary angiography made possible the development of functional coronary angiography. Currently, three technologies are commercially available: quantitative flow ratio(QFR, Medis medical imaging system and Pulse medical imaging technology), FFR_{angio}(CathWorks), and vessel FFR(vFFR, Pie Medical imaging)(**Central illustration and Table 4**). In general, mathematical formula related to the Lance Gould equation has been used for the process of computation(88).

Table 4. Commercially available software for angio-derived fractional flow reserve

	QFR	FFRangio	vFFR
Online computation	Available	Available	Available
Required angiography	2 projections 25 degrees apart	≥ 2 projections	2 projections 30 degrees apart
Process	Integrated mathematical approach	Rapid flow analysis	Integrated mathematical approach
Published clinical data	FAVOR pilot (89), II China (90) and Europe/Japan (91), WiFi II (92)	FAST-FFR (93)	FAST (94)
Incidence of non-analyzable cases in each study	10%, 0.9%, 3.2%, 5.9%, respectively	3.7%	49% (retrospective)
Predictive performance for predicating wire-derived FFR ≤0.80 (AUC)	0.92-0.96	0.94	0.93
Time to computation	5 min	NA*	NA

* An average processing time was reported as 2.7 minutes, however this processing time did not include the manual correction of the coronary reconstruction and lesion identification (93).
AUC = area under the curve, FFR = fractional flow reserve, NA = not available, QFR = quantitative flow ratio, vFFR = vessel fractional flow reserve.

QFR has the largest published data including prospective multicenter trials(89-92). FFR_{angio} has been validated in the prospective multicenter FAST-FFR study(93). Recently retrospective clinical validation data of vFFR was reported(94). Overall, all three technologies show excellent AUC for predicting FFR≤0.80 with a low incidence of non-analyzable cases(0.9-10%) except for the retrospective FAST study(**Table 4**). A systematic review and Bayesian meta-analysis demonstrated that there was no difference in diagnostic performance of angiography derived FFR between methods for computation and online/offline analysis(95).

Time to computation is a major argument in favor of adoption this technology and is relevant for both patients and physicians. Only QFR was prospectively evaluated for “time to computation of the entire procedure” versus FFR. In the FAVOR II Europe/Japan study, the

median time for QFR computation was significantly shorter than time for FFR(5.0min versus 7.0min)(**Table 4**)(91). Whether these differences can be observed outside of clinical trial environment remains to be established.

There are advantages and limitations of angiography-derived FFR compared to wire-based FFR(**Table 3**). Regarding the advantages, there is no requirement of wire and hyperemic agent, and this result in shorter procedure time, less patient discomfort, and elimination of erroneous coronary pressure measurement by pressure wire, which can occur in up to one-third of cases(96). Furthermore, both on-line and off-line analysis can be performed, allowing review of available angiograms from a functional standpoint. The major limitation is of course absence of large RCT evaluating clinical outcomes versus established PCI strategies. However, large RCTs to address this are ongoing: FAVOR III China(NCT03656848) and Europe/Japan(NCT03729739). Some specific lesion types such as LMCA, bifurcation, or ostial lesion are confounding because of differences in interpretation and results may not be reliable in these lesion subsets for the time being. Furthermore, it is understood that the result depends strongly on the quality of acquisition in two or three angiographic views.

Clinical Scenario 3: Physiological assessment after procedure in the Cath Lab

Post-PCI physiological assessment has two potential purposes in clinical practice.
First, post-PCI physiological assessment can be used for the optimization of PCI result. Agarwal et al. reported that in patients with satisfactory angiographic results after stent implantation, post-PCI FFR reclassified 20% as inadequate physiological results which required further intervention for complete functional optimization at the time of the index procedure(97). The DEFINE PCI trial demonstrated that significant epicardial residual ischemia after angiographically successful PCI defined as iFR≤0.89 occurred in 24% of patients(98). Of note, 81.6% of patients with suboptimal post-PCI iFR had focal residual disease. Interestingly, about 60% of residual focal stenoses were located outside the stented segment, although all target vessels were evaluated by iFR prior to PCI(98). Therefore, post-PCI physiological assessment may play a more important role for evaluation and localization of residual disease outside the stented segment rather than for stent optimization, for which intracoronary imaging is the established method.

Second, post-PCI physiological assessment can be used as a predictor of long-term clinical outcomes(**Table 5**). Multiple large observational studies and post hoc analyses of RCTs have established that post-PCI FFR value is an independent predictor of long-term clinical outcomes(99). Previous trials consistently demonstrated that “the higher is better”, although the best cut-off value of post-PCI FFR varied from 0.86 to 0.96 for the prediction of clinical events(97,100,101). Despite increasing evidence, recent study reported a low adoption rate(9%) of post-PCI wire-based physiological assessment even in patients who underwent wire-based physiological assessment prior to PCI(102). The most likely deterrents are the need for pressure-wire, hyperemic agents, and prolonged procedure time. When compared to wire-derived FFR, angio-derived FFR is a more user-friendly tool for interventional cardiologist for the purpose.

Regarding angio-derived FFR, the HAWKEYE trial demonstrated that a low post-PCI QFR(≤0.89) was associated with higher 2-year vessel-oriented clinical endpoint rate

compared to a high post-PCI QFR(>0.89)(**Table 4**)(103). A subanalysis of SYNTAX II also demonstrated same result with slightly different cut off value(0.91) in state-of-the-art PCI practice for 3VD(104). We have no doubt about the "higher is better" concept of post-PCI QFR is similar to post-PCI FFR; however, we need more confirmatory data and also improvements of the QFR software for daily use, since the analyzability of post-PCI QFR is still far from perfect with feasibility of analysis of 85% and 80% in HAWKEYE and SYNTAX II, respectively .

Further studies are warranted to assess whether further intervention for residual ischemia according to post-PCI physiological assessment can improve the clinical outcomes. The issue will be addressed by the ongoing randomized FFR-REACT(105) and Target -FFR trial(NCT03259815).

Table 5. Major trials investigating the impact of post PCI physiological assessment on clinical outcomes.

	Primary end point	Cutoff value of FFR (QFR) for predicting primary endpoint (AUC)	Comparison of low vs. high post PCI FFR (QFR) on primary end point	
Pressure wire derived FFR				
FAME I and II (100) n=838 vessels	2-Y VOCE (vessel-related cardiac death, vessel-related MI, ischemia-driven TVR)	FFR ≤0.92 (NA)	9.2% vs. 3.8% (lower (<0.88) vs. upper (>0.92) tercile)	p=0.037
DKCRUSH VII (101) n=1476 patients	1-Y TVF (cardiac death, target vessel-MI, clinically-driven TVR)	FFR ≤0.88 (0.83)	8.0% vs. 4.0%	p=0.001
Agarwal et al (97) n=574 patients	MACE (death, MI, TVR) Mean follow-up 31±16 months	FFR ≤0.86 (NA)	23% vs. 17%	p=0.02
Angiography derived FFR				
HAWKEYE (103) n=751 vessels	2-Y VOCE (vessel-related cardiac death, vessel-related MI, ischemia driven-TVR)	QFR ≤0.89 (0.77)	25% vs. 3.5%	p<0.001
SYNTAX II (104) n=771 vessels	2-Y VOCE (vessel-related cardiac death, vessel-related MI, TVR)	QFR <0.91 (0.702)	12% vs. 3.7%	p<0.001

AUC = area under the curve, FFR = fractional flow reserve, MACE = major adverse cardiac event, MI = myocardial infarction, NA = not available, PCI = percutaneous coronary intervention, QFR = quantitative flow ratio, TVF = target vessel failure, TVR = target vessel revascularization, VOCE = vessel-oriented composite endpoint.

Clinical Scenario 4: The coronary microvascular circulation

The previous chapters focused only on the coronary physiology of the epicardial arteries. However, CMD is one of the major causes of angina and/or ischemia with non-obstructive coronary artery disease(NOCAD). In a clinical practice, substantial number of patients with

anginal symptom and/or documented ischemia by non-invasive test are diagnosed by ICA as NOCAD(106). The 2019 ESC Guidelines on CCS(1) recommend considering NOCAD in patients with angina and/or documented ischemia, who present either with coronary arteries free of stenoses or with stenoses showing non-ischemic FFR or iFR values. NOCAD should be also considered in cases of persistent angina after complete coronary revascularization(107). The underlying cause of NOCAD should be assessed systematically by non-invasive or invasive testing for diagnosing CMD, since these patients frequently undergo repeated CCTA or ICA with increased health care costs(108). Furthermore, angina and NOCAD are associated with an increased risk of adverse clinical events(109).

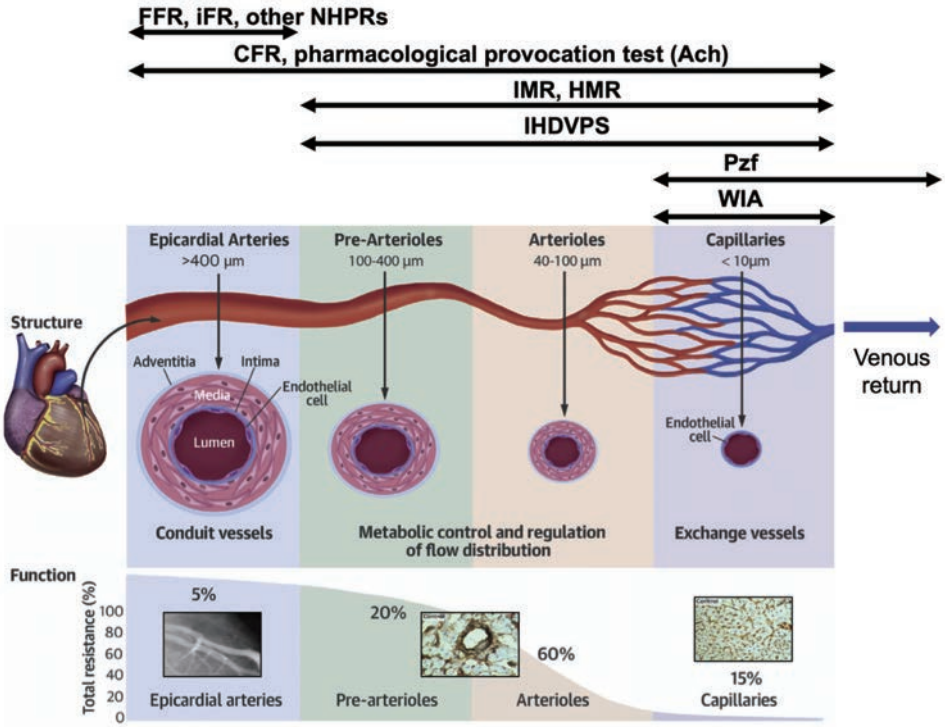


Figure 4. Physiological indices and interrogated coronary domain.
Figure shows the normal structure and function of coronary macro- and microcirculation and the corresponding action-fields of physiology techniques. Myocardial perfusion is governed by adequate orchestration of epicardial arteries, microcirculation and myocardial bed. Different intracoronary physiology tools can approach each of these domains. While CFR encompasses the overall coronary circulation, other indices have been developed to evaluate specific domains of the heart circulation. Adoption with permission with Taqueti et al(69).
CFR=coronary flow reserve, HMR=hyperemic microvascular resistance, IHDVPS=instantaneous hyperemic diastolic velocity pressure slope, IMR=index of microcirculatory resistance, NHPR=non-hyperemic pressure ratio, Pzf=zero flow pressure. Other abbreviations as **Central illustration**.

Pressure-derived indices interrogate a very narrow domain of the coronary circulation. They provide an estimate of the relative contribution of the stenosis to the myocardial flow impairment, which explains why FFR values become non-ischemic when downstream flow-limiting microcirculatory dysfunction is present(110). Furthermore, FFR and NHPR are not applicable to a dynamic scenario of vasomotor disorders that involve the

coronary arterioles, the epicardial vessels, or both(111). While future research may contribute to establish the role of NHPR in the context of CMD(47,48,58-60), it has to be made clear that, like FFR, these new indices cannot be used to interrogate the microvascular domain of the coronary circulation.

The coronary arterial system consists of 4 sequential conduits with different vessel size and function (**Figure 4**): epicardial arteries(>400μm), pre-arterioles(100-400μm), arterioles(40-100μm), capillaries(<10μm). The epicardial arteries have a primary conductance and distribution function, with minimal resistance to coronary flow(5%) in the absence of stenosis, whereas pre-arterioles and arterioles are responsible for regulation and distribution of blood flow to match dynamic needs of local tissue metabolism via the capillaries with maximal resistance to coronary flow(69). The arteriolar tone enables to maintain constant coronary blood flow over a wide range of coronary perfusion pressure, resulting in a mitigation of ischemia during the progression of obstructive epicardial atherosclerosis. Coronary angiography is basically not able to visualize the coronary microcirculation (pre-arterioles, arterioles, and capillaries) with vascular conduits<300μm(111).

In discussing how to interrogate this complex functional and anatomical network we should acknowledge that the term microcirculatory dysfunction is too vague to be used as a diagnostic target, instead the use of distinct functional or pathobiological mechanism, generally called endotypes, is recommended(111). Thus, in patients with CCS and NOCAD the dysfunction mechanisms can be grouped in two dominant endotypes: 1) structural changes in micro-vessels leading to reduced conductance and limited vasodilation; 2) vasomotor disorders affecting the coronary arterioles and/or epicardial vessels. This distinction clearly illustrates why a single physiological tool cannot be used to explore all potential microcirculatory dysfunction pathways(**Figure 4**). The diagnosis of the first endotype (structural remodeling) largely rests on measuring CFR and microcirculatory resistance with endothelium-independent vasodilators, while vasomotor disorders are diagnosed using acetylcholine challenge (Ach, an endothelium-dependent vasodilator) with concomitant ECG monitoring(1). Available methods and technical details on the use of these diagnostic techniques in the Cath Lab are discussed in the following paragraphs.

The invasive CFR is the ratio of hyperemic to resting blood flow by Doppler flow velocity, thermodilution-derived mean transient time, or absolute flow measurement based on thermodilution. In general, endothelium-independent vasodilator such as adenosine is used to induce hyperemia. Studies demonstrating a prognostic value of thermodilution-based CFR used a cut-off value of 2.0(112) as well as that of Doppler-based CFR used a cutoff of 2.5 or lower(113,114). Endothelium-dependent microvascular dysfunction can be assessed by the percent change in coronary blood flow with intracoronary flow doppler in response to acetylcholine(CFR-Ach, increase>50% can be considered as normal)(113). An additional advantage of Ach challenge is that it allows the diagnosis of epicardial vasospastic angina(1).

The measurement of microvascular resistance requires simultaneous recording of intracoronary pressure and flow with thermodilution-based data(IMR: index of microvascular resistance)(115) or Doppler flow velocity(HMR: hyperemic microvascular resistance index)(116).

IMR is calculated as the distal pressure divided by the inverse of the mean transient time during maximal hyperemia. In patients with coronary stenoses with FFR>0.80, an IMR>23 units increased the prognostic value of CFR(112). Furthermore, an abnormal IMR

value immediately after PCI was also associated with adverse events in patients with stable CAD(117). IMR ≥25 unit is considered as abnormal microcirculatory function.

HMR is calculated at the distal pressure divided by distal Doppler average peak flow velocity during maximal hyperemia. Currently available data suggests HMR provides a more accurate reflection of pathological change in the microcirculation compared with IMR(118). The optimal HMR cutoff to predict abnormal microcirculatory function, as estimated by PET, is ≥2.5 mmHg/cm/s(118).

After objective documentation of an abnormal microvascular function, in patients with structural remodeling the aim of treatment is to decrease myocardial oxygen consumption, typically with beta-blockers, while addressing any cardiovascular risk factor accounting for arteriolar thickening or capillary rarefaction (such as hypertension or diabetes). Conversely, in patients with vasomotor disorders (either at epicardial or arteriolar level) calcium channel blockers, ACE inhibitors and statins are recommended to control vasomotor tone and promote normal endothelial function. This tailored approach was demonstrated in the randomized CorMiCa trial, which showed that treatment guided by the result of CFR(<2.0), IMR(≥25), and Ach test resulted in a significant reduction of angina symptom at 6 months compared with conventional non-guided treatment in patients with angina symptoms and/or signs of ischemia and NOCAD(119). This reduction of angina symptom was maintained up to 1 year without any difference in clinical outcomes(120). Furthermore, this tailored approach is recommended by the current ESC guidelines(1).

Clinical perspective

Currently, we have three temporal opportunities to perform physiological assessment of a coronary artery stenosis. Outside the Cath Lab, CT derived FFR may become not only a gate keeper for conventional angiography but also a guide for revascularization when its cost-effectiveness will be established. However, this methodology cannot detect microvascular dysfunction that may lead to myocardial ischemia.

In the Cath Lab before procedure, FFR is the best-known index for coronary physiological assessment due to large and broad evidence. However, iFR should be considered as equivalent to FFR with a reduction in procedure time, cost, and patient discomfort, because discordance between FFR and iFR which did not translate to difference of outcome in the largest two randomized trials.

New NHPR seems promising and may contribute to further adoption of wire-based physiological assessment, although more prospective data are needed. To date, we recommend using new NHPR for non-complex lesions if iFR is not available.

Angio-derived FFR shows comparable diagnostic performance for the diagnosis of hemodynamically significant stenosis defined by FFR ≤0.80. If further data of outcome and cost-effectiveness from ongoing trials are positive, it will be a game changer in the Cath Lab. It is premature to discuss about intracoronary imaging derived FFR.

In the Cath Lab after procedure, physiological assessment may predict future outcome, but clinical impact of physiology guided PCI optimization has still to be demonstrated.

CMD is a very different field of investigation which implies use of flow and pressure since resistance is the issue at stake, but clinically important because in a large substantial number of patients microvascular obstruction contribute to the myocardial ischemia and

cardiovascular events. Further improvement of non-invasive assessment of CMD may enable us to diagnose it easier.

For the time being, it is more important to adopt physiological assessment for patients with its indication rather than which indices to use.

References

1. Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019.
2. Nagel E, Greenwood JP, McCann GP et al. Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. N Engl J Med 2019;380:2418-2428.
3. Melikian N, De Bondt P, Tonino P et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. JACC Cardiovasc Interv 2010;3:307-14.
4. Williams MC, Hunter A, Shah A et al. Symptoms and quality of life in patients with suspected angina undergoing CT coronary angiography: a randomised controlled trial. Heart (British Cardiac Society) 2017;103:995-1001.
5. Investigators S-H, Newby DE, Adamson PD et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. N Engl J Med 2018;379:924-933.
6. Napp AE, Haase R, Laule M et al. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. Eur Radiol 2017;27:2957-2968.
7. Greenwood JP, Ripley DP, Berry C et al. Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial. JAMA 2016;316:1051-60.
8. Chest pain of recent onset: assessment and diagnosis. Clinical guideline [CG95].2010. https://www.nice.org.uk/guidance/cg95?unlid=28903932120171912336 . (November 2016).
9. Haase R, Schlattmann P, Gueret P et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data. BMJ 2019;365:l1945.
10. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. EuroIntervention 2012;8:511-9.
11. 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.
12. Min JK, Leipsic J, Pencina MJ et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237-45.
13. Norgaard BL, Leipsic J, Gaur S et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63:1145-1155.
14. Driessen RS, Danad I, Stuijfzand WJ et al. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. J Am Coll Cardiol 2019;73:161-173.
15. Douglas PS, Pontone G, Hlatky MA et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. Eur Heart J 2015;36:3359-67.
16. Douglas PS, De Bruyne B, Pontone G et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. J Am Coll Cardiol 2016;68:435-445.
17. Patel MR, Norgaard BL, Fairbairn TA et al. 1-Year Impact on Medical Practice and Clinical Outcomes of FFRCT: The ADVANCE Registry. JACC Cardiovasc Imaging 2019.

18. Ihdayhid AR, Norgaard BL, Gaur S et al. Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography. Radiology 2019;292:343-351.
19. Collet C, Miyazaki Y, Ryan N et al. Fractional Flow Reserve Derived From Computed Tomographic Angiography in Patients With Multivessel CAD. J Am Coll Cardiol 2018;71:2756-2769.
20. Collet C, Onuma Y, Andreini D et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. Eur Heart J 2018;39:3689-3698.
21. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT Angiography Medical technologies guidance. 2017. nice.org.uk/guidance/mtg32 (7 March 2018).
22. Norgaard BL, Gaur S, Leipsic J et al. Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial. JACC Cardiovasc Imaging 2015;8:1045-1055.
23. Pontone G, Weir-McCall JR, Baggiano A et al. Determinants of Rejection Rate for Coronary CT Angiography Fractional Flow Reserve Analysis. Radiology 2019;292:597-605.
24. Gaur S, Taylor CA, Jensen JM et al. FFR Derived From Coronary CT Angiography in Nonculprit Lesions of Patients With Recent STEMI. JACC Cardiovasc Imaging 2017;10:424-433.
25. Coenen A, Lubbers MM, Kurata A et al. Coronary CT angiography derived fractional flow reserve: Methodology and evaluation of a point of care algorithm. J Cardiovasc Comput Tomogr 2016;10:105-13.
26. Ko BS, Cameron JD, Munnur RK et al. Noninvasive CT-Derived FFR Based on Structural and Fluid Analysis: A Comparison With Invasive FFR for Detection of Functionally Significant Stenosis. JACC Cardiovasc Imaging 2017;10:663-673.
27. Li Z, Zhang J, Xu L et al. Diagnostic Accuracy of a Fast Computational Approach to Derive Fractional Flow Reserve From Coronary CT Angiography. JACC Cardiovasc Imaging 2020;13:172-175.
28. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. JAMA 2008;300:1765-73.
29. Pijls NH, De Bruyne B, Peels K et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703-8.
30. Silber S, Albertsson P, Aviles FF et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2005;26:804-47.
31. Zimmermann FM, Omerovic E, Fournier S et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. Eur Heart J 2019;40:180-186.
32. Neumann FJ, Sousa-Uva M, Ahlsson A et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
33. Zimmermann FM, Ferrara A, Johnson NP et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J 2015;36:3182-8.
34. Tonino PA, De Bruyne B, Pijls NH et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213-24.
35. Fearon WF, Bornschein B, Tonino PA et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation 2010;122:2545-50.
36. van Nunen LX, Zimmermann FM, Tonino PA et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015;386:1853-60.
37. 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.
38. Xaplanteris P, Fournier S, Pijls NHJ et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med 2018;379:250-259.

39. 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.
40. Hochman J. International Study of Comparative Health Effectiveness With Medical and Invasive Approaches: primary report of clinical outcomes. Presented at: AHA. 2019.
41. Smits PC, Abdel-Wahab M, Neumann FJ et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med 2017;376:1234-1244.
42. Engstrom T, Kelbaek H, Helqvist S et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665-71.
43. Mehta SR, Wood DA, Storey RF et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. The New England journal of medicine 2019;381:1411-1421.
44. Gotberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. J Am Coll Cardiol 2017;70:1379-1402.
45. Sen S, Escaned J, Malik IS et al. 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;59:1392-402.
46. Petraco R, Escaned J, Sen S et al. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. EuroIntervention 2013;9:91-101.
47. Hwang D, Jeon KH, Lee JM et al. Diagnostic Performance of Resting and Hyperemic Invasive Physiological Indices to Define Myocardial Ischemia: Validation With (13)N-Ammonia Positron Emission Tomography. JACC Cardiovasc Interv 2017;10:751-760.
48. de Waard GA, Danad I, Petraco R et al. Fractional flow reserve, instantaneous wave-free ratio, and resting Pd/Pa compared with [15O]H2O positron emission tomography myocardial perfusion imaging: a PACIFIC trial sub-study. Eur Heart J 2018;39:4072-4081.
49. van de Hoef TP, Meuwissen M, Escaned J et al. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. EuroIntervention 2015;11:914-25.
50. Davies JE, Sen S, Dehbi HM et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med 2017;376:1824-1834.
51. Gotberg M, Christiansen EH, Gudmundsdottir IJ et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med 2017;376:1813-1823.
52. Davies J. DEFINE-FLAIR: 2-Year Outcomes From a Randomized Trial of iFR and FFR Decision-Making in Patients With Coronary Artery Disease at TCT. 2019.
53. Nijjer SS, de Waard GA, Sen S et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. Eur Heart J 2016;37:2069-80.
54. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994;330:1782-8.
55. Kikuta Y, Cook CM, Sharp ASP et al. Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Predicts Hemodynamic Outcome In Humans With Coronary Artery Disease: Primary Results of the International Multicenter iFR GRADIENT Registry. JACC Cardiovasc Interv 2018;11:757-767.
56. Modi BN, Rahman H, Ryan M et al. Comparison of Fractional Flow Reserve, Instantaneous Wave Free Ratio and a Novel Technique for Assessing Coronary Arteries with Serial Lesions. EuroIntervention 2019.
57. Jeremias A, Maehara A, Genereux P et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. J Am Coll Cardiol 2014;63:1253-1261.
58. Petraco R, van de Hoef TP, Nijjer S et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study

(Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). Circ Cardiovasc Interv 2014;7:492-502.
59. Cook CM, Jeremias A, Petraco R et al. Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses: An Analysis Using Doppler-Derived Coronary Flow Measurements. JACC Cardiovascular interventions 2017;10:2514-2524.
60. Lee SH, Choi KH, Lee JM et al. Physiologic Characteristics and Clinical Outcomes of Patients With Discordance Between FFR and iFR. JACC Cardiovascular interventions 2019;12:2018-2031.
61. Kobayashi Y, Johnson NP, Berry C et al. The Influence of Lesion Location on the Diagnostic Accuracy of Adenosine-Free Coronary Pressure Wire Measurements. JACC Cardiovasc Interv 2016;9:2390-2399.
62. Sen S, Ahmad Y, Dehbi HM et al. Clinical Events After Deferral of LAD Revascularization Following Physiological Coronary Assessment. J Am Coll Cardiol 2019;73:444-453.
63. Nakayama M, Chikamori T, Uchiyama T et al. Effects of caffeine on fractional flow reserve values measured using intravenous adenosine triphosphate. Cardiovasc Interv Ther 2018;33:116-124.
64. Lee JM, Rhee TM, Choi KH et al. Clinical Outcome of Lesions With Discordant Results Among Different Invasive Physiologic Indices- Resting Distal Coronary to Aortic Pressure Ratio, Resting Full-Cycle Ratio, Diastolic Pressure Ratio, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve. Circ J 2019;83:2210-2221.
65. Seto AH. Instantaneous Wave-Free Ratio Outcomes and the Epistemology of Ischemia. JACC Cardiovasc Interv 2017;10:2511-2513.
66. Hamilos M, Muller O, Cuisset T et al. 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.
67. Warisawa T. Safety of Revascularization Deferral of Left Main Stenosis Based on Instantaneous Wave-Free Ratio Evaluation. Presented at TCT 2019.
68. Warisawa T, Cook CM, Howard JP et al. Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance. Circ Cardiovasc Interv 2019;12:e007494.
69. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. Journal of the American College of Cardiology 2018;72:2625-2641.
70. Collet C, Sonck J, Vandeloo B et al. Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis. J Am Coll Cardiol 2019;74:1772-1784.
71. Andell P, Berntorp K, Christiansen EH et al. Reclassification of Treatment Strategy With Instantaneous Wave-Free Ratio and Fractional Flow Reserve: A Substudy From the iFR-SWEDEHEART Trial. JACC Cardiovasc Interv 2018;11:2084-2094.
72. Serruys PW, Kogame N, Katagiri Y et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019;15:e244-e252.
73. Escaned J, Ryan N, Mejia-Renteria H et al. Safety of the Deferral of Coronary Revascularization on the Basis of Instantaneous Wave-Free Ratio and Fractional Flow Reserve Measurements in Stable Coronary Artery Disease and Acute Coronary Syndromes. JACC Cardiovasc Interv 2018;11:1437-1449.
74. van der Hoeven NW, Janssens GN, de Waard GA et al. Temporal Changes in Coronary Hyperemic and Resting Hemodynamic Indices in Nonculprit Vessels of Patients With ST-Segment Elevation Myocardial Infarction. JAMA Cardiol 2019.
75. Mejia-Renteria H, Lee JM, van der Hoeven NW et al. Coronary Microcirculation Downstream Non-Infarct-Related Arteries in the Subacute Phase of Myocardial Infarction: Implications for Physiology-Guided Revascularization. J Am Heart Assoc 2019;8:e011534.

76. Choi KH, Lee JM, Kim HK et al. Fractional Flow Reserve and Instantaneous Wave-Free Ratio for Nonculprit Stenosis in Patients With Acute Myocardial Infarction. JACC Cardiovasc Interv 2018;11:1848-1858.
77. Pesarini G, Scarsini R, Zivelonghi C et al. Functional Assessment of Coronary Artery Disease in Patients Undergoing Transcatheter Aortic Valve Implantation: Influence of Pressure Overload on the Evaluation of Lesions Severity. Circ Cardiovasc Interv 2016;9.
78. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. Circulation 2003;107:3170-5.
79. Yamanaka F, Shishido K, Ochiai T et al. Instantaneous Wave-Free Ratio for the Assessment of Intermediate Coronary Artery Stenosis in Patients With Severe Aortic Valve Stenosis: Comparison With Myocardial Perfusion Scintigraphy. JACC Cardiovasc Interv 2018;11:2032-2040.
80. Ahmad Y, Vendrik J, Eftekhari A et al. Determining the Predominant Lesion in Patients With Severe Aortic Stenosis and Coronary Stenoses: A Multicenter Study Using Intracoronary Pressure and Flow. Circ Cardiovasc Interv 2019;12:e008263.
81. Wijns W, Serruys PW, Reiber JH et al. Quantitative angiography of the left anterior descending coronary artery: correlations with pressure gradient and results of exercise thallium scintigraphy. Circulation 1985;71:273-9.
82. Kobayashi Y, Johnson NP, Zimmermann FM et al. Agreement of the Resting Distal to Aortic Coronary Pressure With the Instantaneous Wave-Free Ratio. J Am Coll Cardiol 2017;70:2105-2113.
83. Cook CM, Ahmad Y, Shun-Shin MJ et al. Quantification of the Effect of Pressure Wire Drift on the Diagnostic Performance of Fractional Flow Reserve, Instantaneous Wave-Free Ratio, and Whole-Cycle Pd/Pa. Circ Cardiovasc Interv 2016;9:e002988.
84. Van't Veer M, Pijls NHJ, Hennigan B et al. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? J Am Coll Cardiol 2017;70:3088-3096.
85. Lee JM, Choi KH, Park J et al. Physiological and Clinical Assessment of Resting Physiological Indexes. Circulation 2019;139:889-900.
86. Johnson NP, Li W, Chen X et al. Diastolic pressure ratio: new approach and validation vs. the instantaneous wave-free ratio. Eur Heart J 2019;40:2585-2594.
87. Patel MR, Calhoon JH, Dehmer GJ et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:2212-2241.
88. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circulation research 1978;43:242-53.
89. Tu S, Westra J, Yang J et al. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv 2016;9:2024-2035.
90. Xu B, Tu S, Qiao S et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol 2017;70:3077-3087.
91. Westra J, Andersen BK, Campo G et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc 2018;7.
92. Westra J, Tu S, Winther S et al. Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio During Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II). Circulation Cardiovascular imaging 2018;11:e007107.

93. Fearon WF, Achenbach S, Engstrom T et al. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. Circulation 2019;139:477-484.
94. Masdjedi K, van Zandvoort LJC, Balbi MM et al. Validation of 3-Dimensional Quantitative Coronary Angiography based software to calculate Fractional Flow Reserve: Fast Assessment of STenosis severity (FAST)-study. EuroIntervention 2019.
95. Collet C, Onuma Y, Sonck J et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J 2018;39:3314-3321.
96. Jeremias A, Kirtane AJ, Stone GW. A Test in Context: Fractional Flow Reserve: Accuracy, Prognostic Implications, and Limitations. J Am Coll Cardiol 2017;69:2748-2758.
97. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv 2016;9:1022-31.
98. Jeremias A, Davies JE, Maehara A et al. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI Study. JACC Cardiovasc Interv 2019;12:1991-2001.
99. Rimac G, Fearon WF, De Bruyne B et al. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. Am Heart J 2017;183:1-9.
100. Piroth Z, Toth GG, Tonino PAL et al. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. Circ Cardiovasc Interv 2017;10.
101. Li SJ, Ge Z, Kan J et al. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. JACC Cardiovasc Interv 2017;10:986-995.
102. Tebaldi M, Biscaglia S, Fineschi M et al. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. JACC Cardiovasc Interv 2018;11:1482-1491.
103. Biscaglia S, Tebaldi M, Brugaletta S et al. Prognostic Value of QFR Measured Immediately After Successful Stent Implantation: The International Multicenter Prospective HAWKEYE Study. JACC Cardiovasc Interv 2019;12:2079-2088.
104. Kogame N, Takahashi K, Tomaniak M et al. Clinical Implication of Quantitative Flow Ratio After Percutaneous Coronary Intervention for 3-Vessel Disease. JACC Cardiovascular interventions 2019;12:2064-2075.
105. van Zandvoort LJC, Masdjedi K, Tovar Forero MN et al. Fractional flow reserve guided percutaneous coronary intervention optimization directed by high-definition intravascular ultrasound versus standard of care: Rationale and study design of the prospective randomized FFR-REACT trial. Am Heart J 2019;213:66-72.
106. Patel MR, Peterson ED, Dai D et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886-95.
107. Li Y, Yang D, Lu L et al. Thermodilutional Confirmation of Coronary Microvascular Dysfunction in Patients With Recurrent Angina After Successful Percutaneous Coronary Intervention. Can J Cardiol 2015;31:989-97.
108. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA 2005;293:477-84.
109. Jespersen L, Hvelplund A, Abildstrom SZ et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J 2012;33:734-44.
110. Echavarria-Pinto M, Escaned J, Macias E et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: a combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. Circulation 2013;128:2557-66.

111. Mejia-Renteria H, van der Hoeven N, van de Hoef TP et al. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. The international journal of cardiovascular imaging 2017;33:1041-1059.
112. Lee JM, Jung JH, Hwang D et al. Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis. J Am Coll Cardiol 2016;67:1158-1169.
113. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. JACC Cardiovasc Interv 2015;8:1445-53.
114. AlBadri A, Bairey Merz CN, Johnson BD et al. Impact of Abnormal Coronary Reactivity on Long-Term Clinical Outcomes in Women. J Am Coll Cardiol 2019;73:684-693.
115. Fearon WF, Balsam LB, Farouque HM et al. Novel index for invasively assessing the coronary microcirculation. Circulation 2003;107:3129-32.
116. Meuwissen M, Chamuleau SA, Siebes M et al. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. Circulation 2001;103:184-7.
117. Nishi T, Murai T, Ciccarelli G et al. Prognostic Value of Coronary Microvascular Function Measured Immediately After Percutaneous Coronary Intervention in Stable Coronary Artery Disease: An International Multicenter Study. Circ Cardiovasc Interv 2019;12:e007889.
118. Williams RP, de Waard GA, De Silva K et al. Doppler Versus Thermodilution-Derived Coronary Microvascular Resistance to Predict Coronary Microvascular Dysfunction in Patients With Acute Myocardial Infarction or Stable Angina Pectoris. Am J Cardiol 2018;121:1-8.
119. Ford TJ, Stanley B, Good R et al. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol 2018;72:2841-2855.
120. Ford TJ, Stanley B, Sidik N et al. 1-Year Outcomes of Angina Management Guided by Invasive Coronary Function Testing (CorMicA). JACC Cardiovasc Interv 2020;13:33-45.

9

Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: Insight from GLOBAL LEADERS trial.

Norihiro Kogame, Ply Chichareon, Kenneth De Wilder, Kuniaki Takahashi, Rodrigo Modolo, Chun Chin Chang, Mariusz Tomaniak, Hidenori Komiyama, Alaide Chieffo, Antonio Colombo, Scot Garg, Yves Louvard, Peter Jüni, Philippe G Steg, Christian Hamm, Pascal Vranckx, Marco Valgimigli, Stephan Windecker, Hans-Peter Stoll, Yoshinobu Onuma, Luc Janssens, Patrick W Serruys.

Catheter Cardiovasc Interv. 2020 Jul;96(1):100-111.

Abstract

Background:

The aim of this study was to investigate the impact of ticagrelor monotherapy following one-month dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) for bifurcation lesions.

Methods:

GLOBAL LEADERS was a randomized, superiority, all-comers trial comparing one-month DAPT with ticagrelor and aspirin followed by 23-month ticagrelor monotherapy (experimental treatment) with standard 12-month DAPT followed by 12-month aspirin monotherapy (reference treatment) in patients treated with a biolimus A9-eluting stent. The primary endpoint was a composite of all-cause death or new Q-wave myocardial infarction (MI) at 2 years.

Results:

Amongst the 15,845 patients included in this subgroup analysis, 2,498 patients (15.8%) underwent PCI for at least one bifurcation lesion. The incidence of the primary endpoint was similar between the bifurcation and non-bifurcation group (4.7% vs 4.0%, p=0.083). The experimental treatment had no significant effect on the primary endpoint according to the presence/absence of a bifurcation lesion (bifurcation: HR: 0.74; 95% CI: 0.51-1.07, non-bifurcation: HR: 0.90; 95% CI: 0.76-1.07; p for interaction = 0.343), but was associated with significant reduction in definite or probable stent thrombosis (p for interaction = 0.022) and significant excess of stroke (p for interaction = 0.018) when compared with the reference treatment.

Conclusions:

After PCI for bifurcation lesions, using one-month of DAPT, followed by ticagrelor monotherapy for 23-month did not demonstrate explicit benefit regarding all-cause death or new Q-wave MI as in the overall trial.

Introduction

Bifurcation lesions are associated with a lower rate of procedural success and a higher risk of complications compared to non-bifurcation lesions in patients treated with percutaneous coronary intervention (PCI) (1,2). A number of randomized controlled trials have investigated the optimal intervention strategy in patients with bifurcation lesions and showed no benefit in terms of clinical outcomes for the systematic two-stent approach versus main branch-only stenting with provisional stenting of the side branch (2). Therefore, this provisional side branch stenting strategy is the recommended treatment of bifurcation lesions with a Class IA recommendation in current guidelines (3). In 5 to 25% of cases, a second stent for the side branch may be needed (4-6), however the best two-stent technique to use in these situations remains debatable (3).

The complexity and the numerous subtypes of two-stent techniques render their comparison difficult. For that reason, the European bifurcation club (EBC) introduced the MADS classification to standardize reports, that allow comparison between studies, and facilitate interpretation of published results in the evolving literature (7,8). In the GLOBAL LEADERS trial, the dedicated electronic case record form (e-CRF) based MADS classification was achieved in all site-reported bifurcation lesions, which represents a unique opportunity to analyze a cohort stratified for the presence of bifurcation lesions within a large contemporary PCI trial (9).

In terms of antiplatelet therapy, whilst the increased complexity of PCI including 2-stent technique for bifurcation lesions represent a driver for favoring more prolonged dual antiplatelet therapy (DAPT), the evidence regarding the optimal duration of DAPT based on the complexity of intervention is limited, especially due to the low prevalence of bifurcation PCI in the previous clinical trials (10,11). Furthermore, the role of potent P2Y12 inhibitors after bifurcation PCI is uncertain.

In this prespecified subgroup analysis of the primary endpoint such as all-cause death and new Q-wave myocardial infarction (MI) from the GLOBAL LEADERS trial (12), we sought to investigate the impact of ticagrelor monotherapy following one-month DAPT after bifurcation PCI.

Methods

The GLOBAL LEADERS trial

The design and main results of the GLOBAL LEADERS trial have been published previously (13). Briefly, it was a prospective, multicenter, randomized, open-label, superiority trial comparing two antiplatelet regimens in 15,991 all-comers patients who were exclusively treated with a biolimus A9-eluting stent for stable coronary artery disease or acute coronary syndromes.

Patients were randomly assigned in a 1:1 fashion to one-month DAPT with aspirin and ticagrelor followed by 23 months of ticagrelor monotherapy (experimental treatment), or standard DAPT with aspirin plus either clopidogrel (for patients with stable coronary artery disease) or ticagrelor (for patients with acute coronary syndromes) for 12 months, followed by aspirin monotherapy for 12 months (reference treatment). Regarding the primary endpoint of all-cause death or new Q-wave MI at 2 years, the overall trial failed to demonstrate the superiority of experimental treatment compared with the reference

treatment (3.81% in the experimental treatment vs 4.37% in the reference treatment, p=0.073), although at one year the superiority of experimental treatment was demonstrated (1.95% vs 2.47%, p=0.028).

The trial was approved by the institutional review board at each investigating center. The study followed the ethical principles of the Declaration of Helsinki. All the participants provided written informed consent at the time of participation in the trial. The trial is registered with ClinicalTrials.gov, number NCT01813435.

Study population and data collection

According to the all-comers concept, only a limited number of in- and exclusion criteria were applied in the GLOBAL LEADERS trial (Supplementary methods).

In this prespecified subgroup analysis of primary endpoint, patients undergoing bifurcation PCI were identified from the dedicated e-CRF based MADS classification reported by investigators. Bifurcation lesions were defined by investigators in accordance with the practical definition of the European Bifurcation Club (7), as “a coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant side branch.” All bifurcation PCIs were classified whether treated with 1- or 2-stent technique using the results of the MADS classification. Three-stent techniques such as “extended V” and “trouser legs and seat” were included in the 2-stent technique. The stenting technique for trifurcation lesion is not covered by the MADS classification, therefore trifurcation was identified according to the definition of SYNTAX Score (14). The choice of bifurcation treatment technique was left to the discretion of the operators.

As many as seven on-site monitoring visits were done at individual sites, with 20% of reported events checked against source documents. Additionally, the trial was monitored for event under-reporting and event definition consistency. However, no overall central independent adjudication of clinical events was implemented.

Endpoint definitions

The primary endpoint was the composite of all-cause death or new Q-wave MI up to two years after randomization. Deaths from any cause were ascertained without adjudication(15), due to the fact that the survival data were derived from thorough site reports and search for vital status obtained from public domains. Q-wave MI was centrally adjudicated and defined in compliance with the Minnesota classification (new major Q-QS wave abnormalities) or by the appearance of a new left bundle branch block in conjunction with abnormal biomarkers.

The secondary endpoints included individual components of the primary endpoint (all-cause death and new Q-wave MI); composite of all-cause death, stroke or new Q-wave MI; any stroke; ischemic stroke; any MI; any revascularization; target vessel revascularization (TVR); definite stent thrombosis (ST); definite or probable ST (16); and bleeding defined according to the Bleeding Academic Research Consortium (BARC) criteria (type 3 or 5) up to two years (17).

The third universal definition of MI was the recommended criteria to report MI (18). Composite endpoints were analyzed hierarchically. Individual components were reported non-hierarchically (19).

Statistical Analysis

Clinical outcomes were compared between patients treated for at least one bifurcation lesion versus patients not treated for any bifurcation lesion (Bifurcation vs. non-bifurcation).

Thereafter, the effect of experimental versus reference antiplatelet therapy on clinical outcomes according to presence/absence of bifurcation PCI was estimated with a Cox regression model.

Eventually, we did a subgroup analysis of the primary endpoint only in patients treated for at least one bifurcation lesion with tests for treatment-by subgroup interaction according to prespecified baseline characteristics, and type of stenting technique such as 1-stent vs. 2-stent. Due to the absence of classification for trifurcation PCI according to the MADS classification, patients with trifurcation PCI were excluded from the analysis comparing 1-stent vs. 2-stent.

Categorical variables were compared with the $\chi 2$ test or Fisher's exact test. Continuous variables were compared with Student's t test or Mann-Whitney U test for non-normally distributed data. Composite endpoints were calculated using time-to-first of any of the composite event(s) per patient. Patients started being at risk on the day of index PCI, or if no procedure was performed, on the day of randomization. Survival curves were constructed using Kaplan-Meier estimates and the log-rank test was used to compare between-group differences. Landmark analyses were performed with prespecified cut-offs at 30 days (at the time of the planned date of discontinuation of aspirin in the experimental treatment) and one year (at the time of the planned dates of discontinuation of a P2Y12 inhibitor in the reference treatment). In total, there were six outpatient protocol visits at 30 days, 3, 6, 12, 18, and 24 months. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were done in SPSS (version 25.0.0, IBM, New York).

Figure 1

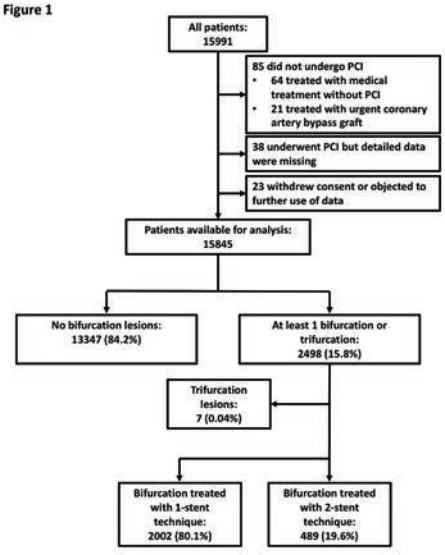


Figure 1. Study flow chart.

Results

The GLOBAL LEADERS trial recruited a total of 15,991 patients(13), of whom 146 patients were excluded from this analysis (**Figure 1**), leaving 15,845 patients of which 2,498 patients (15.7%) underwent PCI for at least one bifurcation lesion and 7 patients (0.04%) at least one trifurcation lesion. Amongst the patients with at least one bifurcation lesion, 2002 (80.1%) were treated with PCI using a 1-stent technique, and 489 (19.6%) a 2-stent technique (**Figure 1**).

Clinical outcomes: Bifurcation versus nonbifurcation group

Patients in the non-bifurcation group had a higher body-mass index and higher prevalence of diabetes mellitus or previous revascularization, whereas patients in the bifurcation group more often presented with acute coronary syndrome (**Table 1**). In terms of procedural characteristics, patients in the bifurcation group as expected had more lesions, stents, and longer total stent length per patient.

In terms of the primary endpoint (a composite of all-cause death or new Q-wave MI) at 2 years, there was a trend towards a higher incidence in the bifurcation group compared with the non-bifurcation group (4.72% vs 3.98%, hazard ratio (HR) 1.19 [95% confidential internal (95%CI): 0.98-1.46], p=0.083) a difference driven by the significantly higher incidence of new Q-wave MI in the bifurcation group (1.84% vs 1.04%, HR 1.78 [95%CI: 1.27-2.48], p=0.001)(**Table 2**). These differences in any revascularization and TVR were also observed at 30-day and 1-year follow-up, but not in the landmark analysis at 1 year.

Table 1. Baseline and procedural characteristics

	Bifurcation n = 2498	Non-bifurcation n = 13347	p Value
Age, years	64.4 ± 10.4	64.6 ± 10.3	0.601
Male	1950/2498 (78.1)	10205/13347 (76.5)	0.082
Body-mass index, kg/m2	28.0 ± 4.5	28.2 ± 4.6	0.034
Medical history			
Diabetes mellitus	590/2495 (23.6)	3414/13339 (25.6)	0.040
Insulin-dependent diabetes mellitus	169/2490 (6.8)	1043/13308 (7.8)	0.071
Hypertension	1856/2491 (74.5)	9774/13300 (73.5)	0.289
Hypercholesterolemia	1722/2429 (70.9)	8965/12915 (69.4)	0.146
Current smoker	638/2498 (25.5)	3501/13347 (26.2)	0.471
Peripheral vascular disease	137/2469 (5.5)	857/13230 (6.5)	0.082
Chronic obstructive pulmonary disease	109/2482 (4.4)	702/13292 (5.3)	0.065
Previous major bleeding	15/2498 (0.6)	83/13326 (0.6)	0.896
Impaired renal function*	322/2488 (12.9)	1836/13273 (13.8)	0.236
Previous stroke	70/2497 (2.8)	348/13325 (2.6)	0.584
Previous myocardial infarction	554/2494 (22.2)	3125/13305 (23.5)	0.167
Previous percutaneous coronary intervention	774/2498 (31.0)	4407/13333 (33.1)	0.043
Previous coronary artery bypass grafting	108/2498 (4.3)	830/13334 (6.2)	<0.001
Clinical presentation			

Stable coronary artery disease	1277/2498 (51.1)	7127/13347 (53.4)	0.036
Acute coronary syndrome	1221/2498 (48.9)	6220/13347 (46.6)	0.036
Unstable angina	348/2498 (13.9)	1659/13347 (12.4)	0.038
Non-ST-elevation myocardial infarction	559/2498 (22.4)	2797/13347 (21.0)	0.110
ST-elevation myocardial infarction	314/2498 (12.6)	1764/13347 (13.2)	0.380
Procedural characteristics			
Vascular access site			
Femoral	679/2458 (27.6)	3589/13188 (27.2)	0.675
Brachial	15/2458 (0.6)	91/13188 (0.7)	0.658
Radial	1872/2458 (76.2)	9827/13188 (74.5)	0.085
Number of lesions treated	1.7 ± 0.9	1.4 ± 0.7	<0.001
Number of stents	2.2 ± 1.4	1.6 ± 1.0	<0.001
Total stent length	47.3 ± 31.6	33.2 ± 23.2	<0.001
Randomization of antiplatelet therapy			
Experimental treatment (one-month DAPT followed by 23-month ticagrelor monotherapy)	1240/2498 (49.6)	6683/13347 (50.1)	0.692
Reference treatment (12-month DAPT followed by 12-month aspirin monotherapy)	1258/2498 (50.4)	6664/13347 (49.9)	

Data are mean ± SD or counts (percentage).
*Impaired renal function is defined as estimated glomerular filtration rate of creatinine clearance of 60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease formula

Table 2. Clinical outcomes at 30 days, one, two years follow-up and landmark analysis at 30 days and 1 year stratified by presence or absence of bifurcation.

	Bifurcation n = 2498	Non-bifurcation n = 13347	HR (95%CI)	p Value
30-day outcomes				
All-cause death or new Q-wave MI	15 (0.60%)	61 (0.46%)	1.32 (0.75-2.31)	0.340
All-cause death	13 (0.52%)	54 (0.40%)	1.29 (0.70-2.36)	0.412
New Q-wave MI	2 (0.08%)	8 (0.06%)	1.34 (0.28-6.30)	0.712
Composite of all-cause death, stroke or new Q-wave MI	18 (0.72%)	86 (0.64%)	1.12 (0.67-1.86)	0.665
POCE*	86 (3.44%)	311 (2.33%)	1.49 (1.17-1.89)	0.001
Stroke	3 (0.12%)	31 (0.23%)	0.52 (0.16-1.69)	0.267
Ischemic stroke	3 (0.12%)	23 (0.17%)	0.70 (0.21-2.32)	0.554
Any MI	38 (1.52%)	112 (0.84%)	1.82 (1.26-2.63)	0.001
Any revascularization	55 (2.20%)	189 (1.42%)	1.56 (1.16-2.11)	0.003
TVR	35 (1.40%)	124 (0.93%)	1.51 (1.04-2.20)	0.030
Definite ST	10 (0.40%)	49 (0.37%)	1.09 (0.55-2.15)	0.802

Definite or probable ST	16 (0.64%)	69 (0.52%)	1.24 (0.72-2.14)	0.439
BARC 3 or 5 bleeding	16 (0.64%)	82 (0.61%)	1.04 (0.61-1.78)	0.876
1-year outcomes				
All-cause death or new Q-wave MI	67 (2.68%)	284 (2.13%)	1.27 (0.97-1.65)	0.082
All-cause death	40 (1.60%)	197 (1.48%)	1.09 (0.77-1.53)	0.630
New Q-wave MI	28 (1.12%)	89 (0.67%)	1.69 (1.10-2.58)	0.015
Composite of all-cause death, stroke or new Q-wave MI	80 (3.20%)	352 (2.64%)	1.22 (0.95-1.55)	0.112
POCE*	276 (11.05%)	1138 (8.53%)	1.32 (1.15-1.50)	<0.001
Stroke	15 (0.60%)	85 (0.64%)	0.94 (0.54-1.63)	0.833
Ischemic stroke	13 (0.52%)	67 (0.50%)	1.04 (0.57-1.88)	0.905
Any MI	64 (2.56%)	266 (1.99%)	1.29 (0.98-1.70)	0.064
Any revascularization	216 (8.65%)	828 (6.20%)	1.41 (1.22-1.64)	<0.001
TVR	125 (5.00%)	433 (3.24%)	1.55 (1.27-1.90)	<0.001
Definite ST	17 (0.68%)	77 (0.58%)	1.18 (0.70-2.00)	0.535
Definite or probable ST	24 (0.96%)	101 (0.76%)	1.27 (0.81-1.98)	0.291
BARC 3 or 5 bleeding	50 (2.00%)	202 (1.51%)	1.33 (0.97-1.81)	0.073
2-year outcomes				
All-cause death or new Q-wave MI	118 (4.72%)	531 (3.98%)	1.19 (0.98-1.46)	0.083
All-cause death	75 (3.00%)	399 (2.99%)	1.01 (0.79-1.29)	0.964
New Q-wave MI	46 (1.84%)	139 (1.04%)	1.78 (1.27-2.48)	0.001
Composite of all-cause death, stroke or new Q-wave MI	138 (5.52%)	634 (4.75%)	1.17 (0.97-1.40)	0.100
POCE*	376 (15.05%)	1771 (13.27%)	1.16 (1.03-1.29)	0.011
Stroke	22 (0.88%)	138 (1.03%)	0.85 (0.54-1.34)	0.483
Ischemic stroke	19 (0.76%)	110 (0.82%)	0.92 (0.57-1.50)	0.746
Any MI	81 (3.24%)	405 (3.03%)	1.07 (0.85-1.36)	0.559
Any revascularization	280 (11.21%)	1227 (9.19%)	1.24 (1.09-1.41)	0.001
TVR	167 (6.69%)	645 (4.83%)	1.40 (1.18-1.66)	<0.001
Definite ST	24 (0.96%)	104 (0.78%)	1.23 (0.79-1.92)	0.353
Definite or probable ST	32 (1.28%)	132 (0.99%)	1.30 (0.88-1.91)	0.188
BARC 3 or 5 bleeding	62 (2.48%)	269 (2.02%)	1.23 (0.94-1.63)	0.134
Landmark analysis at 30 days				
All-cause death or new Q-wave MI	103 (4.15%)	470 (3.54%)	1.18 (0.95-1.46)	0.134
All-cause death	62 (2.50%)	345 (2.60%)	0.96 (0.73-1.26)	0.776
New Q-wave MI	44 (1.77%)	131 (0.99%)	1.80 (1.28-2.54)	0.001
Composite of all-cause death, stroke or new Q-wave MI	120 (4.86%)	548 (4.15%)	1.17 (0.96-1.43)	0.110
POCE*	290 (12.08%)	1460 (11.26%)	1.08 (0.96-1.23)	0.210
Stroke	19 (0.77%)	107 (0.81%)	0.95 (0.58-1.54)	0.831
Ischemic stroke	16 (0.65%)	87 (0.66%)	0.98 (0.58-1.67)	0.948
Any MI	43 (1.76%)	293 (2.23%)	0.79 (0.57-1.09)	0.145
Any revascularization	225 (9.29%)	1038 (7.96%)	1.18 (1.02-1.36)	0.025
TVR	132 (5.40%)	521 (3.98%)	1.37 (1.13-1.66)	0.001

Definite ST	14 (0.57%)	55 (0.42%)	1.36 (0.76-2.45)	0.301
Definite or probable ST	16 (0.65%)	63 (0.48%)	1.36 (0.78-2.35)	0.275
BARC 3 or 5 bleeding	46 (1.87%)	187 (1.42%)	1.32 (0.96-1.82)	0.092
Landmark analysis at 1 year				
All-cause death or new Q-wave MI	51 (2.10%)	247 (1.89%)	1.11 (0.82-1.50)	0.500
All-cause death	35 (1.43%)	202 (1.54%)	0.93 (0.65-1.33)	0.676
New Q-wave MI	18 (0.74%)	50 (0.38%)	1.94 (1.13-3.32)	0.014
Composite of all-cause death, stroke or new Q-wave MI	58 (2.43%)	282 (2.20%)	1.10 (0.83-1.46)	0.492
POCE*	100 (4.56%)	633 (5.25%)	0.86 (0.70-1.07)	0.171
Stroke	7 (0.29%)	53 (0.41%)	0.70 (0.32-1.55)	0.382
Ischemic stroke	6 (0.25%)	43 (0.33%)	0.75 (0.32-1.75)	0.498
Any MI	17 (0.72%)	139 (1.09%)	0.65 (0.40-1.08)	0.097
Any revascularization	64 (2.88%)	399 (3.28%)	0.87 (0.67-1.14)	0.318
TVR	42 (1.82%)	212 (1.69%)	1.07 (0.77-1.50)	0.672
Definite ST	7 (0.29%)	27 (0.21%)	1.39 (0.60-3.18)	0.440
Definite or probable ST	8 (0.33%)	31 (0.24%)	1.38 (0.63-3.00)	0.419
BARC 3 or 5 bleeding	12 (0.50%)	67 (0.52%)	0.96 (0.52-1.78)	0.897

Data are counts (percentage).
*POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.
BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel

Treatment effect of antiplatelet therapy according to presence/absence of bifurcation lesions

There were no significant differences in baseline characteristics between experimental and reference group stratified by presence/absence of bifurcation lesions (**supplementary table 1**).

The results for the experimental versus reference antiplatelet treatment in the bifurcation and non-bifurcation groups are reported in **Figure 2** and **Supplementary table 2**. Compared to the reference strategy, the experimental strategy did not reduce the primary endpoint at 2 years in patients undergoing PCI irrespective of the presence or absence of a bifurcation lesion (bifurcation: HR: 0.74; 95% CI: 0.51-1.07, non-bifurcation: HR: 0.90; 95% CI: 0.76-1.07; p for interaction = 0.343), however it did result in a significant reduction in rates of definite or probable ST at 2 years in patients in the bifurcation (HR: 0.46; 95% CI: 0.22-0.97) versus non-bifurcation group (HR: 1.20; 95% CI: 0.85-1.69; p for interaction = 0.022) (**Supplementary figure 1A**). The same trend was observed on 1-year definite or probable ST (p for interaction = 0.027), whereas this significant benefit of ticagrelor monotherapy against aspirin monotherapy subsided beyond 1 year (p for interaction = 0.482) (**Supplementary figure 1B**). In terms of the 2-year incidence of stroke, the experimental strategy showed a negative effect in patient undergoing bifurcation PCI against the reference strategy (bifurcation: HR: 2.72; 95% CI: 1.06-6.94 in **Supplementary figure 2A**, non-bifurcation: HR: 0.82; 95% CI: 0.58-1.14; p for interaction = 0.018). This negative effect was observed at 1 year follow-up (p for interaction = 0.021), but not at 30 days (p for interaction = 0.480) and beyond 1 year (p for interaction = 0.479). In patients undergoing bifurcation PCI, the majority of stroke was ischemic (experimental group: 13/16

(81.2%), reference group: 6/6 (100%)), and the incidence of ischemic stroke was not different between groups (experimental group: 1.0% versus reference group: 0.5%, HR 2.21; 95% CI: 0.84-5.80, p=0.109 in **Supplementary figure 2B**). Only three hemorrhagic strokes occurred in patient undergoing bifurcation PCI, 2 occurred in the first year (day 135 and 139) and the third one beyond 1 year (day 596) (experimental group: 0.2% versus reference group: 0.0%, p=0.081 in **Supplementary figure 2C**).

Subgroup analysis of the primary endpoint in patients treated for at least one bifurcation lesion

The subgroup analysis in patients with bifurcation PCI demonstrated no variation in treatment effects for the primary endpoint according to prespecified baseline characteristics as well as stenting technique (1-stent vs. 2-stent) (**Figure 3**). In patients treated with 2-stent technique, the experimental treatment was associated with a numerically lower incidence of the primary endpoint at 2 years when compared with the reference treatment, but not statistically significant (4.6% vs 9.1%, HR 0.50 [95%CI: 0.24-1.02], p=0.056).

Discussion

The main findings of the study are following:

1. PCI for bifurcation lesions with a biolimus A9-eluting stent was not associated with higher incidence of primary endpoint of all-cause death or new Q-wave MI compared with PCI for non-bifurcation lesions, whereas significant difference was observed in new Q-wave MI, any revascularization and TVR at 2 years between groups.
2. In patients who underwent bifurcation PCI, one-month of DAPT with aspirin and ticagrelor followed by 23-month ticagrelor monotherapy had no impact on the primary endpoint but was associated with significant reduction in the risk of definite or probable ST and significant excess of stroke compared with 12-month standard DAPT followed by 12-month aspirin monotherapy.

Bifurcation vs. non-bifurcation group

In terms of the primary endpoint of death or new Q-wave MI, the result of the study is in line with previously published data from all-comers trials.(1,20) In contrast the higher rate of new Q-wave MI in the bifurcation group over the non-bifurcation group was observed consistently at 1- and 2-year follow-up and in the and landmark analysis at 1 year, whereas the incidence of any MI was similar between groups. In the bifurcation subanalysis of the Resolute all comers trial, 2-year Q-wave MI rates in bifurcation and non-bifurcation groups were similar to the present trial, but there was no significant difference due to less sample size (1.6% in bifurcation vs. 0.6% in non-bifurcation, p=0.097, n=2,265).(20) Therefore, this finding may suggest that bifurcation PCI can be associated with the occurrence of more severe MI up to 2 years when compared with non-bifurcation PCI.

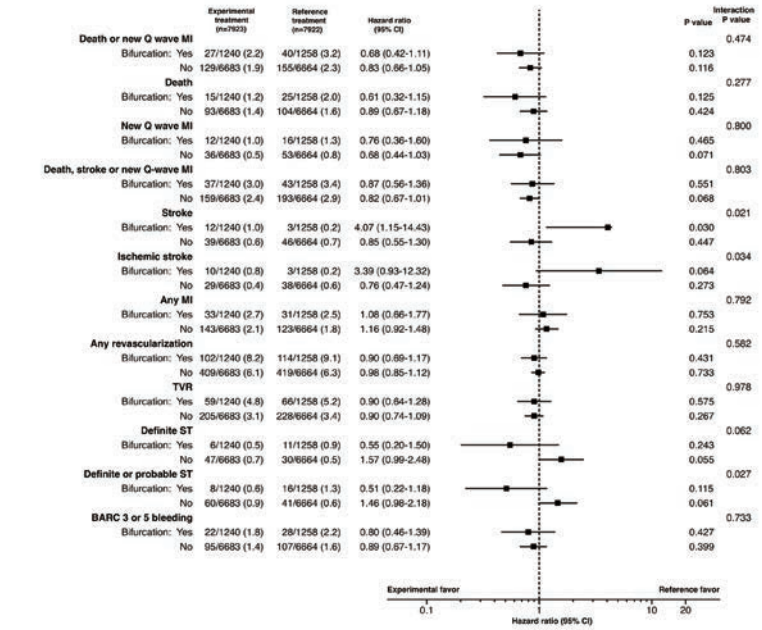


Figure 2. Treatment comparison of experimental versus reference antiplatelet strategy in randomized patients with versus without bifurcation PCI at 1 year (A) and 2 years (B) follow-up

*POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.
#Values were compared with Fisher's exact test.
BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel revascularization.

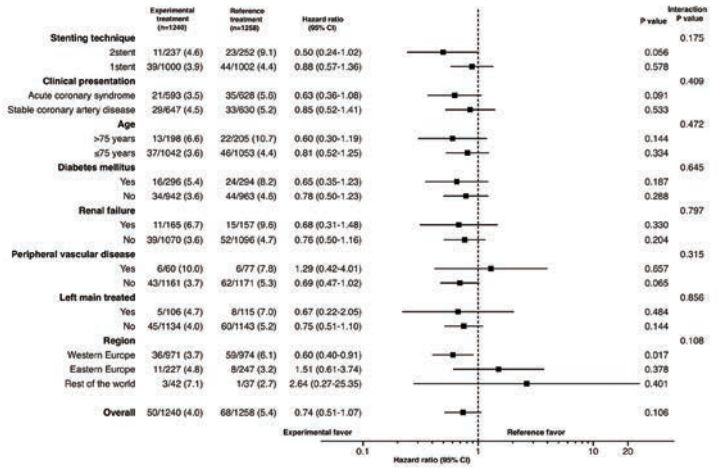


Figure 3. Subgroup analysis of all-cause death or new Q-wave MI at 2 years in patients treated for at least one bifurcation lesion.
CI: confidence interval.

Optimal antiplatelet strategy for patients undergoing bifurcation PCI

The evidence for the optimal antiplatelet strategy after bifurcation PCI is scarce, especially for potent antiplatelet drugs such as ticagrelor and prasugrel. Recent pooled patient-level analysis demonstrated that short DAPT of 3 or 6 months is associated with a higher incidence of 1-year major adverse cardiac events mainly driven by MI, when compared with prolonged DAPT of more than 1 year in patients undergoing PCI for complex lesions including bifurcation lesions treated with a 2-stent technique (10). In addition, a multicenter observational study reported that the risks of a composite of all-cause death or MI, MI, and definite or probable ST at 4 years were significantly lower in the prolonged (≥12 months) versus shorter DAPT group (<12 months) after bifurcation PCI with DES (21). From these results, it seems that patients undergoing bifurcation PCI need at least 12 months of DAPT. The present study also shows no benefit of one-month DAPT followed by ticagrelor monotherapy on the primary endpoint when compared with 12-month DAPT.

Stent thrombosis and stroke after bifurcation PCI

Previously coronary bifurcation lesions were reported as an independent risk factor for ST (22-24) as consequence of several factors. Firstly, bifurcation stenting modifies local hemodynamics and creates low endothelial shear stress and stagnant areas that could result in local thrombogenicity (25). Secondly, pathological studies demonstrated that the flow divider zone was associated with a high percentage of uncovered struts and fibrin deposition several months after DES implantation, which could represent a substrate for ST (26). Thirdly, two-stent strategies have been suspected of inducing overlapping device segments that could result in local thrombogenicity (27). Finally, bifurcation stenting could also encourage stent malapposition due to vessel dimension variation along the different segments and promote future thrombotic events (28). In the present trial, the incidence of ST did not statistically differ between bifurcation and non-bifurcation group. However, ticagrelor monotherapy following one-month DAPT demonstrated significant treatment

effect on definite or probable ST at 2 years compared with conventional aspirin monotherapy following 12-month DAPT. This benefit was observed up to 1 year and subsided beyond, although theoretically this benefit should be derived from the comparison between ticagrelor monotherapy versus aspirin monotherapy beyond 1 year. In addition, overall incidence of ST was quite low, and the treatment effect of the experimental strategy on ST went into opposite directions in bifurcation and non-bifurcation group. Consequently, these significant finding regarding ST can be considered as a play of chance.

On the other hand, in patients who underwent bifurcation PCI, harmful effect of experimental treatment in 2-year stroke was observed compared with reference treatment. This difference in stroke was mainly derived from the result between 30 days to 1 year. Therefore, procedure itself was probably not associated with the occurrence of stroke. These findings may suggest that DAPT is associated with lower incidence of stroke up to 1 year compared with monotherapy of ticagrelor. However, overall incidence of stroke was quite low, and the treatment effect of the experimental strategy on stroke went into opposite directions in bifurcation and non-bifurcation group. Consequently, these apparently significant findings regarding stroke can be also considered as a play of chance similar to ST.

Regarding composite hard endpoint of all-cause death, stroke or new Q-wave MI at 2 years, there was no significant difference between groups in patients undergoing bifurcation PCI, which suggests that early discontinuation of aspirin at 30 days after bifurcation PCI followed by ticagrelor monotherapy may be as safe as conventional 12-month DAPT followed by aspirin monotherapy.

Further evidence from dedicated bifurcation trial testing one-month DAPT followed by P2Y12 monotherapy is warranted in order to further elucidate that possible duality of effect (such as possible prevention of ST and possible increase in stroke) in patients undergoing bifurcation PCI.

Study limitations

This prespecified subgroup analysis of primary endpoint has several limitations.

Firstly, in the context of the overall trial in which the primary endpoint was not met, these findings need to be considered as hypothesis-generating.

Secondly, although this subgroup analysis of primary endpoint was prespecified and information of bifurcation was prospectively collected(12), no formal power calculation was performed. In addition, there exist limitations inherent in subgroup analysis such as diminished power to detect real differences and increasing statistical likelihood of false finding when many subgroups are examined with multiple testing. Therefore, the study findings should be considered as hypothesis-generating (29).

Thirdly, clinical outcomes were not adjudicated by an independent clinical event committee. All events were identified and confirmed by the investigators of each hospital. There might be inaccuracies in determining cause of death or target vessel MI. Therefore, we chose all-cause death or new Q-wave MI centrally adjudicated by core lab instead of cardiac death or target vessel MI as the primary outcome. Nevertheless, the result of secondary endpoint should cautiously be interpreted in conjunction with the individual components of the primary endpoint.

Fourthly, the analysis comparing 2- versus 1-stent was post-randomization and non-prespecified analysis, therefore the findings are likely influenced by unmeasured confounders.

Fifthly, we did not collect the anatomic SYNTAX score including Medina classification in all the patients, which limited the analysis regarding anatomical complexity of each bifurcation lesion.

Finally, a biolimus A9-eluting stent has a relatively thicker strut of 120 μm compared with other current generation DES. This might result in worse outcomes in bifurcation lesions treated with 2-stent technique using a biolimus A9-eluting stent due to the overlap of relatively thicker struts. A meta-analysis published in 2018 showed that DES with ultra-thin struts (strut thickness <70 μm) reduced the incidence of target lesion failure compared with that of contemporary stents with thicker struts (30). However, in the present study, all patients were exclusively treated with a biolimus A9-eluting stent, and this makes the effect of antiplatelet drug more likely.

Conclusion

After PCI for bifurcation lesions, using one-month of DAPT, followed by ticagrelor monotherapy for 23-month did not demonstrate explicit benefit regarding all-cause death or new Q-wave MI as in the overall trial.

References

1. Grundeken MJ, Wykrzykowska JJ, Ishibashi Y, Garg S, de Vries T, Garcia-Garcia HM, Onuma Y, de Winter RJ, Buszman P, Linke A and others. First generation versus second generation drug-eluting stents for the treatment of bifurcations: 5-year follow-up of the LEADERS all-comers randomized trial. Catheter Cardiovasc Interv 2016;87(7):E248-60.
2. Gao XF, Zhang YJ, Tian NL, Wu W, Li MH, Bourantas CV, Jiang XM, Wang ZM, Li B, Mao WX and others. Stenting strategy for coronary artery bifurcation with drug-eluting stents: a meta-analysis of nine randomised trials and systematic review. EuroIntervention 2014;10(5):561-9.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ and others. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018.
4. Hildick-Smith D, Behan MW, Lassen JF, Chieffo A, Lefevre T, Stankovic G, Burzotta F, Pan M, Ferenc M, Bennett L and others. The EBC TWO Study (European Bifurcation Coronary TWO): A Randomized Comparison of Provisional T-Stenting Versus a Systematic 2 Stent Culotte Strategy in Large Caliber True Bifurcations. Circ Cardiovasc Interv 2016;9(9).
5. Zhang F, Dong L, Ge J. Simple versus complex stenting strategy for coronary artery bifurcation lesions in the drug-eluting stent era: a meta-analysis of randomised trials. Heart 2009;95(20):1676-81.
6. Brar SS, Gray WA, Dangas G, Leon MB, Aharonian VJ, Brar SK, Moses JW. Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. EuroIntervention 2009;5(4):475-84.
7. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, Burzotta F, Zelizko M, Dudek D, Ludman P and others. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv 2008;71(2):175-83.
8. Lassen JF, Burzotta F, Banning AP, Lefevre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y and others. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. EuroIntervention 2018;13(13):1540-1553.
9. Katsikis A, Chichareon P, Cavalcante R, Collet C, Modolo R, Onuma Y, Stankovic G, Louvard Y, Vranckx P, Valgimigli M and others. Application of the MADS classification system in a "mega mammoth" stent trial: Feasibility and preliminary clinical implications. Catheter Cardiovasc Interv 2018.
10. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y and others. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol 2016;68(17):1851-1864.
11. Yeh RW, Kereiakes DJ, Steg PG, Cutlip DE, Croce KJ, Massaro JM, Mauri L, Investigators DS. Lesion Complexity and Outcomes of Extended Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. J Am Coll Cardiol 2017;70(18):2213-2223.
12. Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, Garcia-Garcia HM, van Es GA, Serruys PW. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention 2016;12(10):1239-1245.
13. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C and others. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940-949.
14. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T and others. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;5(1):50-6.

15. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A and others. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation 2018;137(9):961-972.
16. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B and others. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Eur Heart J 2018;39(23):2192-2207.
17. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C and others. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32(2):205-17.
18. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Writing Group on the Joint ESCAAHAWHFTFftUDoMI, Thygesen K, Alpert JS, White HD and others. Third universal definition of myocardial infarction. Eur Heart J 2012;33(20):2551-67.
19. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P and others. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.
20. 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):1267-1274.
21. Jang WJ, Ahn SG, Song YB, Choi SH, Chun WJ, Oh JH, Cho SW, Kim BS, Yoon JH, Koo BK and others. Benefit of Prolonged Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stent for Coronary Bifurcation Lesions: Results From the Coronary Bifurcation Stenting Registry II. Circ Cardiovasc Interv 2018;11(7):e005849.
22. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M and others. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293(17):2126-30.
23. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z and others. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113(8):1108-13.
24. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW and others. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53(16):1399-409.
25. Antoniadis AP, Mortier P, Kassab G, Dubini G, Foin N, Murasato Y, Giannopoulos AA, Tu S, Iwasaki K, Hikichi Y and others. Biomechanical Modeling to Improve Coronary Artery Bifurcation Stenting: Expert Review Document on Techniques and Clinical Implementation. JACC Cardiovasc Interv 2015;8(10):1281-96.
26. 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(16):1679-87.
27. Zimarino M, Corazzini A, Ricci F, Di Nicola M, De Caterina R. Late thrombosis after double versus single drug-eluting stent in the treatment of coronary bifurcations: a meta-analysis of randomized and observational Studies. JACC Cardiovasc Interv 2013;6(7):687-95.
28. Lassen JF, Holm NR, Stankovic G, Lefevre T, Chieffo A, Hildick-Smith D, Pan M, Darremont O, Albiero R, Ferenc M and others. Percutaneous coronary intervention for coronary bifurcation disease: consensus from the first 10 years of the European Bifurcation Club meetings. EuroIntervention 2014;10(5):545-60.
29. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, Devereaux PJ, Thabane L. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol 2017;46(2):746-755.

30. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer-Generation Ultrathin Strut Drug-Eluting Stents Versus Older Second-Generation Thicker Strut Drug-Eluting Stents for Coronary Artery Disease. Circulation 2018;138(20):2216-2226.

Supplementary Material

Patients selection criteria

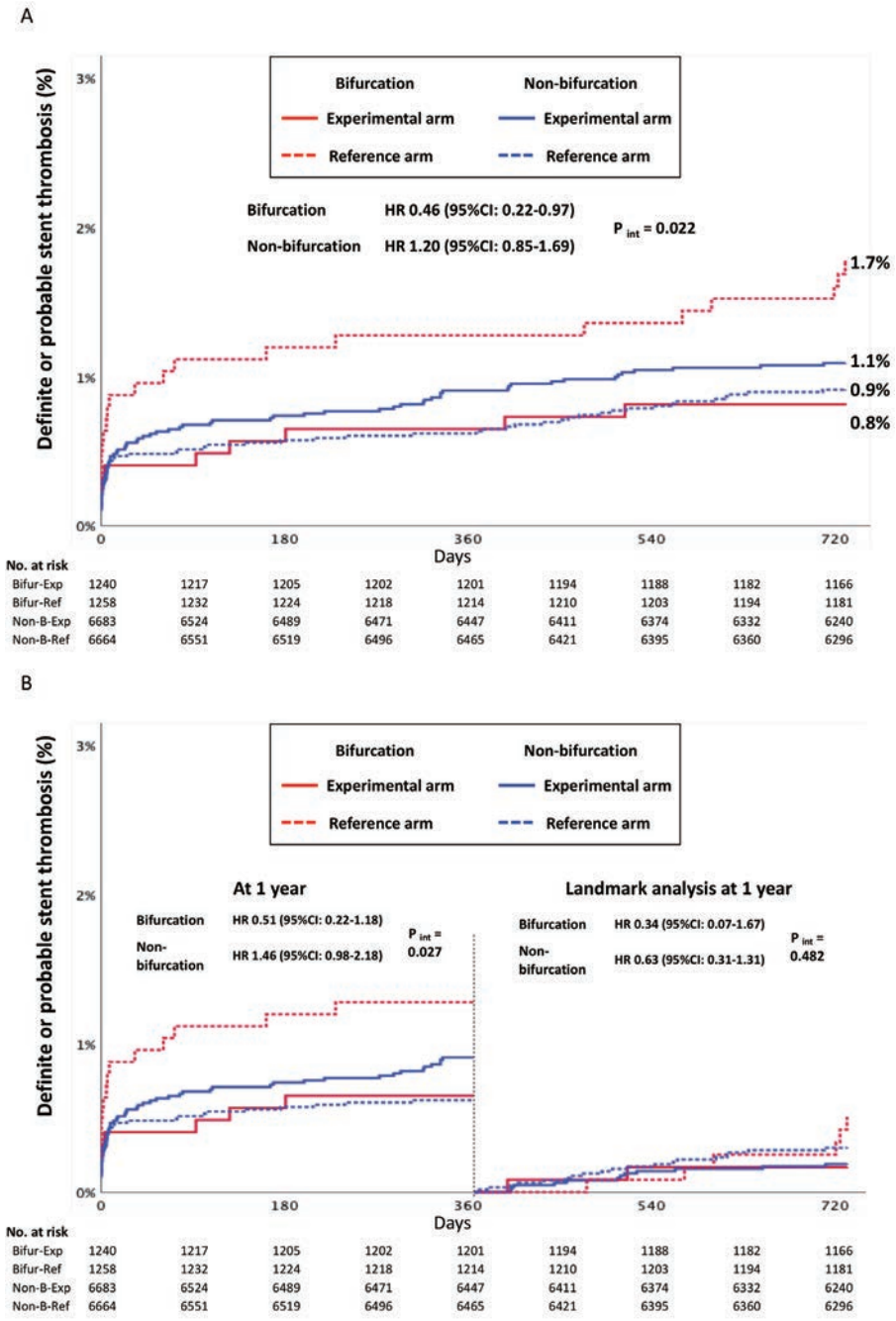
INCLUSION CRITERIA.

For inclusion in the study patients must fulfil the following criteria

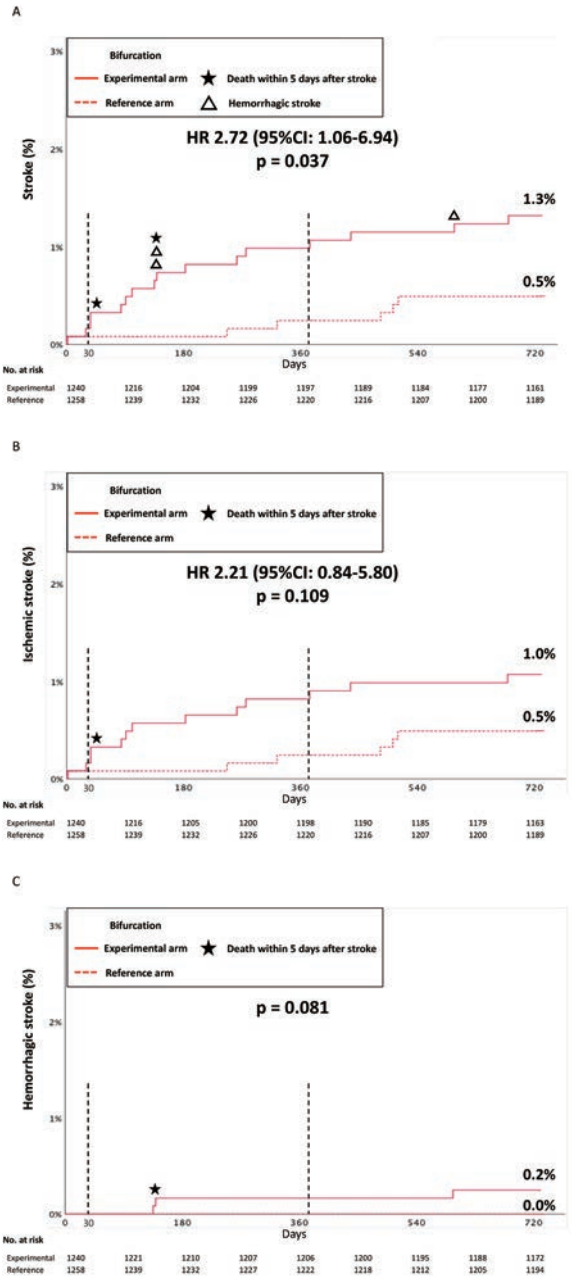
1. Age ≥18 years;
2. Patients with any clinical indication for percutaneous coronary intervention
3. Presence of one or more coronary artery stenosis of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 millimeter.

EXCLUSION CRITERIA.

1. Known intolerance to aspirin, P2Y12 receptor antagonists, bivalirudin, stainless steel or biolimus
2. Known intake of a strong cytochrome P3A4 inhibitor (eg, ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor
3. Use of fibrinolytic therapy within 24 hours of percutaneous coronary intervention
4. Known severe hepatic impairment
5. Planned coronary artery bypass grafting as a staged procedure (hybrid) within 12 months of the index procedure
6. Planned surgery within 12 months of percutaneous coronary intervention unless dual antiplatelet therapy is maintained throughout the peri-surgical period
7. Need for oral anti-coagulation therapy
8. PCI for a priori known stent thrombosis
9. Known overt major bleeding
10. Known history of intracranial hemorrhage
11. Known stroke from ischemic or unknown cause within last 30 days
12. Known pregnancy at time of randomization
13. Inability to provide informed consent
14. Currently participating in another trial before reaching primary endpoint



Supplementary figure 1. Kaplan–Meier estimates of cumulative incidence of definite or probable stent thrombosis for experimental versus reference antiplatelet strategy in patients with or without bifurcation up to 730 days (A) and up to 365 days and landmark analysis at 365 days (B).



Supplementary figure 2. Kaplan–Meier estimates of cumulative incidence of stroke for experimental versus reference antiplatelet strategy in patients with bifurcation up to 730 days.
Kaplan–Meier curves show the cumulative incidence of any stroke (Panel A); ischemic stroke (Panel B); hemorrhagic stroke (Panel C).

Supplementary table 1. Baseline and procedural characteristics between experimental versus reference treatment stratified by presence/absence of bifurcation lesions.

	Bifurcation n=2498			Non-bifurcation n=13347		
	Experimental n = 1240	Reference n = 1258	p Value	Experimental n = 6683	Reference n = 6664	p Value
Age, years	64.5 ± 10.5	64.4 ± 10.4	0.974	64.5 ± 10.3	64.6 ± 10.3	0.790
Male	958/1240 (77.3)	992/1258 (78.9)	0.335	5111/6683 (76.5)	5094/6664 (76.4)	0.960
Body-mass index, kg/m2	28.0 ± 4.6	28.0 ± 4.4	0.908	28.2 ± 4.6	28.2 ± 4.7	0.807
Medical history						
Diabetes mellitus	296/1238 (23.9)	294/1257 (23.4)	0.760	1734/6679 (26.0)	1680/6660 (25.2)	0.330
Insulin-dependent diabetes mellitus	78/1233 (6.3)	91/1257 (7.2)	0.365	523/6665 (7.8)	520/6643 (7.8)	0.967
Hypertension	917/1237 (74.1)	939/1254 (74.9)	0.668	4924/6660 (73.9)	4850/6640 (73.0)	0.244
Hypercholesterolemia	843/1199 (70.3)	879/1230 (71.5)	0.531	4467/6464 (69.1)	4498/6451 (69.7)	0.445
Current smoker	319/1240 (25.7)	319/1258 (25.4)	0.833	1727/6683 (25.8)	1774/6664 (26.6)	0.306
Peripheral vascular disease	60/1221 (4.9)	77/1248 (6.2)	0.173	411/6626 (6.2)	446/6604 (6.8)	0.198
Chronic obstructive pulmonary disease	53/1230 (4.3)	56/1252 (4.5)	0.842	346/6660 (5.2)	356/6632 (5.4)	0.656
Previous major bleeding	5/1240 (0.4)	10/1258 (0.8)	0.205	41/6671 (0.6)	42/6655 (0.6)	0.904
Impaired renal function*	165/1235 (13.4)	157/1253 (12.5)	0.537	929/6642 (14.0)	907/6631 (13.7)	0.607
Previous stroke	37/1239 (3.0)	33/1258 (2.6)	0.583	172/6671 (2.6)	176/6654 (2.6)	0.809
Previous myocardial infarction	267/1236 (21.6)	287/1258 (22.8)	0.467	1547/6663 (23.2)	1578/6642 (23.8)	0.462
Previous percutaneous coronary intervention	367/1240 (29.6)	407/1258 (32.4)	0.136	2225/6677 (33.3)	2182/6656 (32.8)	0.507
Previous coronary artery bypass grafting	52/1240 (4.2)	56/1258 (4.5)	0.751	392/6677 (5.9)	438/6657 (6.6)	0.090
Clinical presentation						
Stable coronary artery disease	647/1240 (52.2)	630/1258 (50.1)	0.294	3553/6683 (53.2)	3574/6664 (53.6)	0.589
Acute coronary syndrome	593/1240 (47.8)	628/1258 (49.9)	0.294	3130/6683 (46.8)	3090/6664 (46.4)	0.589
Unstable angina	159/1240 (12.8)	189/1258 (15.0)	0.112	835/6683 (12.5)	824/6664 (12.4)	0.821
Non-ST-elevation myocardial infarction	283/1240 (22.8)	276/1258 (21.9)	0.597	1391/6683 (20.8)	1406/6664 (21.1)	0.686
ST-elevation myocardial infarction	151/1240 (12.2)	163/1258 (13.0)	0.557	904/6683 (13.5)	860/6664 (12.9)	0.289
Procedural characteristics						

Vascular access site						
Femoral	342/1220 (28.0)	337/1238 (27.2)	0.653	1800/6599 (27.3)	1789/6589 (27.2)	0.871
Brachial	8/1220 (0.7)	7/1238 (0.6)	0.774	45/6599 (0.7)	46/6589 (0.7)	0.910
Radial	924/1220 (75.7)	948/1238 (76.6)	0.626	4915/6599 (74.5)	4912/6589 (74.5)	0.929
Number of lesions treated	1.8 ± 1.0	1.7 ± 0.9	0.067	1.4 ± 0.7	1.4 ± 0.7	0.355
Number of stents	2.3 ± 1.4	2.2 ± 1.4	0.295	1.6 ± 1.0	1.6 ± 1.0	0.695
Total stent length (mm)	48.3 ± 32.4	46.3 ± 30.8	0.135	33.1 ± 22.7	33.4 ± 23.7	0.398
Bifurcation treatment						
2-stent technique used	237/1237 (19.2)	252/1254 (20.1)	0.556			
bifurcation involved left main	99/1240 (8.0)	107/1258 (8.5)	0.636			
Proximal optimization technique performed	411/1240 (33.1)	373/1258 (29.7)	0.060			
Kissing balloon inflation performed	512/1240 (41.3)	533/1258 (42.4)	0.585			

Data are mean ± SD or counts (percentage).

*Impaired renal function is defined as estimated glomerular filtration rate of creatinine clearance of 60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease formula.

Supplementary table 2. Clinical outcomes in all patients according to prevalence of bifurcation and allocated antiplatelet regimen at 30days, and Landmark analysis at 30 days and 1 year

	Bifurcation				Non-bifurcation				
	Experimental treatment	Reference treatment	HR (95%CI)	p value	Experimental treatment	Reference treatment	HR (95%CI)	p value	p for interaction
30 days									
All-cause death or new Q-wave MI	3/1240 (0.2)	12/1258 (1.0)	0.25 (0.07-0.90)	0.033	31/6683 (0.5)	30/6664 (0.5)	1.03 (0.62-1.70)	0.906	0.043
All-cause death	3/1240 (0.2)	10/1258 (0.8)	0.30 (0.08-1.10)	0.070	29/6683 (0.4)	25/6664 (0.4)	1.16 (0.68-1.98)	0.592	0.060
New Q-wave MI	0/1240 (0.0)	2/1258 (0.2)	NA	0.254#	2/6683 (0.02)	6/6664 (0.1)	0.33 (0.07-1.65)	0.177	NA
POCE*	34/1240 (2.7)	52/1258 (4.1)	0.66 (0.43-1.02)	0.060	151/6683 (2.3)	160/6664 (2.4)	0.94 (0.75-1.18)	0.592	0.153
Stroke	2/1240 (0.2)	1/1258 (0.1)	2.02 (0.18-22.33)	0.565	14/6683 (0.2)	17/6664 (0.3)	0.82 (0.41-1.67)	0.587	0.480
Any MI	21/1240 (1.7)	17/1258 (1.4)	1.25 (0.66-2.38)	0.488	61/6683 (0.9)	51/6664 (0.8)	1.19 (0.82-1.73)	0.349	0.897
Any revascularization	17/1240 (1.4)	38/1258 (3.0)	0.45 (0.25-0.80)	0.006	93/6683 (1.4)	96/6664 (1.4)	0.97 (0.73-1.29)	0.815	0.019
TVR	11/1240 (0.9)	24/1258 (1.9)	0.46 (0.23-0.95)	0.035	61/6683 (0.9)	63/6664 (0.9)	0.97 (0.68-1.37)	0.848	0.070
Definite ST	3/1240 (0.2)	7/1258 (0.6)	0.43 (0.11-1.68)	0.227	27/6683 (0.4)	22/6664 (0.3)	1.22 (0.70-2.15)	0.480	0.165
Definite or probable ST	5/1240 (0.4)	11/1258 (0.9)	0.46 (0.16-1.33)	0.150	37/6683 (0.6)	32/6664 (0.5)	1.15 (0.72-1.85)	0.553	0.120
BARC 3 or 5 bleeding	8/1240 (0.6)	8/1258 (0.6)	1.01 (0.38-2.70)	0.978	43/6683 (0.6)	39/6664 (0.6)	1.10 (0.71-1.70)	0.664	0.881
Landmark at 30 days									
All-cause death or new Q-wave MI	47/1236 (3.8)	56/1246 (4.5)	0.84 (0.57-1.24)	0.390	221/6651 (3.3)	249/6632 (3.8)	0.88 (0.74-1.06)	0.177	0.835
All-cause death	28/1236 (2.3)	34/1248 (2.7)	0.83 (0.50-1.37)	0.464	163/6653 (2.5)	182/6637 (2.7)	0.89 (0.72-1.10)	0.291	0.791
New Q-wave MI	20/1236 (1.6)	24/1246 (1.9)	0.84 (0.46-1.52)	0.561	60/6651 (0.9)	71/6632 (1.1)	0.84 (0.60-1.19)	0.325	0.992
POCE*	148/1198 (12.4)	142/1202 (11.8)	1.06 (0.84-1.33)	0.638	704/6497 (10.8)	756/6474 (11.7)	0.93 (0.84-1.03)	0.157	0.313
Stroke	14/1228 (1.1)	5/1243 (0.4)	2.86 (1.03-7.93)	0.044	48/6602 (0.7)	59/6591 (0.9)	0.81 (0.56-1.19)	0.289	0.024
Any MI	22/1209 (1.8)	21/1228 (1.7)	1.07 (0.59-1.94)	0.829	138/6556 (2.1)	155/6559 (2.4)	0.89 (0.71-1.12)	0.333	0.584
Any revascularization	115/1214 (9.5)	110/1209 (9.1)	1.05 (0.81-1.36)	0.718	506/6523 (7.8)	532/6515 (8.2)	0.95 (0.84-1.07)	0.414	0.501
TVR	70/1220 (5.7)	62/1223 (5.1)	1.14 (0.81-1.61)	0.441	242/6555 (3.7)	279/6546 (4.3)	0.87 (0.73-1.03)	0.101	0.154
Definite ST	5/1227 (0.4)	9/1239 (0.7)	0.56 (0.19-1.68)	0.303	29/6587 (0.4)	26/6588 (0.4)	1.12 (0.66-1.90)	0.677	0.267
Definite or probable ST	5/1226 (0.4)	11/1239 (0.9)	0.46 (0.16-1.33)	0.150	35/6587 (0.5)	28/6586 (0.4)	1.25 (0.76-2.06)	0.372	0.093

BARC 3 or 5 bleeding	22/1223 (1.8)	24/1238 (1.9)	0.93 (0.52-1.66)	0.804	90/6579 (1.4)	97/6576 (1.5)	0.93 (0.70-1.24)	0.612	0.999
Landmark at 1Y									
All-cause death or new Q-wave MI	23/1211 (1.9)	28/1218 (2.3)	0.82 (0.47-1.43)	0.490	123/6549 (1.9)	124/6507 (1.9)	0.99 (0.77-1.26)	0.907	0.562
All-cause death	16/1223 (1.3)	19/1233 (1.5)	0.85 (0.44-1.65)	0.625	99/6585 (1.5)	103/6558 (1.6)	0.96 (0.73-1.26)	0.754	0.740
New Q-wave MI	8/1211 (0.7)	10/1218 (0.8)	0.80 (0.32-2.03)	0.642	26/6549 (0.4)	24/6507 (0.4)	1.08 (0.62-1.88)	0.791	0.593
POCE*	48/1087 (4.4)	52/1106 (4.7)	0.94 (0.63-1.39)	0.755	300/6039 (5.0)	333/6018 (5.5)	0.90 (0.77-1.05)	0.168	0.826
Stroke	4/1196 (0.3)	3/1220 (0.2)	1.36 (0.30-6.08)	0.686	23/6460 (0.4)	30/6452 (0.5)	0.77 (0.45-1.32)	0.336	0.479
Any MI	10/1175 (0.9)	7/1195 (0.6)	1.46 (0.56-3.84)	0.442	56/6363 (0.9)	83/6377 (1.3)	0.68 (0.48-0.95)	0.023	0.140
Any revascularization	30/1108 (2.7)	34/1115 (3.0)	0.89 (0.54-1.45)	0.636	190/6096 (3.1)	209/6084 (3.4)	0.91 (0.74-1.10)	0.325	0.942
TVR	22/1150 (1.9)	20/1163 (1.7)	1.12 (0.61-2.05)	0.721	98/6296 (1.6)	114/6271 (1.8)	0.86 (0.65-1.12)	0.258	0.432
Definite ST	2/1200 (0.2)	5/1214 (0.4)	0.41 (0.08-2.09)	0.280	9/6448 (0.1)	18/6466 (0.3)	0.50 (0.23-1.12)	0.091	0.818
Definite or probable ST	2/1200 (0.2)	6/1214 (0.5)	0.34 (0.07-1.67)	0.184	12/6446 (0.2)	19/6463 (0.3)	0.63 (0.31-1.31)	0.216	0.482
BARC 3 or 5 bleeding	8/1188 (0.7)	4/1198 (0.3)	2.02 (0.61-6.71)	0.251	38/6411 (0.6)	29/6403 (0.5)	1.31 (0.81-2.13)	0.272	0.512

Data are counts (percentage).

*POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.

#Values were compared with Fisher's exact test.

BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; NA = not available; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel revascularization.

10

Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD: The ASET Pilot Study.

Norihiro Kogame, Patricia O Guimarães, Rodrigo Modolo, Fernando De Martino, Joao Tinoco, Expedito E Ribeiro, Hideyuki Kawashima, Masafumi Ono, Hironori Hara, Rutao Wang, Rafael Cavalcante, Bruno Moulin, Breno A A Falcão, Rogerio S Leite, Fernanda Barbosa de Almeida Sampaio, Gustavo R Morais, George C Meireles, Carlos M Campos, Yoshinobu Onuma, Patrick W Serruys, Pedro A Lemos.

JACC Cardiovasc Interv. 2020 Oct 12;13(19):2251-2262.

Abstract

Objective:
To evaluate the hypothesis that a prasugrel monotherapy following a successful everolimus-eluting stent (EES) implantation is feasible and safe in patients with stable coronary artery disease (CAD).

Background:
Recent studies suggested that short dual antiplatelet therapy (DAPT) strategies may provide an adequate balance between ischemic and bleeding risks. However, the complete omission of aspirin immediately after percutaneous coronary intervention (PCI) has not been tested so far.

Methods:
The study is a multicenter, single arm, open-label trial with a stopping rule based on the occurrence of definite stent thrombosis (if >3, the trial enrollment would be terminated). Patients undergoing successful EES implantation for stable CAD with a SYNTAX score <23 were included. All Participants were on standard DAPT at the time of index PCI. Aspirin was discontinued on the day of the index procedure but given prior to the procedure; prasugrel was administered in the Cath Lab immediately after the successful procedure and the aspirin-free prasugrel became the therapy regimen from that moment. Patients were treated solely with prasugrel for 3 months. The primary ischemic endpoint was the composite of cardiac death, spontaneous target-vessel myocardial infarction or definite stent thrombosis, whereas the primary bleeding endpoint was Bleeding Academic Research Consortium type 3 and 5 bleeding up to 3 months.

Results:
From February 22, 2018, to May 7, 2019, 201 patients were enrolled. All patients underwent PCI for stable CAD. Overall, 98.5% of patients adhered to prasugrel at 3-month follow-up. The primary ischemic and bleeding endpoints occurred in one patient (0.5%). No stent thrombosis event occurred.

Conclusion:
The aspirin-free prasugrel monotherapy following a successful EES implantation demonstrated feasibility and safety without any stent thrombosis in selected low-risk stable CAD patients. Our findings may help underpinning larger randomized controlled studies to evaluate the aspirin-free strategy compared with traditional DAPT following PCI.

Introduction

Patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) are traditionally treated with aspirin and a P2Y12 inhibitor during the first period post-procedure (the so-called dual antiplatelet therapy [DAPT]), followed by withdrawn of the P2Y12 inhibitor and maintenance of aspirin as the single antiplatelet drug afterwards (1). However, the best antithrombotic approach after stenting is still an open matter, currently under intense clinical investigation. The adequate duration of the DAPT period, as well as the best agent for the subsequent monotherapy phase, have been scrutinized in recent studies (2). In this regard, a number of recent trials have shown promising results with a scheme comprising short DAPT duration (i.e. one to three months) followed by the administration of solely a P2Y12 antagonist, instead of aspirin (3-6). However, the complete omission of aspirin immediately after PCI has not been tested so far.

Prasugrel is an irreversible oral P2Y12 receptor inhibitor that shows less variability in platelet inhibition and has a faster onset of action than clopidogrel. Some data from in vitro study suggested that aspirin demonstrated little additional inhibition in the presence of strong blockade by prasugrel (7). Additionally, the administration of aspirin has been linked to ominous hemorrhagic complications (8). Therefore, we hypothesized that a single antiplatelet therapy with prasugrel started immediately after PCI would result in an adequate stent thrombotic protection while avoiding an excess of bleeding risk. To test this concept, we designed a proof-of-concept single arm trial in which selected low-risk patients with stable CAD received prasugrel monotherapy immediately following a successful PCI with everolimus eluting stent (EES).

Methods

Study design with a stopping rule

The design of the ASET (Acetyl Salicylic Elimination Trial) pilot study (NCT03469856) was previously described elsewhere (9). The study was a multicenter, single arm, open-label, first-in-man, proof-of-concept pilot trial. Due to the exploratory nature of this study, no formal sample size calculations were performed. Based on previous pilot studies with similar design such as BENESTENT-II pilot study which evaluated heparin-coated Palmaz-Schatz stent with or without intravenous heparin infusion immediately post treatment, a sample of 200 patients would be enrolled with a safety stopping rule based on the occurrence of definite stent thrombosis (10). The BENESTENT-II pilot, first-in-man study was successfully completed without any stent thrombosis in 200 patients, and did precede the large randomized BENESTENT II trial with 827 patients (11). In the present trial, if during the enrolment period more than 3 cases of definite stent thrombosis occurred following the index procedure up to 3 months follow-up, patient recruitment would have been terminated.

In the present trial the cut-off rate of definite stent thrombosis was determined based on the incidence of stent thrombosis in the Bern-Rotterdam registry (1.2% at 30 days and 1.7% at 1 year) (12) and considering current development of PCI (13,14). All potential patients provided written informed consent prior to undergoing any study-specific procedures including screening and diagnostic angiography potentially leading to an “ad hoc” PCI. The central ethical committee (Comissão de ética para análise de projetos de

pesquisa - CAPPesq) and local ethical committee in each participating center approved the study protocol.

Study participants

Patients requiring PCI for stable CAD with a baseline SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score <23 were screened and considered eligible for the study. Complete Inclusion and exclusion criteria are listed in **Table 1**. We excluded patients with absolute or relative contraindications for prasugrel use, high risk features for PCI (left main disease, chronic total occlusion, bifurcation lesion requiring two stent treatment, saphenous or arterial graft lesion and severe calcified lesion requiring the use of rotablator) in order to minimize potential ischemic risks of implementing prasugrel monotherapy immediately after PCI. Patients who required staged procedures were also excluded in order to avoid the heterogeneity of duration of pharmacological treatment between index and staged procedure. Patients with history of ACS within 12 months before index procedure were excluded since these patients are recommended to receive DAPT for twelve months.

Patients screening before index PCI

The baseline anatomical SYNTAX score was calculated at each site by the investigators and recorded. A standard 12-lead electrocardiogram (ECG) was performed within 72 hours prior to the PCI and cardiac biomarkers (Creatine kinase myocardial band [CK-MB] or troponin) were collected prior to the PCI to detect and rule out ACS. For inclusion, the value of CK-MB should be less than 2-times the upper limit of normal (ULN). If the value of troponin was elevated more than ULN at baseline (within 72 hours prior to the start of PCI) without any ST-T change and/or typical symptom, an additional blood sample would have to be collected prior to the PCI. If the second blood test showed either stable level of troponin (less than 20% increase of the value of baseline troponin) or a drop of troponin level, with normal range of CK-MB, and normal ECG, the patient could be enrolled in the study.

Index PCI

Participants were loaded with standard DAPT (300 mg of aspirin and 600 mg of clopidogrel unless patients were previously on long-term therapy) at least 2 hours prior to the index PCI. The index PCI was performed with intention to achieve complete revascularization of all vessels with at least 1.5 mm diameter showing a stenosis of 50% or more, as identified by the local interventional cardiologist (15). Peri-procedural anticoagulation was used at the operator's discretion according to local or international guidelines (1,16).

All target lesions were exclusively treated with the everolimus-eluting platinum chromium stent (Pt-EES). The Pt-EES elutes everolimus within three months from a 4 μm biodegradable PLGA (poly [lactic-co-glycolic acid]) coating that is located only on the abluminal side of 74 μm/79 μm/81 μm platinum-chromium struts (for the stent sizes ≤2.5 mm/3.0-3.5 mm/4.0 mm, respectively) and resorbed within four months.

The investigators performed the procedure aiming at achieving optimal stent implantation according to local standard of care by angiography. The use of quantitative coronary angiography (QCA) and/or intracoronary imaging (IVUS or optical coherence tomography [OCT]) was recommended but let at the discretion of the operator. The achievement of optimal stenting was judged by each investigator according to recommended criteria shown in **Online Table 1** and **Online Figure 1** (17-19). All angiography recordings were analyzed offline by an independent academic core lab (Academic research

team, ART, Rotterdam) with a QCA software (Coronary Angiography Analysis System [CAAS], version 5.9, Pie Medical Imaging, Maastricht, the Netherlands).

Table 1. Inclusion and exclusion criteria

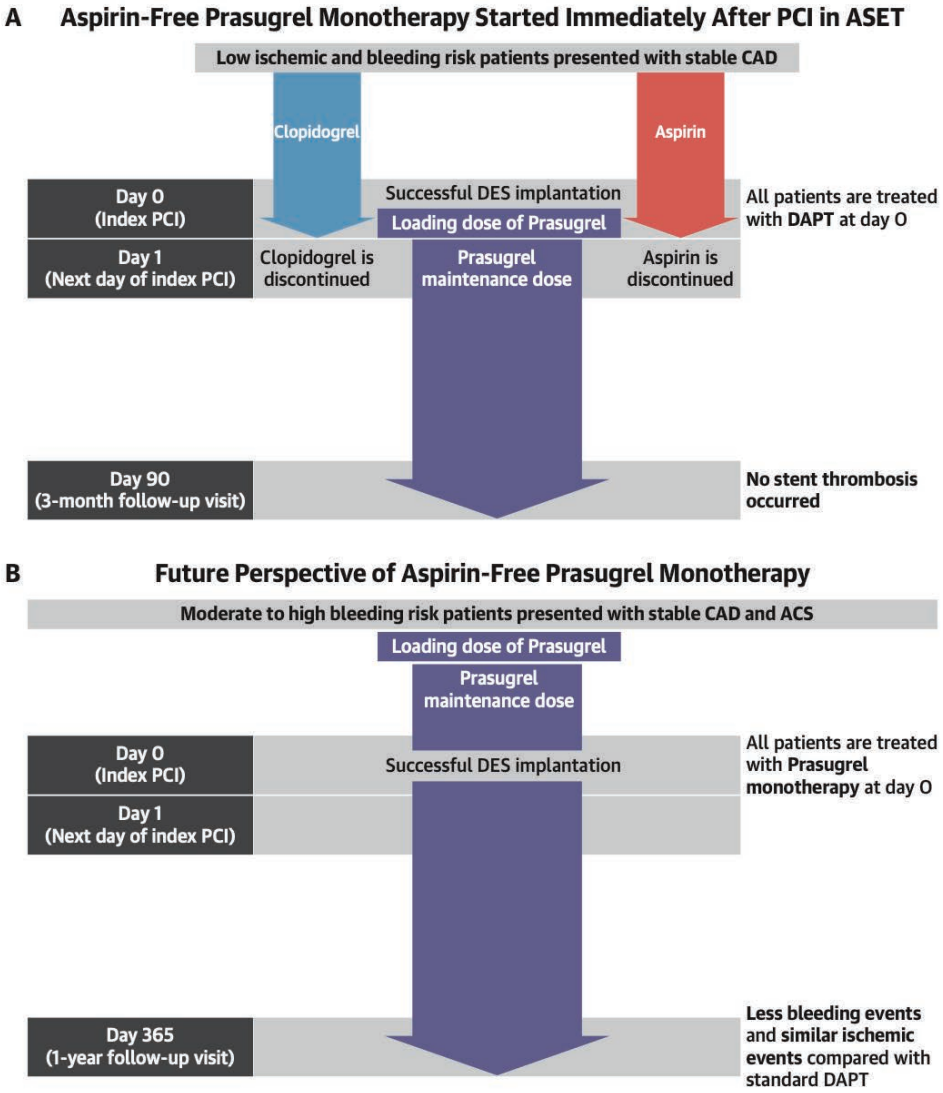
Inclusion criteria
1. Successful PCI with optimal stent implantation of one or more SYNERGY stent(s). 2. SYNERGY stent implantation was performed to treat: a. Presence of one or more de novo lesion with diameter stenosis ≥50% by visual estimation in at least one native coronary artery with a reference vessel diameter ranging from 2.25 mm to 4.00 mm without left main stem involvement. b. Chronic coronary syndrome or stabilized acute coronary syndromes with normal cardiac enzyme values prior to the index PCI, and evidence of myocardial ischemia by symptoms or non-invasive test (e.g. treadmill exercise test, radionuclide scintigraphy, stress echocardiography). c. Anatomic SYNTAX score <23 prior to PCI. 3. Patients has provided written informed consent as approved by the Ethical Committee of the respective clinical site.
Exclusion criteria
1. Under the age of 18 years or ≥75 years. 2. Patients weighing <60 kg. 3. Glomerular filtration rate <60 mL/min 4. Previous PCI in the last 12 months. 5. Current or previous acute coronary syndrome within 12 months. 6. Patients with planned PCI or surgical intervention to treat any cardiac or non-cardiac condition within next 6 months. 7. Concomitant cardiac valve disease requiring surgical therapy. 8. Following lesion characteristics: left main disease, chronic total occlusion, bifurcation lesion requiring two stent treatment, saphenous or arterial graft lesion and severe calcified lesion requiring the use of rotablator. 9. Patients concomitantly treated with any other non-study stent at the same procedure. 10. Previous history of definite stent thrombosis. 11. Previous history of stroke or transient ischemic cerebrovascular accident. 12. Atrial fibrillation or other indication for oral anticoagulant therapy. 13. Hemoglobin <10 g/dL or other evidence of active bleeding. 14. Peptic ulceration documented by endoscopy within the last 3 months unless healing proven by repeat endoscopy. 15. Any other condition deemed by the investigator to place patient at excessive risk of bleeding with prasugrel. 16. Known allergy to aspirin, prasugrel or diagnosed lactose intolerance. 17. Treatment in the last 10 days or requirement for ongoing treatment with a strong CYP3A4 inhibitor or inducer. 18. Females of child-bearing potential unless negative pregnancy test at screening and willing to use effective contraception for the duration of treatment with study medication. 19. Female who is breastfeeding at time of enrolment. 20. Participation in another trial with an investigational drug or stent. 21. Co-morbidity associated with life expectancy less than one year. 22. Assessment that the subject is not likely to comply with the study procedures. 23. Known drug or alcohol dependence within the past 12 months as judged by the investigator.

PCI, percutaneous coronary intervention.

Antiplatelet treatment

After achievement of optimal Pt-EES implantation on standard DAPT administrated prior to the index procedure, patients were finally enrolled in the study and loaded with 60 mg of prasugrel while still in the catheterization laboratory (cath lab) in order to avoid further

delay or omission of the loading dose (**Central Illustration**). In patients already on long-term ticagrelor, we recommended the investigator to administer 60 mg of prasugrel in the cath lab and discontinue ticagrelor just after the procedure. In patients already on long-term prasugrel, there was no need for additional loading dose, and patients were treated with 10 mg of prasugrel once a daily for 3 months. Upon enrollment, aspirin was discontinued on the day of the index procedure, and the prescription was maintained aspirin-free throughout the 3-month follow-up.



Central Illustration. Aspirin-free prasugrel monotherapy.
Panel A shows aspirin-free prasugrel monotherapy in ASET. Panel B shows future perspective of aspirin-free prasugrel monotherapy.
ACS = acute coronary syndrome, CAD = coronary artery disease, DAPT = dual antiplatelet therapy, DES = drug eluting stent, PCI = percutaneous coronary intervention.

Study follow-up

After the index procedure, an assessment of the patient's clinical status was performed. Cardiac biomarkers were measured at discharge or at 3-8 hours post procedure. A standard 12-lead ECG was also performed at discharge or within 24 hours post procedure. Before hospital discharge, all patients were diligently educated about the importance of compliance with medication and the risk of stopping prasugrel using a specific educational study card. This card contained important information on the study drug and a warning on the risks of discontinuing the study drug without consultation of the research staff. If prasugrel needed to be discontinued for any reason, aspirin and clopidogrel should be considered as alternative treatment after consultation with the research staff.

A clinical follow-up was performed at 1 month by telephone contact to assess treatment adherence and clinical events. After 3 months, an in-person visit was performed and prasugrel monotherapy was replaced by aspirin monotherapy or DAPT according to physician's discretion. When switching from prasugrel back to aspirin monotherapy, a loading dose of aspirin was recommended and was to be given in the hospital at the time of the 3 months follow-up visit.

A telephone contact was performed at 4 months (final follow-up) for an observational assessment of the switch to standard of care treatment (aspirin alone or DAPT). An assessment of the angina status, cardiovascular drug use and any serious adverse events were recorded during clinical follow-up visits.

Adherence to prasugrel

The number of remaining prasugrel tablets at 3 months follow-up was recorded in order to assess adherence to prasugrel. Discontinuation and restart of any antiplatelet agents up to 4 months were recorded with the date and reason (20). Adherence to prasugrel was assessed with two methods: cross-sectional binary assessment in each follow-up visit and tablet-level assessment using drug accountability report at 3 months follow-up (i.e. [number of prasugrel tablets prescribed at discharge - number of remaining prasugrel tablets at 3 months follow-up] / number of prasugrel tablets required from discharge to 3 months follow-up).

Study endpoints

The primary ischemic endpoint was a composite of cardiac death, spontaneous target-vessel myocardial infarction (MI) (48 hours after index procedure) or definite stent thrombosis up to 3 months after the index procedure.

The primary bleeding end point was any Bleeding Academic Research Consortium (BARC) type 3 and 5 bleeding up to 3 months after the index procedure. Secondary endpoints included all-cause death, stroke (subclassified as ischemic, hemorrhagic, or unknown), all MI, repeat revascularization, definite/probable/possible stent thrombosis, BARC type 1-5 bleedings and each individual component of the primary endpoint.

All deaths were considered cardiac unless an undisputed non-cardiac cause was present. Spontaneous MI was defined according to Third Universal definitions (21). Periprocedural MI (<48 hours post PCI) was defined according to Society for Cardiovascular Angiography and Interventions (SCAI) 2013 definition (22). Stent thrombosis was defined and classified according to the Academic Research Consortium (ARC)-2 definition (23). BARC bleeding was defined as previously reported (24). All endpoints were independently adjudicated by the Clinical Event Committee (CEC). An independent Data Safety and

Monitoring Board (DSMB) oversaw the individual and collective safety of the patients in the study during enrollment and follow-up period. In order to provide the steering committee with timely feedback on the potential safety issues, the DSMB reviewed the data three times during the trial, when the 50th patient enrolled, when the 125th patient enrolled and when the 200th patient completed 1-month follow-up. The listing of the members of CEC and DSMB is shown in Online appendix.

Statistical analysis

Continuous variables were presented as mean with standard deviation, or median with interquartile range as appropriate. Categorical variables were presented as frequencies and percentages. All analyses were 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).

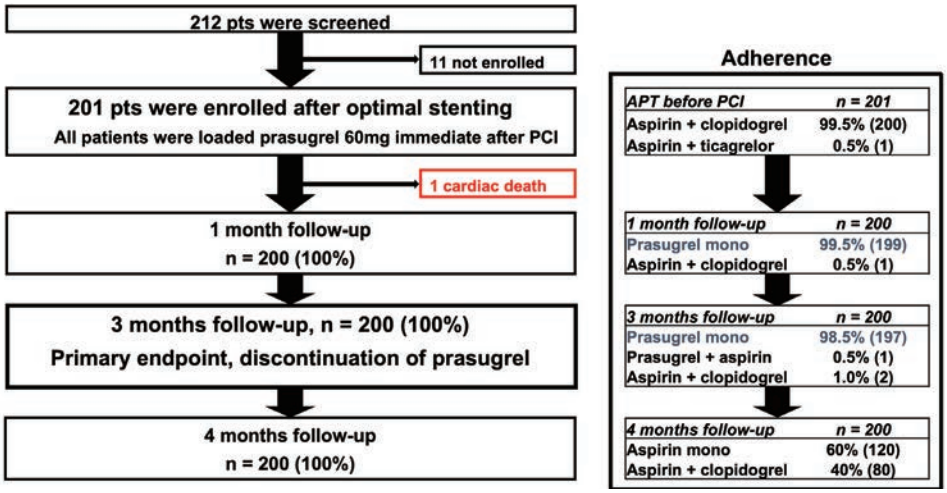


Figure 1. Study flow chart with adherence to antiplatelet agent
APT = antiplatelet therapy, PCI = percutaneous coronary intervention.

Results

Patients screening and enrollment

From February 22, 2018, to May 7, 2019, 212 patients with SYNTAX score <23 were screened, and 201 patients were enrolled after successful PCI in the trial at 9 centers in Brazil (**Figure 1** and **Online Table 2**). Most of the reasons for non-enrollment were related to suboptimal results of PCI such as left main stenting, 2-stent technique for bifurcation lesion and side branch occlusion after stenting in 7 patients. In addition, a few more non eligible cases related to non-significant stenosis and atrial fibrillation have to be mentioned (**Table 2)**.

Baseline characteristics

Baseline characteristics are shown in **Table 3**. Mean age was 59.5 ± 7.7 years and 35.3% of patients were female. Diabetes mellitus was observed in 36.8% of patients. Before the

procedure, 96.5% of patients (194/201) were diagnosed as stable CAD with normal troponin I or T value (<upper limit of normal [ULN]), and 6 patients had CK-MB values <2 x ULN. One patient was diagnosed as stable CAD without any pre-procedural measurement of cardiac enzyme, whereas the post-procedural troponin T and CK-MB value was below ULN in this patient. The mean site-reported SYNTAX score was 7.2 ± 4.5.

Table 2. The reasons of screened but not enrolled.

Reasons of not enrolled	Number of patients
Non-significant stenosis (diameter stenosis <50%)	2
Left main disease	2
Bifurcation lesion requiring 2-stent technique	2
Stent edge dissection	1
Sidebranch occlusion after stent implantation	1
Presence of transient total occlusion	1
Atrial fibrillation	1
Enrollment was closed at the time of screening	1
Total	11

Table 3. Baseline characteristics

Characteristics	n = 201
Age, mean (SD), y	59.5 (7.7)
Male, No. (%)	130 (64.7)
Female, No. (%)	71 (35.3)
Body Mass Index, mean (SD), kg/m2	28.8 (4.4)
Medical history	
Current smoker, No. (%)	33 (16.4)
Diabetes Mellitus, No. (%)	74 (36.8)
Insulin dependent, No. (%)	16 (8.0)
Hypertension, No. (%)	186 (92.5)
Dyslipidemia, No. (%)	140 (69.7)
Family history of coronary artery disease, No. (%)	118 (61.8)
Previous Myocardial Infarction, No. (%)	18 (9.0)
Established Peripheral Vascular Disease, No. (%)	11 (5.5)
Chronic Obstructive Pulmonary Disease, No. (%)	4 (2.0)
Heart failure, No. (%)	5 (2.5)
Major bleeding, No. (%)	1 (0.5)
Renal insufficiency, No. (%)*	0 (0)
Previous Percutaneous Coronary Intervention, No. (%)	25 (12.4)
Previous Coronary Artery Bypass Grafting, No. (%)	3 (1.5)
Left ventricular ejection fraction, mean (SD), %	64.3 (7.7)
SYNTAX Score, mean (SD)	7.2±4.5
Clinical presentation	
Non-ST elevation myocardial infarction, No. (%)	0 (0)
Unstable angina, No. (%)	0 (0)
Chronic coronary syndrome, No. (%)	201 (100)
Stable angina, No. (%)	189 (94)
Silent ischemia, No. (%)	4 (2)
Angina equivalent, No. (%)	8 (4)

* Impaired renal function is defined as estimated glomerular filtration rate of creatinine clearance < 60 mL/min per 1.73 m2 based on the Modification of Diet in Renal Disease formula.
SD = standard deviation.

Table 4. Lesion and procedural characteristics

Characteristics	n=201
Vascular access site per patient	
Femoral, No. (%)	31 (15.4)
Radial, No. (%)	170 (84.6)
Brachial, No. (%)	0 (0)
Lesions treated per patient	
One lesion, No. (%)	159 (79.1)
Two lesions, No. (%)	36 (17.9)
Three or more lesions, No. (%)	6 (3.0)
Treated lesions (n=250 lesions)	
Left Main coronary artery, No. (%)	0 (0)
Left anterior descending artery, No. (%)	131 (52.4)
Left circumflex artery, No. (%)	47 (18.8)
Right coronary artery, No. (%)	72 (28.8)
AHA lesion classification	
A, No. (%)	39 (15.6)
B1, No. (%)	80 (32.0)
B2, No. (%)	51 (20.4)
C, No. (%)	80 (32.0)
Direct stenting, No. (%)	168 (67.2)
IVUS used for stent optimization, No. (%)	42 (16.8)
Minimal lumen area, mean (SD), mm2	7.1 (3.5)
Stent area, mean (SD), mm2	7.5 (3.0)
Post dilatation performed, No. (%)	144 (57.6)
Diameter stenosis by quantitative coronary angiography	
Pre-procedure, mean (SD), %	58.9 (11.9)
Post-procedure, mean (SD), %	11.4 (7.1)
<30%, No. (%)	1 (0.4)
Pre-procedural TIMI flow	
Flow 0, No. (%)	0 (0)
Flow 1, No. (%)	4 (1.6)
Flow 2, No. (%)	6 (2.4)
Flow 3, No. (%)	240 (96.0)
Post-procedural TIMI flow	
Flow 0, No. (%)	0 (0)
Flow 1, No. (%)	0 (0)
Flow 2, No. (%)	1 (0.4)
Flow 3, No. (%)	249 (99.6)
Number of stents used per patient, median (IQR1-3)	1 (1-2)
Patients with:	
No Stent, No. (%)	0 (0)
One Stent, No. (%)	142 (70.6)
Two Stents, No. (%)	50 (24.9)
Three or more Stents, No. (%)	9 (4.5)
Total stent length per patient, mean (SD), mm	32.7 (18.0)
Per stent characteristics (n= 272 stents)	
Pt-EES used, No (%)	272 (100)
Stent length, mean (SD), mm	24.2 (8.4)
Stent nominal diameter, mean (SD), mm	3.00 (0.43)
Procedure time, mean (SD), minutes	45.8 (26.5)
Days in hospital, median (IQR1-3), days	2 (2-3)
Prasugrel loading dose given after successful PCI procedure, No. (%)	201 (100)

AHA = American Heart Association, IVUS = intravascular ultrasound, PCI = percutaneous coronary intervention, Pt-EES = everolimus-eluting platinum chromium stent, TIMI = Thrombolysis in Myocardial Infarction.

Table 5. Clinical outcomes at 3 months follow-up

Outcomes at 3 months follow-up	n=201
Primary ischemic endpoint: a composite of cardiac death, TV-spontaneous myocardial infarction, or definite stent thrombosis	1 (0.5)
Cardiac death	1 (0.5)
TV-spontaneous myocardial infarction (48 hours after PCI)	0 (0)
Definite stent thrombosis	0 (0)
Primary bleeding endpoint: BARC type 3 or 5 bleeding	1 (0.5)
BARC type 3a	0 (0)
BARC type 3b	0 (0)
BARC type 5a	0 (0)
BARC type 5b	1 (0.5)
Secondary endpoints	
All cause death	1 (0.5)
Cardiac	1 (0.5)
Stroke	1 (0.5)
Ischemic	0 (0)
Hemorrhagic	1 (0.5)
Unknown	0 (0)
Transient ischemic attack	0 (0)
Myocardial Infarction	2 (1.0)
Spontaneous	0 (0)
- TV related	0 (0)
- Non-TV related	0 (0)
Peri-procedural	2 (1.0)
- TV related	2 (1.0)
- Non-TV related	0 (0)
Bleeding: BARC type 1 to 5	1 (0.5)
BARC Type 5b	1 (0.5)
All revascularizations	1 (0.5)
Non-TV revascularization	1 (0.5)
Stent Thrombosis	0 (0)
Definite	0 (0)
Probable	0 (0)
Possible	0 (0)

BARC = Bleeding Academic Research Consortium, TV = target vessel.

Lesion and procedural characteristics

Lesion and procedural characteristics are shown in **Table 4**. Diagnostic coronary angiograms from all 201 enrolled patients are shown in **Online Figure 2**. The majority of patients underwent PCI using radial access (84.6%). Half of lesions were classified as AHA lesion classification B2 or C (52.4%). All patients were treated exclusively with Pt-EES. The median number of implanted stents per patients was 1 (IQR1-3:1-2) and the mean total stent length per patients was 32.7 ± 18.0 mm. Overlapping stent was observed in 19 patients. Direct stenting was performed in 67.2% of lesions, whereas post dilatation was performed in 57.6% of lesions with mean maximum pressure of 18.6 atm. IVUS guided stent optimization was performed in 16.8% of lesions. After the procedure, TIMI flow 3 was achieved in 99.6% of lesions (249/250). All lesions achieved post PCI diameter stenosis (DS) <20% by visual estimation, whereas 99.5% of lesions (249/250) achieved DS <30% by QCA with mean DS of 11.4 ± 7.1%. Peri-procedural MI occurred in 2 patients (1.0%).

Outcomes

All enrolled patients completed study follow-up over 4 months except one patient who died 3 days after index procedure (**Figure 1**). The primary ischemic endpoint occurred in one patient up to 3 months follow-up (0.5%). The primary bleeding endpoint occurred in one patient (0.5%). These primary endpoints occurred in the same patient. The patient was a 68-year-old female with SYNTAX score of 3. She underwent successful PCI for a non-complex target lesion in the mid right coronary artery. She was on long-term therapy of clopidogrel before index procedure, so that clopidogrel loading dose was not administrated before index procedure. Prasugrel 60mg was loaded immediately after PCI. The patient maintained constant high blood pressure and a few hours after the index procedure, she presented with severe headache and altered level of consciousness, becoming then comatose and needing orotracheal intubation. Computed tomography revealed massive intracranial bleeding and the patient was referred to emergency neurosurgical decompression. After surgery there was severe deterioration of the neurological status and the patient eventually died 3 days after index procedure. This event was adjudicated as cardiac death, BARC type 5b bleeding, and hemorrhagic stroke. The complete list of clinical outcomes is presented in **Table 5**. In terms of secondary endpoints, no spontaneous MI and stent thrombosis were observed up to 3 months follow-up, while one non-target vessel revascularization was observed.

Adherence to antiplatelet agents

Adherence to antiplatelet agents is shown in Figure 1. First of all, before index procedure, all participants were on standard DAPT by design. Of these 99.5% were on DAPT with aspirin plus clopidogrel. One hundred four patients were prescribed clopidogrel loading dose, whereas 96 were on long-tern therapy of clopidogrel with maintenance dose. Only one patient was on long-term DAPT with aspirin plus ticagrelor before PCI. Immediately after PCI, all 201 patients received loading dose of prasugrel 60 mg and aspirin was discontinued on the day of the index procedure. At 3-month follow-up, three patients did not adhere to study medication. Two patients presented with recurrent angina during follow-up. One underwent revascularization for a non-target vessel and subsequently restarted the DAPT (aspirin and clopidogrel). The other restarted DAPT (aspirin and clopidogrel) without having undergone an invasive coronary angiography and subsequently angina subsided. The remaining patient did not discontinue prasugrel up to 3-month follow-up, but restarted aspirin 10 days before 3-month visit on his own decision. Overall, 98.5% of patients adhered study medication at 3-month follow-up in the cross-sectional analysis. In drug accountability analysis for prasugrel among 198 patients with available data, the adherence to prasugrel was 98.3% (18055/18353 tablets). Both analyses demonstrated high adherence to prasugrel monotherapy without any side effect. At 4-month follow-up, 60% of patients received aspirin monotherapy, and the remaining patients received DAPT with aspirin and clopidogrel.

Discussion

We present here a proof-of-concept trial in which selected stable CAD patients were treated with aspirin-free prasugrel monotherapy following a successful Pt-EES implantation. One patient presented a primary bleeding endpoint. Importantly, no stent thrombosis event occurred. This finding is not surprising, but to the best of our knowledge, this is the first

prospective experience of withholding aspirin the next day of index PCI while administrating a monotherapy of P2Y12 inhibitor (25).

Recently, several randomized controlled trials (RCT) have been conducted to investigate different antithrombotic strategies including a monotherapy of P2Y12 inhibitor, aiming to assess the best balance between ischemic and bleeding risks after PCI. The STOPDAPT-2 trial showed that 1-month DAPT followed by clopidogrel monotherapy provided a beneficial net clinical effect for ischemic and bleeding events, compared with 12-month DAPT with aspirin and clopidogrel (3). Likewise, in the SMART-CHOICE study, 3 months of DAPT followed by P2Y12 inhibitor monotherapy for 9 months was noninferior to 12 months of DAPT (4). Similar results were reported in a high-risk population from the large-scale randomized TWILIGHT study (5) and in ACS patients from the TICO trial (6). Additionally, albeit not showing superiority, the GLOBAL LEADERS trial suggested no harm of a scheme comprising one-month DAPT (aspirin and ticagrelor) followed by 23-month ticagrelor monotherapy (26). It is interesting to note that all those trials included patients undergoing PCI in both acute and stable settings.

When compared with patients treated with standard DAPT, patients with moderate to high bleeding risk should derive benefit from a strategy of aspirin-free prasugrel monotherapy by reducing the bleeding events without increasing the ischemic events. In numerous RCTs with short DAPT followed by P2Y12 inhibitor monotherapy, P2Y12 inhibitor monotherapy was started at least one month after index procedure (3-6). But until now, no trial has evaluated a P2Y12 monotherapy strategy initiated immediately after DES implantation and this type of strategy should be evaluated with special consideration for safety due to the high frequency of stent thrombosis observed during the first month (13). Therefore, before starting a RCT to prove the superiority of aspirin-free strategy in reducing bleeding, the safety concern with regard to an excess of early stent thrombosis should be excluded. If we aim to demonstrate the non-inferiority of aspirin-free therapy against standard DAPT on definite stent thrombosis at three months, we need more than 11,000 patients in each arm (Expected 3-month definite stent thrombosis rate of standard DAPT group: 0.44% from SYNTAX II [using Pt-EES and IVUS guided stent optimization], non-inferiority margin: 0.22%, one-sided alpha: 0.05, 80% power) (27). It is unrealistic or even unethical to implement such a trial without any evidence of feasibility and safety. Therefore, we needed such a small first-in-man study with maximum consideration for safety (i.e. early stent thrombosis prevention) such as careful patient selection using SYNTAX Score, strict screening based on cardiac enzyme, strong recommendation of imaging guided stent optimization, strict protocol of switching antiplatelet drugs and extended follow-up up to 4 months as well as patient education using specific study card, and a stringent careful data monitoring by DSMB. In terms of changes in antiplatelet therapy regimen, we decided to initiate prasugrel monotherapy in the catheterization laboratory immediately after confirmation of a successful EES implantation in order to minimize the risk of stent thrombosis, since suboptimal stent implantation or unexpected complex stenting are performed with a certain probability (3.3% [7/212] among all the patients screened in the present trial). This strategy of switching P2Y12 inhibitor is in line with international consensus on switching therapies and being supported by the pharmacodynamic studies (28-31). In a previous trial, it has been demonstrated that a prasugrel loading dose following a clopidogrel loading dose results in rapid and substantial decrease in high platelet reactivity in patients undergoing PCI (31).

The safety profile of prasugrel monotherapy following DES implantation in this study may be attributed, at least in part, to the exclusive use of newer generation thin-strut biodegradable polymer EES, since these new stents demonstrated lower rate of thrombotic complications compared with those of first-generation DES (14). Additionally, we included only patients with non-complex, non-acute CAD in whom optimal PCI results were achieved. Although intracoronary imaging guided stent optimization was strongly recommended by the protocol, only 16% of patients underwent IVUS guided stent optimization. A low adoption of IVUS for stent optimization was somewhat disappointing, but in-stent DS <30% by QCA was achieved in almost all lesions (99.5%) with a mean DS of 11.4 ± 7.1%.

Potent P2Y12 blockage by prasugrel monotherapy with an excellent adherence (98.5%) may have led to downregulation of other markers of platelet reactivity including arachidonic acid- and collagen-induced aggregation (32,33), resulting in no case of stent thrombosis. The adherence to prasugrel in the present trial was relatively higher compared with those in the trials which implemented P2Y12 monotherapy with ticagrelor (at 3 months: 86.0% and 87.3% in the GLOBAL LEADERS trial and the TWILIGHT trial, respectively), although the present trial enrolled far less patients than the others. In the ISAR-REACT 5 trial, among 4018 patients with ACS randomized to either prasugrel or ticagrelor, the incidence of death, MI, or stroke was significantly lower among those who received prasugrel than among those who received ticagrelor, and the incidence of major bleeding was not significantly different between the two groups. In addition to the main findings, prasugrel was associated with a lower incidence of drug discontinuation at 1-year follow-up compared with ticagrelor (12.5% in the prasugrel arm vs 15.2% in the ticagrelor arm, p = 0.03) (34), which can be at least partially explained by the specific side effects of ticagrelor (e.g. dyspnea) and its BID prescription. Furthermore, in the present study we diligently educated participants about the importance of compliance with medication and the risk of stopping prasugrel using a specific study card, which may have contributed to the high adherence to prasugrel. These findings may suggest that prasugrel is a preferable drug as P2Y12 inhibitor monotherapy when compared with ticagrelor.

In the present trial, maximal consideration for early stent thrombosis resulted in the enrollment of very low bleeding risk patients, but the efficacy of aspirin-free strategy in reducing bleeding among high bleeding risk patients is of interest and should be investigated in a large-scale RCT. The completion of the present trial without any stent thrombosis allows us ethically to plan further trials. Theoretically, patients with moderate to high bleeding risk are ideal candidates for a large RCT to prove efficacy in bleeding reduction as shown in the recent trials with short DAPT strategy followed by P2Y12 monotherapy (35-37). Of note, these patients frequently have complex PCI features and ACS presentation which are well known ischemic risk factors and were systematically excluded from the present trial according to the exclusion criteria applied in this first in man study investigating for the first time a regimen of aspirin-free prasugrel monotherapy. Therefore, before starting large RCT, additional pilot study may be needed to demonstrate safety (absence of early stent thrombosis) in patients with a more complex coronary syndrome (e.g. Non-ST elevation ACS population like in the ASET Japan trial).

Limitations

The present trial has several limitations. First, this was a non-randomized study without any comparator. Therefore, no conclusion could be drawn in terms of superiority or inferiority of prasugrel monotherapy compared with conventional DAPT, since this was not the

objective of this study. Second, the external validity of the result of the present pilot study may be limited to a population selected with the stringent criteria of selection applied in the present study which is only one exploratory step toward "an aspirin-free era post PCI" (38). However, the completion of the present trial without any stent thrombosis allows us to plan further trials and expansion of the inclusion criteria (e.g. Non-ST elevation ACS population in the ASET Japan trial). Third, the cut-off rate of definite stent thrombosis adopted in the present study was relatively high when compared with the stent thrombosis outcome of current stent trials with contemporary DES in which a definite stent thrombosis rate of 0.72% at a median follow-up of 3.8 years in Cobalt Chromium or Platina Chromium EES is reported (14). Fourth, the administration of prasugrel loading dose immediately after PCI potentially may have contributed to the fatal intracranial bleeding in one patient who was on long-term therapy of aspirin plus clopidogrel before PCI. A single event of intracranial hemorrhage in a very small sample size population as in the ASET trial represents theoretically a rate of 0.5% over 3 months in very low-risk patients and is concerning, since in previous RCTs with short DAPT strategies among higher-risk patients than in the present trial, intracranial hemorrhage rate ranged from 0 to 0.13% over an observation period of 1 year (3,26). This single case of intracranial hemorrhage may have been caused more specifically by the switching between P2Y12 inhibitors with loading dose of prasugrel rather than by the aspirin-free prasugrel monotherapy itself. Initiation of prasugrel with or without aspirin prior to the procedure might be a desirable alternative in future trials, since the switching from clopidogrel to prasugrel could be then avoided. Although prasugrel monotherapy starting before PCI is the desirable final strategy (Central Illustration B), it was premature to implement that strategy during this first in man study without applying the switching of P2Y12 recommended in the literature (28). Finally, the lack of platelet functional test is a major limitation, since we have missed the opportunity to evaluate the incidence and impact of high platelet reactivity (HPR) under prasugrel treatment without aspirin in clinical practice. HPR has been observed in around 10% of patients treated with prasugrel (39), and might be associated with worse ischemic outcome in patient on prasugrel monotherapy than on standard DAPT. However, an individual patient-level meta-analysis from more than 6000 patients showed that HPR was not predictive of recurrent ischemic events in low-risk patients treated with clopidogrel (40). In the present trial, careful patient selection and strong recommendation of imaging guided stent optimization may have minimized the risk of ischemic event in patients with HPR on prasugrel monotherapy.

Conclusion

The aspirin-free prasugrel monotherapy was feasible and safe following a successful DES implantation in a population of selected stable CAD patients with low anatomical complexity. Our findings may help underpinning larger randomized controlled studies to evaluate the aspirin-free strategy compared with traditional DAPT following PCI.

References

1. Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.
2. Yin SH, Xu P, Wang B et al. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis. BMJ 2019;365:l2222.
3. Watanabe H, Domei T, Morimoto T et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA 2019;321:2414-2427.
4. Hahn JY, Song YB, Oh JH et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA 2019;321:2428-2437.
5. Mehran R, Baber U, Sharma SK et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019;381:2032-2042.
6. Jang Y. Ticagrelor with or without aspirin in acute coronary syndrome after PCI: randomized evaluation of ticagrelor monotherapy after 3-month dual antiplatelet therapy in acute coronary syndrome (the TICO trial). Presented on: March 30, 2020. ACC 2020.
7. Armstrong PC, Leadbeater PD, Chan MV et al. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. J Thromb Haemost 2011;9:552-61.
8. Palmerini T, Bacchi Reggiani L, Della Riva D et al. Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting. J Am Coll Cardiol 2017;69:2011-2022.
9. Kogame N, Modolo R, Tomaniak M et al. Prasugrel monotherapy after PCI with the SYNERGY stent in patients with chronic stable angina or stabilised acute coronary syndromes: rationale and design of the ASET pilot study. EuroIntervention 2019;15:e547-e550.
10. Serruys PW, Emanuelsson H, van der Giessen W et al. Heparin-coated Palmaz-Schatz stents in human coronary arteries. Early outcome of the Benestent-II Pilot Study. Circulation 1996;93:412-22.
11. Serruys PW, van Hout B, Bonnier H et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet 1998;352:673-81.
12. Daemen J, Wenaweser P, Tsuchida K et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667-78.
13. Raber L, Magro M, Stefanini GG et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation 2012;125:1110-21.
14. Palmerini T, Benedetto U, Biondi-Zoccai G et al. Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. J Am Coll Cardiol 2015;65:2496-507.
15. 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.
16. Neumann FJ, Sousa-Uva M, Ahlsson A et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
17. Chang CC, Kogame N, Onuma Y et al. Defining Device Success for Percutaneous Coronary Intervention Trials: A Position Statement from the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. EuroIntervention 2019.

18. de Jaegere P, Mudra H, Figulla H et al. 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;19:1214-23.
19. Prati F, Romagnoli E, Burzotta F et al. Clinical Impact of OCT Findings During PCI: The CLI-OPCI II Study. JACC Cardiovasc Imaging 2015;8:1297-305.
20. Valgimigli M, Garcia-Garcia HM, Vrijens B et al. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC). Eur Heart J 2019;40:2070-2085.
21. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
22. Moussa ID, Klein LW, Shah B et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). Catheter Cardiovasc Interv 2014;83:27-36.
23. Garcia-Garcia HM, McFadden EP, Farb A et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Eur Heart J 2018;39:2192-2207.
24. Mehran R, Rao SV, Bhatt DL et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
25. Colombo A, Hall P, Nakamura S et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676-88.
26. Vranckx P, Valgimigli M, Juni P et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940-949.
27. Escaned J, Collet C, Ryan N et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. Eur Heart J 2017;38:3124-3134.
28. Angiolillo DJ, Rollini F, Storey RF et al. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. Circulation 2017;136:1955-1975.
29. Angiolillo DJ, Saucedo JF, Deraad R et al. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: results of the SWAP (SWitching Anti Platelet) study. J Am Coll Cardiol 2010;56:1017-23.
30. Diodati JG, Saucedo JF, French JK et al. Effect on platelet reactivity from a prasugrel loading dose after a clopidogrel loading dose compared with a prasugrel loading dose alone: Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients (TRIPLET): a randomized controlled trial. Circ Cardiovasc Interv 2013;6:567-74.
31. Diodati JG, Saucedo JF, Cardillo TE et al. Transferring from clopidogrel loading dose to prasugrel loading dose in acute coronary syndrome patients. High on-treatment platelet reactivity analysis of the TRIPLET trial. Thromb Haemost 2014;112:311-22.
32. Capodanno D, Mehran R, Valgimigli M et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018.
33. Tello-Montoliu A, Thano E, Rollini F et al. Impact of aspirin dose on adenosine diphosphate-mediated platelet activities. Results of an in vitro pilot investigation. Thromb Haemost 2013;110:777-84.
34. Schupke S, Neumann FJ, Menichelli M et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. N Engl J Med 2019;381:1524-1534.
35. Mehran R, Baber U, Sharma SK et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019.

36. Serruys PW, Takahashi K, Chichareon P et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. Eur Heart J 2019;40:2595-2604.
37. Dangas G, Baber U, Sharma S et al. Ticagrelor With Aspirin or Alone After Complex PCI: The TWILIGHT-COMPLEX Analysis. J Am Coll Cardiol 2020.
38. Serruys PW, Takahashi K, Chichareon P, Onuma Y. Twilight, the Dawn of a New Era of Aspirin-Free PCI? Journal of the American College of Cardiology 2020;75:2425-2429.
39. Lemesle G, Schurtz G, Bauters C, Hamon M. High on-treatment platelet reactivity with ticagrelor versus prasugrel: a systematic review and meta-analysis. J Thromb Haemost 2015;13:931-42.
40. Reny JL, Fontana P, Hochholzer W et al. Vascular risk levels affect the predictive value of platelet reactivity for the occurrence of MACE in patients on clopidogrel. Systematic review and meta-analysis of individual patient data. Thromb Haemost 2016;115:844-55.

Supplementary Material

Patients selection criteria

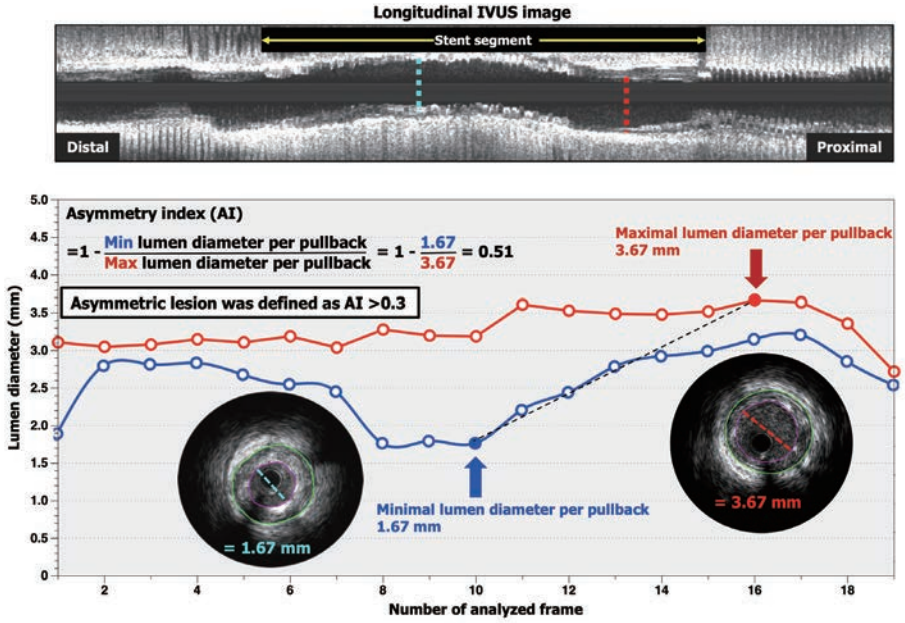
Supplementary methods

Definitions of the study endpoints

All deaths will be considered cardiac unless an undisputed non-cardiac cause is present. Spontaneous MI will be defined according to Third Universal definitions. Periprocedural MI (<48 hours post PCI) will be defined according to Society for Cardiovascular Angiography and Interventions (SCAI) 2013 definition. Stent thrombosis will be defined according to the Academic Research Consortium (ARC)-2 definition. BARC bleeding will be defined as previously reported.

Listing of the members of clinical event committee (CEC) and data safety and monitoring board (DSMB)

- CEC
  Dr. E. McFadden (Cork University Hospital, Ireland)
  Dr B.J.W.M. Rensing (St. Antonius Hospital, the Netherlands)
  Dr O. Soliman (National University of Ireland Galway, Ireland)
  Dr. S. Garg (Royal Blackburn Hospital, UK)
  Prof. G. Andersen (Aarhus University Hospital, Denmark)
- DSMB
  Prof. F.W.A. Verheugt (Radboud UMC, the Netherlands)
  Prof. J. Tijssen (Academisch Medisch Centrum, University of Amsterdam, the Netherlands)
  Dr. P.C. Smits (Maasstad Ziekenhuis, the Netherlands)

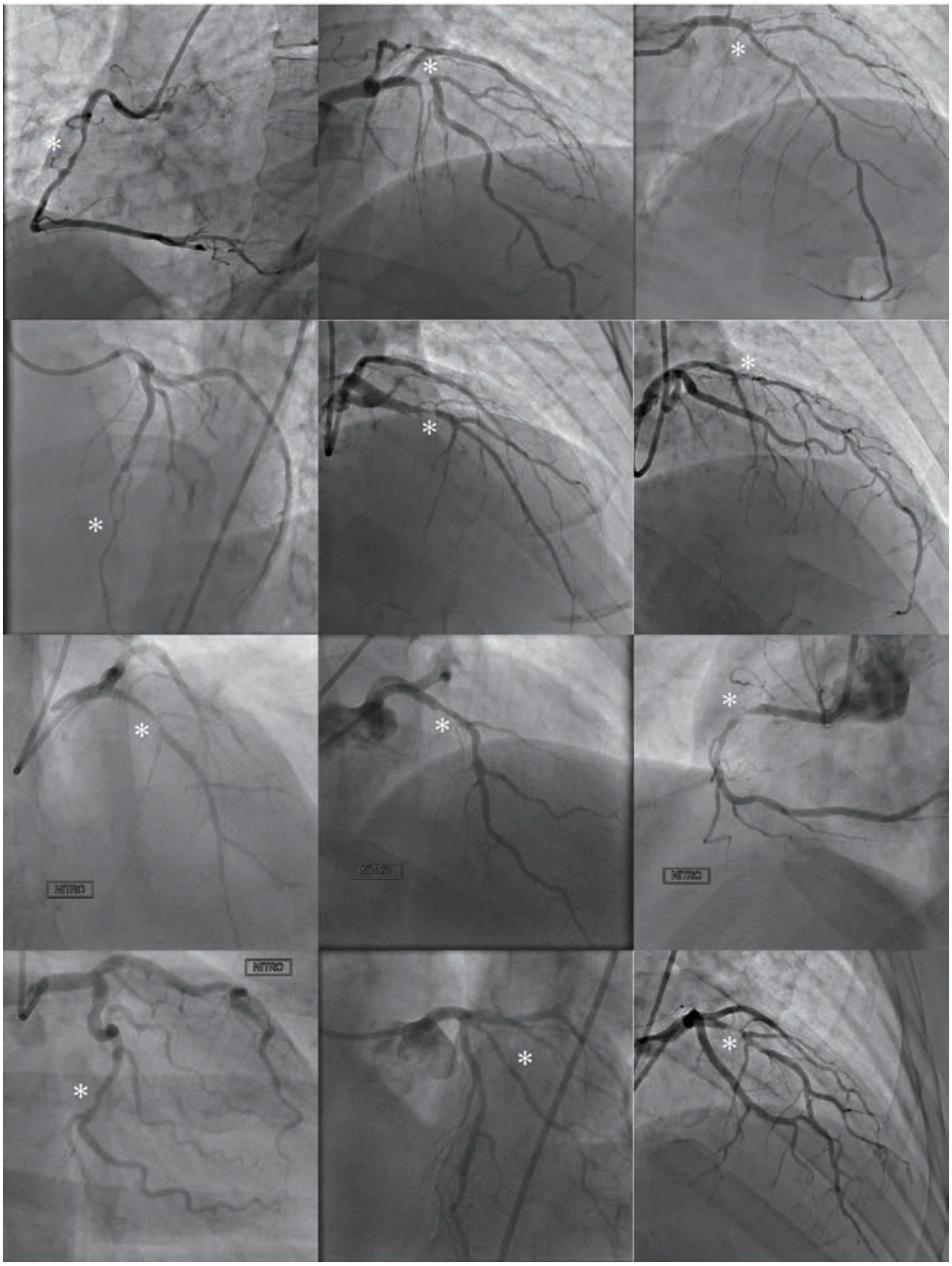


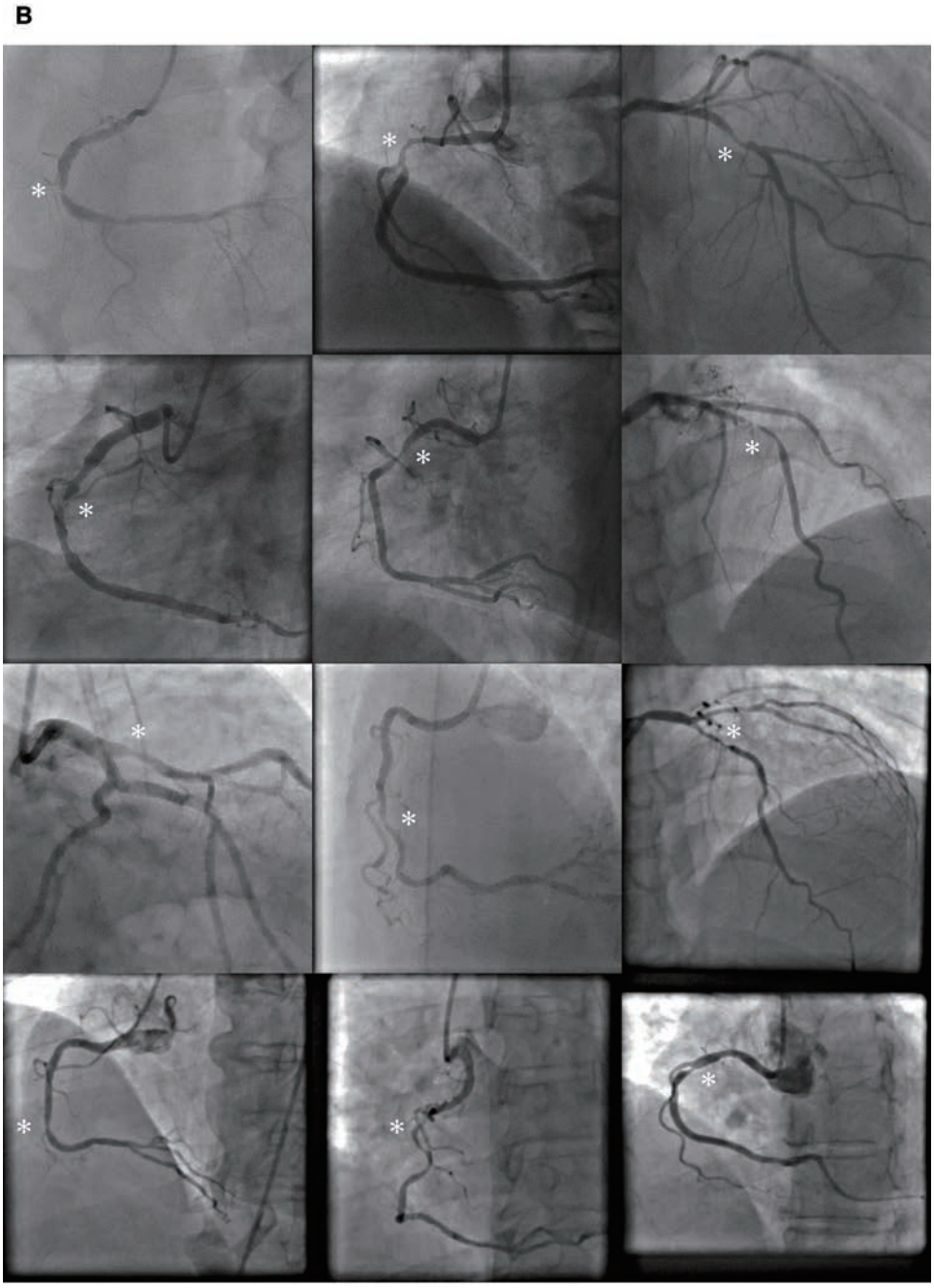
Online Figure 1. Assessment of symmetric stent expansion with asymmetry index in longitudinal IVUS image
Asymmetry index was calculated per stented segment as (1 – minimal lumen diameter/maximal lumen diameter). Minimal lumen diameter was the minimal value of minimal lumen diameter throughout stent segment (red arrow), maximal lumen diameter was the maximal value of maximal lumen diameter throughout stent segment (blue arrow). Therefore, the minimum lumen diameter and maximum lumen diameter could derive from different cross-sections in the stent segment.

AI = asymmetry index, IVUS = intravascular ultrasound.

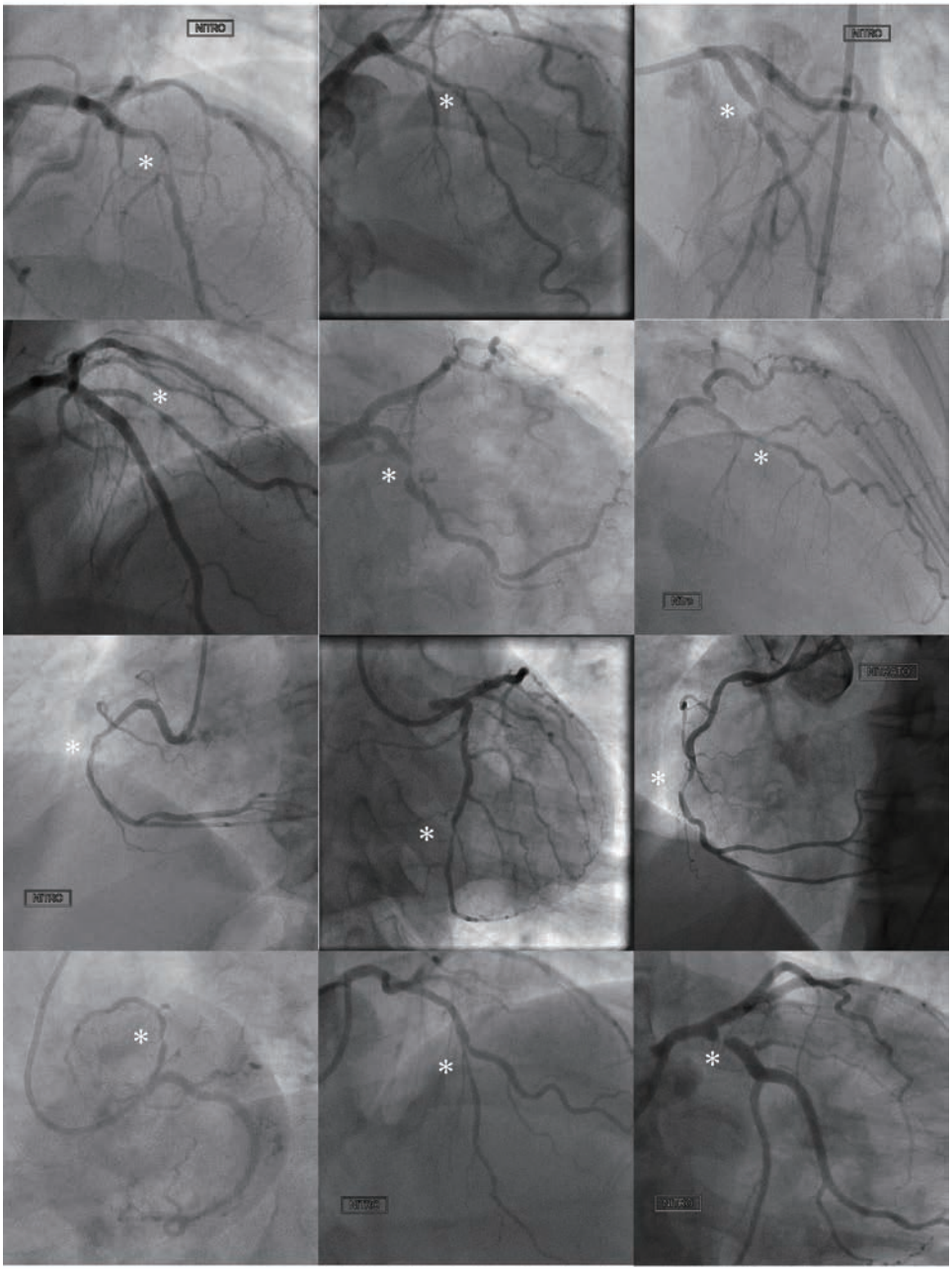
Online Figure 2. Diagnostic coronary angiograms from all 201 enrolled patients
Panel A to S show the pictures of diagnostic coronary angiogram from all participants. The target lesion is marked with an asterisk.

A

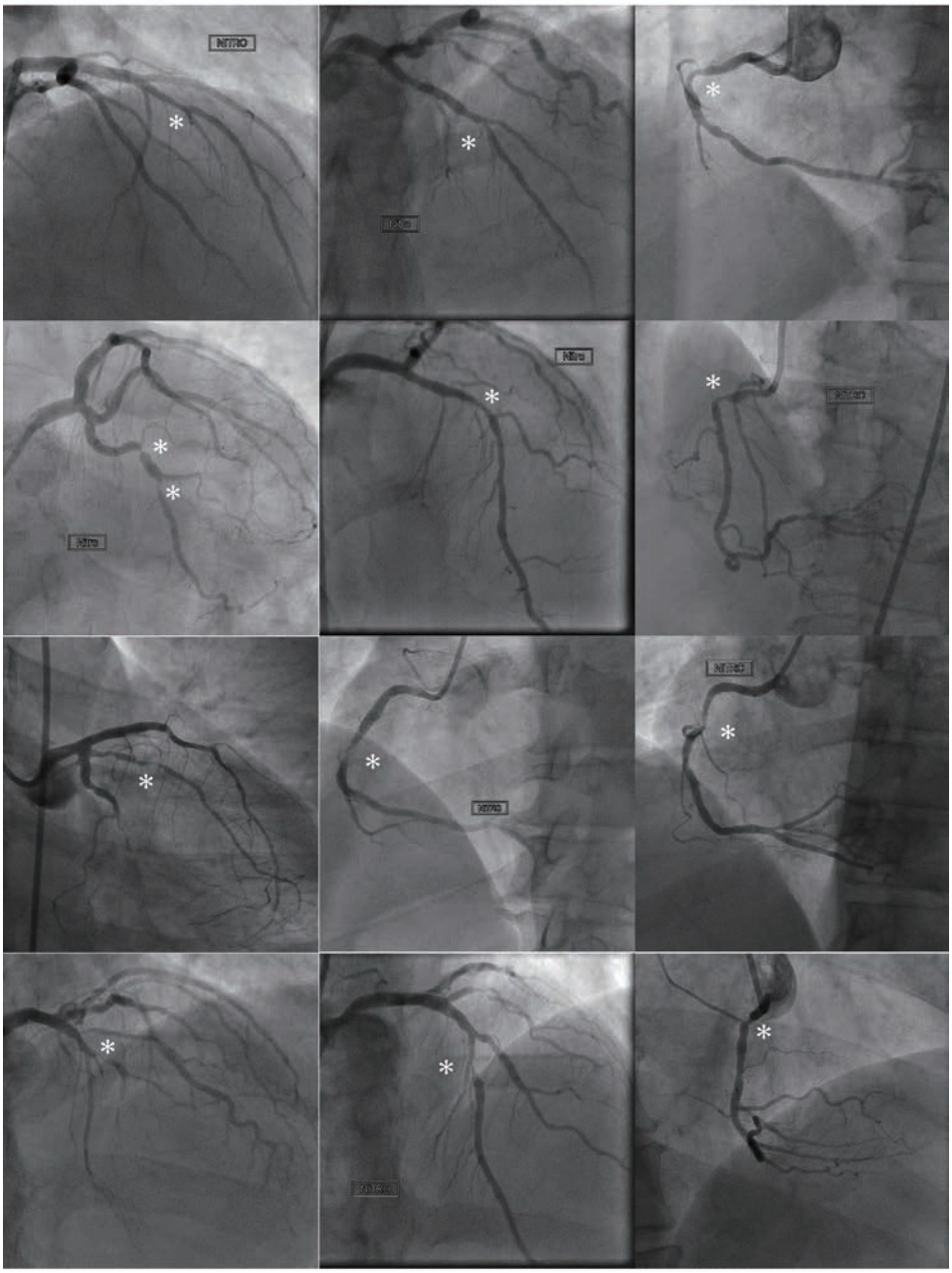


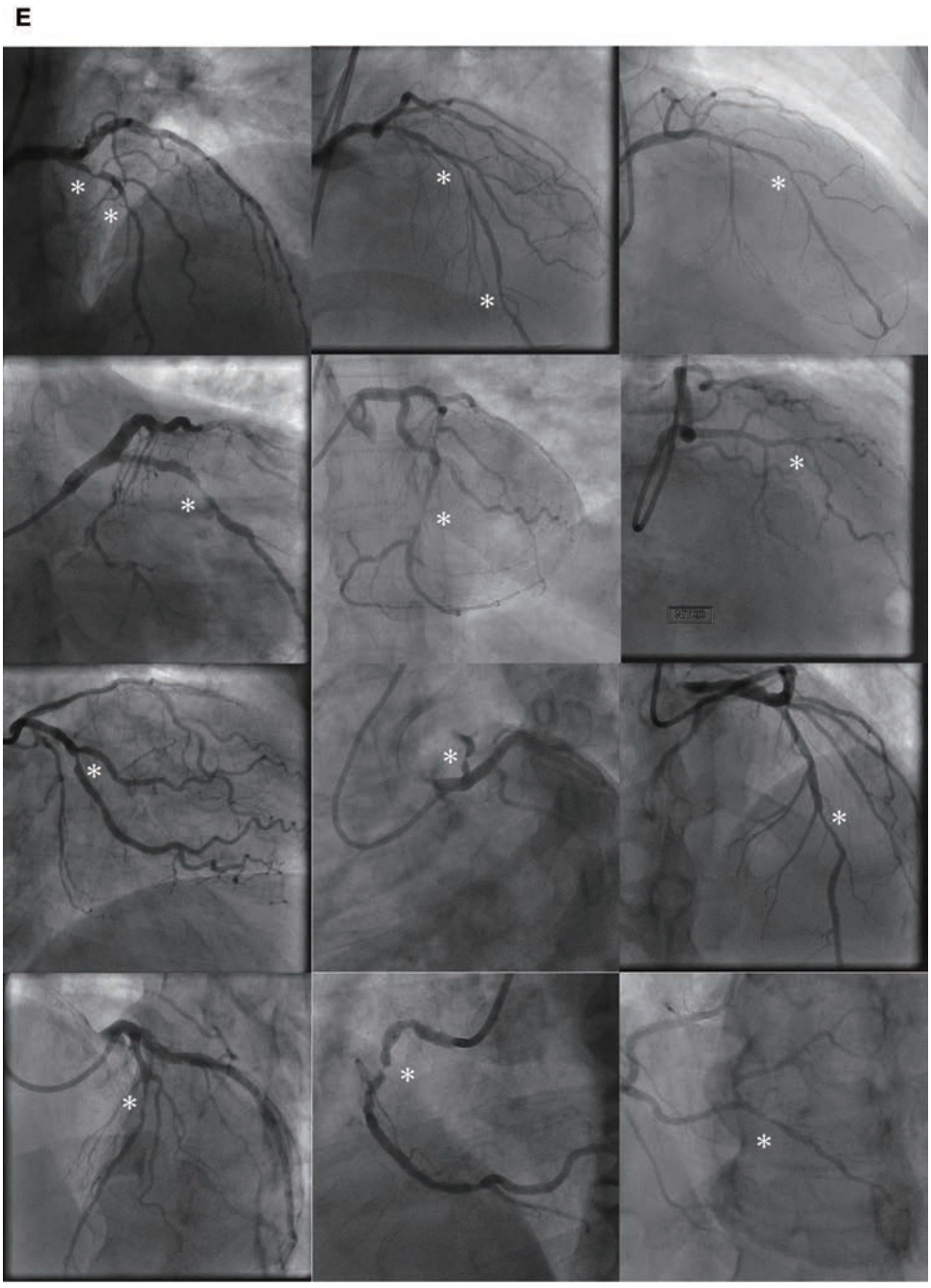

B

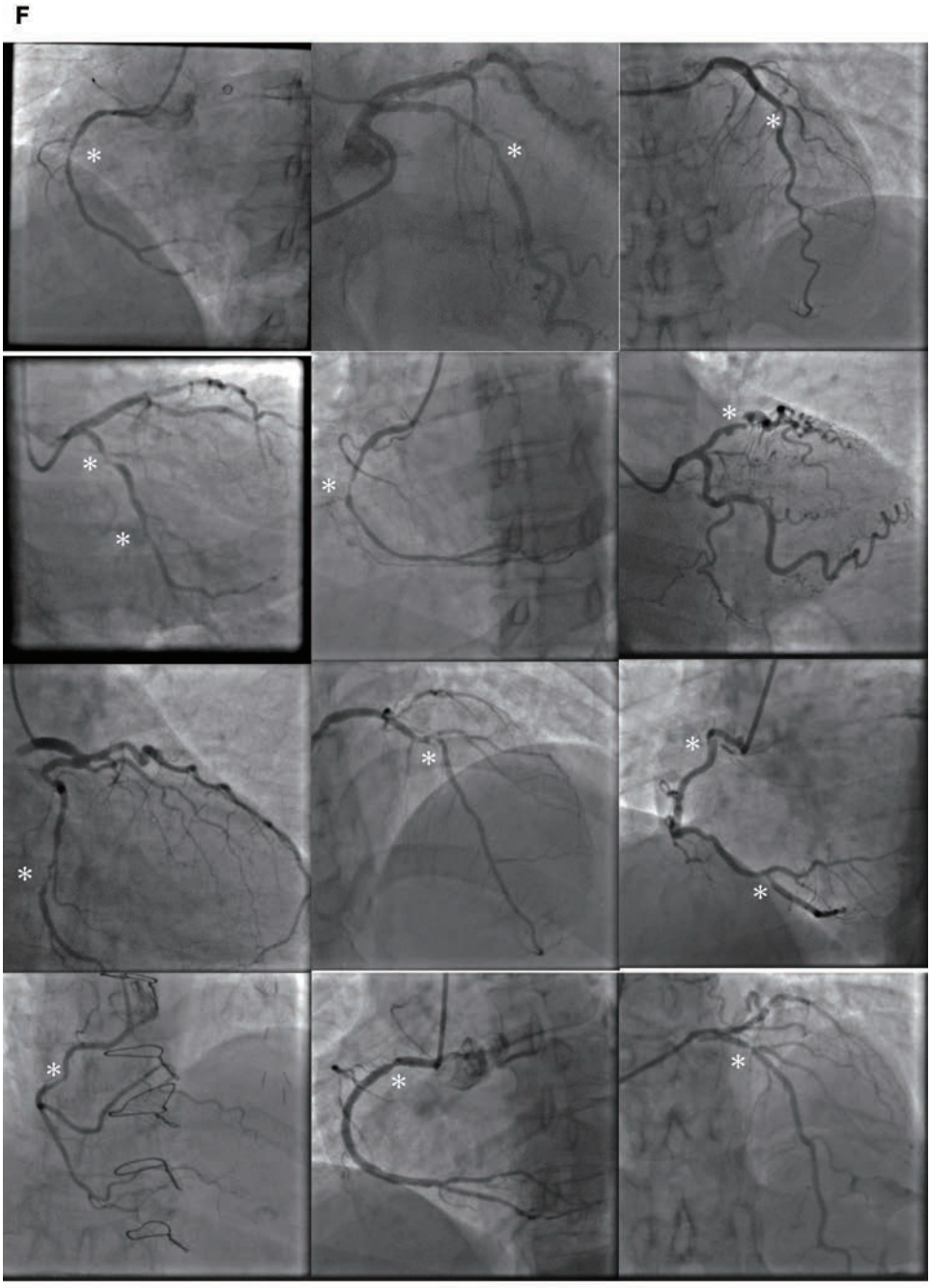
C



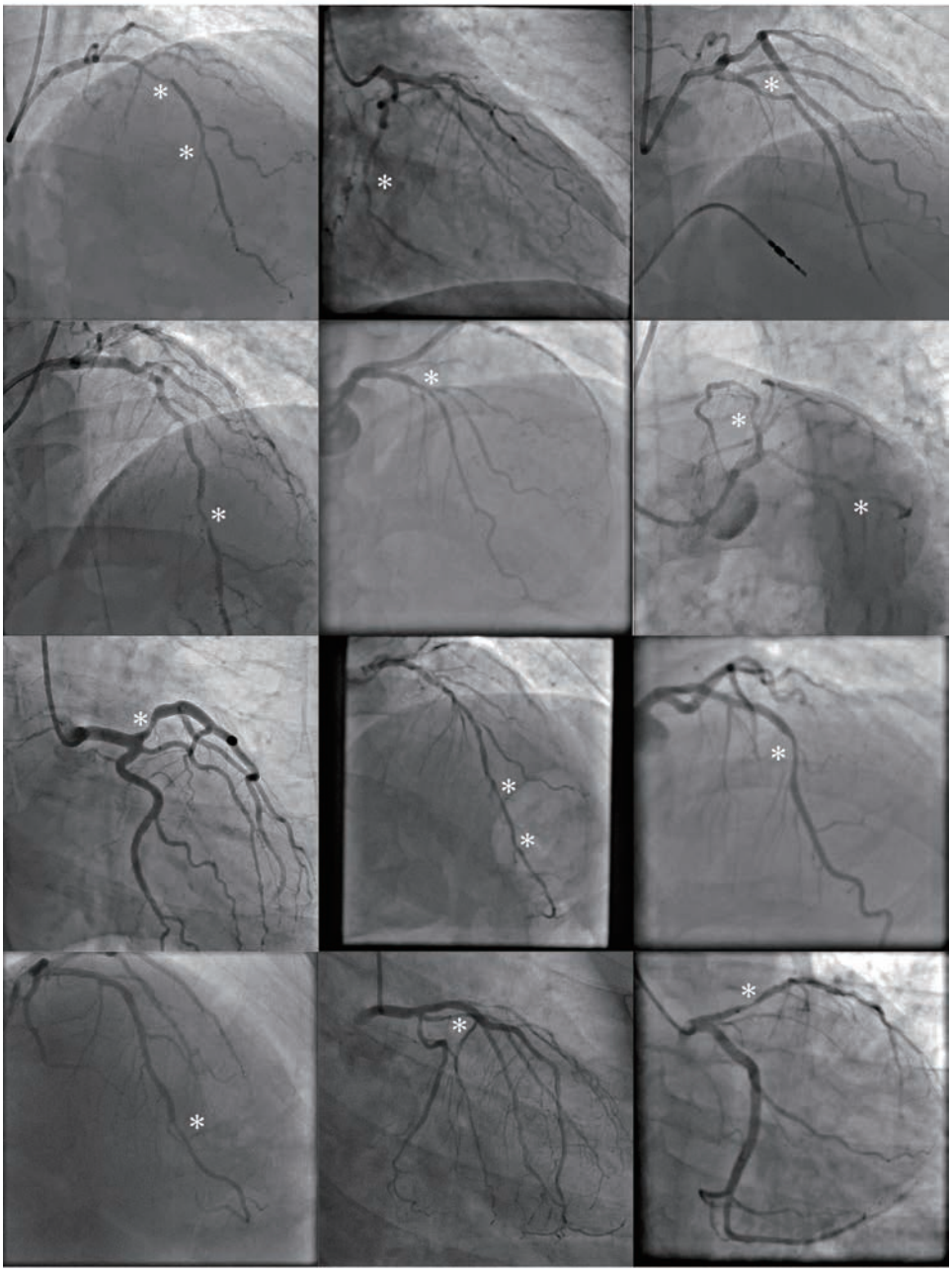
D



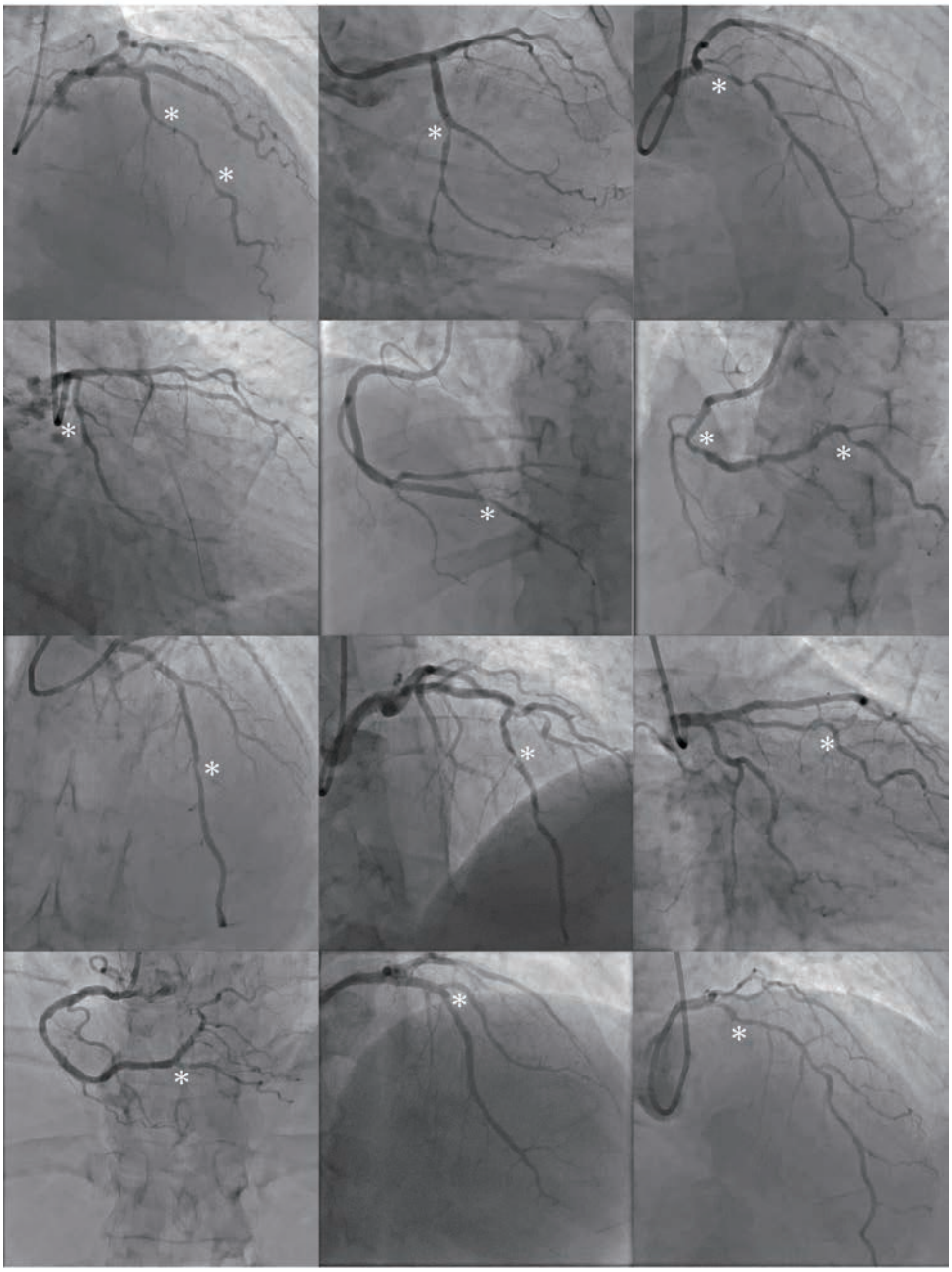

E


F

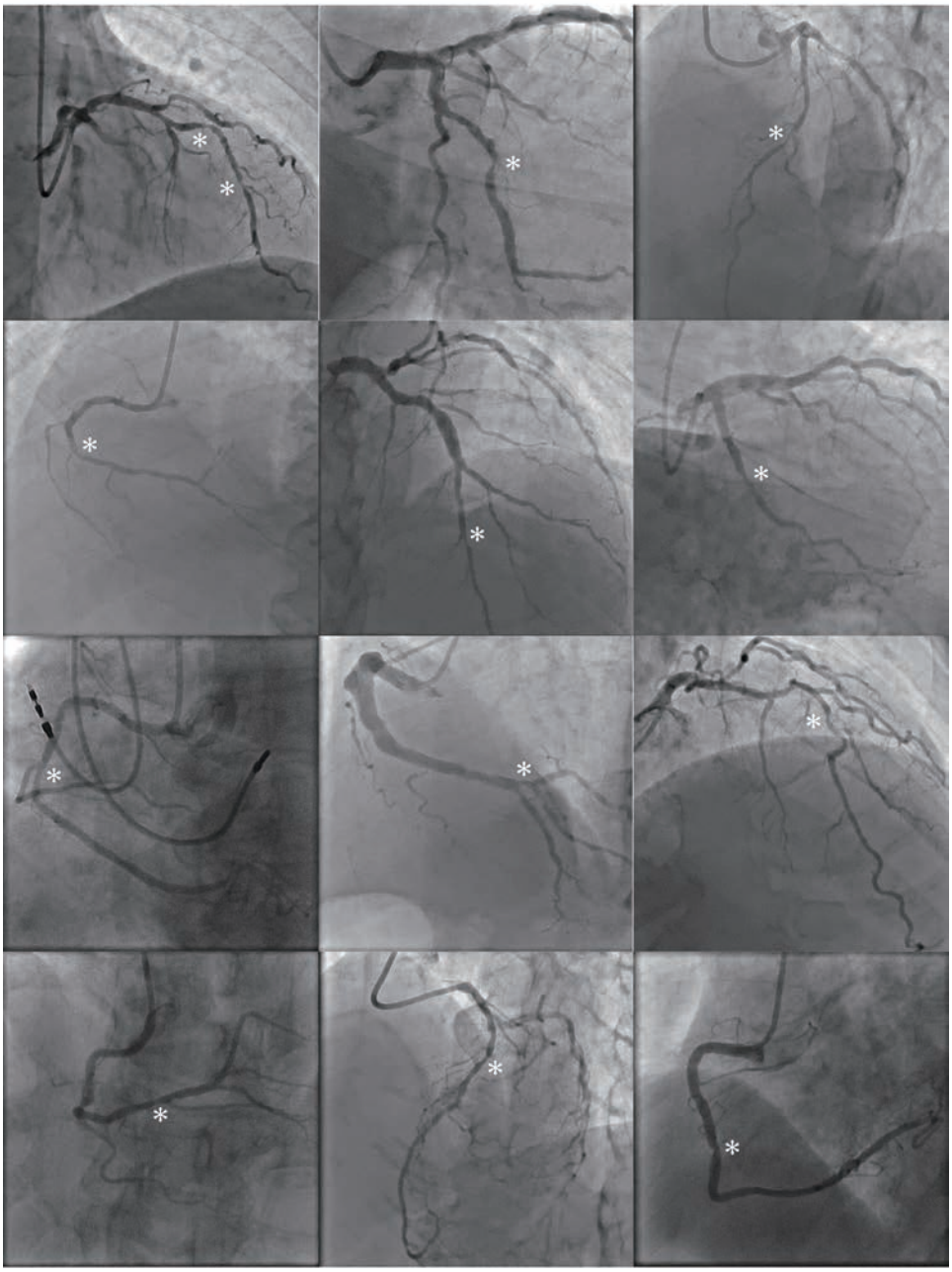
G



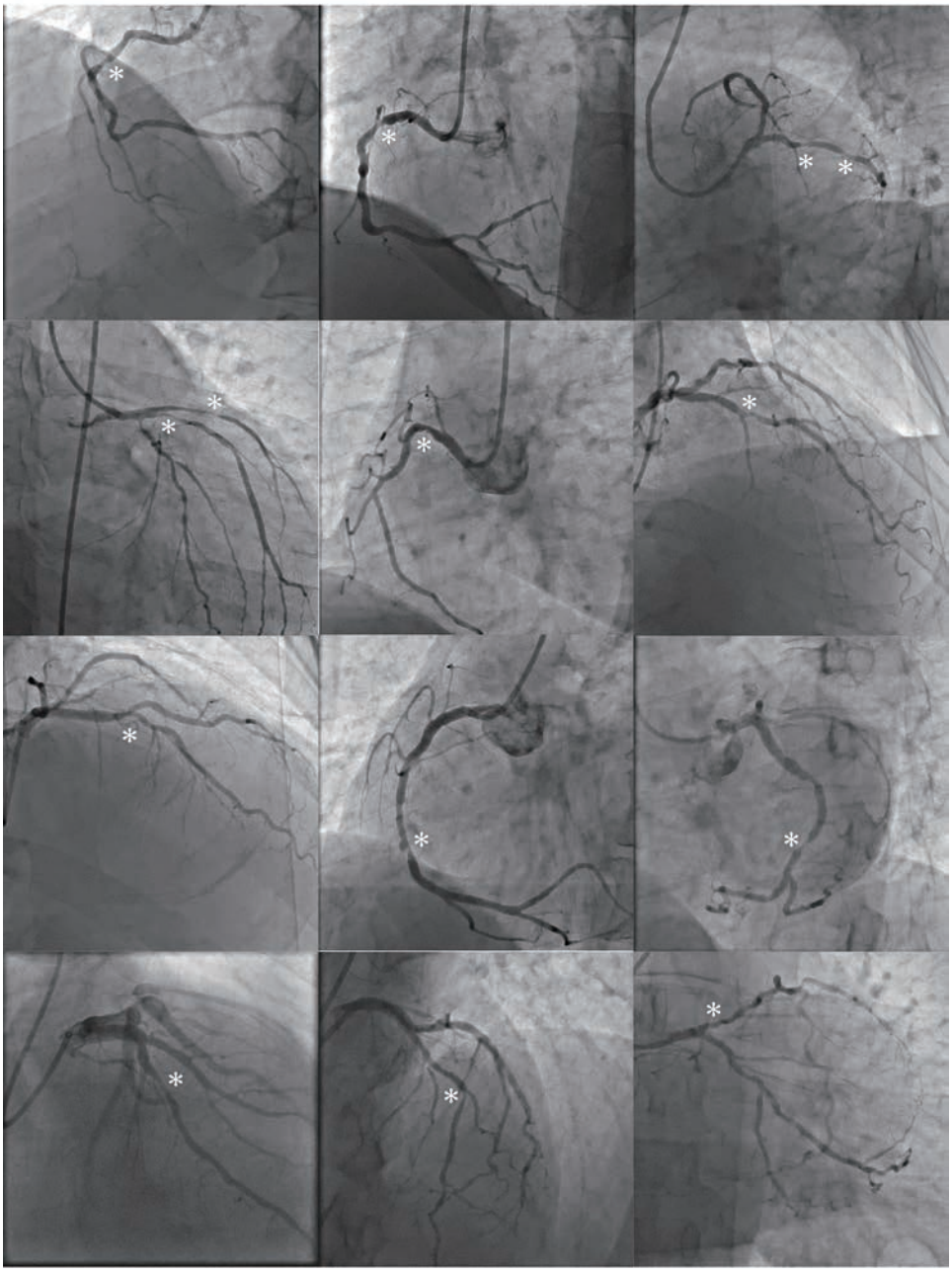
H

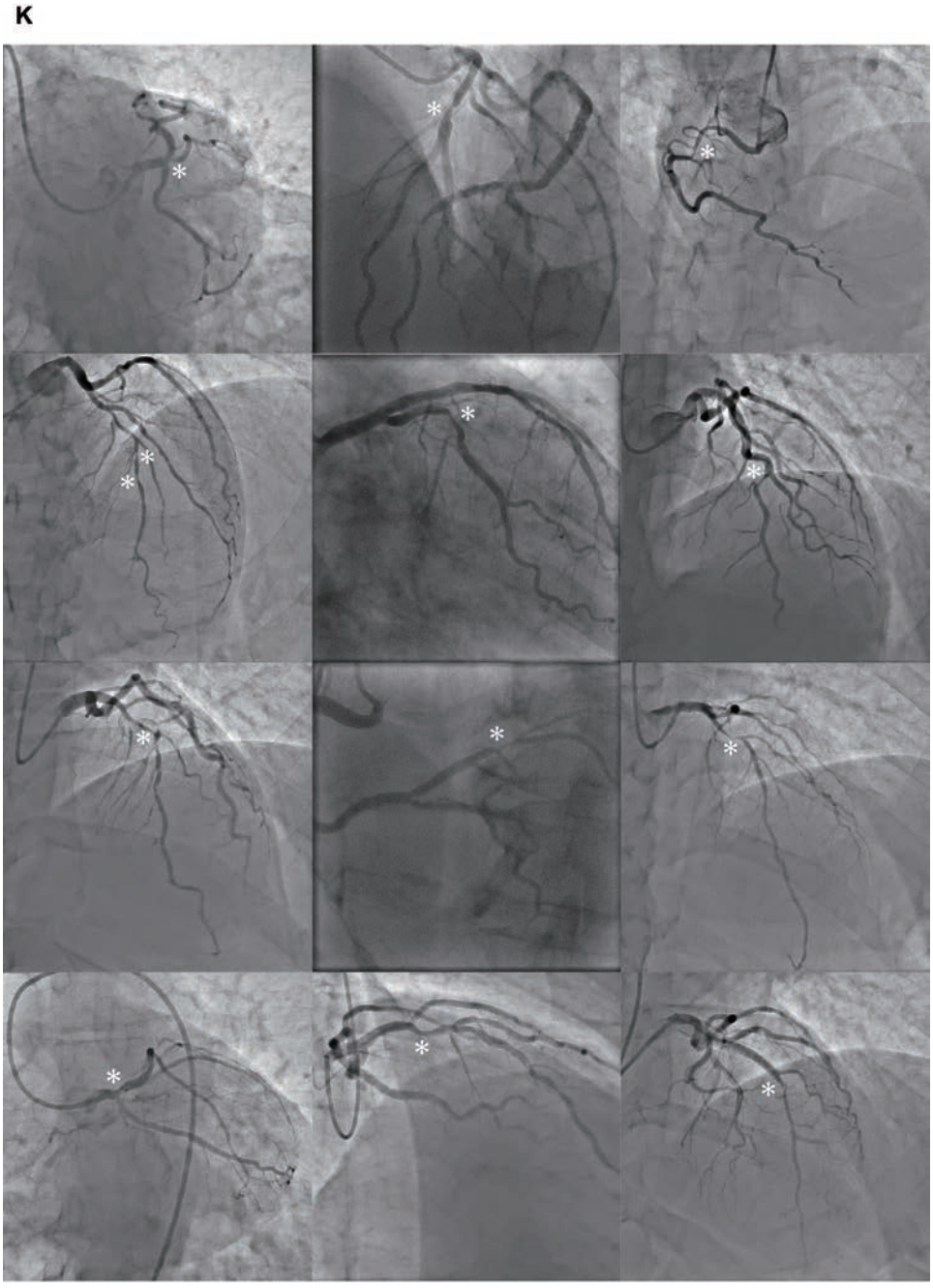


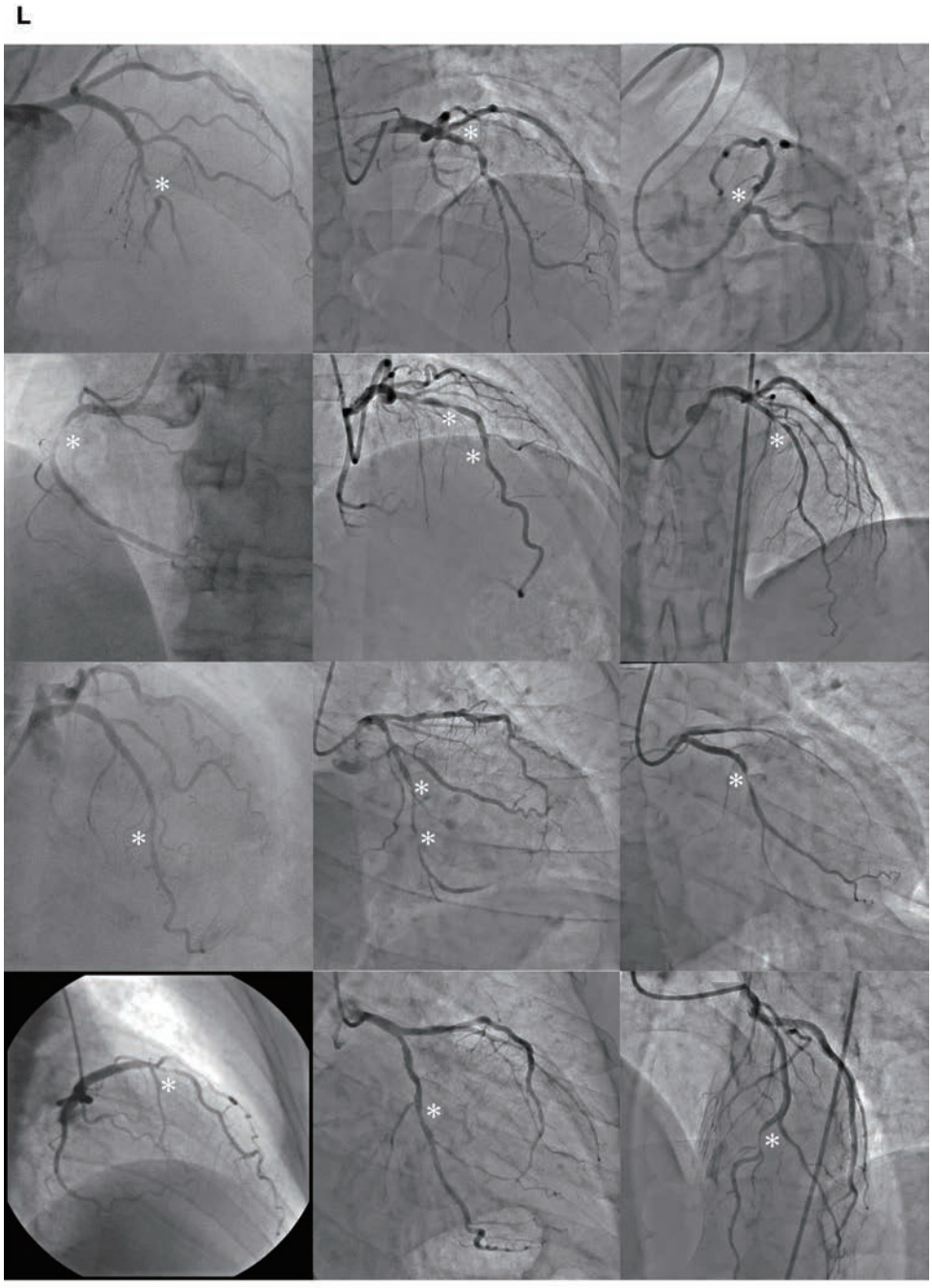
I

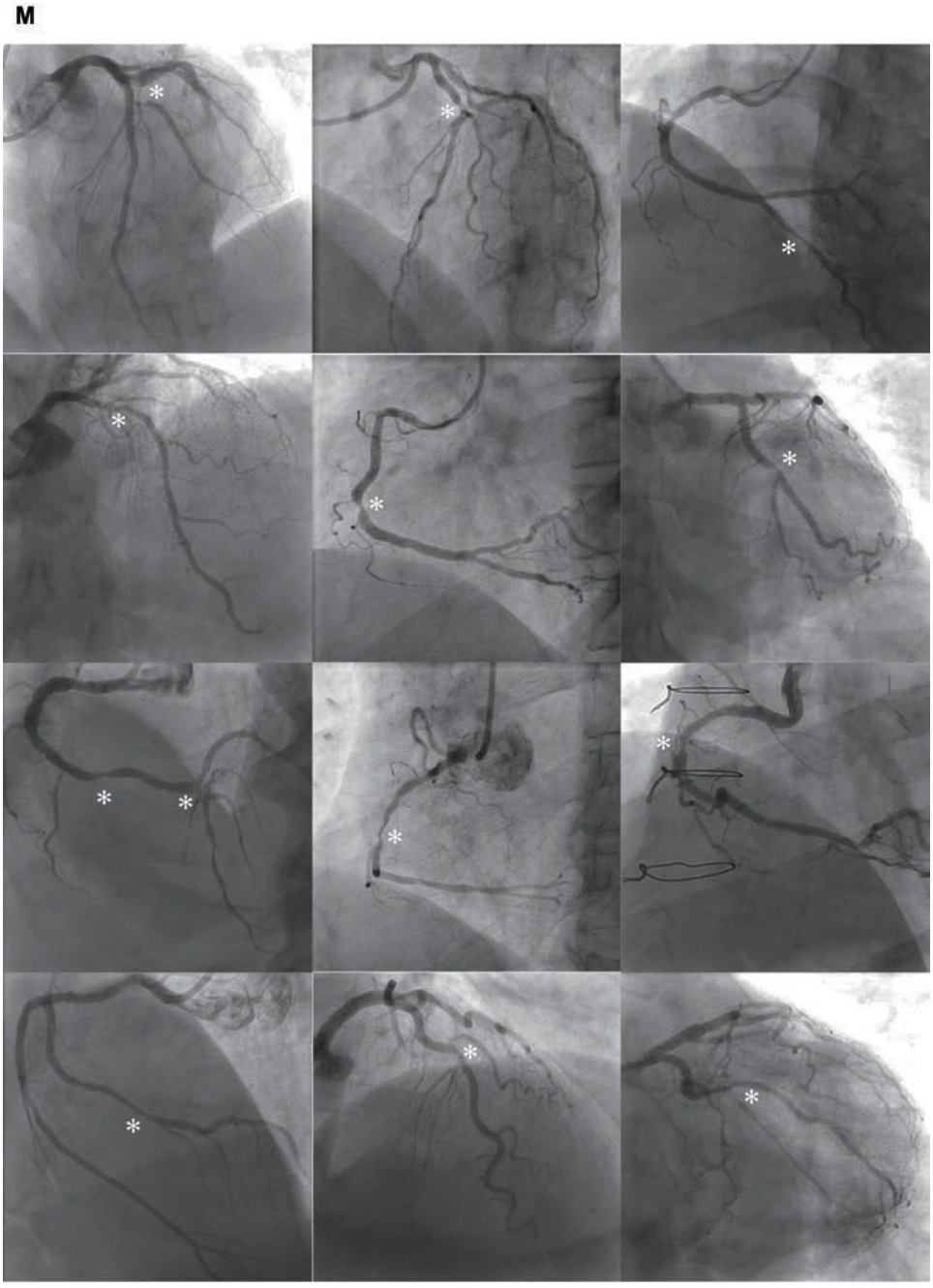


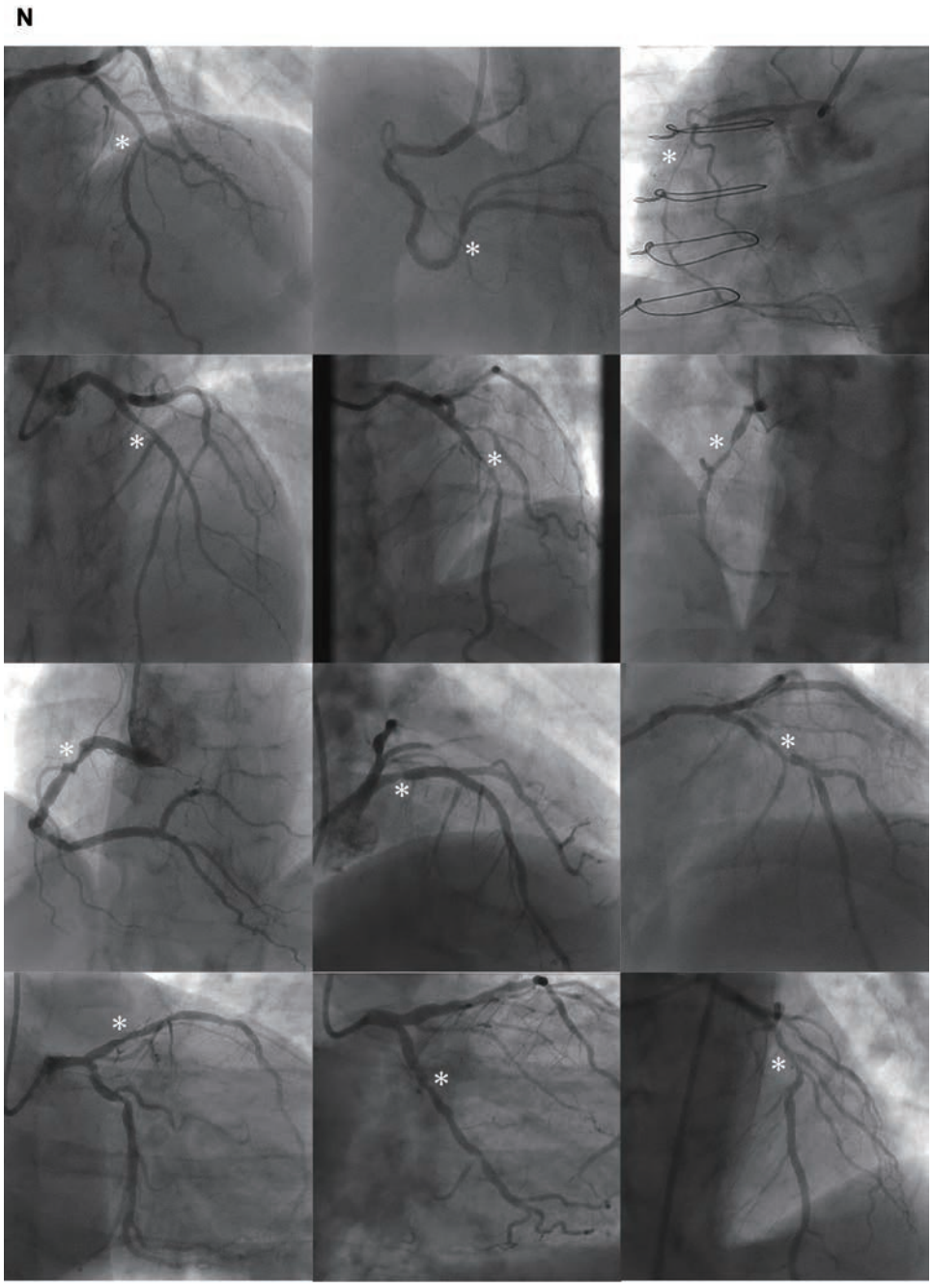
J



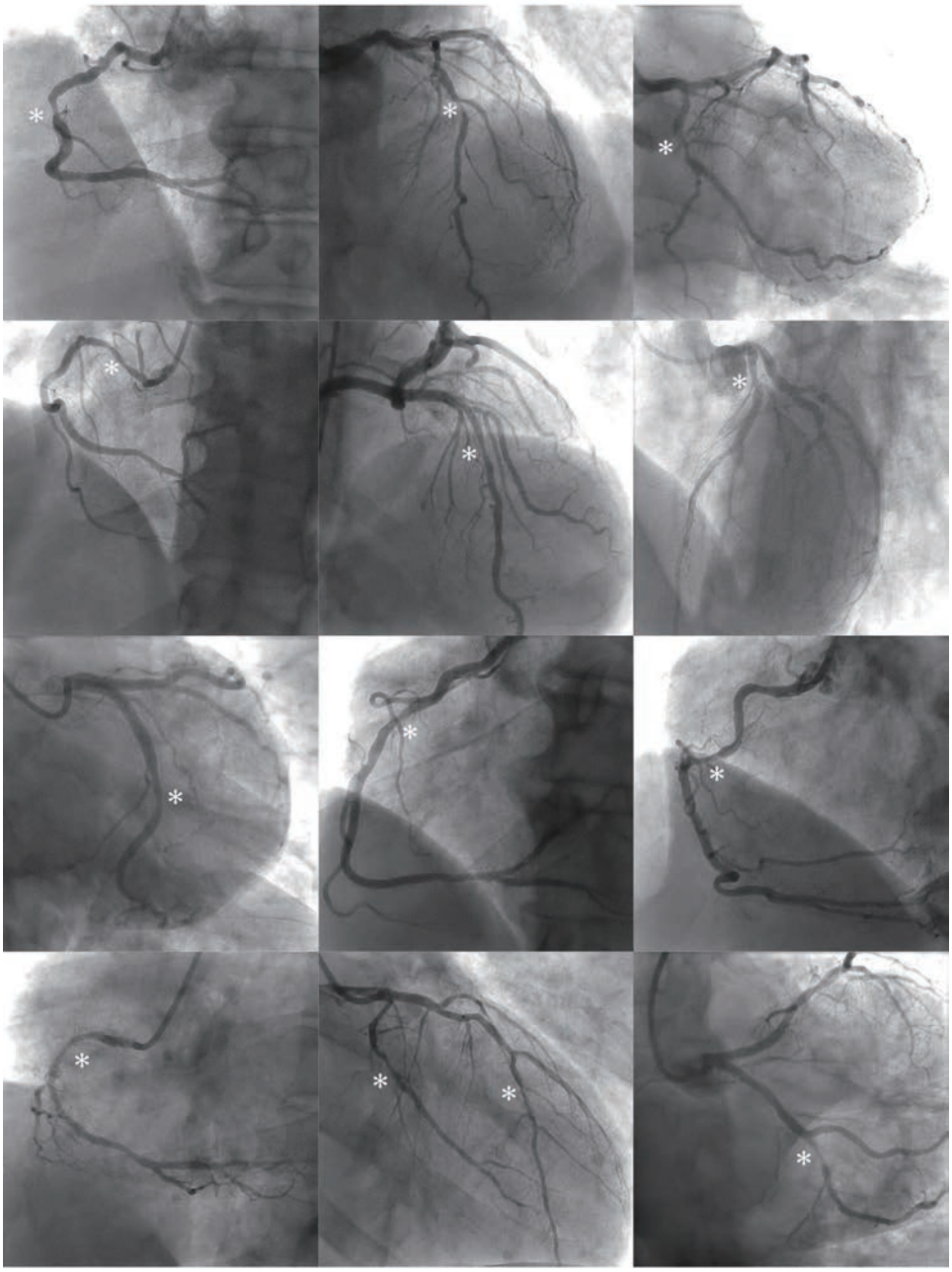

K

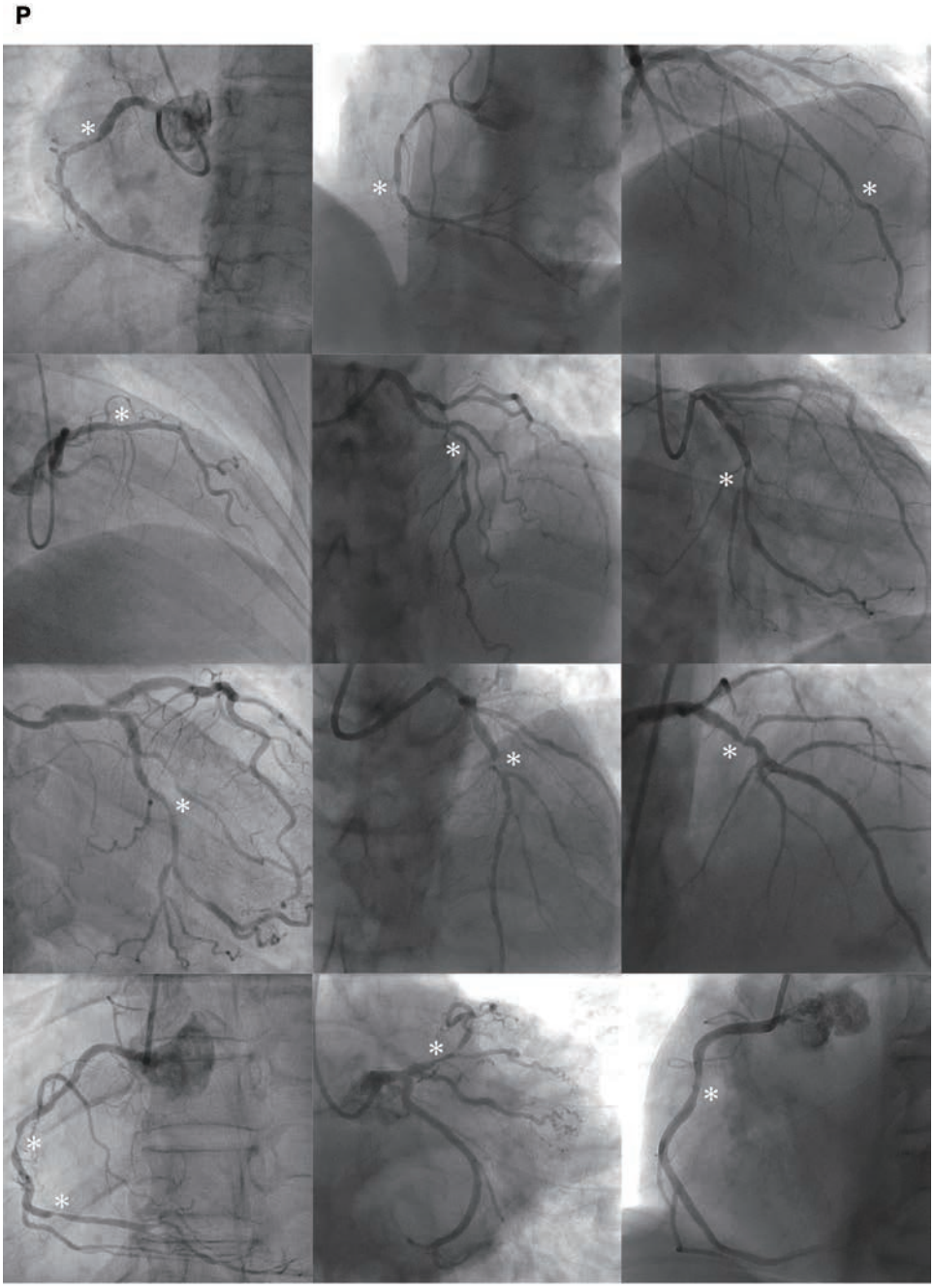

L


M

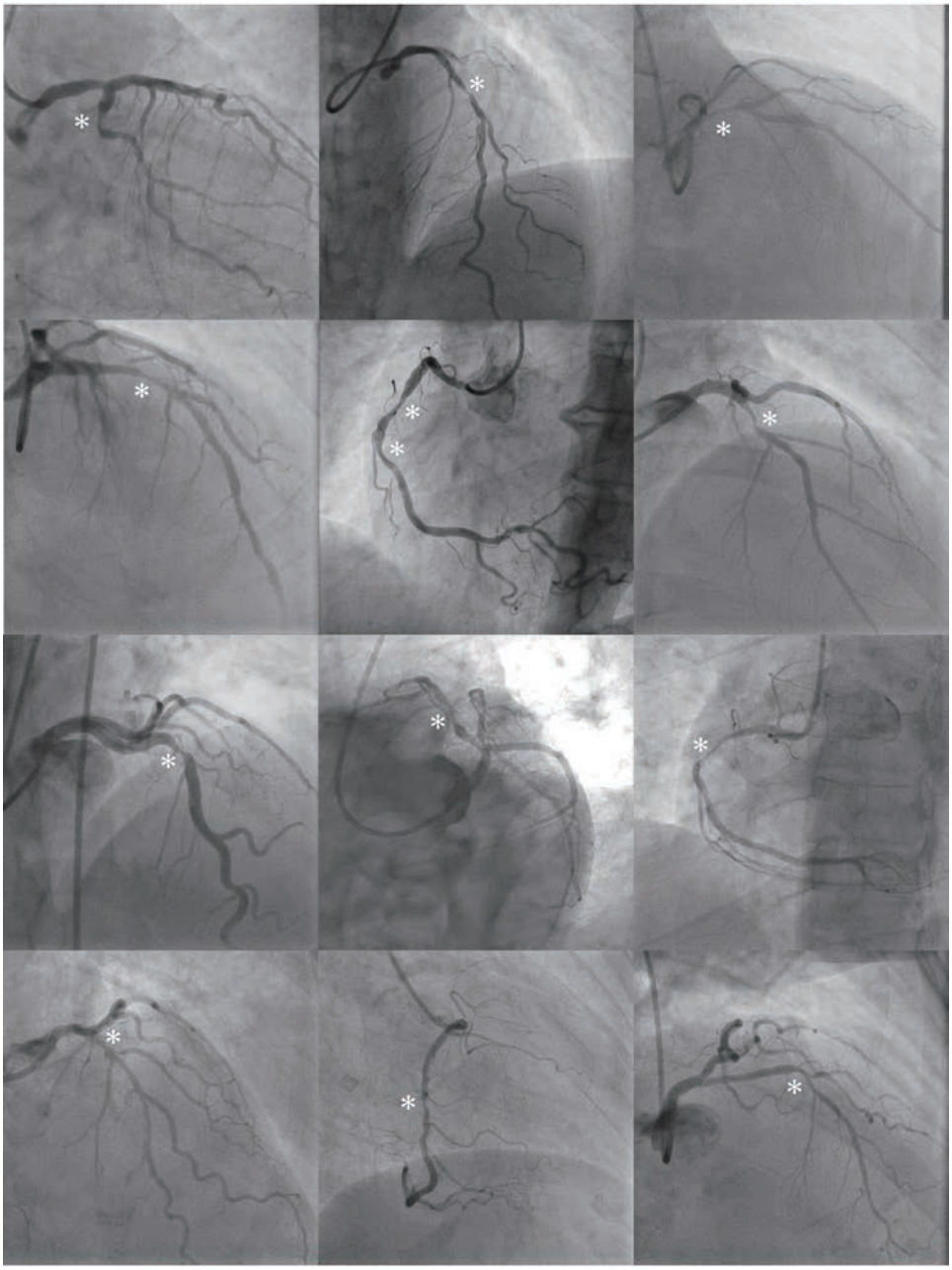

N

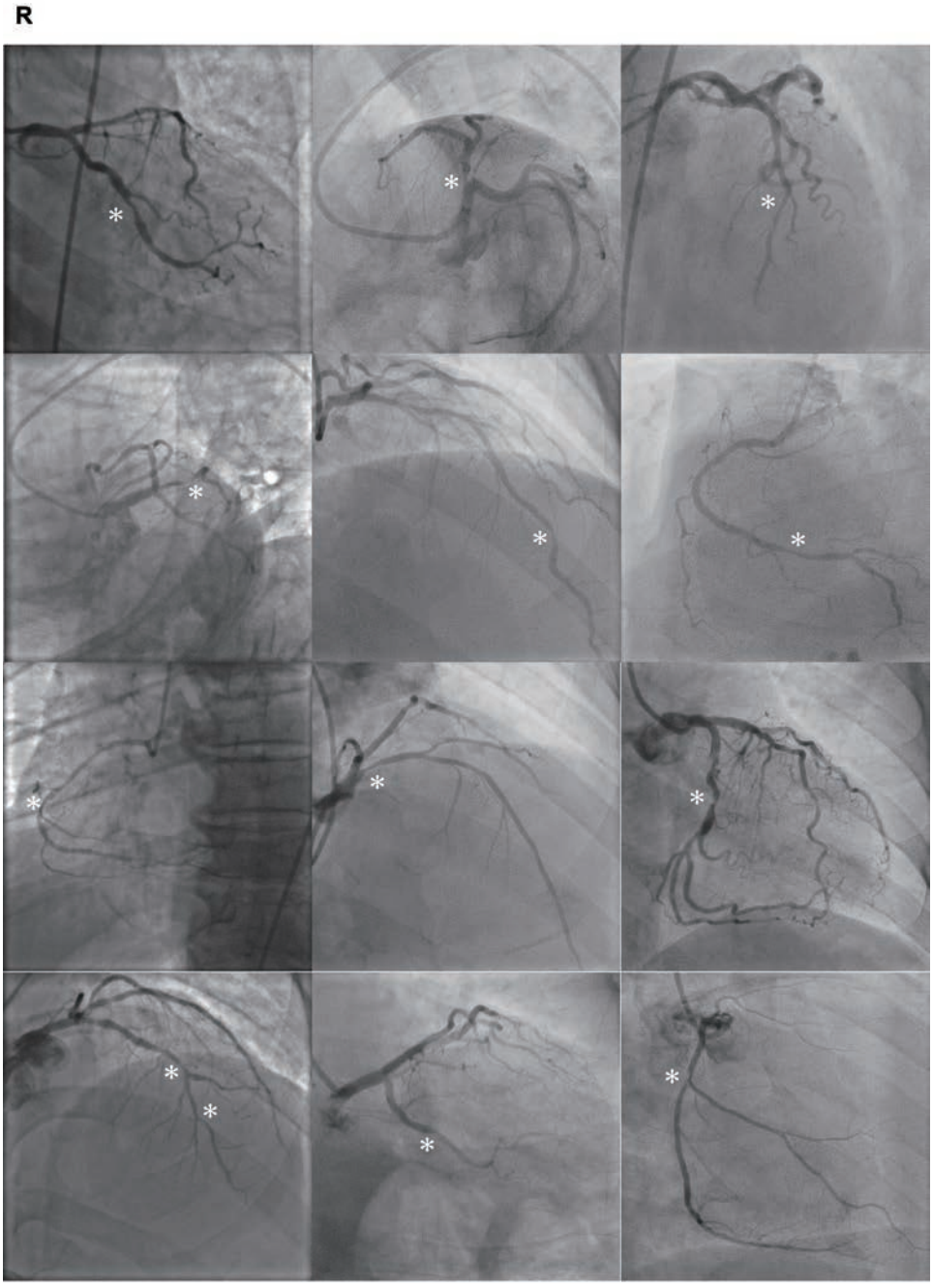
o

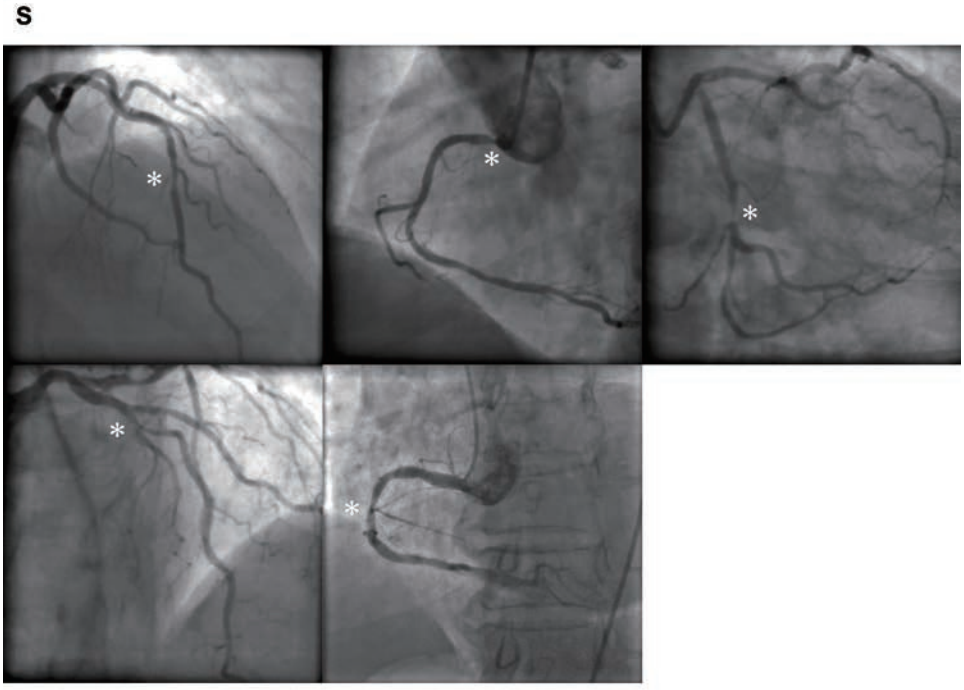



P

Q




R


S

Online Table 1. Recommended criteria of optimal stent implantation

Angiography including quantitative coronary angiography
Residual diameter stenosis <20% by visual estimation or <30% by quantitative coronary angiography (QCA) without edge dissection, thrombus, major side branch occlusion, no-reflow.
Intravascular ultrasound (IVUS) criteria (Modified MUSIC Criteria) [1]
Stent deployment is suboptimal when at least one of the below IVUS findings is present: 1. Complete apposition against the vessel wall of the entire stent. 2. Adequate stent expansion: a) In case in-stent minimal lumen area (MLA) ≤5.5 mm^2, In-stent MLA ≥90% of the average reference lumen area or ≥100% of lumen area of the reference segment with the lowest lumen area; or b) In case in-stent MLA >5.5 mm^2, in-stent MLA ≥80% of the average reference lumen area or ≥90% of lumen area of the reference segment with the lowest lumen area. 3. Symmetric stent expansion defined by asymmetry index (1 – minimal lumen diameter per pullback / maximal lumen diameter per pullback) ≤0.3 (Online Figure 1).
OCT criteria [Prati et al.] [2]
Stent deployment is suboptimal when at least one of the below OCT findings is present: 1) Edge dissection: the presence of a linear rim of tissue with a width ≥200 μm and a clear separation from the vessel wall or underlying plaque that was adjacent (<5 mm) to a stent edge. 2) Reference lumen narrowing: lumen area <4.5 mm^2 in the presence of significant residual plaque adjacent to stent endings. 3) Malapposition: stent-adjacent vessel lumen distance >200 μm. 4) In-stent MLA <4.5 mm^2. 5) In-stent MLA <70% of the average reference lumen area; 6) Intrastent plaque/thrombus protrusion: tissue prolapsing between stent struts extending inside a circular arc connecting adjacent struts or intraluminal mass ≥500 μm in thickness, with no direct continuity with the surface of the vessel wall or highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal free shadowing.

IVUS, intravascular ultrasound; MLA, minimum lumen area; OCT, optical coherence tomography.

Online references

1. de Jaegere P, Mudra H, Figulla H, et al. 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):1214-1223.
2. Prati F, Romagnoli E, Burzotta F, et al. Clinical Impact of OCT Findings During PCI: The CLI-OPCI II Study. *JACC Cardiovasc Imaging.* 2015;8(11):1297-1305.

Online Table 2. Number of patients enrolled per site (Total number of patients: 201).

Center ID	Center name	Principal investigator	City	Enrollment	Date first patient enrolled	Date last patient enrolled
BR007	Universidade Federal do Triangulo Mineiro	Fernando de Martino	Uberaba	49	July 26, 2018	May 6, 2019
BR010	Instituto Cardiovascular de Linhares LTDA - UNICOR	João Eduardo Tinoco de Paula	Linhares	49	July 23, 2018	May 7, 2019
BR001	Incor	Expedito Eustaquio Ribeiro	São Paulo	44	February 21, 2018	May 6, 2019
BR009	Associação Evangélica Beneficiente Espírito Santense - AEBES	Bruno Moulin Machado	Vila Velha	18	September 3, 2018	May 3, 2019
BR012	Hospital de Messejana Dr. Carlos Alberto Studart Gomes	Breno de Alencar Araripe Falcão	Fortaleza	16	November 5, 2018	May 7, 2019
BR006	Instituto de Cardiologia do RS / Fundação Universitária de Cardiologia	Rogerio Eduardo Gomes Sarmento Leite	Porto Alegre	12	August 23, 2018	May 2, 2019
BR004	Instituto Nacional de Cardiologia - INC	Fernanda Barbosa de Almeida Sampaio	Rio de Janeiro	7	January 10, 2019	March 27, 2019
BR013	Hospital Nossa Senhora das Neves - HNSN	Gustavo Rique Morais	João Pessoa	4	December 14, 2018	April 13, 2019
BR017	Instituto de Assist Medica ao Serv. Pub, Estadual (Iamspe)	George Cesar Ximenes Meireles	São Paulo	2	January 23, 2019	April 16, 2019

Summary and future perspectives

Samenvatting van het proefschrift

Deel A: Beste praktijk bij coronaire revascularisatie van drie-vatslijden

Ondanks de enorme evoluties in drug-eluting stent (DES), implantatietechnieken en post-procedurele anti-bloedplaatjestherapie, blijft drie-vatslijden (3VD) de meest uitdagende subgroep van patiënten voor PCI [1]. Van de verschillende onderzoeken die coronaire bypass-transplantatie (CABG) vergelijken met PCI bij patiënten met 3VD, identificeerde de SYNergy tussen percutane coronaire interventie met TAXus en hartchirurgie (SYNTAX trial), CABG als de voorkeursstrategie voor revascularisatie, vergeleken met PCI met eerste generatie DES [2]. Sinds de patienten inclusie van de SYNTAX-I trial in 2007 waren er grote technische en procedurele vorderingen die de resultaten na PCI beïnvloedden. In hoofdstuk 2 hebben we de 2-jarige uitkomst van de SYNTAX II studie gerapporteerd. De SYNTAX II-studie was een multicenter, eenarmige studie die de impact onderzocht van een hedendaagse beste praktijk PCI-strategie (SYNTAX-II-strategie) op klinische resultaten bij 454 patiënten met de novo 3VD zonder linker hoofdstam ziekte. Klinische resultaten in SYNTAX II werden vergeleken met de vooraf gedefinieerde PCI (SYNTAX-I PCI) en CABG (SYNTAX-I CABG) cohorten uit de historische SYNTAX-studie (SYNTAX-I), geselecteerd op basis van evenwicht (equipoise) voor lange termijn (vier- jaar) sterfte met behulp van de SYNTAX-Score II [3-5]. De SYNTAX-II-strategie omvat: besluitvorming door het hartteam met behulp van de SYNTAX Score II (een klinisch hulpmiddel dat anatomische en klinische factoren combineert), coronaire fysiologie begeleide revascularisatie, implantatie van dunne biologisch afbreekbare polymere drug-eluting stents, intravasculaire echografie (IVUS) begeleide stentimplantatie, chronische totale occlusie revascularisatie met hedendaagse technieken en medische therapie volgend de richtlijnen. Na twee jaar waren ernstige ongunstige cardiale en cerebrovasculaire gebeurtenissen (MACCE: een samenstelling van overlijden door alle oorzaken, elke beroerte, myocardinfarct of revascularisatie) in SYNTAX II significant lager in vergelijking met SYNTAX-I PCI (13,2% vs. 21,9%, p=0,001). Dit verschil werd veroorzaakt door een vermindering van 66% bij alle myocardinfarcten (MI) en 38% bij alle revascularisaties. Bovendien waren vergelijkbare resultaten over twee jaar voor MACCE duidelijk tussen SYNTAX II PCI en SYNTAX-I CABG (13,2% vs. 15,1%, p=0,42). Er is een duidelijke verbetering in klinische resultaten tot 2 jaar na PCI binnen een tijdsverloop van 9 jaar tussen de inclusie van patiënten van de SYNTAX I en II.

Deel B: Standaardisering van de beoordeling van het succes van het hulpmiddel in de hedendaagse stent studies.

De evolutie van coronaire stents heeft het meest bijgedragen aan het verbeteren van de algehele PCI-prestaties. Het gebruik van DES van de tweede generatie maakt deel uit van de best praktijk PCI-strategie. Onlangs toonde een meta-analyse aan dat DES met ultradunne struts (strutdikte <70 m) de incidentie van het falen van het behandelde bloedvat verminderde in vergelijking met die van de hedendaagse tweede generatie DES met dikkere struts [6]. Het gebruik van DES met ultradunne stut zal waarschijnlijk deel uitmaken van de best praktijk PCI-strategie, maar het mechanische vermogen van DES met ultradunne struts moet nauwkeurig worden geëvalueerd. Daarom hebben we in hoofdstuk 3 een systematische evaluatie van definities en rapportage van het succes van het hulpmiddel (stents) in klinische onderzoeken uitgevoerd. De meeste PCI-onderzoeken die rapporteren

over succes, hebben de definitie overgenomen die wordt aanbevolen door de Europese Commissie en de Amerikaanse Food and Drug Administration, maar het is opmerkelijk dat de succespercentages van hulpmiddelen niet op dezelfde manier worden gerapporteerd en niet in alle onderzoeken worden gerapporteerd. De meest voorkomende variatie is de definitie van definitieve stenose in de stent, die varieert van <20% tot <50%. We hebben een uitgebreide definitie voorgesteld die niet alleen een succesvolle implantatie van het hulpmiddel verklaart, maar ook een succesvolle ballonexpansie en terugtrekking van het plaatsingssysteem. Bovendien wordt het bereiken van een uiteindelijke in-stent residuele stenose van <20% met gegevens gerapporteerd door de QCA van het core laboratorium (voorkeurs methodologie) overgenomen in de uitgebreide definitie volgens de belangrijkste angiografische eindpunten aanbevolen door de ESC/EAPCI Task Force op de evaluatie van coronaire stents [7]. We hebben ook speciale overwegingen voorgesteld, zoals op laesie gebaseerde analyseproblemen, gebruik van meerdere hulpmiddelen/stents en laesiesucces versus succes van het hulpmiddel.
In hoofdstuk 4 rapporteerden we het primaire eindpunt van de TALENT-studie, een gerandomiseerde, gecontroleerde studie voor iedere patiënt om de non-inferioriteit van klinische uitkomsten te onderzoeken na implantatie van de ultradunne Supraflex DES in vergelijking met de Xience DES. Na 12 maanden was het primaire eindpunt van een device (hulpmiddel) georiënteerd samengesteld eindpunt opgetreden bij 35 patiënten (4,9%) in de Supraflex-groep en bij 37 patiënten (5,3%) in de Xience-groep. Non-inferioriteit van de Supraflex-stent vergeleken met de Xience-stent werd aangetoond, met een absoluut verschil van –0,3% en een eenzijdige 95% bovengrens van 1,6% (p voor non-inferioriteit <0,0001, p voor superioriteit=0,801). Het succespercentage van het hulpmiddel per laesie in beide groepen was hoog, maar er was een significant verschil tussen de Supraflex- en de Xience-groep (973 [97,6%] van 997 laesies versus 998 [99,5%] van 1003; verschil –1,9%, 95 % BI –3·0 tot –0·9; p=0,0003). Dit verschil werd voornamelijk veroorzaakt door een grotere cross-over naar de niet-toegewezen stent in de Supraflex-groep in vergelijking met die in de Xience-groep. Er waren geen verschillen in de resterende in-stent stenose van 30% of meer tussen groepen. Dit verschil in het succes van het hulpmiddel had geen invloed op de resultaten van de patiënt in het ziekenhuis (in het ziekenhuis gericht samengesteld eindpunt 11 [1,5%] van 720 patiënten versus 10 [1,4%] van 715; verschil 0,1%, 95% CI –1,2 tot 1,5; p=0,837). In de TALENT-studie is de definitie van succes van het hulpmiddel vergelijkbaar met de uitgebreide definitie, met slechts een klein verschil in de mate van een resterende stenose (<30%). Verder onderzoek is nodig om de superioriteit van de ultradunne DES stent struts aan te tonen in vergelijking met DES van de 2e generatie.

Deel C: Beoordeling van optimale coronaire stenting met intracoronaire beeldvorming

Intravasculaire echografie (IVUS) en optische coherentietomografie (OCT) zijn de afgelopen drie decennia ontwikkeld en verbeterd als diagnostische en begeleidingsinstrumenten voor interventionele procedures. IVUS heeft een resolutie van 100 µm met een hoge weefselpenetratie en het vermogen om de volledige structuur van een kransslagader te beoordelen, inclusief het externe elastische membraan, terwijl OCT een hogere resolutie heeft van 10-20 µm om endoluminale structuren met een beperkte weefselpenetratie te beoordelen in vergelijking met IVUS [8]. In hoofdstuk 5 onderzochten we de impact van minimaal stentoppervlak (MSA) geëvalueerd door post-procedurele IVUS op klinische

uitkomsten na beste praktijk PCI bij patiënten met 3VD in de SYNTAX II-studie. In de SYNTAX II-studie was post-procedurele IVUS-beoordeling verplicht en uitgevoerd bij 84,1% van de patiënten (76,4% van de laesies) om stentappositie, expansie en symmetrie te optimaliseren op basis van MUSIC criteria [9]. Van de 819 laesies die werden behandeld met de beste praktijk PCI strategie, was grotere post-procedurele MSA onafhankelijk geassocieerd met het lagere percentage van target laesie revascularisatie (TLR) na 2 jaar (16/288 [5,6%], 12/265 [4,5%] en 4/266 [1,5%] [P = 0,042]). Een MSA-drempel van 5,2 mm2 of minder voorspelde TLR na 2 jaar door ROC-analyse met een relatief lage c-statistiek van 0,620. In hoofdstuk 6 onderzochten we de klinische implicaties van 3-dimensionale optische frequentiedomein-beeldvorming (3D-OFDI)-geleide stents voor bifurcatielaesies in de gerandomiseerde OPTIMUM-studie (Online 3-Dimensional Optical Frequency Domain Imaging to Optimize Bifurcation Stenting Using UltiMaster Stent). In deze studie rapporteerden we uitstekende haalbaarheid van online 3D-OFDI (98,2%) en superioriteit van online 3D-OFDI-begeleide bifurcatie-PCI ten opzichte van angiografie-begeleide bifurcatie-PCI in termen van acute onvolledige stentaanbrenging bij bifurcatie (19,5 ± 15,8% versus 27,5 ±14,2%, P=0,008). Verdere onderzoeken zijn nodig om het klinische voordeel op lange termijn van online 3D-OFDI-begeleide stents voor bifurcatielaesies te bevestigen.

Deel D: Coronaire fysiologie voor optimale revascularisatiestrategie

In de context van de groeiende belangstelling voor functionele beoordeling van coronaire stenosen, hebben vorderingen in rekenkracht en driedimensionale coronaire angiografie de ontwikkeling van functionele coronaire angiografie mogelijk gemaakt. In het algemeen is een wiskundige formule met betrekking tot de Lance Gould-vergelijking gebruikt voor het proces van berekening [10]. Een van de commercieel beschikbare technologieën is de kwantitatieve stroomverhouding (QFR) (Medis Medical Imaging System, Leiden, Nederland, en Pulse Medical Imaging Technology, Shanghai, China), met de meest gepubliceerde gegevens, waaronder prospectieve multicenter-onderzoeken. In hoofdstuk 7 werden alle vaten die werden behandeld in de SYNTAX II studie retrospectief gescreend en geanalyseerd op post-PCI QFR. In deze analyse wordt een hogere post-PCI QFR-waarde (≥0,91) geassocieerd met verbeterde bloedvat gerelateerde klinische resultaten in de beste PCI-praktijk voor de novo 3VD (12,0% in post-PCI QFR <0,91 vs. 3,7% in post-PCI QFR ≥0,91; hazard ratio: 3,37; 95% betrouwbaarheidsinterval: 1,91 tot 5,97; p < 0,001). Volgens deze bevinding kan het bereiken van een post-PCI QFR-waarde van ≥0,91 in alle behandelde vaten deel uitmaken van de beste praktijk PCI-strategie bij de behandeling van de novo 3VD. In hoofdstuk 8 hebben we uitgebreid de klinische waarde van post-PCI fysiologische beoordeling besproken. Post-PCI fysiologische beoordeling heeft twee mogelijke doelen in de klinische praktijk. Ten eerste kan post-PCI fysiologische beoordeling worden gebruikt als een voorspeller van klinische resultaten op lange termijn, zoals onderzocht in hoofdstuk 7. Ten tweede kan post-PCI fysiologische beoordeling worden gebruikt voor de optimalisatie van PCI-resultaten. Post-PCI fysiologische beoordeling kan een belangrijkere rol spelen voor evaluatie en lokalisatie van resterende ziekte buiten het stentsegment dan voor stentoptimalisatie, waarvoor intracoronaire beeldvorming de gevestigde methode is. Verdere studies zijn nodig om te beoordelen of verdere interventie voor resterende ischemie volgens post-PCI fysiologische beoordeling de klinische resultaten kan verbeteren.

Deel E: Optimale antitrombotische therapie na stentimplantatie

In het SYNTAX II-onderzoek werd de dubbele antibloedplaatjestherapie (DAPT) voortgezet bij 99,3% van de patiënten na 1 maand, 59,7% na 1 jaar en 7,0% na 2 jaar. Ongeveer 70% van de patiënten kreeg clopidogrel als P2Y12-remmer en P2Y12-remmer werd zelden gebruikt als monotherapie na stopzetting van DAPT. Na de voltooiing van het SYNTAX II-onderzoek hebben een aantal recente onderzoeken veelbelovende resultaten opgeleverd met een schema dat een korte DAPT-duur omvat, gevolgd door de toediening van alleen een P2Y12-antagonist in plaats van aspirine [11]. Daarom moet een nieuw antitrombotisch regime na het plaatsen van een stent worden toegepast in de beste praktijk PCI-strategie.
In hoofdstuk 9 onderzochten we de klinische impact van ticagrelor monotherapie na 1 maand DAPT na PCI voor bifurcatielaesies, een van de meest uitdagende anatomische kenmerken voor PCI. In de GLOBAL LEADERS-studie ondergingen, van de 15.845 patiënten die in deze subgroepanalyse waren opgenomen, 2.498 patiënten (15,8%) PCI voor ten minste één bifurcatielaesie. Na PCI voor bifurcatielaesies met 1 maand DAPT gevolgd door ticagrelor monotherapie gedurende 23 maanden was er geen hogere incidentie van overlijden door alle oorzaken of een nieuw Qwave-myocardinfarct vergeleken met conventionele DAPT-strategie. De verkorte DAPT-strategie was echter geassocieerd met een significante vermindering van definitieve of waarschijnlijke stenttrombose (p voor interactie = .022) en significante overmaat aan beroerte (p voor interactie = .018) in vergelijking met de referentiebehandeling. Verder bewijs van speciale bifurcatiestudies die DAPT van 1 maand testen, gevolgd door P2Y12-monotherapie, zijn gerechtvaardigd om die mogelijke dualiteit van het effect (zoals mogelijke preventie van ST en mogelijke toename van beroerte) bij patiënten die een bifurcatie-PCI ondergaan, verder op te helderen.
In hoofdstuk 10 evalueerden we de hypothese dat prasugrel monotherapie na succesvolle everolimus-eluting stent implantatie haalbaar en veilig is bij patiënten met stabiel CAD. De ASET-studie (Acetyl Salicylic Elimination Trial) was een multicenter, eenarmige, open-label studie met een stopregel op basis van het optreden van definitieve stenttrombose (indien >3 zou de studie worden beëindigd). Patiënten die een succesvolle everolimus-afgevende stentimplantatie ondergingen voor stabiel CAD met SYNTAX-scores <23 werden geïncludeerd. Alle deelnemers waren op standaard dual-antiplatelet-therapie op het moment van index-PCI. Aspirine werd voorafgaand aan de procedure gegeven maar stopgezet op de dag van de indexprocedure; prasugrel werd direct na een succesvolle procedure in het katheterisatielaboratorium toegediend en vanaf dat moment werd prasugrel zonder aspirine het therapie regime. Patiënten werden gedurende 3 maanden uitsluitend met prasugrel behandeld. Bij 201 patiënten toonde prasugrel-monotherapie de haalbaarheid en veiligheid aan na succesvolle everolimus-afgevende stentimplantatie zonder enige stenttrombose bij geselecteerde laagrisicopatiënten met stabiel CAD. Deze bevindingen kunnen helpen bij het ondersteunen van grotere gerandomiseerde gecontroleerde onderzoeken om de aspirinevrije strategie te evalueren in vergelijking met traditionele dubbele antibloedplaatjestherapie na PCI.

Toekomstperspectieven

In de laatste 5 jaar follow-up van het SYTNTAX II-onderzoek blijven de voordelen van de beste praktijk PCI-strategie voor de novo 3VD behouden [12]. Er is een duidelijke verbetering in klinische resultaten tot 5 jaar na PCI binnen een tijdsverloop van 9 jaar tussen de inclusie van patiënten in de SYNTAX I en II studies. Vooraf gedefinieerde verkennende analyse vond geen significant verschil in ernstige ongunstige cardiale en cerebrovasculaire gebeurtenissen (MACCE) tussen SYNTAX II PCI en gelijksoortige SYNTAX I CABG-patiënten bij een follow-up

van 5 jaar. Over een periode van 5 tot 7 jaar wordt echter ook een significante verbetering van de gebeurtenisvrije overleving na CABG gesuggereerd in een propensity-matched analyse van patiënten gerandomiseerd naar CABG in de SYNTAX (inclusieperiode 2005 tot 2007) en EXCEL (inclusieperiode 2010 tot 2014) proeven [13].
Onlangs is de FAME 3-studie uitgevoerd om FFR-begeleide PCI, uitgevoerd met DES van de huidige generatie, te evalueren in vergelijking met CABG met betrekking tot de incidentie van MACCE bij patiënten met 3VD. In deze studie toonde FFR-begeleide PCI geen non-inferioriteit aan CABG in termen van MACCE na 1 jaar (10,6% vs. 6,9%, HR 1,5 [1,1-2,2], p voor non-inferioriteit = 0,35) [14]. Hoewel intravasculaire beeldvorming werd gebruikt bij slechts 12% van de patiënten die werden behandeld met PCI, en ultradunne DES werd niet gebruikt in de FAME 3-studie.
Deze bevindingen suggereren dat de beste PCI-praktijk richtlijnen moet worden bijgewerkt na de voltooiing van de SYNATX II-studie (inclusie periode 2014-2015). Volgens de bevindingen van dit proefschrift hebben we de mogelijkheid overwogen van verdere updates in individuele componenten van de beste praktijk PCI-strategie:
i) gebruik van ultradunne strut DES; ii) gebruik van angiografie afgeleide FFR-begeleide PCI; iii) nieuw antibloedplaatjesregime zoals korte DAPT gevolgd door krachtige P2Y12-monotherapie. Een nieuwe beste praktijk PCI-strategie, inclusief voorgestelde updates, zal worden geëvalueerd bij patiënten met 3VD in de lopende Multivessel TALENT-studie [15].
Naarmate de beste PCI-strategie evolueert, moeten we ook de haalbaarheid ervan in de dagelijkse klinische praktijk overwegen. Vanuit het dagelijkse praktijkperspectief maken de lage acceptatiegraad van intravasculaire beeldvorming en fysiologische beoordeling het moeilijk om de beste praktijk PCI-strategie te implementeren. Een angiografie afgeleide FFR kan operators helpen om fysiologische beoordeling uit te voeren, aangezien een van angiografie afgeleide FFR het gebruik van een drukdraad en hyperemie niet vereist, wat leidt tot kortere proceduretijden dan met een draad afgeleide FFR. In termen van minder invasieve onderzoeken zou FFRCT-afgeleide revascularisatie de ultieme optie zijn voor besluitvorming tussen CABG en PCI bij patiënten met 3VD. Het nut hiervan werd aangetoond in de SYNTAX III-studie, waar het combineren van niet-invasieve verworven anatomie en fysiologie van coronaire CT-angiografie en FFRCT hart-teams in staat stelde complexe coronaire revascularisatie te plannen bij patiënten met linker hoofdstam- of 3VD [16].

Summary of the thesis

Part A: Best practice in coronary revascularization of three-vessel disease

Despite the tremendous evolutions in drug eluting stent (DES), three-vessel disease (3VD) remains the most challenging subset of patients for PCI and the optimal stent implantation techniques and post-procedural anti-platelet therapy after PCI of the high-risk population are still to be determined [1]. Among several trials comparing coronary bypass grafting (CABG) with PCI in patients with 3VD, the pivotal SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trial identified CABG as the preferred revascularization strategy, compared with PCI with first-generation DES [2]. However, since the completed enrolment of SYNTAX-I in 2007 there have been major technical and procedural advances influencing outcomes after PCI. In **chapter 2** we reported 2-year outcome of the SYNTAX II trial. The SYNTAX II study was a multicenter, single-arm study that investigated the impact of a contemporary best practice PCI strategy (SYNTAX-II strategy) on clinical outcomes in 454 patients with de novo 3VD without left main disease. Clinical outcomes in SYNTAX II were compared to the predefined PCI (SYNTAX-I PCI) and CABG (SYNTAX-I CABG) cohorts from the landmark SYNTAX trial (SYNTAX-I), selected based on equipoise for long-term (four-year) mortality utilizing the SYNTAX score II [3-5]. The SYNTAX-II strategy includes: heart team decision-making utilizing the SYNTAX Score II (a clinical tool combining anatomical and clinical factors), coronary physiology guided revascularization, implantation of thin strut bioresorbable-polymer drug-eluting stents, intravascular ultrasound (IVUS) guided stent implantation, contemporary chronic total occlusion revascularization techniques and guideline-directed medical therapy. At two years, major adverse cardiac and cerebrovascular events (MACCE: a composite of all-cause death, any stroke, myocardial infarction, or revascularization) in SYNTAX II were significantly lower compared to SYNTAX-I PCI (13.2% vs. 21.9%, p=0.001). This difference was driven by a reduction of 66% in any MI and 38% in any revascularization. Furthermore, similar two-year outcomes for MACCE were evident between SYNTAX II PCI and SYNTAX-I CABG (13.2% vs. 15.1%, p=0.42). There has been a clear improvement in clinical outcomes up to 2 years after PCI within a 9-year lapse of time between the enrolment periods of the SYNTAX I and II.

Part B: Standardization of the assessment of the device success in the contemporary stent trials

The evolution of coronary stent has contributed most to the overall improvement of PCI performance. Use of second-generation DES is part of the best practice PCI strategy. Recently, a meta-analysis showed that DES with ultra-thin struts (strut thickness <70 μm) reduced the incidence of target lesion failure compared with that of contemporary second-generation DES with thicker struts[6]. The use of ultra-thin strut DES is likely to be part of best practice PCI strategy, but the mechanical ability of ultra-thin strut DES should be evaluated precisely. Therefore, in **chapter 3**, we performed a systematic evaluation of definitions and reporting of device success in clinical trials. Most PCI trials reporting on device success adopted the definition recommended by the European Commission and the U.S. Food and Drug Administration, but it is noteworthy that device success rates are not reported in the same fashion and are not reported in all studies. The most common variation is the definition of final in-stent residual stenosis, which ranges from <20% to <50%. We proposed an extended definition accounting for not only successful delivery and deployment but also successful balloon expansion and withdrawal of the delivery system. In addition, attainment of a final in-stent residual stenosis of <20% with final data reported by core

laboratory QCA (preferred methodology) is added to the extended definition according to the principal angiographic endpoints recommended by the ESC/EAPCI Task Force on the evaluation of coronary stents [7]. We also proposed special considerations such as lesion-based analysis issues, use of multiple devices, and lesion success versus device success.

In **chapter 4** we reported the primary endpoint of The TALENT trial, which was an all-comers randomized controlled trial to investigate non-inferiority of clinical outcomes after implantation of the ultra-thin strut Supraflex DES compared with the Xience DES. At 12 months, the primary endpoint of a device oriented composite endpoint had occurred in 35 patients (4.9 %) in the Supraflex group and in 37 patients (5.3%) in the Xience group. Non-inferiority of the Supraflex stent compared with the Xience stent was shown, with an absolute difference of –0.3% and one-sided 95% upper confidence bound of 1.6% (p for non-inferiority <0.0001, p for superiority=0.801). The device success proportion per lesion in both groups was high, but there was significant difference between the Supraflex and the Xience group (973 [97.6%] of 997 lesions vs 998 [99.5%] of 1003; difference –1·9%, 95% CI –3·0 to –0·9; p=0·0003). This difference was mainly driven by increased crossover to non-allocated stent in the Supraflex group compared with that in the Xience group. There were no differences in the residual in-stent stenosis of 30% or greater between groups. This difference in device success did not affect in-hospital patient outcomes (in-hospital device-oriented composite endpoint 11 [1.5%] of 720 patients vs 10 [1.4%] of 715; difference 0.1%, 95% CI –1.2 to 1.5; p=0.837). In the TALENT trial, the definition of device success is similar to the extended definition, with only a slight difference in the degree of a residual stenosis (<30%). Further trial is needed to demonstrate a superiority of ultra-thin strut DES compared to 2nd generation DES.

Part C: Assessment of optimal coronary artery stenting with intracoronary imaging

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have been developed and improved as both diagnostic and guidance tools for interventional procedures over the past three decades. IVUS has a resolution of 100μm with a high tissue penetration and capability of assessing the entire structure of a coronary artery including the external elastic membrane, whereas OCT has a higher resolution of 10–20 μm to assess endoluminal structures with a limited tissue penetration compared to IVUS [8]. In **chapter 5** we investigated the impact of minimal stent area (MSA) evaluated by post-procedural IVUS on clinical outcomes after best practice PCI among patients with 3VD in the SYNTAX II trial. In the SYNTAX II trial, post-procedural IVUS assessment was mandatory and performed in 84.1% of the patients (76.4% of the lesions) to optimize stent apposition, expansion and symmetry based on MUSIC criteria [9]. Among 819 lesions treated with best practice PCI strategy, larger post-procedural MSA was independently associated with the lower rate of target lesion revascularization (TLR) at 2 years (16/288 [5.6%], 12/265 [4.5%], and 4/266 [1.5%] [P = 0.042]). An MSA threshold of 5.2 mm^2 or less predicted TLR at 2 years by ROC analysis with a relatively low c-statistic of 0.620. In **chapter 6** we investigated clinical implication of 3-dimensional optical frequency domain imaging (3D-OFDI)-guided stenting for bifurcation lesions in the randomized OPTIMUM (Online 3-Dimensional Optical Frequency Domain Imaging to Optimize Bifurcation Stenting Using UltiMaster Stent) trial. In this trial, we reported excellent feasibility of online 3D-OFDI (98.2%) and superiority of Online 3D-OFDI-guided bifurcation PCI to angiography-guided bifurcation PCI in terms of acute incomplete stent apposition at bifurcation (19.5±15.8% versus 27.5±14.2%, P=0.008). Further trials are warranted to confirm the long-term clinical benefit of online 3D-OFDI guided stenting for bifurcation lesions.

Part D: Coronary physiology for optimal revascularization strategy

In the context of growing interest in functional assessment of coronary stenoses, advances in computational power and 3- dimensional coronary angiography have made possible the development of functional coronary angiography. In general, a mathematical formula related to the Lance Gould equation has been used for the process of computation [10]. One of the commercially available technologies is quantitative flow ratio (QFR) (Medis Medical Imaging System, Leiden, the Netherlands, and Pulse Medical Imaging Technology, Shanghai, China), which has the most published data, including prospective multicenter trials. In **chapter 7** all vessels treated in the SYNTAX II trial were retrospectively screened and analyzed for post-PCI QFR. In this analysis, a higher post-PCI QFR value (≥0.91) is associated with improved vessel-related clinical outcomes in best PCI practice for de novo 3VD (12.0% in post-PCI QFR <0.91 vs. 3.7% in post-PCI QFR ≥0.91; hazard ratio: 3.37; 95% confidence interval: 1.91 to 5.97; $p < 0.001$). According to this finding, achieving a post-PCI QFR value ≥0.91 in all treated vessels can be part of best practice PCI strategy when treating de novo 3VD.

In **chapter 8** we extensively reviewed clinical value of post-PCI physiological assessment. Post-PCI physiological assessment has 2 potential purposes in clinical practice. First, post-PCI physiological assessment can be used as a predictor of long-term clinical outcomes as investigated in **chapter 7**. Second, post-PCI physiological assessment can be used for the optimization of PCI result. Post-PCI physiological assessment may play a more important role for evaluation and localization of residual disease outside the stented segment rather than for stent optimization, for which intracoronary imaging is the established method. Further studies are warranted to assess whether further intervention for residual ischemia according to post-PCI physiological assessment can improve clinical outcomes.

Part E: Optimal antithrombotic therapy after stent implantation

In the SYNTAX II trial, dual antiplatelet therapy (DAPT) was continued in 99.3% of patients at 1month, 59.7% at 1 year, and 7.0% at 2 years. About 70% of patients received clopidogrel as P2Y12 inhibitor and P2Y12 inhibitor was rarely used as monotherapy after discontinuation of DAPT. After the completion of the SYNTAX II trial, several recent trials have shown promising results with a scheme comprising short DAPT duration followed by the administration of a P2Y12 antagonist as a single antiplatelet therapy, instead of aspirin[11]. Therefore, novel antithrombotic regimen after stenting should be adopted in best practice PCI strategy.

In **chapter 9** we investigated the clinical impact of ticagrelor monotherapy following 1-month DAPT after PCI for bifurcation lesions which are the one of the most challenging anatomical characteristics for PCI. In the GLOBAL LEADERS trial, among the 15,845 patients included in this subgroup analysis, 2,498 patients (15.8%) underwent PCI for at least one bifurcation lesion. After PCI for bifurcation lesions using 1-month of DAPT followed by ticagrelor monotherapy for 23 months was not associated with higher incidence of all-cause death or new Q-wave myocardial infarction compared with conventional DAPT strategy. However, abbreviated DAPT strategy was associated with a significant reduction in definite or probable stent thrombosis (p for interaction = .022) and a significant excess of stroke (p for interaction = .018) when compared with the reference treatment. Further evidence from dedicated bifurcation trial testing 1-month DAPT followed by P2Y12 monotherapy is warranted to further elucidate that possible duality of effect (such as possible prevention of ST and possible increase in stroke) in patients undergoing bifurcation PCI.

In **chapter 10** we evaluated the hypothesis that prasugrel monotherapy following successful everolimus-eluting stent implantation is feasible and safe in patients with stable CAD. The ASET

(Acetyl Salicylic Elimination Trial) trial was a multicenter, single-arm, open-label trial with a stopping rule based on the occurrence of definite stent thrombosis (if >3, trial enrollment would be terminated). Patients undergoing successful everolimus- eluting stent implantation for stable CAD with SYNTAX scores <23 were included. All participants were on standard dual-antiplatelet therapy at the time of index PCI. Aspirin was discontinued on the day of the index procedure but given prior to the procedure; prasugrel was administered in the catheterization laboratory immediately after the successful procedure, and aspirin-free prasugrel became the therapy regimen from that moment. Patients were treated solely with prasugrel for 3 months. In 201 patients, aspirin-free prasugrel monotherapy following successful everolimus-eluting stent implantation demonstrated feasibility and safety without any stent thrombosis in selected low-risk patients with stable CAD. These findings may help underpin larger randomized controlled studies to evaluate the aspirin-free strategy compared with traditional dual-antiplatelet therapy following PCI.

Future perspectives

In final 5 years follow-up of STNTAX II trial, the benefits of best practice PCI strategy for de novo 3VD are maintained [12]. There has been a clear improvement in clinical outcomes up to 5 years after PCI within a 9-year lapse of time between the enrolment periods of the SYNTAX I and II. Predefined exploratory analysis found no significant difference in major adverse cardiac and cerebrovascular events (MACCE) between SYNTAX II PCI and matched SYNTAX I CABG patients at 5-year follow-up. However, over a 5- to 7-year period, significant improvement in event-free survival after CABG is also suggested in a propensity-matched analysis of patients randomized to CABG in the SYNTAX (enrollment period 2005 to 2007) and EXCEL (enrollment period 2010 to 2014) trials [13].

Recently, the FAME 3 trial was conducted to evaluate FFR-guided PCI performed with current-generation DES as compared with CABG with respect to the incidence of MACCE among patients with 3VD. In this trial, FFR-guided PCI did not show noninferiority to CABG in terms of MACCE at 1 year (10.6% vs. 6.9%, HR 1.5 [1.1-2.2], p for noninferiority = 0.35) [14]. However, intravascular imaging was used in only 12% of the patients treated with PCI, and ultra-thin strut DES was not used in the FAME 3 trial.

These findings suggest that the best PCI practice should be updated after the completion of the SYNATX II trial (enrollment period 2014-2015). According to the finding of this thesis, we considered the possibility of further updates in individual components of the best practice PCI strategy:

i) use of ultra-thin strut DES; ii) angiography-derived FFR guided-PCI; iii) novel antiplatelet regimen such as short DAPT followed by potent P2Y12 monotherapy. A novel best practice PCI strategy including suggested updates will be evaluated among patients with 3VD in the ongoing Multivessel TALENT trial [15].

As the best PCI strategy evolves, we also need to consider its feasibility in routine clinical practice. From a daily practice perspective, the low adoption rates of intravascular imaging and physiological assessment make it difficult to implement the best practice PCI strategy. An angiography-derived FFR may prompt operators to perform physiological assessment, since an angiography-derived FFR do not require the use of a pressure wire and induced hyperemia, leading to shorter procedure times than wire-derived FFR. In terms of less invasive investigations, CT-derived FFR guided revascularization would be the ultimate option for decision making between CABG and PCI among patients with 3VD. The utility of this was demonstrated in the SYNTAX III trial, where combining non-invasively acquired anatomy and physiology from coronary CT angiography and FFR_{CT} allowed heart teams to plan complex coronary revascularization among patients with left main or 3VD [16].

References

1. 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.
2. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, Holmes DR, Jr., Curzen N, Davierwala P, Noack T, Milojevic M, Dawkins KD, da Costa BR, Juni P, Head SJ, Investigators SES. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019;**394**(10206):1325-1334.
3. 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.
4. Serruys PW, Chichareon P, Modolo R, Leaman DM, Reiber JHC, Emanuelsson H, Di Mario C, Pijls NHJ, Morel MA, Valgimigli M, Farooq V, van Klaveren D, Capodanno D, Andreini D, Bourantas CV, Davies J, Banning AP, Escaned J, Piek JJ, Echavarria-Pinto M, Taylor CA, Thomsen B, Collet C, Pompilio G, Bartorelli AL, Glocker B, Dressler O, Stone GW, Onuma Y. The SYNTAX score on its way out or ... towards artificial intelligence: part I. EuroIntervention 2020;**16**(1):44-59.
5. Serruys PW, Chichareon P, Modolo R, Leaman DM, Reiber JHC, Emanuelsson H, Di Mario C, Pijls NHJ, Morel MA, Valgimigli M, Farooq V, van Klaveren D, Capodanno D, Andreini D, Bourantas CV, Davies J, Banning AP, Escaned J, Piek JJ, Echavarria-Pinto M, Taylor CA, Thomsen B, Collet C, Pompilio G, Bartorelli AL, Glocker B, Dressler O, Stone GW, Onuma Y. The SYNTAX score on its way out or ... towards artificial intelligence: part II. EuroIntervention 2020;**16**(1):60-75.
6. Madhavan MV, Howard JP, Naqvi A, Ben-Yehuda O, Redfors B, Prasad M, Shahim B, Leon MB, Bangalore S, Stone GW, Ahmad Y. Long-term follow-up after ultrathin vs. conventional 2nd-generation drug-eluting stents: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J 2021;**42**(27):2643-2654.
7. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, Joner M, Oktay S, Juni P, Kastrati A, Sianos G, Stefanini GG, Wijns W, Windecker S. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur Heart J 2015;**36**(38):2608-20.
8. Ono M, Kawashima H, Hara H, Gao C, Wang R, Kogame N, Takahashi K, Chichareon P, Modolo R, Tomaniak M, Wykrzykowska JJ, Piek JJ, Mori I, Courtney BK, Wijns W, Sharif F, Bourantas C, Onuma Y, Serruys PW. Advances in IVUS/OCT and Future Clinical Perspective of Novel Hybrid Catheter System in Coronary Imaging. Front Cardiovasc Med 2020;**7**:119.
9. 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.
10. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circulation research 1978;**43**(2):242-53.

11. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J 2020.
12. Banning AP, Serruys P, De Maria GL, Ryan N, Walsh S, Gonzalo N, Jan van Geuns R, Onuma Y, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, Hoole SP, Piek JJ, Appleby C, Fath-Ordoubadi F, Zaman A, Van Mieghem NM, Uren N, Zueco J, Buszman P, Iniguez A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, de Vries T, Taggart D, Farooq V, Spitzer E, Tijssen J, Escaned J. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. Eur Heart J 2021.
13. Modolo R, Chichareon P, Kogame N, Dressler O, Crowley A, Ben-Yehuda O, Puskas J, Banning A, Taggart DP, Kappetein AP, Sabik JA, Onuma Y, Stone GW, Serruys PW. Contemporary Outcomes Following Coronary Artery Bypass Graft Surgery for Left Main Disease. J Am Coll Cardiol 2019;**73**(15):1877-1886.
14. Fearon WF, Zimmermann FM, De Bruyne B, Piroth Z, van Straten AHM, Szekely L, Davidavicius G, Kalinauskas G, Mansour S, Kharbanda R, Ostlund-Papadogeorgos N, Aminian A, Oldroyd KG, Al-Attar N, Jagic N, Dambrink JE, Kala P, Angeras O, MacCarthy P, Wendler O, Casselman F, Witt N, Mavromatis K, Miner SES, Sarma J, Engstrom T, Christiansen EH, Tonino PAL, Reardon MJ, Lu D, Ding VY, Kobayashi Y, Hlatky MA, Mahaffey KW, Desai M, Woo YJ, Yeung AC, Pijls NHJ, Investigators F. Fractional Flow Reserve-Guided PCI as Compared with Coronary Bypass Surgery. N Engl J Med 2022;**386**(2):128-137.
15. Hara H, Gao C, Kogame N, Ono M, Kawashima H, Wang R, Morel MA, O'Leary N, Sharif F, Mollmann H, Reiber JHC, Sabate M, Zaman A, Wijns W, Onuma Y, Serruys PW. A randomised controlled trial of the sirolimus-eluting biodegradable polymer ultra-thin Supraflex stent versus the everolimus-eluting biodegradable polymer SYNERGY stent for three-vessel coronary artery disease: rationale and design of the Multivessel TALENT trial. EuroIntervention 2020;**16**(12):e997-e1004.
16. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, La Meir M, Miyazaki Y, de Mey J, Gaemperli O, Ouda A, Maureira JP, Mandry D, Camenzind E, Macron L, Doenst T, Teichgraber U, Sigusch H, Asano T, Katagiri Y, Morel MA, Lindeboom W, Pontone G, Luscher TF, Bartorelli AL, Serruys PW. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. Eur Heart J 2018;**39**(41):3689-3698.

Appendices

Authors and affiliations
Curriculum vitae
Portfolio
List of publications
Acknowledgement

Authors and affiliations

Daniele Andreini	Centro Cardiologico Monzino, IRCCS, Milan, Italy; Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
Taku Asano	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
Adrian P. Banning	Department of Cardiology, John Radcliffe Hospital, Oxford, United Kingdom
Andreas Baumbach	Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom
Christos V Bourantas	Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom
Pawel E. Buszman	Center for Cardiovascular Research and Development, American Heart of Poland, Katowice, Poland
Robert A. Byrne	Cardiovascular Research Institute (CVRI), Mater Private Hospital and, School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin, Ireland
Carlos M Campos	Heart Institute - InCor, University of São Paulo, São Paulo, Brazil
Davide Capodanno	Division of Cardiology, C.A.S.T., P.O. “G. Rodolico”, Azienda Ospedaliero-Universitaria “Policlinico-Vittorio Emanuele”, Uni- versity of Catania, Catania, Italy

Rafael Cavalcante Boston Scientific, Marlborough, Massachusetts

Angel Cequier University Hospital of Bellvitge, Barcelona, Spain

Chun Chin Chang Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands

Ply Chichareon Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

Alaide Chieffo Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

Anirban Choudhury Department of Cardiology, University Hospital of Wales, Cardiff, UK

Carlos Collet Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium

Antonio Colombo Interventional Cardiology Unit, Villa Maria Cecila Hospital GVM, Cotignola (RA), Italy

Ignacio Cruz-Gonzalez Department of Cardiology, Hospital Universitario de Salamanca, Salamanca, Spain

Donald E. Cutlip Baim Institute for Clinical Research, Boston, MA, USA

Justin Davies	Department of Cardiology, Imperial College London, London, United Kingdom
Fernanda Barbosa de Almeida Sampaio	Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil
Giovanni Luigi De Maria	Department of Cardiology, John Radcliffe Hospital, Oxford, United Kingdom
Fernando De Martino	Department of Internal Medicine, Discipline of Cardiology, University of Triangulo Mineiro, Uberaba, Brazil
Kenneth De Wilder	Heart Centre, Imelda Hospital Bonheiden, Bonheiden, Belgium
Robbert J de Winter	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
Dariusz Dudek	Institute of Cardiology, Jagiellonian University, Krakow, Poland
Javier Escaned	Hospital Clinico San Carlos IDISSC and Universidad Complutense de Madrid, Madrid, Spain
Breno A A Falcão	Hospital Dr. Carlos Alberto Studart Gomes de Messejana, Fortaleza, Brazil
Vasim Farooq	The Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, United Kingdom

Farzin Fath-Ordoubadi Manchester Heart Centre, Manchester Royal Infirmary, Manchester University Foundation Trusts, Manchester, United Kingdom

Alan G. Fraser School of Medicine, Cardiff Univer- sity, University Hospital of Wales, Cardiff, United Kingdom

Scot Garg Department of Cardiology, Royal Blackburn Hospital, Blackburn, UK

Robert J Gil Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland

Javier Goicolea Department of Cardiology, Hospital Puerta de Hierro, Madrid, Spain

Patricia O Guimarães Heart Institute - InCor, University of São Paulo, São Paulo, Brazil.

Christian Hamm Kerckhoff Heart and Thorax Center, University of Giessen, Giessen, Germany

Hironori Hara Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

David Hildick-Smith Brighton & Sussex University Hospitals NHS Trust, Brighton, United Kingdom

Sjoerd Hofma Medical Centre Leeuwarden, Leeuwarden, Netherlands

Angela Hoye	Department of Academic Cardiology, University of Hull, Castle Hill Hospital, UK
Sander Ijsselmuiden	Amphia Ziekenhuis, Breda, Netherlands
Andres Iniguez	Department of Cardiology, Hospital Meixoeiro, Pontevedra, Spain
Luc Janssens	Heart Centre, Imelda Hospital Bonheiden, Bonheiden, Belgium
Peter Jüni	Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Ontario, Canada
Yuki Katagiri	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
Upendra Kaul	Academics and Research, Batra Hospital and Medical Research Center, New Delhi, India
Hideyuki Kawashima	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
Hidenori Komiyama	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
Mitchell W. Krucoff	Duke Clinical Research Institute, Durham, NC, USA

Neville Kukreja Department of Cardiology, East and North Hertfordshire NHS Trust, Hertfordshire, UK

Hiroyuki Kyono Division of Cardiology, Teikyo University School of Medicine, Tokyo, Japan

Alexandra Lansky Section for Cardiology, Yale University School of Medicine, New Haven, CT, USA

Jonathan Leipsic Department of Radiology, University of British Columbia, Vancouver, British Columbia, Canada

Rogerio S Leite Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia, Porto Alegre, Brazil

Pedro A Lemos Heart Institute - InCor, University of São Paulo, São Paulo, Brazil

Amir Lerman Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota

Maciej Lesiak 1st Department of Cardiology, University of Medical Sciences, Poznañ, Poland

Yves Louvard Department of Cardiology, Ramsay Générale de Santé, Institut Cardiovasculaire Paris Sud, Hopital Privé Jacques Cartier, Massy, France

Anthony Mathur Department of Cardiology, Barts Heart Centre, Barts Health NHS Trust, London, UK

Roxana Mehran	The Zena and Michael A. Wiener Cardiovascular Institute, The Icahn School of Medicine at Mount Sinai, New York, NY, USA
George C Meireles	Hospital do Servidor Público Estadual - IAMSPE, São Paulo, Brazil
Bela Merkely	Heart and Vascular Center, Semmelweis University, Budapest, Hungary
Yosuke Miyazaki	Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan
Rodrigo Modolo	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
Gustavo R Morais	Hospital Nossa Senhora das Neves, João Pessoa, Brazil
Marie-Angèle Morel	Department of Cardiology, National University of Ireland, Galway (NUIG) and CORRIB Corelab and Center for Research and Imaging, Galway, Ireland.
Raul Moreno	Cardiology Department, La Paz University Hospital, Madrid, Spain
Bruno Moulin	Associação Evangélica Beneficiente Espírito Santense, Vila Velha, Brazil
Takashi Muramatsu	Department of Cardiology, Cardiovascular Center, Fujita Health University Hospital, Toyoake, Japan

Shimpei Nakatani Department of Cardiology, Osaka Police Hospital, Japan

Andrzej Ochala Medical University of Silesia, Katowice, Poland

Takayuki Okamura Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan

Masafumi Ono Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

Yoshinobu Onuma Department of Cardiology, National University of Ireland Galway, Galway, Ireland

Yukio Ozaki Department of Cardiology, Cardiovascular Center, Fujita Health University Hospital, Toyoake, Japan

Manesh R Patel Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina

Ivo Petrov Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria

Jan J. Piek Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

Janusz Prokopczuk PAKS Kędzierzyn, Koźle, Poland

Johan H C Reiber	Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands
Expedito E Ribeiro	Heart Institute - InCor, University of São Paulo, São Paulo, Brazil
Manel Sabate	Thorax Institute, Hospital Clinic I Provincial de Barcelona, Barcelona, Spain
Antonio Serra	Unidad de Cardiología Intervencionista, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Patrick W. Serruys	Department of Cardiology, National University of Ireland Galway, Galway, Ireland
Faisal Sharif	Department of Cardiology, National University of Ireland Galway, Galway, Ireland
Pieter C Smits	Maasstad Ziekenhuis, Rotterdam, Netherlands
Osama Soliman	Department of Cardiology, National University of Ireland Galway, Galway, Ireland
Yohei Sotomi	Department of Cardiology, Osaka Police Hospital, Japan
Ernest Spitzer	Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands

Rod Stables Institute of Cardiovascular Medicine and Science, Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, United Kingdom

Philippe G Steg French Alliance for Cardiovascular Trials (FACT), Université Paris-Diderot, Paris, France

Hans-Peter Stoll Biosensors Clinical Research, Morges, Switzerland

Gregg W. Stone The Zena and Michael A. Wiener Cardiovascular Institute, The Icahn School of Medicine at Mount Sinai, New York, NY, USA

Kuniaki Takahashi Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

Joao Tinoco Instituto Cardiovascular de Linhares LTDA - UNICOR, Linhares, Brazil

Mariusz Tomaniak Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands

Gincho Tonev Multi-profile Hospital for Active Treatment, St George's University, Plovdiv, Bulgaria

Pim Tonino Department of Cardiology, Catharina Hospital, Eindhoven, Netherlands

Shengxian Tu Med-X Research Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

Imre Ungi	Division of Invasive Cardiology, Second Department of Internal Medicine and Cardiology Center, University of Szeged, Szeged, Hungary
Marco Valgimigli	Department of Cardiology, Inselspital, University of Bern, Bern, Switzerland
Robert-Jan van Geuns	Cardiology Department, Radboud UMC, Nijmegen, the Netherlands
Pascal Vranckx	Faculty of Medicine and Life Sciences, Jessa Ziekenhuis, the Hasselt University, Hasselt, Belgium
Simon Walsh	Department of Cardiology Belfast Health & Social Care Trust, Belfast, UK
Rutao Wang	Department of Cardiology, Radboud University, Nijmegen, the Netherlands
Nick E J West	Department of Interventional Cardiology, Royal Papworth Hospital, Cambridge, United Kingdom
William Wijns	The Lambe Institute for Translational Medicine and Curam, National University of Ireland Galway, Galway, Ireland; Saolta University Healthcare Group, University College Hospital Galway, Galway, Ireland
Stephan Windecker	Swiss Cardiovascular Center Bern, Bern University Hospital, Bern, Switzerland
Joanna J. Wykrzykowska	Amsterdam UMC, University of Amsterdam, Heart Center; department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

Bo Xu Fu Wai Hospital, National Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China

Azfar Zaman Freeman Hospital, Newcastle University, and Newcastle upon Tyne Hospitals NHS Trust, Newcastle, UK

Aleksander Zurakowski Małopolskie Centrum Sercowo-Naczyniowe PAKS, Chrzanow, Poland

CURRICULUM VITAE

Norihiro Kogame
Date and Place of Birth: 13 Dec. 1982, Okayama, Japan
Nationality: Japan
E-mail: kamexon@gmail.com

Education

2001-2007	School of Medicine, Toho University, Tokyo, Japan

Training and Work Experience

2007 – 2009	Resident program in Toho University Ohashi Medical Center, Tokyo, Japan.
2009	Division of Respiratory Medicine, Tokyo National Hospital, Tokyo, Japan.
2009 – 2010	Division of Gastroenterological Medicine, Kohsei Chuo General Hospital, Tokyo, Japan.
2010 – 2011	Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan.
2011 – 2015	Division of Cardiology, Ota Memorial Hospital, Ota, Japan.
2015 – 2017	Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan.
2018 – 2019	Research Fellow at Amsterdam University Medical Center, Amsterdam, the Netherland.
2020 – present	Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan.

License and Certification

2011	Board Certified Membership of the Japanese Society of Internal Medicine
2014	CVIT board-certified cardiovascular interventionist
2017	Board Certified Membership of the Japanese Society of Cardiology

Academic Membership

Japanese Association of Cardiovascular Intervention and Therapeutics
The Japanese Circulation Society
The Japanese Society of Internal Medicine

PhD PORTFOLIO

PhD student: Norihiro Kogame
PhD period: January 2018 – December 2019
Supervisors: prof. dr. J.J. Piek and prof. dr. P.W.J.C. Serruys
Co-supervisors: dr. J.J. Wykrzykowska and prof. dr. Y. Onuma

PhD training	Year	ECTS
Presentations and international conferences*		
EuroPCR, Paris, France (attendant)	2018	1.0
Transcatheter Cardiovascular Therapeutics (TCT), San Diego, US (2 oral presentations)	2018	2.25
EuroPCR, Paris, France (3 poster presentations)	2019	2.5
European Society of Cardiology (ESC) scientific sessions, Paris, France (1 oral presentation)	2019	1.75
Transcatheter Cardiovascular Therapeutics (TCT), San Francisco, US (1 oral presentation)	2019	1.75
Other academic activities		
Local associated editor and regular reviewer for EuroIntervention and AsiaIntervention	2018 - 2020	3.0

*Presentation at scientific conference (oral or poster) = 0.5 ECTS, Visiting scientific conference (per day) = 0.25 ECTS.

LIST OF PUBLICATIONS
Included in thesis

1. Serruys PW*, Kogame N*, Katagiri Y, Modolo R, Buszman PE, Íñiguez-Romo A, Goicolea J, Hildick-Smith D, Ochala A, Dudek D, Piek JJ, Wykrzykowska JJ, Escaned J, Banning AP, Farooq V, Onuma Y. Clinical outcomes of state-of-the-art percutaneous coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019;15(3):e244-e252. *Authors contributed equally

2. Katagiri Y, De Maria GL, Kogame N, Chichareon P, Takahashi K, Chang CC, Modolo R, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, West NEJ, Piek JJ, Wykrzykowska JJ, Farooq V, Escaned J, Banning AP, Onuma Y, Serruys PW. Impact of post-procedural minimal stent area on 2-year clinical outcomes in the SYNTAX II trial. Catheter Cardiovasc Interv 2019;93(4):E225-e234.

3. Zaman A, de Winter RJ, Kogame N, Chang CC, Modolo R, Spitzer E, Tonino P, Hofma S, Zurakowski A, Smits PC, Prokopczuk J, Moreno R, Choudhury A, Petrov I, Cequier A, Kukreja N, Hoye A, Iniguez A, Ungi I, Serra A, Gil RJ, Walsh S, Tonev G, Mathur A, Merkely B, Colombo A, Ijsselmuiden S, Soliman O, Kaul U, Onuma Y, Serruys PW. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherosclerotic lesions (TALENT): a prospective multicentre randomised controlled trial. Lancet 2019;393(10175):987-997.

4. Kogame N, Takahashi K, Tomaniak M, Chichareon P, Modolo R, Chang CC, Komiyama H, Katagiri Y, Asano T, Stables R, Fath-Ordoubadi F, Walsh S, Sabaté M, Davies JE, Piek JJ, van Geuns RJ, Reiber JHC, Banning AP, Escaned J, Farooq V, Serruys PW, Onuma Y. Clinical Implication of Quantitative Flow Ratio After Percutaneous Coronary Intervention for 3-Vessel Disease. JACC Cardiovasc Interv 2019;12(20):2064-2075.

5. Onuma Y*, Kogame N*, Sotomi Y, Miyazaki Y, Asano T, Takahashi K, Kawashima H, Ono M, Katagiri Y, Kyono H, Nakatani S, Muramatsu T, Sharif F, Ozaki Y, Serruys PW, Okamura T. A Randomized Trial Evaluating Online 3-Dimensional Optical Frequency Domain Imaging-Guided Percutaneous Coronary Intervention in Bifurcation Lesions. Circ Cardiovasc Interv 2020;13(12):e009183. *Authors contributed equally

6. Chang CC*, Kogame N*, Onuma Y, Byrne RA, Capodanno D, Windecker S, Morel MA, Cutlip DE, Krucoff MW, Stone GW, Lansky AJ, Mehran R, Spitzer E, Fraser AG, Baumbach A, Serruys PW. Defining device success for percutaneous coronary intervention trials: a position statement from the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. EuroIntervention 2020;15(13):1190-1198. *Authors contributed equally

7. Kogame N, Chichareon P, De Wilder K, Takahashi K, Modolo R, Chang CC, Tomaniak M, Komiyama H, Chieffo A, Colombo A, Garg S, Louvard Y, Jüni P, P GS, Hamm C, Vranckx P, Valgimigli M, Windecker S, Stoll HP, Onuma Y, Janssens L, Serruys PW. Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: Insight from GLOBAL LEADERS trial. Catheter Cardiovasc Interv 2020;96(1):100-111.

8. Kogame N, Ono M, Kawashima H, Tomaniak M, Hara H, Leipsic J, Andreini D, Collet C, Patel MR, Tu S, Xu B, Bourantas CV, Lerman A, Piek JJ, Davies JE, Escaned J, Wijns W, Onuma Y, Serruys PW. The Impact of Coronary Physiology on Contemporary Clinical Decision Making. JACC Cardiovasc Interv 2020;13(14):1617-1638.

9. Kogame N, Guimarães PO, Modolo R, De Martino F, Tinoco J, Ribeiro EE, Kawashima H, Ono M, Hara H, Wang R, Cavalcante R, Moulin B, Falcão BAA, Leite RS, de Almeida Sampaio FB, Morais GR, Meireles GC, Campos CM, Onuma Y, Serruys PW, Lemos PA. Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD: The ASET Pilot Study. JACC Cardiovasc Interv 2020;13(19):2251-2262.

Published articles, not included in thesis

10. 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(1):113-9.

11. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Impact of carotid artery ultrasound and ankle-brachial index on prediction of severity of SYNTAX score. Circ J 2013;77(3):712-6.

12. Nakamura M, Kogame N, Iijima R, Ono T, Ikeda N, Tokue M, Hayashi F, Watanabe M, Takenaka H, Fukui R, Hara H. Individualized antiplatelet therapy after drug-eluting stent deployment: Implication of clinical trials of different durations of dual antiplatelet therapy. J Cardiol 2017;70(6):511-517.

13. Niikura H, Iijima R, Anzai H, Kogame N, Fukui R, Takenaka H, Kobayashi N. Clinical utility of early use of tolvaptan in very elderly patients with acute decompensated heart failure. Anatol J Cardiol 2017;18(3):206-212.

14. Asano T, Jin Q, Katagiri Y, Kogame N, Takahashi K, Chang CC, Chichareon P, Wang C, Shi B, Su X, Fu G, Wu Y, Zhou X, Yuan Z, Wykrzykowska JJ, Piek JJ, Serruys PW, Onuma Y, Chen Y. A randomised comparison of healing response between the BuMA Supreme stent and the XIENCE stent at one-month and two-month follow-up: PIONEER-II OCT randomised controlled trial. EuroIntervention 2018;14(12):e1306-e1315.

15. Iijima R, Kogame N, Hara H, Moroi M, Nakamura M. Clinical Outcomes of Drug-Coated Balloons in Coronary Artery Disease Unsuitable for Drug-Eluting Stent Implantation. Circ J 2018;82(8):2025-2031.

16. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940-949.

17. Komiyama H, Modolo R, Chang CC, Chichareon P, Kogame N, Takahashi K, Tomaniak M, Onuma Y, Cuisset T, Fajadet J, Amin H, Al Rashdan I, Serruys PW. Interventional cardiology 2018: the year in review. EuroIntervention 2019;14(18):e1861-e1878.

18. Onuma Y, Kogame N, Serruys PW. Unconfirmed Very Long-Term Clinical Benefit of Xience Over Cypher: Should We Reset Our Vision? JACC Cardiovasc Interv 2019;12(7):648-650.

19. Modolo R, Chichareon P, Kogame N, Dressler O, Crowley A, Ben-Yehuda O, Puskas J, Banning A, Taggart DP, Kappetein AP, Sabik JA, Onuma Y, Stone GW, Serruys PW. Contemporary Outcomes

Following Coronary Artery Bypass Graft Surgery for Left Main Disease. J Am Coll Cardiol 2019;73(15):1877-1886.

20. Chichareon P, Onuma Y, van Klaveren D, Modolo R, Kogame N, Takahashi K, Chang CC, Tomaniak M, Asano T, Katagiri Y, van Geuns RM, Bolognese L, Tumscitz C, Vrolix M, Petrov I, Garg S, Naber CK, Sabaté M, Iqbal J, Wykrzykowska JJ, Piek JJ, Spitzer E, Jüni P, Hamm C, Steg PG, Valgimigli M, Vranckx P, Windecker S, Serruys PW. Validation of the updated logistic clinical SYNTAX score for all-cause mortality in the GLOBAL LEADERS trial. EuroIntervention 2019;15(6):e539-e546.

21. Kogame N, Modolo R, Tomaniak M, Cavalcante R, de Martino F, Tinoco J, Ribeiro EE, Mehran R, Campos CM, Onuma Y, Lemos PA, Serruys PW. Prasugrel monotherapy after PCI with the SYNERGY stent in patients with chronic stable angina or stabilised acute coronary syndromes: rationale and design of the ASET pilot study. EuroIntervention 2019;15(6):e547-e550.

22. Serruys PW, Takahashi K, Chichareon P, Kogame N, Tomaniak M, Modolo R, Chang CC, Komiyama H, Soliman O, Wykrzykowska JJ, de Winter RJ, Ferrario M, Dominici M, Buszman P, Bolognese L, Tumscitz C, Benit E, Stoll HP, Hamm C, Steg PG, Onuma Y, Jüni P, Windecker S, Vranckx P, Colombo A, Valgimigli M. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. Eur Heart J 2019;40(31):2595-2604.

23. Chang CC, Spitzer E, Chichareon P, Takahashi K, Modolo R, Kogame N, Tomaniak M, Komiyama H, Yap SC, Hoole SP, Gori T, Zaman A, Frey B, Ferreira RC, Bertrand OF, Koh TH, Sousa A, Moschovitis A, van Geuns RJ, Steg PG, Hamm C, Jüni P, Vranckx P, Valgimigli M, Windecker S, Serruys PW, Soliman O, Onuma Y. Ascertainment of Silent Myocardial Infarction in Patients Undergoing Percutaneous Coronary Intervention (from the GLOBAL LEADERS Trial). Am J Cardiol 2019;124(12):1833-1840.

24. Serruys PW, Tomaniak M, Chichareon P, Modolo R, Kogame N, Takahashi K, Chang CC, Spitzer E, Walsh SJ, Adlam D, Hildick-Smith D, Édes I, van de Harst P, Krackhardt F, Tijssen JGP, Rademaker-Havinga T, Garg S, Steg PG, Hamm C, Jüni P, Vranckx P, Onuma Y, Verheugt FWA. Patient-oriented composite endpoints and net adverse clinical events with ticagrelor monotherapy following percutaneous coronary intervention: insights from the randomised GLOBAL LEADERS trial. EuroIntervention 2019;15(12):e1090-e1098.

25. Asano T, Katagiri Y, Chang CC, Kogame N, Chichareon P, Takahashi K, Modolo R, Tenekecioglu E, Collet C, Jonker H, Appleby C, Zaman A, van Mieghem N, Uren N, Zueco J, Piek JJ, Reiber JHC, Farooq V, Escaned J, Banning AP, Serruys PW, Onuma Y. Angiography-Derived Fractional Flow Reserve in the SYNTAX II Trial: Feasibility, Diagnostic Performance of Quantitative Flow Ratio, and Clinical Prognostic Value of Functional SYNTAX Score Derived From Quantitative Flow Ratio in Patients With 3-Vessel Disease. JACC Cardiovasc Interv 2019;12(3):259-270.

26. Asano T, Hytönen J, Chichareon P, Taavitsainen J, Kogame N, Katagiri Y, Miyazaki Y, Takahashi K, Modolo R, Komiyama H, Tenekecioglu E, Sotomi Y, Wykrzykowska JJ, Piek JJ, Martin J, Baumbach A, Mathur A, Onuma Y, Ylä-Herttuala S, Serruys PW. Serial Optical Coherence Tomography at Baseline, 7 Days, and 1, 3, 6 and 12 Months After Bioresorbable Scaffold Implantation in a Growing Porcine Model. Circ J 2019;83(3):556-566.

27. Tijssen RYG, Kerkmeijer LSM, Katagiri Y, Kraak RP, Takahashi K, Kogame N, Chichareon P, Modolo R, Asano T, Nassif M, Kalkman DN, Sotomi Y, Collet C, Hofma SH, van der Schaaf RJ, Arkenbout EK, Weevers A, Beijk MAM, Piek JJ, Tijssen JGP, Henriques JP, de Winter RJ, Onuma Y,

Serruys PW, Wykrzykowska JJ. The relationship of pre-procedural Dmax based sizing to lesion level outcomes in Absorb BVS and Xience EES treated patients in the AIDA trial. The international journal of cardiovascular imaging 2019;35(7):1189-1198.

28. Chichareon P, Modolo R, van Klaveren D, Takahashi K, Kogame N, Chang CC, Katagiri Y, Tomaniak M, Asano T, Spitzer E, Buszman P, Prokopczuk J, Fath-Ordoubadi F, Buysschaert I, Anderson R, Oldroyd KG, Merkely B, Garg S, Wykrzykowska JJ, Piek JJ, Jüni P, Hamm C, Steg PG, Valgimigli M, Vranckx P, Windecker S, Onuma Y, Serruys PW. Predictive ability of ACEF and ACEF II score in patients undergoing percutaneous coronary intervention in the GLOBAL LEADERS study. International journal of cardiology 2019;286:43-50.

29. Modolo R, Chichareon P, Kogame N, Asano T, Chang CC, de Winter RJ, Kaul U, Zaman A, Spitzer E, Takahashi K, Katagiri Y, Soliman OII, van Es GA, Morel MA, Onuma Y, Serruys PW. A prospective multicentre randomised all-comers trial to assess the safety and effectiveness of the thin-strut sirolimus-eluting coronary stent SUPRAFLEX: rationale and design of the Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent (TALENT) trial. EuroIntervention 2019;15(4):e362-e369.

30. Chichareon P, Katagiri Y, Asano T, Takahashi K, Kogame N, Modolo R, Tenekecioglu E, Chang CC, Tomaniak M, Kukreja N, Wykrzykowska JJ, Piek JJ, Serruys PW, Onuma Y. Mechanical properties and performances of contemporary drug-eluting stent: focus on the metallic backbone. Expert review of medical devices 2019;16(3):211-228.

31. Sonck J, Miyazaki Y, Collet C, Onuma Y, Asano T, Takahashi K, Kogame N, Katagiri Y, Modolo R, Serruys PW, Bartorelli AL, Andreini D, Doenst T, Maureira JP, Plass A, La Meir M, Pompillio G. Feasibility of planning coronary artery bypass grafting based only on coronary computed tomography angiography and CT-derived fractional flow reserve: a pilot survey of the surgeons involved in the randomized SYNTAX III Revolution trial. Interact Cardiovasc Thorac Surg 2019.

32. Katagiri Y, Serruys PW, Asano T, Miyazaki Y, Chichareon P, Modolo R, Takahashi K, Kogame N, Wykrzykowska JJ, Piek JJ, Onuma Y. How does the failure of Absorb apply to the other bioresorbable scaffolds? An expert review of first-in-man and pivotal trials. EuroIntervention 2019;15(1):116-123.

33. Tomaniak M, Chichareon P, Onuma Y, Deliargyris EN, Takahashi K, Kogame N, Modolo R, Chang CC, Rademaker-Havinga T, Storey RF, Dangas GD, Bhatt DL, Angiolillo DJ, Hamm C, Valgimigli M, Windecker S, Steg PG, Vranckx P, Serruys PW. Benefit and Risks of Aspirin in Addition to Ticagrelor in Acute Coronary Syndromes: A Post Hoc Analysis of the Randomized GLOBAL LEADERS Trial. JAMA Cardiol 2019;4(11):1092-1101.

34. Takahashi K, Serruys PW, Chichareon P, Chang CC, Tomaniak M, Modolo R, Kogame N, Magro M, Chowdhary S, Eitel I, Zweiker R, Ong P, Ottesen MM, Tijssen JGP, Wykrzykowska JJ, de Winter RJ, Garg S, Stoll HP, Hamm C, Steg PG, Onuma Y, Valgimigli M, Vranckx P, Carrie D, Windecker S. Efficacy and Safety of Ticagrelor Monotherapy in Patients Undergoing Multivessel PCI. J Am Coll Cardiol 2019;74(16):2015-2027.

35. Serruys PW, Kogame N, Onuma Y. Was the Ball Inside or Outside the Court?: Ask the Hawk-Eye System. JACC Cardiovasc Interv 2019;12(20):2089-2092.

36. Ono M, Kawashima H, Hara H, Gao C, Wang R, Kogame N, Takahashi K, Chichareon P, Modolo R, Tomaniak M, Wykrzykowska JJ, Piek JJ, Mori I, Courtney BK, Wijns W, Sharif F, Bourantas

C, Onuma Y, Serruys PW. Advances in IVUS/OCT and Future Clinical Perspective of Novel Hybrid Catheter System in Coronary Imaging. Front Cardiovasc Med 2020;7:119.

37. Tijssen RYG, Kerkmeijer LSM, Takahashi K, Kogame N, Katagiri Y, Kraak RP, Chichareon P, Modolo R, Asano T, Nassif M, Kalkman DN, Sotomi Y, Collet C, Hofma SH, van der Schaaf RJ, Arkenbout EK, Weevers A, Piek JJ, Tijssen JGP, Henriques JP, de Winter RJ, Onuma Y, Serruys PW, Wykrzykowska JJ. The influence of implantation techniques on lesion oriented-outcomes in Absorb BVS and Xience EES lesions treated in routine clinical practice at complete three year follow-up: AIDA trial QCA substudy. The international journal of cardiovascular imaging 2020;36(4):565-575.

38. Tomaniak M, Chichareon P, Modolo R, Takahashi K, Chang CC, Kogame N, Spitzer E, Buszman PE, van Geuns RM, Valkov V, Steinwender C, Geisler T, Prokopczuk J, Sabaté M, Zmudka K, Rademaker-Havinga T, Tijssen JGP, Jüni P, Hamm C, Steg PG, Onuma Y, Vranckx P, Valgimigli M, Windecker S, Baber U, Anderson R, Dominici M, Serruys PW. Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a pre-specified analysis of the GLOBAL LEADERS trial. EuroIntervention 2020;15(18):e1605-e1614.

39. Hara H, van Klaveren D, Takahashi K, Kogame N, Chichareon P, Modolo R, Tomaniak M, Ono M, Kawashima H, Wang R, Gao C, Niethammer M, Fontos G, Angioi M, Ribeiro VG, Barbato E, Leandro S, Hamm C, Valgimigli M, Windecker S, Jüni P, Steg PG, Verbeeck J, Tijssen JGP, Sharif F, Onuma Y, Serruys PW. Comparative Methodological Assessment of the Randomized GLOBAL LEADERS Trial Using Total Ischemic and Bleeding Events. Circ Cardiovasc Qual Outcomes 2020;13(8):e006660.

40. Garg S, Chichareon P, Kogame N, Takahashi K, Modolo R, Chang CC, Tomaniak M, Fath-Ordoubadi F, Anderson R, Oldroyd KG, Stables RH, Kukreja N, Chowdhary S, Galasko G, Hoole S, Zaman A, Hamm CW, Steg PG, Jüni P, Valgimigli M, Windecker S, Onuma Y, Serruys PW. Impact of established cardiovascular disease on outcomes in the randomized global leaders trial. Catheter Cardiovasc Interv 2020;96(7):1369-1378.

41. Chang CC, Kogame N, Asano T, von Birgelen C, Sabaté M, Onuma Y, Serruys PW. BuMA Supreme biodegradable polymer sirolimus-eluting stent versus a durable polymer zotarolimus-eluting coronary stent: three-year clinical outcomes of the PIONEER trial. EuroIntervention 2020;16(11):e900-e903.

42. Hara H, Gao C, Kogame N, Ono M, Kawashima H, Wang R, Morel MA, O'Leary N, Sharif F, Möllmann H, Reiber JHC, Sabaté M, Zaman A, Wijns W, Onuma Y, Serruys PW. A randomised controlled trial of the sirolimus-eluting biodegradable polymer ultra-thin Supraflex stent versus the everolimus-eluting biodegradable polymer SYNERGY stent for three-vessel coronary artery disease: rationale and design of the Multivessel TALENT trial. EuroIntervention 2020;16(12):e997-e1004.

43. Chichareon P, Modolo R, Kogame N, Takahashi K, Chang CC, Tomaniak M, Botelho R, Eeckhout E, Hofma S, Trendafilova-Lazarova D, Kőszegi Z, Iñiguez A, Wykrzykowska JJ, Piek JJ, Garg S, Hamm C, Steg PG, Jüni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Serruys PW. Association of diabetes with outcomes in patients undergoing contemporary percutaneous coronary intervention: Pre-specified subgroup analysis from the randomized GLOBAL LEADERS study. Atherosclerosis 2020;295:45-53.

44. Kogame N, Serruys PW, Onuma Y. Cracking (the code of) coronary artery calcification to win the last battle of percutaneous coronary intervention: still in the middle of a rocky road. Eur Heart J 2020;41(6):797-800.

45. Katagiri Y, Onuma Y, Lurz P, Buszman P, Piek JJ, Wykrzykowska JJ, Asano T, Kogame N, Takahashi K, Chang CC, de Winter RJ, Serruys PW, Wijns W. Clinical outcomes of bioabsorbable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents: two-year follow-up of the DESSOLVE III trial. EuroIntervention 2020;15(15):e1366-e1374.

46. Chang CC, Chichareon P, Modolo R, Takahashi K, Kogame N, Tomaniak M, Gao C, Royaards KJ, Cequier A, Oldroyd K, Steg PG, Hamm C, Jüni P, Valgimigli M, Windecker S, Onuma Y, Stables RH, Jan van Geuns R, Serruys PW. Association between post-percutaneous coronary intervention bivalirudin infusion and net adverse clinical events: a post hoc analysis of the GLOBAL LEADERS study. Eur Heart J Cardiovasc Pharmacother 2020;6(1):22-30.

47. Chichareon P, Modolo R, Kerkmeijer L, Tomaniak M, Kogame N, Takahashi K, Chang CC, Komiyama H, Moccetti T, Talwar S, Colombo A, Maillard L, Barlis P, Wykrzykowska J, Piek JJ, Garg S, Hamm C, Steg PG, Jüni P, Valgimigli M, Windecker S, Onuma Y, Mehran R, Serruys PW. Association of Sex With Outcomes in Patients Undergoing Percutaneous Coronary Intervention: A Subgroup Analysis of the GLOBAL LEADERS Randomized Clinical Trial. JAMA Cardiol 2020;5(1):21-29.

48. Kawashima H, Ono M, Kogame N, Takahashi K, Chang CC, Hara H, Gao C, Wang R, Tomaniak M, Modolo R, Wykrzykowska JJ, De Winter RJ, Sharif F, Serruys PW, Onuma Y. Drug-eluting bioresorbable scaffolds in cardiovascular disease, peripheral artery and gastrointestinal fields: a clinical update. Expert opinion on drug delivery 2020;17(7):931-945.

49. Modolo R*, Kogame N*, Komiyama H, Chichareon P, de Vries T, Tomaniak M, Chang CC, Takahashi K, Walsh S, Lesiak M, Moreno R, Farrooq V, Escaned J, Banning A, Onuma Y, Serruys PW. Two years clinical outcomes with the state-of-the-art PCI for the treatment of bifurcation lesions: A sub-analysis of the SYNTAX II study. Catheter Cardiovasc Interv 2020;96(1):10-17. *Authors contributed equally

50. Takahashi K, Kogame N, Tomaniak M, Chichareon P, Chang CC, Modolo R, Benit E, Liebetrau C, Janssens L, Ferrario M, Zurakowski A, van Geuns RJ, Dominici M, Huber K, Buszman P, Bolognese L, Tumscitz C, Żmudka K, Aminian A, Vrolix M, Petrov I, Wykrzykowska JJ, de Winter RJ, Hamm C, Steg PG, Onuma Y, Valgimigli M, Windecker S, Vranckx P, Garg S, Serruys PW. Impact of recruitment and retention on all-cause mortality in a large all-comers randomised controlled trial: insights from the GLOBAL LEADERS trial. Clin Res Cardiol 2020;109(7):918-929.

51. Tomaniak M, Chichareon P, Klimczak-Tomaniak D, Takahashi K, Kogame N, Modolo R, Wang R, Ono M, Hara H, Gao C, Kawashima H, Rademaker-Havinga T, Garg S, Curzen N, Haude M, Kochman J, Gori T, Montalescot G, Angiolillo DJ, Capodanno D, Storey RF, Hamm C, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Serruys PW, Anderson R. Impact of renal function on clinical outcomes after PCI in ACS and stable CAD patients treated with ticagrelor: a prespecified analysis of the GLOBAL LEADERS randomized clinical trial. Clin Res Cardiol 2020;109(7):930-943.

52. Tomaniak M, Chichareon P, Takahashi K, Kogame N, Modolo R, Chang CC, Spitzer E, Neumann FJ, Plante S, Hernández Antolin R, Jambrik Z, Gelev V, Brunel P, Konteva M, Beygui F, Morelle JF, Filipiak KJ, van Geuns RJ, Soliman O, Tijssen J, Rademaker-Havinga T, Storey RF, Hamm C, Steg PG, Windecker S, Onuma Y, Valgimigli M, Serruys PW. Impact of chronic obstructive pulmonary disease and dyspnoea on clinical outcomes in ticagrelor treated patients undergoing percutaneous coronary intervention in the randomized GLOBAL LEADERS trial. Eur Heart J Cardiovasc Pharmacother 2020;6(4):222-230.

53. Takahashi K, Serruys PW, Kogame N, Buszman P, Lurz P, Jessurun GAJ, Koch KT, Troquay RPT, Hamer BJB, Oude Ophuis T, Milewski KP, Hofma SH, Wykrzykowska JJ, Onuma Y, de Winter RJ, Wijns W. Final 3-Year Outcomes of MiStent Biodegradable Polymer Crystalline Sirolimus-Eluting Stent Versus Xience Permanent Polymer Everolimus-Eluting Stent: Insights From the DESSOLVE III All-Comers Randomized Trial. Circ Cardiovasc Interv 2020;13(6):e008737.

54. Wang R, Takahashi K, Chichareon P, Gao C, Kogame N, Modolo R, Tomaniak M, Kawashima H, Ono M, Hara H, Schächinger V, Tonev G, Ungi I, Botelho R, Eeckhout E, Hamm C, Jüni P, Vranckx P, Windecker S, Garg S, Van Geuns RJ, Onuma Y, Serruys PW. The impact of pre-procedure heart rate on adverse clinical outcomes in patients undergoing percutaneous coronary intervention: Results from a 2-year follow-up of the GLOBAL LEADERS trial. Atherosclerosis 2020;303:1-7.

55. Chichareon P, Modolo R, Kawashima H, Takahashi K, Kogame N, Chang CC, Tomaniak M, Ono M, Walsh S, Suryapranata H, Cotton J, Koning R, Akin I, Kukreja N, Wykrzykowska J, Piek JJ, Garg S, Hamm C, Steg PG, Jüni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Serruys PW. DAPT Score and the Impact of Ticagrelor Monotherapy During the Second Year After PCI. JACC Cardiovasc Interv 2020;13(5):634-646.

56. de Faria AP, Modolo R, Chichareon P, Chang CC, Kogame N, Tomaniak M, Takahashi K, Rademaker-Havinga T, Wykrzykowska J, de Winter RJ, Ferreira RC, Sousa A, Lemos PA, Garg S, Hamm C, Juni P, Vranckx P, Valgimigli M, Windecker S, Onuma Y, Steg PG, Serruys PW. Association of Pulse Pressure With Clinical Outcomes in Patients Under Different Antiplatelet Strategies After Percutaneous Coronary Intervention: Analysis of GLOBAL LEADERS. Can J Cardiol 2020;36(5):747-755.

57. Hara H, Kogame N, Takahashi K, Modolo R, Chichareon P, Tomaniak M, Ono M, Kawashima H, Gao C, Wang R, Valkov VD, Vom Dahl J, Steinwender C, Geisler T, Lemos Neto PA, Macaya Miguel C, Garg S, Jüni P, Hamm C, Steg PG, Valgimigli M, Vranckx P, Windecker S, Farooq V, Onuma Y, Serruys PW. Usefulness of the updated logistic clinical SYNTAX score after percutaneous coronary intervention in patients with prior coronary artery bypass graft surgery: Insights from the GLOBAL LEADERS trial. Catheter Cardiovasc Interv 2020;96(5):E516-e526.

58. Asano T*, Kogame N*, Onuma Y, Modolo R, Chichareon P, Lefèvre T, Legutko J, Digne F, Morel MA, Serruys PW, Gil RJ. Treatment with a dedicated bifurcation sirolimus-eluting cobalt-chromium stent for distal left main coronary artery disease: rationale and design of the POLBOS LM study. EuroIntervention 2020;16(8):654-662. *Authors contributed equally

59. Takahashi K, Chichareon P, Modolo R, Kogame N, Chang CC, Tomaniak M, Moschovitis A, Curzen N, Haude M, Jung W, Holmvang L, Garg S, Tijssen JGP, Wykrzykowska JJ, de Winter RJ, Hamm C, Steg PG, Stoll HP, Onuma Y, Valgimigli M, Vranckx P, Windecker S, Serruys PW. Impact of ticagrelor monotherapy on two-year clinical outcomes in patients with long stenting: a post hoc analysis of the GLOBAL LEADERS trial. EuroIntervention 2020;16(8):634-644.

60. Hara H, Takahashi K, Kogame N, Tomaniak M, Kerkmeijer LSM, Ono M, Kawashima H, Wang R, Gao C, Wykrzykowska JJ, de Winter RJ, Neumann FJ, Plante S, Lemos Neto PA, Garg S, Jüni P, Vranckx P, Windecker S, Valgimigli M, Hamm C, Steg PG, Onuma Y, Serruys PW. Impact of Bleeding and Myocardial Infarction on Mortality in All-Comer Patients Undergoing Percutaneous Coronary Intervention. Circ Cardiovasc Interv 2020;13(9):e009177.

61. Ono M, Chichareon P, Tomaniak M, Kawashima H, Takahashi K, Kogame N, Modolo R, Hara H, Gao C, Wang R, Walsh S, Suryapranata H, da Silva PC, Cotton J, Koning R, Akin I, Rensing B, Garg S,

Wykrzykowska JJ, Piek JJ, Jüni P, Hamm C, Steg PG, Valgimigli M, Windecker S, Storey RF, Onuma Y, Vranckx P, Serruys PW. The association of body mass index with long-term clinical outcomes after ticagrelor monotherapy following abbreviated dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: a prespecified sub-analysis of the GLOBAL LEADERS Trial. Clin Res Cardiol 2020;109(9):1125-1139.

62. Ono M, Kawashima H, Hara H, Katagiri Y, Takahashi K, Kogame N, Wykrzykowska JJ, Piek JJ, Doshi M, Sharif F, Onuma Y, Colombo A, Serruys PW, Cortese B. A Prospective Multicenter Randomized Trial to Assess the Effectiveness of the MagicTouch Sirolimus-Coated Balloon in Small Vessels: Rationale and Design of the TRANSFORM I Trial. Cardiovasc Revasc Med 2021;25:29-35.

63. Hara H, van Klaveren D, Kogame N, Chichareon P, Modolo R, Tomaniak M, Ono M, Kawashima H, Takahashi K, Capodanno D, Onuma Y, Serruys PW. Statistical methods for composite endpoints. EuroIntervention 2021;16(18):e1484-e1495.

64. Chichareon P, van Klaveren D, Modolo R, Kogame N, Takahashi K, Chang CC, Tomaniak M, Yuan J, Xie L, Song Y, Qiao S, Yang Y, Guan C, Zurakowski A, van Geuns RJ, Sabate M, Ong PJ, Wykrzykowska JJ, Piek JJ, Garg S, Hamm C, Steg G, Vranckx P, Valgimigli M, Windecker S, Juni P, Onuma Y, Steyerberg E, Xu B, Serruys PW. Predicting 2-year all-cause mortality after contemporary PCI: Updating the logistic clinical SYNTAX score. Catheter Cardiovasc Interv 2021;98(7):1287-1297.

65. Biscaglia S, Uretsky B, Barbato E, Collet C, Onuma Y, Jeremias A, Tebaldi M, Hakeem A, Kogame N, Sonck J, Escaned J, Serruys PW, Stone GW, Campo G. Invasive Coronary Physiology After Stent Implantation: Another Step Toward Precision Medicine. JACC Cardiovasc Interv 2021;14(3):237-246.

66. Gao C, Buszman P, Buszman P, Chichareon P, Modolo R, Garg S, Takahashi K, Kawashima H, Wang R, Chang CC, Kogame N, Tomaniak M, Ono M, Hara H, Slagboom T, Aminian A, Naber CK, Carrie D, Hamm C, Steg PG, Onuma Y, Geuns RV, Serruys PW, Zurakowski A. Influence of Bleeding Risk on Outcomes of Radial and Femoral Access for Percutaneous Coronary Intervention: An Analysis From the GLOBAL LEADERS Trial. Can J Cardiol 2021;37(1):122-130.

67. Lemos PA, Kogame N, Guimarães PO, Modolo R, Serruys PW. Reply: Elimination of Aspirin From PCI Pharmacotherapy. JACC Cardiovasc Interv 2021;14(2):230-231.

68. Nakamura K, Takagi T, Kogame N, Hashimoto H, Asami M, Toyoda Y, Enomoto Y, Hara H, Noro M, Sugi K, Moroi M, Nakamura M. The Association of Cardio-Ankle Vascular Index (CAVI) with Biatrial Remodeling in Atrial Fibrillation. J Atheroscler Thromb 2021;28(6):590-603.

69. Gao C, Kogame N, Modolo R, Takahashi K, Wang R, Kawashima H, Ono M, Hara H, Tomaniak M, Zaman A, de Winter RJ, van Geuns RJ, Kaul U, Serruys PW, Onuma Y. The ultra-thin strut sirolimus-eluting coronary stent: SUPRAFLEX. Future Cardiol 2021;17(2):227-237.

70. Gao C, Kogame N, Sharif F, Smits PC, Tonino P, Hofma S, Moreno R, Choudhury A, Petrov I, Cequier A, Colombo A, Kaul U, Zaman A, de Winter RJ, Onuma Y, Serruys PW. Prospective Multicenter Randomized All-Comers Trial to Assess the Safety and Effectiveness of the Ultra-Thin Strut Sirolimus-Eluting Coronary Stent Supraflex: Two-Year Outcomes of the TALENT Trial. Circ Cardiovasc Interv 2021;14(3):e010312.

71. Miyazaki Y, Muramatsu T, Asano T, Katagiri Y, Sotomi Y, Nakatani S, Takahashi K, Kogame N, Higuchi Y, Ishikawa M, Kyono H, Yano M, Ozaki Y, Serruys PW, Okamura T, Onuma Y. Online three-

dimensional OFDI-guided versus angiography-guided PCI in bifurcation lesions: design and rationale of the randomised OPTIMUM trial. EuroIntervention 2021;16(16):1333-1341.

72. Nakamura K, Takagi T, Kogame N, Asami M, Toyoda Y, Enomoto Y, Hara H, Moroi M, Noro M, Sugi K, Nakamura M. Impact of atrial mitral and tricuspid regurgitation on atrial fibrillation recurrence after ablation. J Electrocardiol 2021;66:114-121.

73. Hara H, Ono M, Kawashima H, Kogame N, Mack MJ, Holmes DR, Morice MC, Davierwala PM, Mohr FW, Thuijs D, Head SJ, Kappetein AP, Onuma Y, Serruys PW. Impact of stent length and diameter on 10-year mortality in the SYNTAXES trial. Catheter Cardiovasc Interv 2021;98(3):E379-e387.

74. Ono M, Serruys PW, Patel MR, Escaned J, Akasaka T, Lavieren MAV, Haase C, Grass M, Kogame N, Hara H, Kawashima H, Wykrzykowska JJ, Piek JJ, Garg S, O'Leary N, Inderbitzen B, Onuma Y. A prospective multicenter validation study for a novel angiography-derived physiological assessment software: Rationale and design of the radiographic imaging validation and evaluation for Angio-iFR (ReVEAL iFR) study. Am Heart J 2021;239:19-26.

Acknowledgement

This thesis would not have been accomplished without huge supports from my family, promoters, co-promoters, colleagues, and friends. I would like to express my sincere appreciation to all from the bottom of my heart.

Promoters

Dear Prof. Patrick W. Serruys,

I am very grateful to you for your kindness, patience, and guidance to a fellow like me who cannot speak English. I will never forget you pronouncing the words 10 times with me and checking the correct pronunciation on Longman's website for my English instruction. Your passion for education is top of the world. Working in your home was also the ultimate luxury for me.

Despite being an outstanding individual yourself, I was also impressed by your respect for the importance of the team. I believe this is one of the reasons why you have been able to continue to produce a vast amount of scientific output for many years. I am proud to have been a part of your team. I was also amazed by your extensive academic network, and it was a wonderful experience to have very rare and meaningful collaborations with researchers from all over the world.

Your passion for clinical trial is the best in the world. I was surprised by your refusal to allow even a single missing data. I learned that this attitude is essential for completion of high-quality clinical trials.

Please take care of yourself. I and my family will be forever grateful to you.

Dear Prof. Jan. J. Piek,

Thank you for accepting me for the PhD course of the University of Amsterdam. This thesis would not be accomplished without your invaluable supports. I am proud to have worked with a legend like you about coronary physiology.

Co-promoters

Dear Prof. Yoshinobu Onuma sensei,

I can never thank you enough. You are Superman for me. When I was terribly upset with Prof, when my manuscript was rejected, when soup was spilled on my mac, when my mother's bag was stolen, and so on, you were always there to help me. Of course, I have good memories of having almost all of my manuscript revised in LaBru. I am especially proud that Optimum study is one of my thesis chapters. Hope we can keep our collaboration for the rest of our career.

Dear Dr. Joanna J. Wykrzykowska,

Many thanks for your continuous and invaluable support. I deeply appreciated your swift responses and positive advice on our papers. I am always encouraged by your comments. I hope to continue our global collaborations in the future.

Dear Marie-Angèle,

Prof always says, "you are the boss". I think so, and you are absolutely the oasis for all fellows. I am really proud to have worked with mother of BENESTENT. Finally, I deeply appreciated your help for translating the summary into Dutch.

Dear Hanny,
Many thanks for your help over the past two years. You always supported me on a variety of issues, such as setting up my life, writing email in English, travel arrangement, etc. You were always cheerful, passionate, and energizing. I look forward to meeting you again.

Great fellows from all over the world,

Dear Erhan,
Super hard worker, mainly at midnight. Please do not forget my name on your manuscript. I admire sincere attitude to the works.

Dear Yosuke sensei,
Thank you for your very kind help. It was my pleasure working with you on the OPTIMUM study. I also appreciate you giving me your airbed. Finally, I can sleep.

Dear Taku sensei,
Thank you for your continuous consideration and supports. My career and this thesis would never exist without your invitation. I respect you for initiating the clinical trial in Japan.

Dear Yuki sensei,
I deeply appreciated your excellent advice on all fellow's life in Rotterdam including this thesis. I just had to walk the path you paved. I hope to continue our collaborations in the future.

Dear Ply,
Master of R like statistician. I will never forget how kindly you taught me about GLOBAL LEADERS trial in the beginning of my fellowship.

Dear Rodrigo,
Gentle giant. I admire your smartness and excellent presentation skills. You always helped me when I was in trouble at meetings. Traveling to San Diego with you was also fun and interesting.

Dear Kuni sensei,
I appreciate your continuous consideration and heartfelt supports. I really admire your sincere attitude to the works.

Dear Chun-Chin,
My great Taiwanese friend. Thank you very much for working with me through good and bad times. I have the best memory of having the manuscript of TALENT accepted by the Lancet after really hard work with you and Rodrigo. I look forward to meeting you in Taiwan or Japan.

Dear Mariusz,
I appreciate your continuous and invaluable supports on my works. Some of the papers in this thesis would not be accomplished without your help.

Dear Masa sensei, Kawa sensei, Hiro sensei, Charlie, and Rutao,
I would like to thank all my colleagues in Rotterdam. It was a pleasant moment working with you all. I hope that we will have an opportunity to have international collaboration in the future.

EuroIntervention team,
Dear Sylvie, Amy, and Devia,
Thank you very much for your patience and kind instruction for submitting manuscripts. I really appreciate a lot of opportunity to work together with you as a part of the editorial team.

Amsterdam research team
Dr. Ruben, Laura,
Thank you for letting me join your great team. AIDA QCA project was quite tough, but it was nice opportunity to work together. Many thanks for your kind friendship.

Dear Ms. Margreet de Bruin,
I deeply appreciate your great supports for all procedures of the PhD and the thesis defense ceremony.

Toho University Medical Center Ohashi Hospital
Dear Prof. Masato Nakamura, Dr.Hidehiko Hara, Dr. Raisuke Iijima, Ms. Yoriko Sudo, and colleagues,
I would like to my deepest gratitude for giving an opportunity to study abroad for two years. Without your kind supports from Japan, this thesis would not be accomplished.

Family
I would like to express my sincere appreciation to my parents **Noriko** and **Yoshiharu**, my brother **Hirotaka**, and **Takehiro** for their invaluable supports. Furthermore, I would like to sincerely appreciate kind support from the **family of Ishida**.
finite love and endless supports. I love you all so much that I can't even describe with words.
Lastly, I would like to extend my sincere thanks to my dearest wife, **Emiko**, and my children, **Natsuno**, **Fumika**, and **Rikuto**. Without their tremendous understanding and encouragement in the past few years, it would be impossible for me to complete my thesis. Our family thoroughly enjoyed our time in the Netherland and had great unforgettable experiences.

Implementation of the best practice principle in contemporary percutaneous coronary intervention

Norihiro Kogame