

Risk Assessment in Coronary Artery Disease: Stratifying Plaques, Stratifying Patients

Carlos M. Campos

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Risk Assessment in Coronary Artery Disease: Stratifying Plaques, Stratifying

Risico analyse in coronaire hartziekte:
stratificatie plaques, stratificatie patiënten

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To Fabiana, Natália and Isabela

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Introduction and Overview of the Thesis

INTRODUCTION AND OVERVIEW OF THE THESIS

Few topics have received as much attention in the recent cardiovascular literature as risk stratification¹. The assessment of risk has been a key element in efforts to define factors for coronary artery disease (CAD), to identify novel markers for cardiac events, to identify and assess potential targets of therapy, to enhance the decision making and implementing therapies for both primary and secondary prevention of CAD. Extensive efforts are needed to quantify an individual's risk of an event according to each component of vulnerability (from coronary plaque to a comprehensive clinical profile assessment).

Advances in the field of cardiovascular imaging have made possible invasive and non-invasive assessment of the coronary atherosclerotic burden. Since the beginning of interventional cardiology, coronary angiography has been the reference tool for the quantification of coronary artery disease burden in both clinical practice and scientific investigation. With growing knowledge about the pathophysiology of atherothrombosis it became of interest to visualise *in vivo* different processes taking place at the level of the coronary plaque for the purpose of improving cardiovascular outcomes.^{2,3} Intracoronary imaging techniques overcome the lumenographic limitations of angiography by enabling a pathology-like cross-sectional view of the vessel wall and implanted devices. These invasive imaging methods have succeeded to demonstrate good correlations with plaque vulnerability, patients' clinical profile and cardiovascular events⁴⁻⁶. Moreover, in recent years, coronary CT angiography (CCTA) has become a widely adopted technique, not only

due to its high diagnostic accuracy, but also to the fact that CCTA provides a non-invasive evaluation of the total (obstructive and non-obstructive) coronary atherosclerotic burden, being also able to assess patient's risk of cardiovascular events⁷.

However, the coronary atherosclerotic disease burden is not the only factor that affect patients' prognosis. In patients with complex coronary artery disease, other factors beyond plaque (ex. : thrombogenic blood and electrical instability of myocardium) are components of the final outcome. Therefore, it is needed a comprehensive risk-stratification tool capable of predicting cardiovascular events improving the decision-making process.

In addition, the cardiovascular science community has pursued the quest to modify the natural history of coronary atherosclerosis. Recently, the implantation of coronary bioresorbable scaffolds have emerged as a promising strategy for plaque sealing and modification of natural history of CAD. These devices have the unique ability to provide a temporary scaffold that is necessary to maintain the patency of the vessel after intervention, before they gradually dissolve, liberating the vessel from its cage, and permitting the restoration of vascular physiology and integrity. Neointimal tissue develops following either Absorb BVS implantation and shields lipid tissues and permitting late lumen enlargement^{8,9}. This thesis will provide an insight into the development of these methods and their clinical application.

The first chapter reviews the imaging (invasive and non-invasive) methods for quantifying patient risk at a coronary level. For successfully utilising these methods in research and clinics, it is necessary to understand their strengths and limitations.

Chapter 2 describes the rational of combining anatomic and clinical factors in the risk assessment of coronary artery disease. Clinical characteristics are able to differentiate the manifestation of coronary artery disease as assessed by angiography and intravascular methods and affect patient symptoms and prognosis.

In chapter 3, we describe the risk stratification of patients with complex coronary artery disease. We compare the improvement of the predictive performance of the combination of anatomical and clinical factors (SYNTAX score II) versus coronary anatomy in isolation (SYNTAX score). We evaluate in details the ability of these models in decision making for coronary revascularization, its cost-effectiveness, prognostic implications and future perspectives.

Chapter 4 depicts post-revascularization risk assessment. We quantify the proportion of coronary artery disease burden treated by PCI and evaluate its impact on outcomes using

a new prognostic instrument - the Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) Revascularization Index (SRI). In addition, we describe the importance and challenges in modifying risk factors for secondary prevention after coronary revascularization.

In chapter 5, we describe the potential benefits of bioresorbable scaffolds (BRS) in percutaneous coronary revascularization. Bioresorbable vascular scaffolds (BRS) are a novel approach to the interventional treatment of coronary artery disease (CAD), providing short-term vascular scaffolding combined with drug-delivery capability. These devices present important differences with respect to metallic stents when imaged. We express in the details the methods for short and long-term assessment of bioresorbable scaffolds. Finally, we discuss the potential impact of BRS in the natural history of coronary atherosclerosis.

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PART 1

IMAGING METHODS FOR ASSESSING CARDIOVASCULAR RISK

Chapter 1.1

How Can The Vulnerable Plaque Be Identified?

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ABSTRACT

The precise identification of a vulnerable plaque may have substantial clinical impact since the absolute majority of cases of sudden death are related to acute coronary syndromes. Recent advances in imaging techniques have allowed the development of numerous invasive and noninvasive tools for the investigation of coronary atherosclerosis. Contemporary natural history of atherosclerosis studies added information on changes in the morphological and compositional plaque characteristics. The objective of understanding these temporal changes is to being able to predict plaques prone to have future events changing the way we approach its treatment and strengthening the concept of plaque passivation. This review article summarizes the current definitions on vulnerable plaque, describes the recent advances in the study of atherosclerosis, cites the current evidence, highlights our limitations in understanding the evolution of the plaque and in predicting plaque destabilization.

INTRODUCTION

Despite the recent medical advances, according to the last report from the World Health Organization, 7.3 million people die of ischaemic heart disease every year¹. Included in this population, there is a large number of individuals who are apparently healthy and die suddenly without prior symptoms. In this regard, plaque rupture is the most common type of plaque complication, accounting for 70% of fatal acute myocardial infarctions and/or sudden coronary deaths². These reasons have been fueling a great scientific effort to understand, diagnose and treat properly the plaque that is prone to rupture. Therefore, there are currently several diagnostic imaging techniques aiming to specifically evaluate indicators of plaque vulnerability. These techniques can provide information on the vessel,

lumen and wall size, tissue composition, and the status of inflammation (table1). This article aims to review the current histopathological definitions and state-of-the-art of imaging techniques.

DEFINITIONS

Cardiologists describe the plaque responsible for coronary occlusion and death as a *culprit* plaque. However, clinicians need a similar term for prospective evaluation, to describe such plaques *before* an event occurs, so called vulnerable plaque.

There are two major types of vulnerable plaques, rupture-prone and erosion-prone³⁻⁵. The prototype of a rupture-prone plaque contains a large and soft lipid-rich necrotic core (>30% of plaque) covered by a thin

Table 1. Ability of the available imaging modalities to detect plaque features associated with increased vulnerability

Plaque characteristics associated with increased vulnerability	Thin fibrous cap	Necrotic core	Assessment of plaque burden	Positive remodeling	Neoangio-genesis	Active inflammation
IVUS/IVUS-RF	++	++	+++	+++	-	-
OCT	+++	+++	++	+	++	+
Angioscopy	-	++	-	-	-	-
IV-MRI spectroscopy*	-	++	-	-	-	-
NIRS	-	+++	-	-	-	-
IV-MRI*	-	+	+	+	-	-
Photoacoustic imaging*	-	++	-	-	-	-
TRFS*	+	++	-	-	-	-
CTCA	-	+	++	++	-	-
Thermography	-	-	-	-	-	+
NIRF*	-	-	-	-	+	+++
PET*	-	-	-	-	-	++

Abbreviations: IVUS= intravascular ultrasound; RF=radiofrequency; OCT=optical coherency tomography, IV-MRI, Intravascular MRI; NIRS, near-infrared spectroscopic; TRFS, time-resolved fluorescence imaging; CTCA, Computed Tomography Coronary Angiography; NIRF= Near-infrared fluorescence, PET, Positron emission tomography. The ability of the presented modalities to detect plaque characteristics associated with increased instability is graded as: unable (-), low (+), moderate (++), and high (+++). The modalities marked with an asterisk are in their initial development, and therefore, the data provided for these techniques derive from small scale in vivo or histology-based in vitro studies.

(thickness usually < 65 μm) and inflamed fibrous cap. Associated features include large plaque size, expansive remodelling mitigating luminal obstruction (mild stenosis by angiography), neovascularization plaque haemorrhage, adventitial inflammation, and a "spotty" pattern of calcifications^{4,6}.

The erosion-prone vulnerable plaque type are heterogeneous and defined only by their fate (thrombosis, mostly mural).⁷ The surface endothelium is missing, but whether it vanished before or after thrombosis remains unknown. No single morphological features have been identified but, in general, eroded plaques with thrombosis are scarcely calcified, rarely associated with expansive remodelling, and only sparsely inflamed⁷. Thus, it remains a challenge to distinguish erosion-prone plaques from stable plaques by imaging⁸.

INVASIVE IMAGING OF VULNERABLE PLAQUES

Intravascular ultrasound (IVUS). Intravascular ultrasound (IVUS) was the first invasive modality that allowed imaging of the lumen and vessel wall, quantification of plaque burden, and characterization of its composition. Positive vessel remodeling can readily be evaluated with IVUS⁹⁻¹¹. Visual assessment of plaque echogenicity provides semiquantitative tissue characterization¹². Calcification can be identified with a sensitivity and specificity of approximately 90%¹³. Large eccentric plaques containing an echolucent zone by IVUS were associated with the development of ACS in a prospective study¹⁴. Another feature that can be obtained by IVUS is attenuated plaque, defined as plaques with >30° ultrasonic attenuation of deeper arterial structures despite the

absence of bright calcium. In an assessment of 131 native lesions, attenuated plaques have confluent necrotic core in 93.5% when matched by VH-IVUS and 90.3% of lipid core on the block chemogram¹⁵. Microbubble contrast-enhanced IVUS can measure activity and inflammation within atherosclerotic plaques by imaging vasa vasorum density, which is considered as a marker for plaque vulnerability¹⁶. The main limitation of IVUS is its 100–150 μm axial resolution, whereas the fibrous cap of a TCFA is thinner than 65 μm and, therefore, cannot be visualized by IVUS.

Intravascular ultrasound radiofrequency analysis (RF-IVUS). RF-IVUS involves spectral analysis of the IVUS gray-scale data and evaluates different spectral parameters. Different plaque components are assigned different color codes: calcified (white), fibrous (green), fibrolipidic (greenish–yellow) and necrotic core (red)¹⁷.

The PROSPECT trial has been the largest natural history of atherosclerosis study and used RF-IVUS to detect anatomical and compositional features associated with an increased risk for a plaque to evolve to a culprit lesion¹⁸. Six hundred ninety-seven patients treated for an acute coronary syndrome underwent RF-IVUS post intervention at the 3 epicardial coronary arteries. At 3-year follow-up, 104 new symptomatic lesions became manifest in the nontreated segments. Multivariable analysis demonstrated that the presence of TCFA, a minimum lumen area $\leq 4 \text{ mm}^2$, and a plaque burden $\geq 70\%$ were associated with future events. Similar results were reported by the VH-IVUS in Vulnerable Atherosclerosis Study study that had a similar design¹⁹. The PROSPECT trial not only showed the potential predictive value of intravascular imaging but also highlighted its limited prognostic accu-

racy as only 4% of the detected TCFA evolved to culprit lesions. This should be attributed to the fact that the included patients were on optimal treatment and to the inherited limitations of IVUS imaging²⁰.

Optical coherence tomography. Optical coherence tomography (OCT) is an optical analogue of ultrasound; however, it uses light instead of sound to create an image. It can provide a resolution of 10–20 μm *in vivo*. This resolution permits visualization of details, which cannot be imaged by other intravascular techniques such as evaluation of the thickness of the fibrous cap, detection of macrophages, and neovascularization and identification of plaque erosion²¹. A limitation of OCT is its poor penetration, which often does not allow complete visualization of the vessel wall and assessment of vessel remodeling. In addition, OCT signal cannot penetrate lipid tissue, and thus, it is unable to quantify the lipid component.

Invasive techniques for the detection of inflammation. Thermography was the first invasive imaging technique developed to identify vessel wall inflammation and relies on the measurement of plaque heat. High temperatures indicate increased inflammatory activity and, sometimes, vulnerability of the plaque. Initial reports demonstrated the efficacy of thermography in detecting high-risk plaques, but recent studies have raised concerns about its effectiveness in patent coronaries suggesting that blood flow obstruction is necessary to obtain accurate estimations, fact that has limited its current applications^{22,23,24}.

Near-infrared fluorescence (NIRF) imaging is a novel technique introduced to detect vascular activity. It involves injection of agents that bind molecules related to plaque's inflamma-

tion and have the ability to fluoresce after being irradiated with near-infrared light emitted by a specially designed catheter. Experimental studies demonstrated the feasibility and the potential of this technology²⁵. Recently, a hybrid NIRF-OCT catheter (diameter 2.4F) has been designed that allows simultaneous molecular functional imaging (provided by NIRF) and visualization of vessel pathology (given by OCT)²⁶. The feasibility of this approach has been tested *ex vivo* and *in vivo* in animal models and the first results appear promising. However, the safety of this technique has to be proven before being implemented in humans.

Near-Infrared Spectroscopy (NIRS). NIRS is based on the principle that different organic molecules absorb and scatter NIRS light to different degrees and wavelengths. Spectral analysis of the obtained signal provides a color-coded display, called a chemogram, which provides the probability that lipid core is present in the superficial plaque (studied depth approximately: 1 mm). Several studies have examined the reliability of this technique using histology as the gold standard and demonstrated a high overall accuracy in detecting lipid-rich plaques while others demonstrated its feasibility in the clinical setting^{27,28}. In NIRS sub-study of the European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis (NCT01789411) lipid plaque burden is being weighting as a predictor of cardiac events.

NONINVASIVE IMAGING MODALITIES

Computed Tomography Coronary Angiography (CTCA). CTCA seems that it provides useful prognostic information²⁹, assess the progression of coronary atherosclerosis³⁰,

provides a promising noninvasive method for identifying ischemia-causing stenosis³¹ and gives information about anatomical complexity³². However, CTCA has limited capability in differentiating lipid-rich from fibrotic plaques and has low resolution, which does not permit visualization of plaque characteristics associated with increased vulnerability³³. However, in this field, an ambitious prospective study commenced - the BioImage trial - that aims to include >6,000 asymptomatic subjects who will undergo noninvasive imaging (including CTCA if they have a high-risk cardiovascular profile) to identify new imaging-based predictors of future cardiovascular events.

Magnetic resonance imaging (MRI). Magnetic resonance imaging appears to be able to detect the composition of the plaque and has been used to study the atherosclerotic process in the aorta and the carotids, but it has a limited value in assessing coronary pathology, as it requires prolonged acquisition time and has poor spatial resolution³⁴. Further improvements in external coils as well as the development of contrast agents that will allow more accurate plaque characterization are required so as this modality to be useful in this setting.

Noninvasive imaging of vessel wall inflammation. Nuclear imaging constitutes the leading noninvasive modality for the evaluation of vascular activity. Recent reports demonstrated the feasibility of the combined CTCA-18F-FDG imaging for the identification of inflamed plaques on the coronary tree^{35,36}. The concept of fusing 2 noninvasive modalities that provide anatomical (derived from CTCA) and biological (given by PET) information constitutes a breakthrough in the study of atherosclerosis as it will allow detailed imaging of plaque pathology in larger populations and it is expected

to provide additional information about the distribution of plaque inflammation and its association with different plaque components. Apart from 18F-FDG, several other tracers have been developed to assess vascular activity, such as the 99mTc-AA5, which binds phosphatidylserine produced by apoptotic cells; the 99mTc matrix metalloproteinase inhibitor that binds active metalloproteinases; and the IK17 tracer, which is labeled with I125 and is able to detect the presence of oxidized low density lipoprotein, without however being used in clinical setting yet³⁷⁻³⁹.

FUTURE TRENDS AND CONCLUSIONS

Intravascular magnetic imaging⁴⁰, photoacoustic imaging, Raman spectroscopy, and time-resolved fluorescence spectroscopy are emerging techniques that still under evaluation and are expected to provide additional information about plaque. In parallel, an effort is being made to overcome the limitations of the prominent intravascular imaging modalities either by developing new methodologies that would allow better processing of the acquired data (eg, focused acoustic computed tomography, micro-OCT, polarized OCT) or by creating hybrid catheters that would permit multimodality intravascular imaging^{41,42}. A hybrid catheter that combines an IVUS and a NIRS probe (TVC, MC 7 system; InfraRedx, Burlington, MA) is currently available and being used in research arena⁴³. Catheters that permit fusion of IVUS with OCT, photoacoustic imaging, or time resolved fluorescence spectroscopy are also under evaluation⁴⁴. Initial experimental studies have shown promising results⁴⁵⁻⁴⁷. However, the large dimensions of the available catheters, the concerns regarding

the safety of the new techniques, and the low image acquisition rate as well as the moderate image quality that they provide have not allowed their implementation in humans yet. These

advances are expected to result in a better understanding of the composition and evolution of the atherosclerotic plaque in an attempt to anticipate and prevent acute coronary

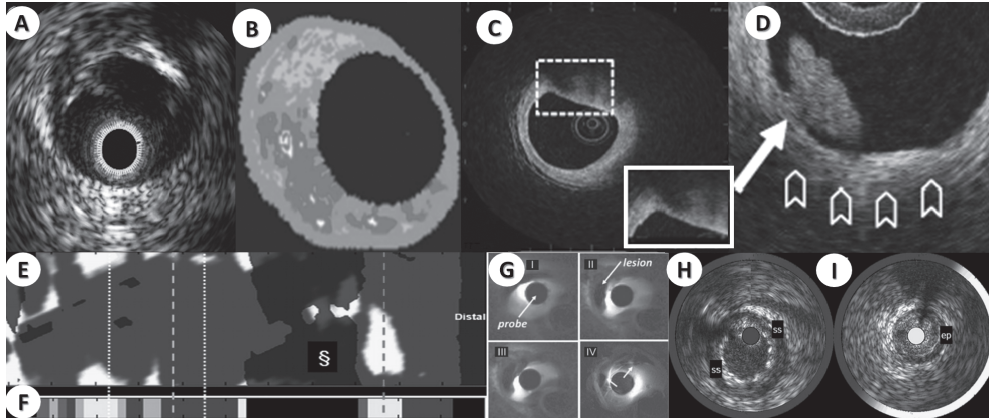


Figure 1. (A) IVUS gray scale plaque rupture represented by a large empty cavity from 11 to 2 o'clock. (B) Plaque to lumen with high content of necrotic core (red), adjacent to lumen, by intravascular ultrasound radiofrequency analysis. (C) The optical coherence tomography image shows a thin-capped fibroatheroma and a (D) ruptured plaque with thrombus at that site (white arrow). (E,F) The output of the near-infrared spectroscopic (NIRS) catheter is illustrated (E, chemogram; F, block chemogram). The yellow-red color-coded map illustrates the probability of the presence of a lipid core (yellow corresponds to high probability and red to low probability). (G) Output of a recently developed intravascular magnetic resonance probe (I-IV); the images were obtained in vitro from an atherosclerotic iliac artery. The dark areas at 9 (II, III) and 12 o'clock (IV) indicate the presence of calcific tissue. (H,I) Data Acquired by a Combined IVUS and NIRS Catheter showing IVUS cross-sections with the corresponding chemogram obtained in a stented and a nonstented segment, respectively. The probability of the presence of a lipid-rich plaque is low in the stented segment (H) but high in the frame portrayed in (I), between 1 and 7 o'clock. ep = echolucent plaque; ss = stent struts. # Area with insufficient NIRS signal.

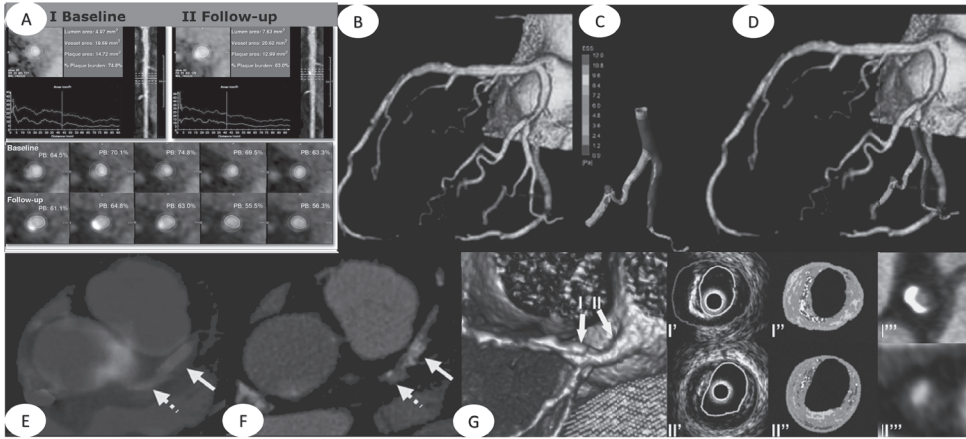


Figure 2. Implications of CTCA in the study of atherosclerosis. (A) Assessment of progression/regression: Example of vessel analyzed at baseline (I) and 3-year follow-up (II). In both panels, 5 lines indicate the location in the vessel of the cross-sections shown at the bottom of the figure (from proximal to distal). In this lesion, the plaque burden (PB, %) decreases consistently from baseline to follow-up in the 5 cross-sections analyzed. (B) Reconstruction of coronary tree from CTCA. (C) These data were used to model the distal circumflex, simulate blood flow, and evaluate the shear stress distribution (portrayed in a color-coded map). (D) Superimposition of the reconstructed model onto the coronary tree provided by CTCA. (E) Fusion of CTCA and positron emission computed tomography. Increased 18F-FDG uptake was noted in the aorta, left main stem, and left anterior descending artery (arrows) of a patient admitted with an acute coronary syndrome. (F) On the other hand, minor inflammation was detected in the aorta and coronary tree of a patient with stable angina. (G) Ability of CTCA to detect the composition of the plaque. The arrows indicate the location of the IVUS and CTCA cross-sectional images. Panels (I'-I''') portray IVUS, IVUS radiofrequency backscatter analysis, and CTCA cross-sections for the distal calcified plaque, whereas the panels (II'-II'''), the corresponding cross-sections for the proximal plaque. The luminal morphology and the distribution of the plaque are similar in the CTCA and IVUS images. CTCA appears to allow accurate differentiation between calcified from noncalcified plaques.

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Chapter 1.2

Ex Vivo Validation of 45 MHz Intravascular Ultrasound Backscatter Tissue Characterization

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ABSTRACT

Aims:

The objectives of the present study are to describe the algorithm for VH[®] IVUS using the 45 MHz rotational IVUS catheter and the associated *ex vivo* validation in comparison to the gold-standard histology.

Methods and Results:

The first phase of the present study was to construct the 45 MHz VH IVUS algorithm by using a total of 55 human coronary artery specimens [111 independent coronary lesions and 510 homogenous regions of interest (ROIs)], obtained at autopsy. Regions were selected from histology and matched with their corresponding IVUS data to build the plaque classification system using spectral analysis and statistical random forests. In the second phase, the *ex vivo* validation of the VH IVUS algorithm assessed a total of 1060 ROIs (120 lesions from 60 coronary arteries) in comparison with histology. In an independent manner, two interventional cardiologists also classified a randomly selected subset of the ROIs for assessment of inter- and intra-observer reproducibility of VH IVUS image interpretation.

When including all ROIs the predictive accuracies were 90.8% for fibrous tissue, 85.8% for fibro fatty tissue, 88.3% for necrotic core and 88.0% for dense calcium. The exclusion of ROIs in the acoustically attenuated areas improved the predictive accuracies, ranging from 91.9 to 96.8%. The independent analysis of randomly selected 253 ROIs showed substantial agreement for inter-observer ($k=0.66$) and intra-observer ($k=0.88$) reproducibility.

Conclusion:

Tissue classification by 45 MHz VH IVUS technology, when not influenced by calcium-induced acoustic attenuation, provided combined tissue accuracy >88% to identify tissue types as compared with the gold-standard histologic assessment, with high inter- and intra-observer reproducibility.

Keywords: Atherosclerosis; coronary disease; spectral analysis; plaque; VH IVUS; IVUS

INTRODUCTION

One of the biggest challenges the cardiologist has currently is to identify lesions precursor of acute coronary events, which sometimes manifest as sudden death. In patients under optimal medical treatment, it has been shown that the occurrence of death and acute coronary syndromes may be associated with the total number of segments with significant disease rather than the ischemic burden¹. This suggests that plaque disruption might be the main cause of major cardiac outcomes rather than the ischemia induced by obstructive plaques. Therefore, assessment of plaque composition - identifying high risk plaques - and the effectiveness of a treatment to alter plaque composition are fields of significant clinical relevance.

In recent years, cardiovascular imaging research has sought potential strategies for detecting high-risk plaques. A number of intravascular ultrasound (IVUS) backscatter analysis techniques are promising and multiple approaches have been developed to produce colour-coded tissue maps, such as spectral analysis^{2,3}, spectral analysis combined with statistical learning⁴⁻⁶, and radiofrequency (RF) elastography analysis⁷.

IVUS RF backscatter analyses technologies, such as VH[®] IVUS (Volcano Corporation, San Diego, California, USA), are aimed at identification of patients at risk, plaque monitoring and eventually to guide targeted therapy. High risk plaque interpretation via VH IVUS analysis, has been shown to be correlated with high risk clinical features as defined by the Framingham Risk Score⁸ and to have the ability to predict cardiac events⁹⁻¹¹. Previously published *in vivo* and *ex vivo* studies^{4,5,12-14} on VH IVUS accuracy

have reported on plaque characterization with the 20 MHz VH IVUS algorithm using the digital 20MHz IVUS catheter (Eagle Eye[®] Catheter, Volcano Corporation, San Diego, California, USA), but this algorithm is restricted in detecting thin-caps associated with vulnerable fibroatheromas⁵. IVUS of higher frequency has higher axial resolution, which could provide improved visualization of a thin-cap, albeit with loss of ultrasound penetration-depth. Herewith we report a new higher frequency IVUS backscatter analysis algorithm for a 45 MHz rotational IVUS catheter and the associated *ex vivo* validation in comparison to the gold-standard histology.

METHODS

Subjects

Similar to the development of the 20 MHz VH IVUS algorithm⁵, data were collected from 55 coronary artery specimens obtained at autopsy with IRB approval from the Cleveland Clinic, Cleveland, Ohio. The study sample was limited to those without prior cardiac percutaneous interventions or surgical revascularization. Additionally, data was not acquired from alcohol and drug abuse cases or those with known blood-borne pathogen diseases (HIV, hepatitis, etc.). All vessels were excised within 24 hours of death and data were collected within 24 hours of vessel procurement.

Data Acquisition. Each vessel was pressure perfused using phosphate buffered saline (PBS) solution at systolic pressure (approximately 120 mmHg) and submerged within PBS to minimize any PBS-air interface reflections in the ultrasound data. Ans5[™] IVUS imaging system (Volcano Corporation, San Diego, California) capable of saving the in-phase

and quadrature (IQ) backscattered signals, and the Revolution[®] 45 MHz rotational catheter (Volcano Corporation, San Diego, California) were used for data collection and for visually locating ROI. Sections-of-interest were identified on the gray-scale IVUS images as having $\geq 30\%$ plaque burden and IQ data were collected at the 8 mm field-of-view setting. A suture was attached to the surrounding tissue of the vessel to mark the location. Adjacent lesions were separated by at least 1 cm to permit histology processing. In addition to placing the catheter at these specific sites, an automated IVUS pullback data collection was performed over the length of the artery specimen from the distal to the proximal site. The automated pullback rate was set to 0.5 mm/sec with a 60 beats per minute simulated heart rate, to allow the ECG-gated IQ data acquisition. This triggers the imaging system to save an IVUS backscatter data-set once per simulated heartbeat, approximately 0.5 mm apart.

Following imaging and IVUS data collection, the artery specimens were pressure fixed using 10% buffered formalin at systolic pressure for at least four hours. The vessels were then sectioned into 1 cm lengths so that the sutures representing the location of the imaged lesions were centered within each section. The sections of artery specimens were then sent for histology processing, which included a decalcification stage, if needed. Following paraffin embedding, pairs of histology slides were prepared at multiple locations (100 μm apart) proximal, at, and distal to the suture location. Each pair of histology slides were stained using hematoxylin and eosin (H&E) and the Movat pentachrome stains, respectively.

Image Correlation. Following data acquisition, matches between corresponding

histology slides and gray-scale IVUS images were determined by observing plaque burden and orientation and the surrounding tissue structures, such as side branch location, veins, location of the myocardium and pericardium, etc. The matching process with histology has been described previously⁵. The slides were reviewed by an expert to identify regions-of-interest (ROI) within the plaque that represent homogenous areas for each of the four tissue types, as described in previous work: FT - fibrous, FF - fibro-fatty, NC - necrotic core, and DC - dense calcium. Slides were reviewed both proximal and distal to the matched slide, to insure that the ROIs were consistent over a length along the vessel comparable to the out-of-plane resolution of the 45 MHz IVUS catheter. It was critical to have homogenous regions with respect to the ultrasound resolution both within the imaging plane and beyond the imaging plane, to successfully train the statistical classifier.

The ROIs obtained from the histology review were then translated onto regions within the matched gray-scale IVUS image by a second expert (different than the expert used for the histology review). Sectors of an annulus were drawn on the reconstructed gray scale image using customized software run with MATLAB[®] (Mathworks, Natick, Massachusetts). The software calculates the ultrasound backscatter signal location in the de-convolved IQ data for each ROI. Each of these homogenous ROIs comprised of 64 digitized IVUS samples in depth and 10 IVUS scan lines in width out of the total 256 scan lines that are used to construct one gray-scale IVUS image.

45 MHz VH IVUS Algorithm. A total of 111 independent lesions and 510 homogenous ROIs were selected to train the 45 MHz VH IVUS algorithm. The homogenous ROIs com-

prised 153 fibrous, 61 fibro-fatty, 112 necrotic core, and 184 dense calcium regions. The IQ signals representing each ROI were converted back to RF data and the signals were processed to remove system effects comparable to previously described efforts¹⁵. In addition, an adjustment factor was applied to the data to compensate for acoustic attenuation due to blood in the *in vivo* environment. This was to compensate for the higher attenuation of IVUS at 45 MHz *in vivo*, in an environment with blood as compared to the attenuated power spectra were then computed and spectral parameters were obtained. These included mid-band fit, intercept, slope, integrated backscatter, maximum power, frequency at maximum power, minimum power, and frequency at minimum power. These spectral parameters were calculated from the normalized power spectra for each homogenous ROI. The spectral parameters and corresponding homogenous tissue type categorization from histology formed the data set for further statistical classification using a Random Forest^{16,17} as an ensemble classification method. The statistical random forests technique is an extension of tree classification schemes and is known for improved predictive power for a diagnostic test with multiple outcomes. Fifty classification trees were used in the 45 MHz VH IVUS algorithm with randomly chosen spectral parameters and a sub-sample of data to build each tree. The VH IVUS classification is a result of a voting scheme from all 50 trees in the forest, resulting in a robust and statistically stable algorithm. The 'randomForest' package was used within the R software environment¹⁸ to implement this approach.

45 MHz VH IVUS Image Construction. The 45 MHz VH IVUS algorithm was applied to multiple backscatter data sets after user-

defined plaque lumen and medial-adventitial boundaries were obtained. Each lesion dataset was analyzed using a finite sized data-window that was 0.0736 radians in the lateral, or circumferential direction (approximately 147 μm at 2 mm depth) and approximately 250 μm in depth. This window of analysis was translated along each scan line one digitized sample at a time to construct a VH colorized tissue map out of the 256 scan lines that represent each IVUS backscattered image dataset.

45 MHz VH IVUS Algorithm *Ex Vivo* Accuracy Assessment. The data utilized for creating the 45 MHz VH algorithm is based on relatively 'homogenous' regions representing the four VH IVUS plaque types compared to the majority of plaque composition. In contrast, most plaques are not as homogenous as these ROIs. Thus, to validate the accuracy of the VH IVUS algorithm, a systematic approach was used to blindly and randomly choose heterogeneous regions and compare the results from histology to the results from the reconstructed VH IVUS images; similar to the approach described for the 20 MHz VH IVUS *ex vivo* validation⁵. VH tissue maps were constructed from 45 MHz IVUS data collected from a total of 120 lesions from 60 coronary artery specimens. Majority of these data were also used in training the VH algorithm, although an independent and different cohort of ROIs was used for training than the cohort of ROIs used for the accuracy assessment.

A team of four investigators analysed the data in a manner that minimizes potential bias. The first step was performed by two of the investigators and involved selecting random ROIs within the histology slides. A square grid pattern was printed on clear plastic overhead projection sheets. These were positioned over scaled printouts of the matched histology

Movat pentachrome stained slide images so that each square was $1/3$ mm x $1/3$ mm, or approximately a 333 μ m sized square. The two investigators then traced the boundary of the plaque on the overhead projection sheet for each section. Next, they numbered every other square that was contained within the plaque boundary following a checkerboard pattern. This overhead (without the underlying histology image) was provided to the third investigator who translated the numbered squares to corresponding positions on the matched and scaled VH image printouts. This step is necessary since the paraffin embedding process in histology preparation, results in warping of the tissue. A third investigator interpreted and recorded the dominant VH IVUS tissue type within each of these heterogeneous ROIs. This third investigator was blinded to the histology data. The traced overhead projection sheets were then provided to a fourth investigator who interpreted the dominant feature of the histology slide for each of the numbered ROIs and was blinded to the matched VH IVUS image. A total of 1060 regions were thus analysed (see Figure1).

In addition to this analysis the third investigator also identified ROIs that were located behind densely calcified ROIs in the radial direction of the ultrasound backscatter. Calcium is known to attenuate or inhibit ultrasound and hence cast a 'shadow' on tissue located at deeper locations radially with respect to the IVUS transducer. This phenomenon is more common with the rotational IVUS modality where the IVUS catheter is constructed of a single unfocused ultrasound transducer. The singularity of the transducer lends it more prone to shadowed regions due to calcifications, because the single unfocused transducer responsible for imaging has backscatter

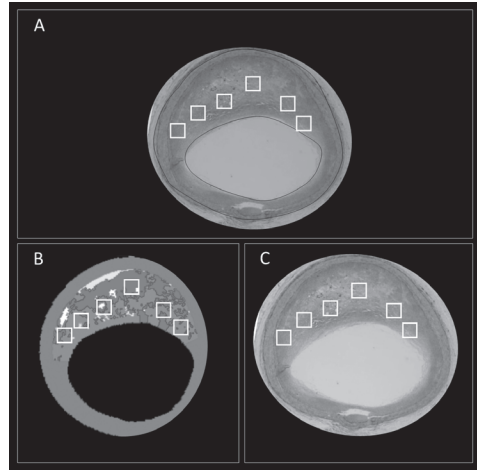


Figure 1. Region-of-interest (ROI) selection for ex vivo accuracy assessment. Four investigators were engaged in the separate tasks of (A) drawing histology image outlines on transparent paper with a grid of $1/3 \times 1/3$ mm regions and highlighting alternating regions; (B) finding matching regions on corresponding VH IVUS images and interpreting the VH IVUS outcome in each ROI; and finally (C) interpreting the pathology outcome in all ROIs. The investigators were blinded to each other's results.

blocked from the calcium in the path of the ultrasound. In contrast, the previous work with the 20 MHz solid-state IVUS modality⁵ was less prone to the calcium-induced shadowing due to the synthetic aperture image formation from a multi-element transducer array. Thus, in the present study, the accuracy results were determined by both, including and excluding regions that were potentially shadowed by the heavily calcified areas.

In an independent manner, two interventional cardiologists (CMC and HMG) analysed 253 randomly selected heterogeneous ROIs (30 random lesions). The comparison was performed blinded to the histologic findings to assess the inter- and intra-observer reproducibility of VH IVUS image interpretation. At

first, the VH IVUS tissue type classification was performed in consensus between the two physicians to compare with the validation analysis done by the four investigators. Later, after a period of one month, the same 253 ROIs were re-analysed by the same two interventional cardiologists, to assess the intra-observer reproducibility.

Data Analysis. The statistical computation that was applied is based on a test for a single state. Thus for each computation, the results were interpreted as being in one of two states: chosen tissue type or not of the chosen tissue type. Since this manuscript addresses four plaque tissue types, one of the types is

chosen (Type X) and the three remaining tissue types are combined as 'not of type X'. Then the common definitions for sensitivity, specificity, and accuracy can be applied. Finally the Kappa statistic was computed for determining the inter- and intra-observer reproducibility of the 45 MHz VH IVUS images.

RESULTS

45 MHz VH IVUS Algorithm *Ex Vivo* Accuracy Assessment. VH IVUS tissue maps were constructed from 45 MHz IVUS data collected from a total of 120 lesions from 60 coronary artery

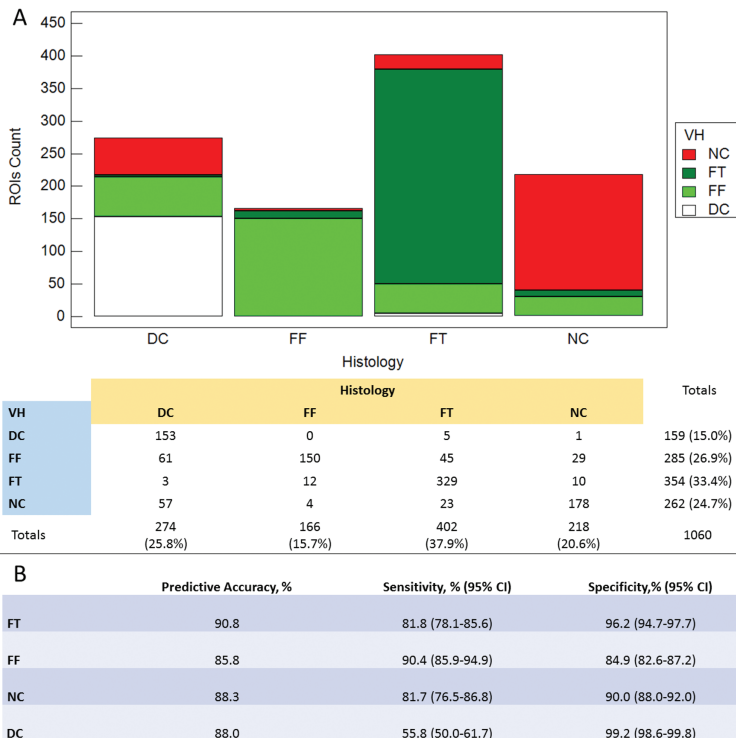


Figure 2. VH IVUS predictive accuracy for tissue types including all regions-of-interest (ROIs; n=1060). (A) Agreement between VH IVUS and histology and truth-table for the accuracy measurements. (B) VH IVUS predictive accuracy, sensitivity and specificity by tissue types as compared with histology. DC = dense calcium; FT = fibrous tissue; FF = fibro fatty; NC = necrotic core.

specimens (51 hearts, 42 male, 9 female; 14 black, 37 white; average age 57.0 ± 12.7 years). The *ex vivo* accuracy was determined for all 1060 ROIs and again after excluding the 290 ROIs shadowed by calcium. Figure 2 describes the truth-table for inclusion of all ROIs and the corresponding accuracy statistics of sensitivity, specificity, and predictive accuracy. When including all ROIs the predictive accuracy ranged from a low of 85.8% for fibro-fatty to a high of 90.8% for fibrous tissue type, with an overall accuracy of 76.7% for all tissue types combined. The sensitivities were all greater than 81% except for dense calcium which is relatively low at 55.8%. The lowest specificity

was for fibro-fatty at 84.9% with the other three tissue types at 90% or higher. The truth-table resulting from the removal of the ROIs positioned behind calcium with the corresponding accuracy statistics is presented in Figure 3. The predictive accuracy ranged from a low of 93.0% for fibrous to a high of 96.8% for fibro-fatty tissue, with an overall accuracy of 88.6% for all tissue types combined. The sensitivities fall in the 82% to 93% range, while the specificity values remain high with all values greater than 90%.

Observer Reproducibility for VH IVUS Image Interpretation. Table 1 describes the inter-observer reproducibility analysis of VH IVUS

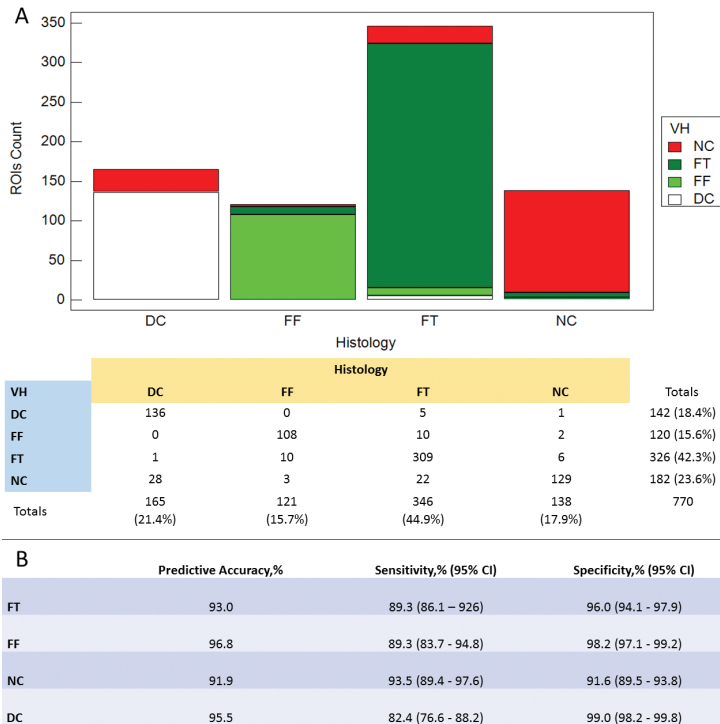


Figure 3. VH IVUS predictive accuracy for tissue types excluding all calcium-shadowed ROIs (n=770). (A) Agreement between VH IVUS and histology and truth-table for the accuracy measurements. (B) VH IVUS predictive accuracy, sensitivity and specificity by tissue types as compared with histology. DC = dense calcium; FT = fibrous tissue; FF = fibro fatty; NC= necrotic core.

Table 1. Inter-observer reproducibility of VH IVUS interpretation without exclusion of shadowed ROIs (n=253). IC=interventional cardiologist

Developer	IC				Totals
	DC	FF	FT	NC	
DC	17	0	1	7	25(9.9%)
FF	1	50	9	3	63(24.9%)
FT	0	11	93	8	112(44.3%)
NC	1	2	15	35	53(20.9%)
Totals	19 (7.5%)	63 (24.9%)	118 (46.6%)	53 (20.9%)	253

Table 2. Intra-observer reproducibility of VH IVUS interpretation without exclusion of shadowed ROIs (n=253). IC=interventional cardiologist

IC 2 nd Analysis	IC 1 st Analysis				Totals
	DC	FF	FT	NC	
DC	17	0	0	2	19(7.5%)
FF	0	61	3	0	64(25.3%)
FT	0	2	112	9	123(48.6%)
NC	2	0	3	42	47(18.6%)
Totals	19 (7.5%)	63 (24.9%)	118 (46.6%)	53 (20.9%)	253

image interpretations, without exclusion of shadowed ROIs (n=253). There was substantial agreement¹⁹ ($k=0.66$) between the assessment performed by the four investigators and the assessment performed by the independent interventional cardiologists. Table 2 summarizes the intra-observer reproducibility analysis without exclusion of shadowed ROI, where there was higher agreement ($k=0.88$).

DISCUSSION

The main findings of the present manuscript can be summarized as follows: first, a statistically robust algorithm was designed to yield analysis of 45 MHz IVUS backscatter, resulting in colour-coded tissue maps of the data; second, the VH IVUS algorithm with the 45MHz catheter had predictive accuracy >85.8% for each tissue type as compared with histology;

third, the predictive accuracy for each tissue type improved to >91.9% when calcium shadowed areas were not taken into consideration; fourth, tissue types classification and resulting interpretation of VH IVUS images showed high intra- and inter-observer reproducibility.

The present work is the first histologic validation of VH IVUS using a 45MHz rotational IVUS catheter. Adapting the VH IVUS algorithm to the 45 MHz catheter is nontrivial since the physical properties of the target plaque tissue types are quite distinct from the same tissue at the lower 20 MHz bandwidth, that was previously reported. One key difference is that the attenuation at 45 MHz is considerably greater than at 20 MHz for both blood and tissue^{20, 21}. Another consideration is the fact that the 20 MHz catheter has a multi-element transducer array with synthetic aperture image formation, while the 45 MHz catheter has a single mechanically rotated unfocused transducer. It has

been shown that these factors influence the ultrasound's depth of field and characteristic resolution²². Figure 4 illustrates an example of IVUS grey-scale images obtained at 20 MHz and 45 MHz from the same location in an *ex vivo* coronary artery sample, with the corresponding VH IVUS images and histologic findings. It is evident, that the 20 MHz image has greater IVUS depth of penetration and the 45 MHz image has greater axial resolution (i.e., in the direction of the ultrasound beam) while it lacks in the depth of penetration due to higher attenuation (see Figure 4). In this 45 MHz IVUS study, the greater effect of calcium-induced shadowing and loss of signal with depth can be observed in the increased amount of fibro-fatty tissue appearing behind dense calcifications as demonstrated in the 45

MHz VH IVUS image in Figure 4. This is due to the fact that spectral properties of backscatter from atherosclerotic fibro-fatty tissue can overlap with properties of backscatter from attenuated ultrasound, resulting in an incorrect classification of tissue type. This phenomenon also explains the low sensitivity observed for dense calcium and the low specificity observed for fibro-fatty tissue in the ROI-cohort without exclusion of calcium-shadowed ROIs. Hence, for clinical studies utilizing the 45 MHz VH IVUS algorithm, regions with dominant shadowing can be excluded from analysis. This greatly increases the sensitivity of dense calcium and to a lesser extent the sensitivity of necrotic core tissue type while increasing the specificity of the fibro-fatty tissue type.

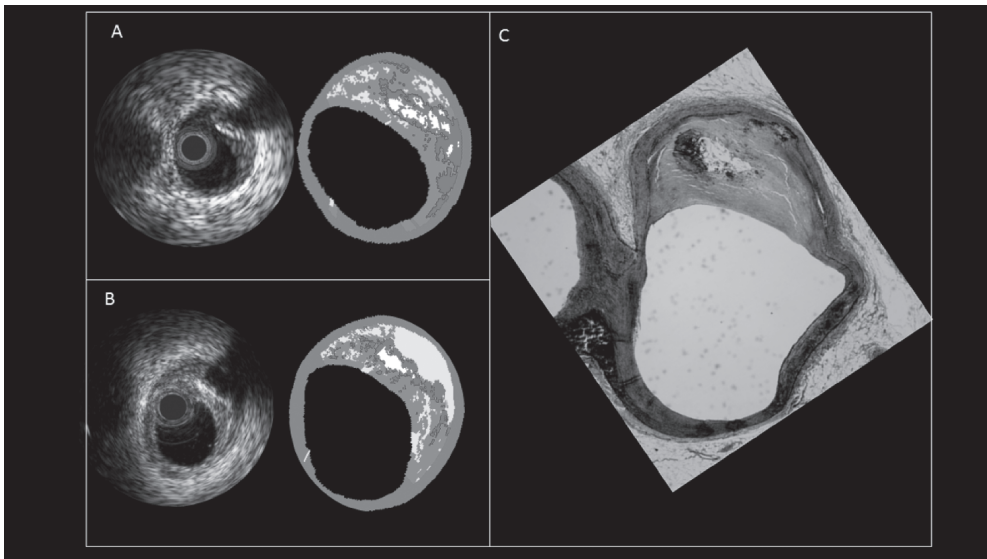


Figure 4. Examples of (A) 20 MHz and (B) 45 MHz IVUS images with corresponding VH IVUS images, collected *ex vivo* in a human coronary lesion (C). The 20 MHz IVUS image has lower axial resolution, but lesser attenuation in signal behind an area of dense calcification, and is displayed with a 10 mm field-of-view. Whereas, the 45 MHz IVUS image has higher axial resolution, but higher attenuation of signal behind the dense calcification (evident from the increased fibro-fatty tissue in the VH IVUS image), and is displayed with an 8 mm field-of-view. This plaque phenotype is classified as a calcified fibroatheroma as it has a visible fibrous cap covering a more than 10% confluent dense calcium and necrotic core.

The results lend themselves to direct comparison with previously reported measurements for the 20 MHz VH IVUS algorithm⁵. The previous manuscript reported predictive accuracy in the range of 93.5% to 96.7% which is comparable to the 45 MHz VH IVUS results when excluding ROIs located behind heavy calcifications (93-95.5%) and ranged from approximately 85% to 90% when including all ROIs.

It may be argued that, with similar catheter accuracy for tissue types, the change for the 45 MHz IVUS catheter is inconsequential. However, the similar accuracy between the 20 and the 45 MHz is in terms of correct colour code interpretation related to histology, and not to any dimensional assessment. The higher axial resolution of the 45 MHz IVUS has potential to improve the coronary atherosclerosis research and raises several questions to be answered in the future. The higher resolution may improve the discernment of the *in vivo* plaque phenotype, identifying with more precision, for instance, if a necrotic core is in contact with the lumen or not. In addition, the better resolution may enhance the ability to quantify tissue type changes with application in natural history of atherosclerosis trials, bioresorbable coronary scaffold degradation, pharma interventions, etc.

The reported inter-observer reproducibility analysis showed consistent agreement between the four investigators and the two

independent interventional cardiologists and may translate to clinical utility for this tool. Additionally, the intra-observer reproducibility demonstrated stable response in a relatively large sample of ROIs.

Limitations. Although the 45MHz catheter has improved axial resolution, the detection of a thin fibrous cap, which defines plaque vulnerability (less than 65 μm in thickness)²³ is still below the axial resolution of current IVUS and this may lead to false positive identification of some vulnerable atheromas. However, with similar accuracy and yet lower resolution, the spectral analysis approach of ultrasound backscatter used with the 20 MHz IVUS catheter has shown prognostic relevance⁹⁻¹¹.

CONCLUSION

Tissue classification by 45 MHz VH IVUS technology, when not influenced by significant calcium-induced acoustic attenuation, provided combined tissue accuracy >88% to identify tissue types as compared with the gold-standard histologic assessment, with high inter- and intra-observer reproducibility.

Conflicts of interest: Anuja Nair is an employee of Volcano Corporation. The other authors did not receive grants or financial support from industry or from any other source to prepare this manuscript.

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Chapter 1.3

Computed tomography angiography for the interventional cardiologist

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ABSTRACT

In recent years, coronary CT angiography(CCTA) has become a widely adopted technique, not only due to its high diagnostic accuracy, but also to the fact that CCTA provides a comprehensive evaluation of the total (obstructive and non-obstructive) coronary atherosclerotic burden. More recently, this technique has become mature, with a large body of evidence addressing its prognostic validation. In addition, CT angiography has moved from the field of 'imagers' and clinicians and entered the interventional cardiology arena, aiding in the planning of both coronary and structural heart interventions, being transcatheter aortic valve implantation one of its most successful examples. It is therefore of utmost importance that interventional cardiologists become familiar with image interpretation and up-to-date regarding several CTA features, taking advantage of this information in planning the procedure, ultimately leading to improvement in patient outcomes. On the other hand, the increasing use of CCTA as a gatekeeper for invasive coronary angiography is expected to lead to an increase in the ratio of interventional to diagnostic procedures and significant changes in the daily cath-lab routine. In a foreseeable future, cath-labs will probably offer an invasive procedure only to patients expected to undergo an intervention, perhaps becoming in this change true interventional-labs.

INTRODUCTION

Advances in the field of computed tomography (CT) have made possible the non-invasive evaluation of coronary artery disease (CAD) and in recent years coronary CT angiography (CCTA) has become a widely adopted technique. This was due not only to its high diagnostic accuracy, but also to the fact that CCTA provides a comprehensive evaluation of both obstructive and non-obstructive CAD and, more recently, its prognostic information has been validated.

The initial studies of CCTA addressed mainly its diagnostic accuracy. This was done both by comparison with the gold standard invasive coronary angiography (ICA) and with intravascular ultrasound (IVUS). As the technique became more robust and widely adopted in clinical practice, data were gathered regarding cardiovascular outcomes and this opened a second phase of studies addressing its prognostic value.

The latest technological advances have significantly improved CCTA temporal resolution and volume coverage, leading to a decrease in radiation and contrast dose, and improvements in image quality, that will further reinforce the role of CCTA for the evaluation of patients with possible CAD and potentially for making clinical decisions based on these findings (e.g. CT-based coronary atherosclerotic burden scores and functional assessment of coronary lesions).

CORRELATION WITH ICA: CARDIAC CT DIAGNOSTIC ACCURACY

Many studies have been published evaluating the diagnostic accuracy of CCTA, by comparing

with the gold standard ICA. These were initially done with four-detector row,¹⁻⁴ followed by 16-detector row scanners,⁵⁻⁹ but by that time significant limitations existed related to the dose of contrast, long breath-hold times, and high percentage of segments excluded from analysis due to insufficient image quality. In a meta-analysis of 27 studies comparing CCTA (with scanners of at least 16-detector row) with ICA, the per-patient sensitivity was very high (96%), but the specificity was only modest (74%), leading to a positive predictive value (PPV) of 68%.¹⁰

The 64-detector row scanners are now considered to be the minimum requirement for CCTA.¹¹ In a more recent meta-analysis, including only studies with 64-detector row scanners, the reported per-patient sensitivity was 99%, specificity 89%; PPV was 93% and negative predictive value (NPV) was 100%.¹² Nevertheless, even with 64-detector row scanners, some multicentre trials, have reported low specificity and PPV when evaluating consecutive non-selected patients. In the assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography (ACCURACY) trial, a prospective multicentre evaluating stable patients without known CAD who underwent CCTA before clinically indicated ICA, CCTA had a diagnostic sensitivity, specificity, PPV, and NPV of 94, 83, 48, and 99%, respectively.¹³ The low specificity and PPV reported in this trial could be related to the fact that patients were consecutively included irrespective of the baseline coronary calcium score, body mass index, or heart rate, variables that are well known to influence image quality.

In another multicentre study, Meijboom et al.¹⁴ evaluated the diagnostic performance of CCTA in a population including both stable and

acute chest pain patients without known CAD referred for ICA. No patients or segments were excluded because of impaired image quality attributable to either coronary motion or calcifications and the prevalence of obstructive CAD was 68%, factors that could explain the low per-patient specificity of 64% for CCTA found in this study, leading to a PPV of 86%. Once again, the per-patient sensitivity was 99% and the NPV was 97%.

With the development of dual source scanners, there was a significant increase in temporal resolution, leading to a less dependence on heart rate control.¹⁵ The introduction of new acquisition protocols with prospective ECG-triggering¹⁶ lead to a significant reduction in radiation dose, which was further reduced to ,1

mSv doses with high-pitch spiral acquisitions, without compromising diagnostic accuracy^{17,18} (Figure1).

Likewise, 320-detector row scanners also lead to significant improvements, reducing the radiation dose and amount of contrast while maintaining high diagnostic accuracy.^{19,20}

Addressing another important technical issue in CCTA, the improved spatial resolution of the high-definition scanners are also expected to lead to significant improvements, especially in the evaluation of calcified lesions, in-stent restenosis, lesions stenosis, and plaque composition, without increasing radiation dose.^{21,22}

The possibility of extracting both anatomical and functional information from CT data sets could ultimately lead to significant improve-

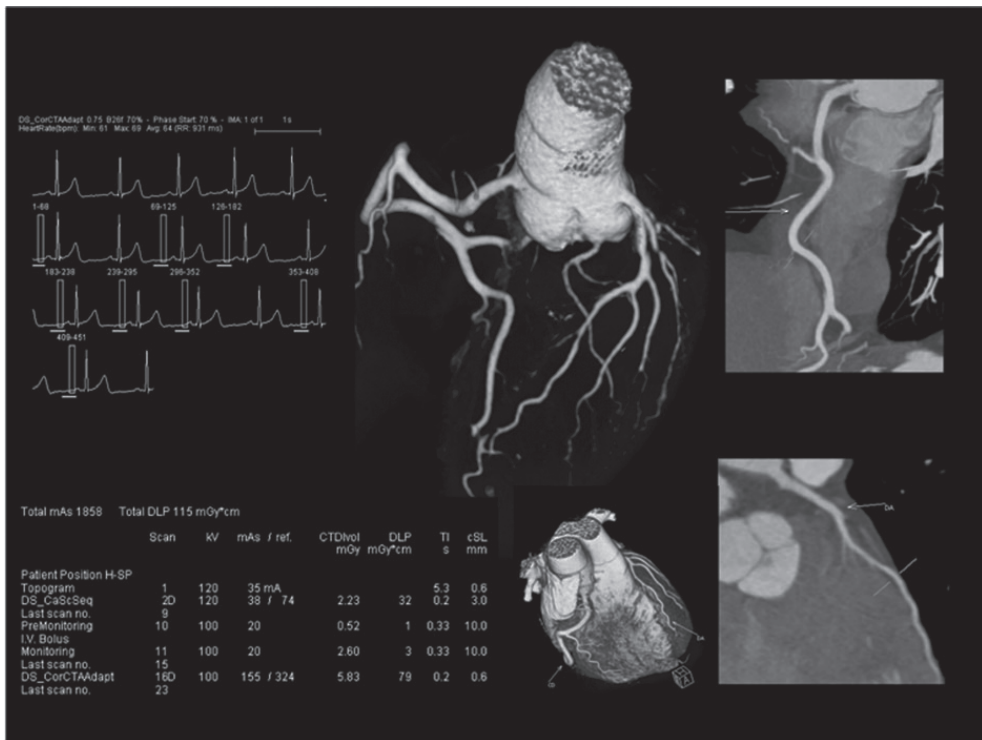


Figure 1: CCTA with prospective triggering with an estimated radiation dose of 1.1mSv (79DLP, conversion factor of 0.014), in a patient with normal coronary arteries.

ments in specificity and PPV, especially in the setting of lesions with intermediate stenosis. This concept has been recently reinforced by the DISCOVER-FLOW,²³ DeFACTO,²⁴ and NXT²⁵ studies that demonstrated a significant improvement in CCTA diagnostic performance when combined with non-invasive fractional flow reserve (FFRCT). This novel method derives the physiological significance of CAD by applying the principles of computational fluid dynamics, taking in consideration not only CAD severity, but also left ventricular mass.

Summing up the different multicentre trials and meta-analysis addressing this issue, it has become clear now that this non-invasive imaging technique has a very high sensitivity for detecting patients with significant CAD, leading to a very high (virtually 100%) NPV, which makes CCTA a perfect gatekeeper for invasive angiography.

The selection of patients for ICA is traditionally based on noninvasive stress testing aimed at identifying patients with obstructive CAD who could benefit from revascularization. Nevertheless, many patients undergoing ICA have normal coronary arteries or nonobstructive lesions, which decrease its diagnostic yield. In a large contemporary registry, with data from almost 400 000 patients referred for ICA, obstructive CAD was found in only 37.6% of the patients, reflecting the low diagnostic yield in routine clinical practice.²⁶ This way, better strategies for the identification of patients in need for ICA are needed and in this regard CT angiography (CTA), by having a high NPV, can be a useful gatekeeper.

In a recent analysis of the large CONFIRM registry, the rates of ICA and revascularization after a CCTA with no CAD (2.5 and 0.3%, respectively) or mild CAD (8.3 and 2.5%,

respectively) were very low. On the other hand, in this registry, obstructive CAD ($\geq 50\%$ stenosis) by CCTA was associated with a high percentage of revascularization, ranging from 28% for 1 vessel to 66.8% for 3 vessel CAD, supporting the concept of CCTA as a gatekeeper for ICA.²⁷

Presently, some patients are referred for ICA for pure diagnostic purposes, like the evaluation of possible CAD in patients scheduled to undergo non-coronary cardiac surgery, to evaluate the need of concomitant myocardial revascularization. In those patients, CCTA seems to be a valid alternative^{28,29} and is considered to be appropriate when the pre-test probability of CAD is not high^{11,30} (Figure 2).

CCTA might also become an alternative to ICA for a routine evaluation of coronary arteries following heart transplantation,³¹ although this can be difficult in the setting of more advanced diffuse disease of chronic transplant arteriopathy, in face of the current limitations of CCTA spatial resolution.

Patients with new-onset or newly diagnosed heart failure and no prior CAD are recommended to undergo the evaluation of possible CAD and are frequently referred for ICA.^{11,32,33} In this setting, CCTA might be a valid alternative to exclude CAD as the underlying aetiology for dilated cardiomyopathy, with the advantage of providing in the same scan information on cardiac vein anatomy that might be potentially relevant in candidates for cardiac resynchronization therapy.^{34,35} Owing to its non-invasive nature and the ability to evaluate the coronary wall, CCTA has also been considered as a valuable imaging modality for coronary dissections and intramural haematomas, especially in the follow-up of patients managed conservatively.³⁶

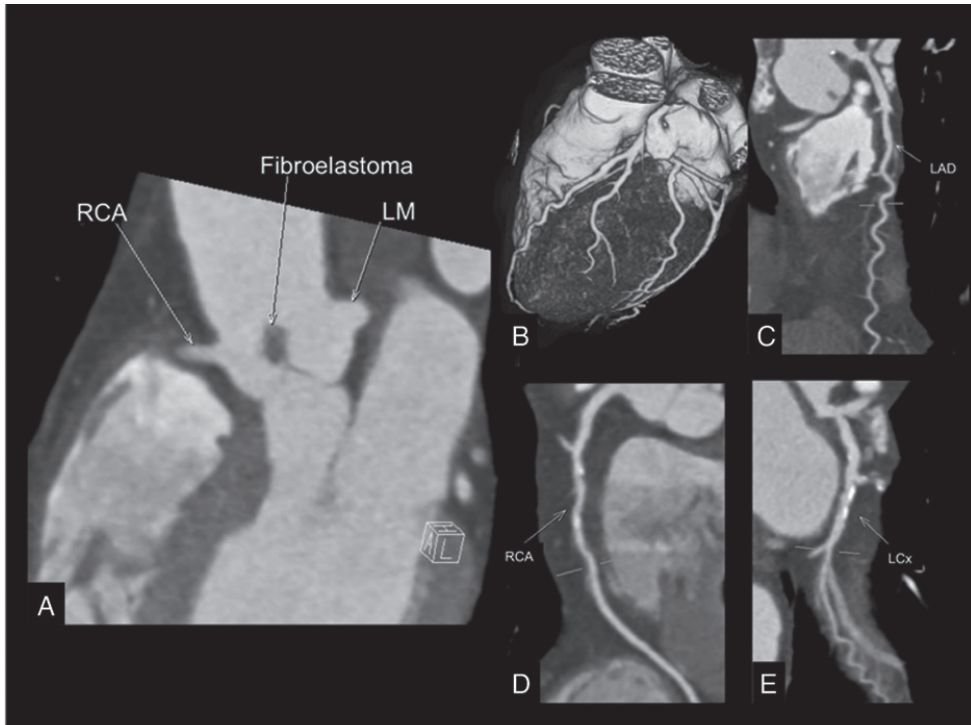


Figure 2: CCTA for the exclusion of obstructive CAD prior to valvular surgery, in a patient with a fibroelastoma of the aortic valve. Multiplanar (A, C, D, and E) and volume-rendering technique (B) reconstructions showing the mass attached to the aortic cusps and predominantly calcified non-obstructive coronary lesions in the RCA and LCx. This 66-year-old female patient underwent surgery without the need for invasive coronary angiography.

The use of CCTA in these purely diagnostic indications, coupled with a better selection of patients for ICA using CCTA as a gatekeeper, are expected to lead to an increase in the ratio of interventional to diagnostic procedures in the catheterizations laboratories.

In conclusion, when evaluating the diagnostic accuracy of CCTA, some factors have to be considered, that could influence the performance of the exam, and could explain the differences between different studies:

- type of scanner technology (64-detector row scanners are now considered to be the typical minimum standard).

- population studied, regarding expected prevalence of obstructive CAD (can be calculated with pre-test CAD probability scores—CCTA is indicated in low-to-intermediate CAD probability).
- inclusion of non-evaluable segments in the analysis (considering non-evaluable segments as positive improves sensitivity but reduces specificity).
- inclusion of patients with a high body mass index, high calcium score or high heart rates, factors known to negatively affect image quality.

EVALUATION OF PATIENTS WITH PREVIOUS REVASCLARIZATION

The evaluation of patients with previous revascularization procedures can be challenging for CCTA and these patients are usually recommended to undergo stress imaging.³⁷

In the evaluation of patients after PCI, there are two sets of difficulties faced by CCTA. Metallic artefacts caused by the struts (influenced by the type of alloy and strut thickness), impairing the assessment of stents with a diameter ≥ 3 mm and/or stents with thick struts (≥ 140 μm).^{38,39} In a meta-analysis of studies with 64-rows scanners including

1398 stents, the sensitivity and specificity for the detection of in-stent restenosis was only 79 and 81%, respectively.⁴⁰ The increasing adoption of bioresorbable scaffolds in clinical practice might lead to an improvement in the diagnostic accuracy of

CCTA for stent evaluation, since the metallic artefacts are only limited to the radio-opaque markers at scaffold margins.⁴¹

Besides the aforementioned difficulties imposed to the evaluation of the stented lesions, these patients frequently have other lesions in the coronary tree, some of them of intermediate degree of stenosis, that could impair specificity on a patient-based level,

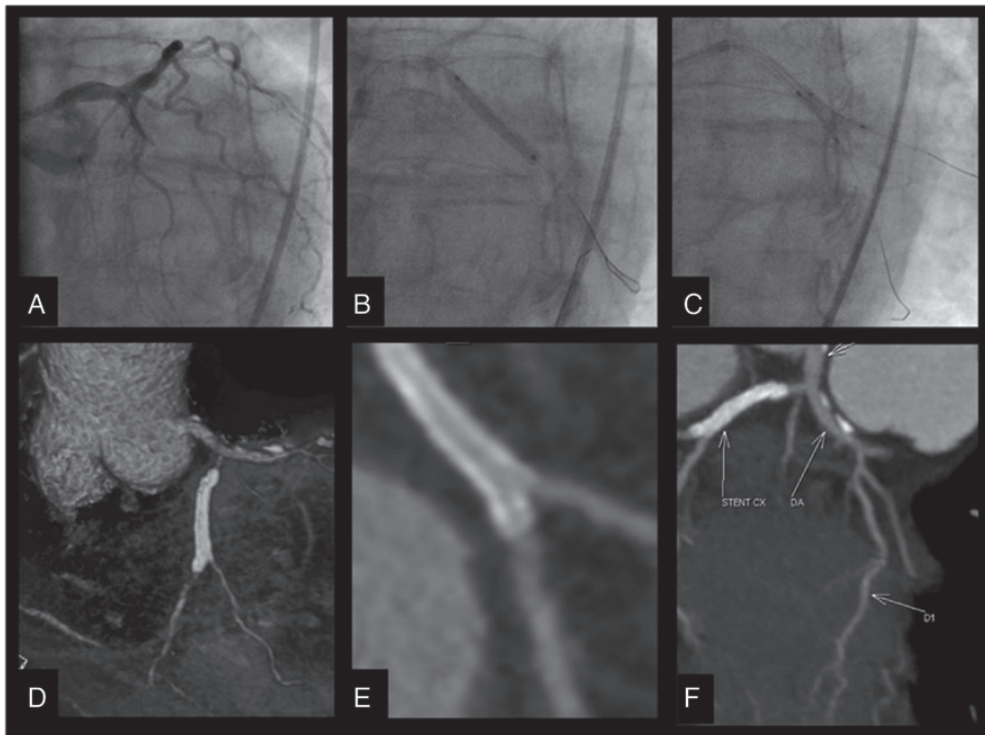


Figure 3: CCTA evaluation of a patient with previous PCI. (A) Chronic total occlusion of the proximal circumflex; (B) implantation of a Xience 2.5/23 mm stent; (C) final kissing-balloon; (D) CCTA with volume-rendering technique reconstruction; (E) multiplanar reconstruction with a detail of the ostial scaffolding to the first obtuse marginal; (F) mixed plaque in proximal LAD with intermediate stenosis.

since specificity and/or PPV of CCTA has been shown to be lower in cohorts with higher disease prevalence^{13,14,24} (Figure 3). This last limitation is also true regarding the evaluation of the native vessels in patients with prior coronary artery bypass grafts, because of the extent of CAD, often associated with severe calcifications and small vessel calibre, leading to a decrease in CCTA accuracy in this setting.^{42,43}

In contrast, CCTA has a high accuracy for the evaluation of graft patency, due to the larger diameter, less motion and less frequently calcified, when compared with the native arteries (Figure 4). In addition, disease in grafts more often presents as occlusion rather than stenosis, which are easy to depict in CCTA. In

a meta-analysis including studies with both 16- and 64-rows scanners, the sensitivity and specificity for the detection of significant ($\geq 50\%$) graft stenosis was 96 and 97%,⁴⁴ documenting a high overall performance for noninvasive graft assessment.

PLAQUE CHARACTERIZATION AND CORRELATION WITH OTHER IMAGING MODALITIES: PUSHING THE LIMITS OF SPATIAL RESOLUTION

Since many myocardial infarctions present in previously asymptomatic patients and not infrequently the first manifestation of CAD is sudden cardiac death, the main challenge

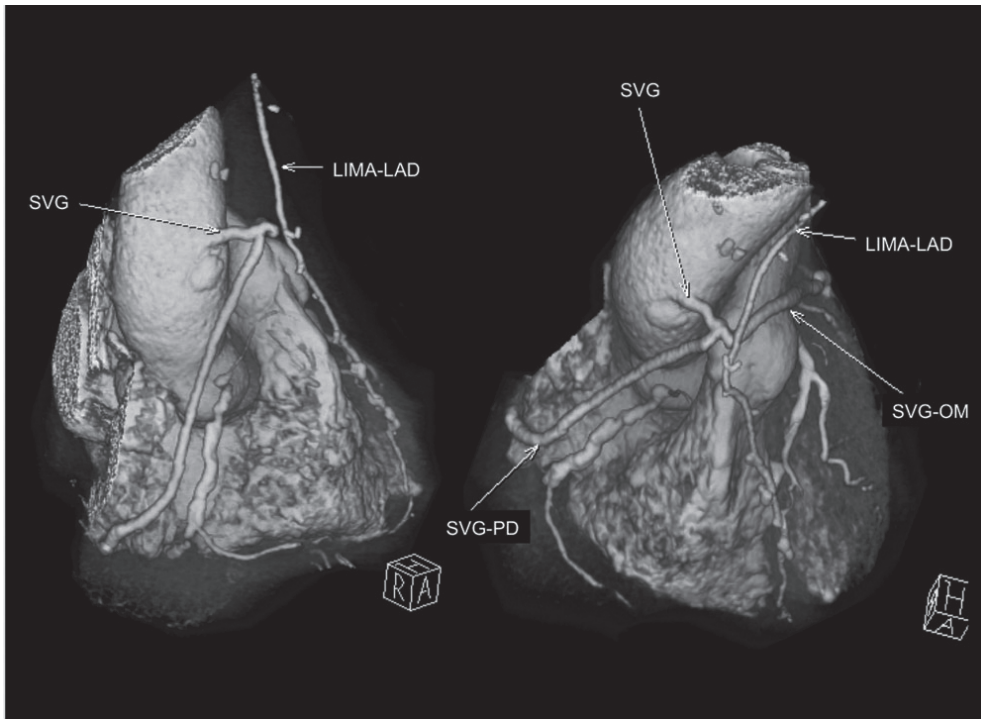


Figure 4: Evaluation of bypass grafts by CCTA. Volume-rendering technique reconstructions showing saphenous vein grafts (SVG) to the posterior-descending (PD) and obtuse marginal (OM) branches and a left internal mammary artery to the left anterior descending artery (LIMA-LAD).

that we face today is to identify patients at risk before those events occur. In this regard, clinical evaluation alone might be insufficient, since only a minority of patients experiencing and acute myocardial infarction would have been identified as high risk by the available risk factors based scores, prior to the event.⁴⁵

Coronary plaque characterization, namely the identifications of features of vulnerability, has been the focus of extensive research by different coronary imaging modalities such as IVUS, IVUS-virtual histology (IVUS-VH), and optical coherence tomography (OCT). These imaging modalities, although providing the highest possible spatial resolution, have their applicability limited by their invasive nature, and are usually employed in patients already referred for invasive angiography because

of suspected CAD or with acute coronary syndromes (ACS). Many of these patients will be (independent of the result of the imaging modality) under secondary prevention of CAD, which changes natural history and reduces the risk of subsequent cardiovascular events.^{46,47}

In the multicentre PROSPECT study,⁴⁷ a large plaque burden, a small lumen area and the presence of a thin cap fibroatheromas (TCFA) assessed by IVUS-VH in non-culprit lesions, were independent predictors of future major adverse cardiac events. In this study, lesions that led to major adverse cardiac event had a high plaque burden by IVUS, but were mild by baseline angiography, with a mean diameter stenosis of only 32%.

On the other hand, ischaemia based imaging modalities have also some limitation in

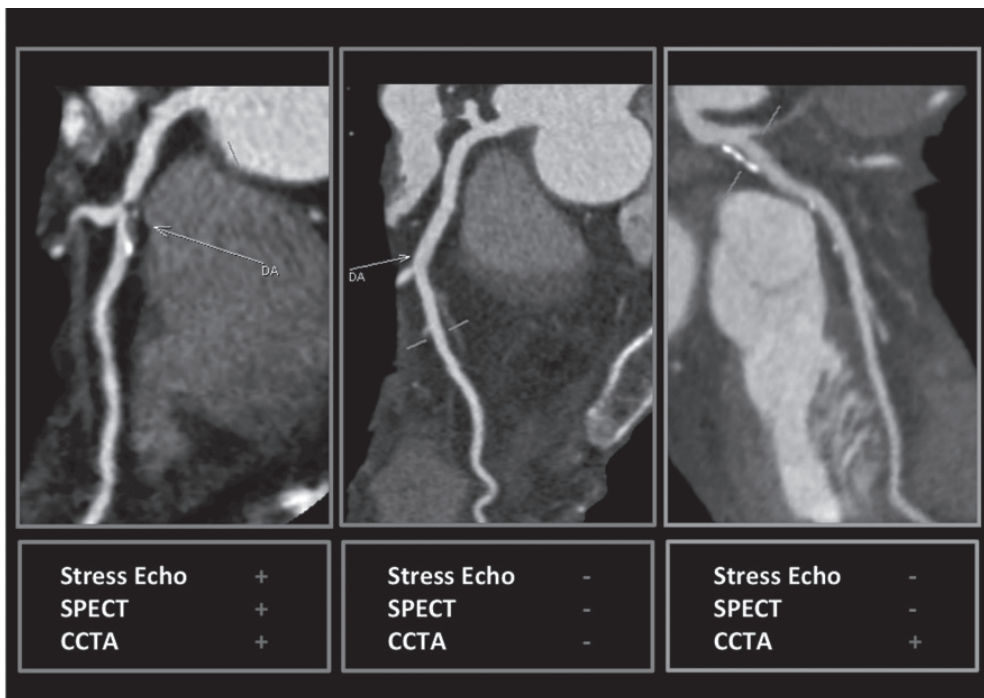


Figure 5: Identification of non-obstructive CAD as a unique feature of CCTA as a non-invasive CAD imaging modality.

this regard, especially related to the fact that nonobstructive lesions are not associated with ischaemia, but can also be the culprit of coronary events⁴⁷⁻⁵⁰ (Figure5).

Several studies have reported on the correlation between CCTA plaque features with invasive coronary imaging modalities like IVUS, IVUS-VH, and OCT. In a meta-analysis published in 2011, CCTA had a good diagnostic accuracy to detect coronary plaques compared with the gold standard IVUS, with an area under the curve for the receiver operating characteristics analysis of 0.94, a sensitivity of 90%, and a specificity of 92%, with small differences in the assessment of plaque area and volume, percent area stenosis, and a slight overestimation of lumen area.⁵¹

Several CCTA plaque characteristics have now been shown to be more prevalent in culprit lesions in the setting of ACSs. In a study done by Hoffman et al.⁵², a significantly larger plaque area and positive remodelling were found in culprit lesions of ACS patients, compared with patients with stable CAD. Positive remodelling has been considered for many years a surrogate marker of plaque vulnerability, and many of these lesions have a high plaque burden, that is, underestimated by luminal angiograms because they undergo expansive or positive outward enlargement and are frequently non-stenotic⁴⁹ (Figure6). In another small study, Motoyama et al.⁵³ found that culprit lesions of patients with ACS had more frequently positive remodelling, low

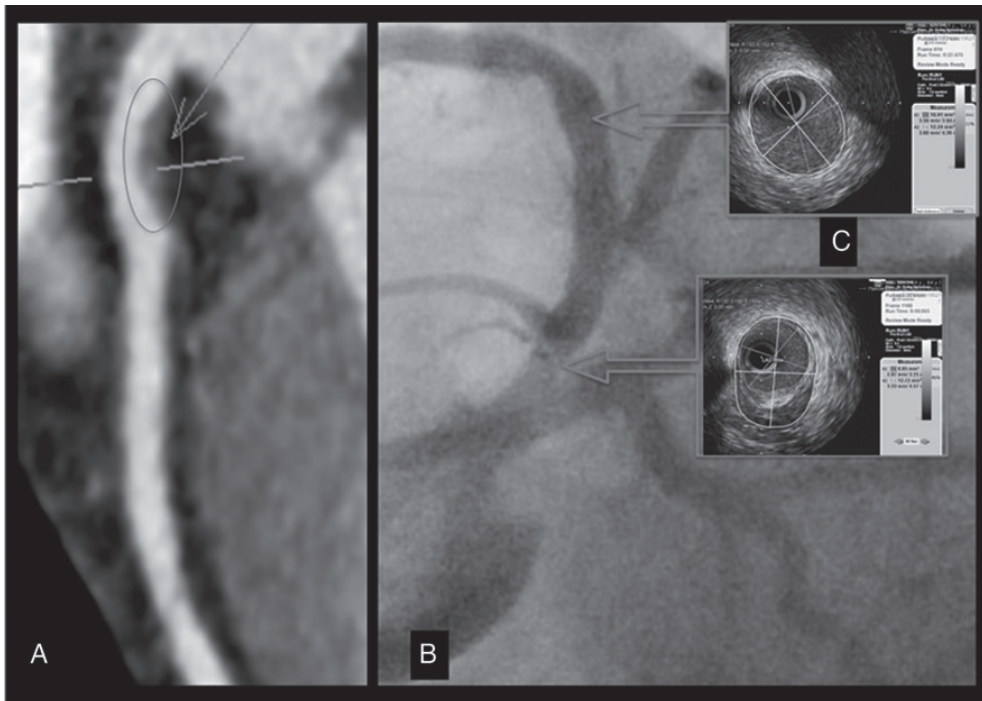


Figure 6: CCTA depicting a non-calcified plaque in the proximal left anterior descending artery without significant stenosis (A). In invasive angiography (B), this lesion was not apparent but was confirmed with IVUS (C).

density plaque [<30 Hounsfield units (HU)] and spotty calcifications.

Extending on these results, the same authors conducted a large prospective trial including 1059 patients who underwent CCTA, and demonstrated that positive remodelling and low-attenuation plaques were associated with the subsequent development of ACSs.⁴⁸ In this study, the percentage of patients with these two features that subsequently developed and ACS was 22.2%, compared with only 3.7% for patients with only one feature and 0.5% for patients with neither positive remodelling nor low-attenuation plaques.

In a study by Kashiwagi et al.,⁵⁴ evaluating 105 patients with CAD, CCTA findings have been also validated against OCT. In this study, TCFA had higher remodelling indexes, lower CT attenuation values and more often 'ring-like' enhancement by CCTA (44% in the TCFA group vs. 4% for the non-TCFA group).

In a recent study, Papadopoulou et al.⁵⁵ evaluated the distribution and composition of coronary plaques at bifurcations with both CCTA and IVUS-VH. They found that plaques with a high-risk phenotype as assessed by IVUS-VH were more commonly found in segments proximal to the bifurcation, rather than in the bifurcation or distal to the bifurcation. Interestingly, by evaluating the geometry of the bifurcation, a feature easily assessed with CCTA, they found that a wide angle was more often associated with high-risk plaques.

As a group, these studies provide evidence on how CCTA can noninvasively provide information on several plaque characteristics—like plaque volume, remodelling, plaque composition, distribution, and geometry of the coronary tree—that can be associated with the development of future coronary events.

LIMITATIONS OF CCTA FOR PLAQUE CHARACTERIZATION

Despite significant improvements in image quality, spatial resolution has not seen significant improvements and remains presently one of the major technical limitations of CCTA. The spatial resolution of currently available scanners (in the range of 400–600 μm) prevents the detailed assessment of several features associated with vulnerable plaques, as is the case of the evaluation of a thin fibrous cap.⁵¹ This spatial resolution is significantly worse than that of IVUS (200–250 μm) or OCT (10–15 μm)⁵⁶ and this has to be taken in consideration and should temper our expectations regarding the potential of CCTA for plaque assessment in face of the limitations already faced by other invasive imaging modalities regarding the identification of the vulnerable plaque.

Another limitation faced by CCTA plaque characterization is related to the fact that coronary plaque attenuation values are significantly modified by differences in lumen contrast densities, as has been demonstrated both *ex vivo* and *in vivo*.^{57,58} This is important because lumen attenuation can be influenced by different contrast and scanning protocols and therefore makes it difficult to establish thresholds for the definition of low-attenuation plaque as a surrogate of vulnerable plaque that can be widely adopted.

One last important limitation in this regard is related to the reproducibility of CCTA plaque measurements, as many previous studies have reported significant inter-observer variability in the assessment of several CCTA plaque characteristics.^{59,60} This is dependent on image quality, vessel size and degree of calcification, features that are dependent again on spatial resolution. In the future, improvements in

spatial resolution and the development of robust dedicated automated quantification software could contribute to overcome these difficulties.

PROGNOSTIC VALUE: CARDIAC CT REACHING ADULTHOOD

As the technique became more robust and more data become available, CCTA proved also to be a strong prognostic tool for the evaluation of patients with suspected CAD.⁶¹⁻⁶⁶ Pundziute et al.⁶¹ in 100 patients with known or suspected CAD, showed that there were no major cardiac events on the subset of patients without CAD, contrasting with the 30% event rate of patients with CCTA documented CAD upto 16 months. More importantly, the cumulative event rate of patients with non-obstructive CAD was higher and different from the excellent prognosis of patients without plaques on CCTA. This earlier study had some limitations, both related to the small sample size and the fact that some of the included cardiovascular events (revascularization and unstable angina requiring hospitalization) are not 'hard' endpoints and could be influenced by the CCTA result.

Min et al.⁶² evaluated the prognostic value of identifying CAD with CCTA in a single-centre cohort of 1127 patients with stable chest symptoms. A negative CCTA was associated with an excellent prognosis and some CCTA-derived CAD indexes were developed and prognostically validated. Some of those indexes were expected to convey prognostic information, as these observations extend on what was previously documented for ICA, as was the case of number of diseased vessels, degree of stenosis and more proximal location.

More importantly was the fact that they were able to demonstrate the prognostic value of more CCTA-specific indexes derived from the comprehensive information of both obstructive and non-obstructive plaque: the segment involvement score (SIS), obtained as the total number of segments with plaque (1 point for each segment with plaque, irrespective of the degree of luminal stenosis) and the segment stenosis score (SSS), obtained by grading the stenosis severity of each segment with plaque (segments graded from 0 to 3 according to the degree of stenosis). For both SIS and SSS, a value of 5 was identified as the best cut-off to predict all-cause mortality.

In 2011, two meta-analyses were published^{63,64} evaluating the prognostic value of CCTA and (not surprisingly) had the same two main conclusions: (i) that the presence and extent of CAD on CCTA are strong and independent predictors of future with an excellent prognosis. Of note, in both meta-analysis, it was possible to distinguish between the excellent prognosis of patients in the absence of CAD from that of patients with non-obstructive CAD, as documented by CCTA.

In the CCTA registry CONFIRM (Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: an International Multicentre Registry),⁶⁵ which included >20 000 patients, the absence of CAD was associated with an excellent prognosis (annualized death rate of 0.28%). At 2.3 years follow-up, both obstructive and non-obstructive CAD conferred an increased mortality risk with hazard ratios of 2.6 and 1.6, respectively.

In another report of the CONFIRM database, it was demonstrated that CCTA measures of CAD severity yield independent and incremental prognostic value to that of left ventricle ejection fraction (LVEF) and routine clinical

predictors.⁶⁶ In this report, all-cause mortality occurred in 0.65% of patients without CAD, in 1.99% of patients with non-obstructive CAD, 2.90% of patients with non-high-risk CAD, and 4.95% with high-risk CAD.

In what concerns the incremental prognostic value of CCTA over other CAD imaging modalities, Werkhoven et al.⁶⁷ have evaluated the potential synergistic effect of a functional test (single-positron emission CT-SPECT) and CCTA (as an anatomical test). They found CCTA to be an independent predictor of cardiovascular events and its prognostic information was incremental to that of SPECT, in line with previous studies that showed an incremental value over exercise ECG testing.⁶⁸ Nevertheless, although the potential synergistic role of both anatomical and functional imaging modalities can be appealing, for both diagnostic and prognostic purposes, this concept might be difficult to prove as a cost-effective strategy and probably not desirable to perform both exams in the same patient. In addition, some studies evaluating the relative prognostic value of CCTA and exercise ECG testing suggested that CCTA may be used as a first line exam, since a normal CCTA is always associated with a good prognosis, independent of the results of exercise ECG, and a non-negligible percentage of patients with a normal exercise ECG are found to have significant stenosis on CCTA, a finding associated with worse outcomes.^{69,70}

This way, more research is needed to further evaluate the role and relative position of the different imaging modalities in the algorithm for the evaluation of patients presenting with possible CAD. One proposed approach is to select the type of exam according to the patient CAD probability, favouring functional exams in the intermediate probability and CCTA for the

lower probability patient, as recommended by the National Institutes of Clinical Excellence (NICE) Clinical guidelines on 'chest pain of recent onset'.⁷¹ The prognostic evaluation of CCTA data (as is the case for other CAD imaging modalities) is dependent on the baseline risk of the population included and the outcomes evaluated. Studies including a higher percentage of patients with intermediate-to-high CAD probability and/or risk, or even with known CAD, can more easily document the prognostic power of CCTA. This is also the case for studies evaluating the impact on total cardiovascular events (instead of only 'hard' CV events). This is especially true regarding the inclusion of revascularizations after CCTA, as the result of this anatomical test could influence and increase subsequent procedures. For this reason, many studies addressing this issue have now excluded earlier revascularizations from the outcome analyses.^{63,72}

In another recently published study, Andreini et al. evaluated the long-term (.4 years follow-up) prognostic value of CCTA in a cohort of 1304 patients with suspected CAD.⁷² Although the authors excluded patients with known CAD, the mean pre-test probability of CAD in the study population was high (42.5%, with one quarter of the patients having a high CAD probability) and they also included patients with possible ACSs. This led to a higher than expected hard event rate for a stable CAD population (event-free survival of 54% for patients with obstructive CAD). Therefore, the design of studies to address the prognostic value of CCTA can be influenced by these two important aspects: inclusion of many high risk/high-CAD probability patients and of revascularization as a cardiovascular event can lead to an overestimation of the prognostic power of CCTA.

When comparing the prognostic information conveyed by CCTA with that of other non-invasive imaging modalities such as SPECT or stress echo, it is remarkable that the excellent prognosis of a normal CCTA—no plaque—0.17% annual event rate in a CCTA metaanalysis⁶⁴ is even lower than what was previously demonstrated for patients with normal perfusion on SPECT (0.6% annual event rate) or normal wall motion on stress echo (1.0% annual event rate) in previous meta-analysis.^{73,74}

This difference could be explained by the fact that CCTA identifies non-obstructive

CAD (usually negative of stress-based exams) and in this way provides a more comprehensive evaluation of the total coronary atherosclerotic burden that has a stronger prognostic meaning (Figure 7).

Scores that reflect the comprehensive information provided by CCTA have already been developed and they can be useful tools to quantify the coronary atherosclerotic burden. One of these is the CT-SYNTAX score, a CCTA adaptation of its angiographic counterpart,

known to reflect the severity of CAD which has prognostic implications and is a useful tool for decision-making on myocardial revascular-

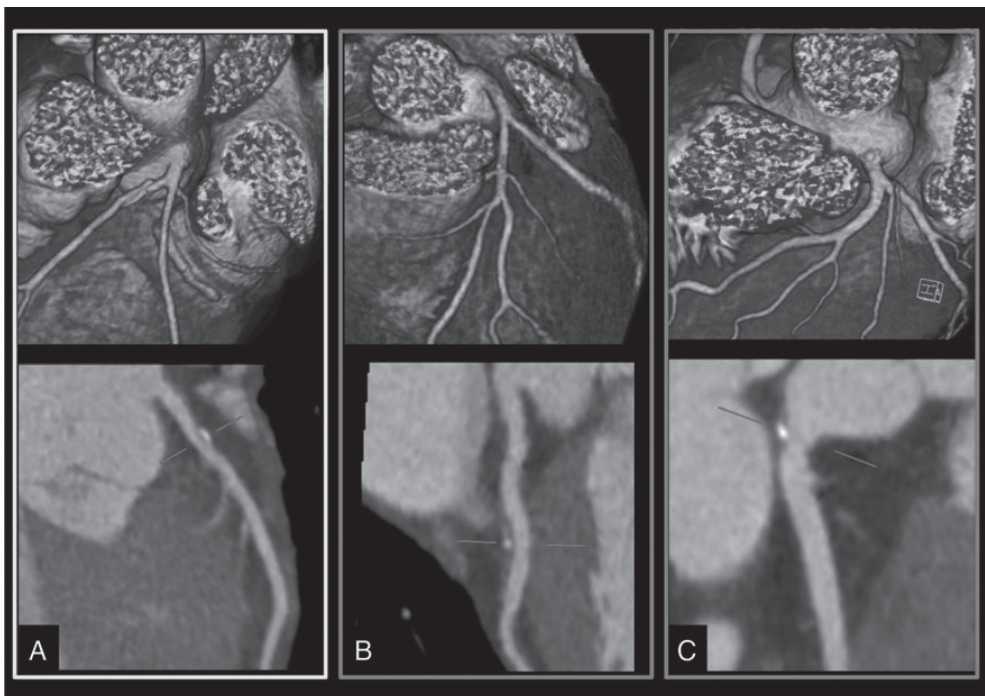


Figure 7: Non-obstructive (but probably not non-significant!) coronary lesions identified with CCTA. Upper panel with a volume-rendering technique and lower panel with multiplanar reconstructions. (A) Mixed plaque in the proximal LAD with 25–50% stenosis in a 54-year-old female with dyslipidaemia and smoking habits; (B) mixed plaque in the proximal LAD with 25% stenosis in a 31-year-old male with a family history of premature CAD; (C) mixed plaque in the left main with 25% stenosis in a 51-year-old male with hypertension and dyslipidaemia. None of these patients had a high ($\geq 5\%$) 10-year risk of cardiovascular death, as estimated by the HeartScore.

ization. The score calculated with CCTA data acquired with last generation scanners has been shown to correlate well with the invasive SYNTAX and to have a high reproducibility.⁷⁵ This way it is also expected to be a useful prognostic tool for risk stratification of patients with obstructive CAD. In addition, this information can be made available in advance, which could help in the planning of the revascularization procedure.

Another CCTA score that was recently described is the CT-Leaman score, in which all the atherosclerotic lesions are taken in consideration (both obstructive and non-obstructive) in a comprehensive score that has three sets of weighting factors: lesion localization (taking in consideration the anatomical dominance), degree of stenosis (obstructive and non-obstructive), and type of plaque (calcified, non-calcified, and mixed plaques).⁷⁶ This score

can become a useful tool to quantify a total coronary atherosclerotic burden and is expected to convey the strong prognostic information of CCTA. This could even be more useful in patients with non-obstructive lesions, whose prognosis has been shown to be worse than that of patients without coronary plaques^{65,72} and is a very prevalent subset,^{77,78} for whom risk stratification will be of utmost importance.

CCTA AS A TOOL IN THE PLANNING OF INTERVENTIONAL PROCEDURES

CCTA can also be used as a tool for the appropriate selection and planning of interventional procedures, and has been routinely used in this setting in chronic total occlusions (CTOs), transcatheter aortic valve implantation (TAVI),

and potentially many other coronary and structural heart procedures. Regarding CTOs, which still remain a challenging subset of lesions for percutaneous revascularization, appropriate selection of the cases is of utmost importance, since PCI in this setting is not only associated with higher contrast and radiation dosages, but also with a non-negligible rate of procedural complications. In this regard, several CCTA features have been associated with success of PCI for CTOs like the length of the occluded segment, the amount of calcification, the presence of a blunt stump and bending and tortuosity of the proximal vessel and/or occluded segment.^{79,80} The evaluation of myocardial perfusion by CT is also becoming a reality^{81,82} and patients with CTOs might be an important subset to benefit from this combined anatomic and viability assessment for decision-making regarding intervention.⁸³

CCTA plays also an important role in the evaluation of the candidate for implantation of a catheter-based aortic valve. CCTA provides information in correct sizing of the prosthesis since it is acknowledged that 3D imaging techniques, with a greater extent of evidence for CCTA, yield larger aortic annulus dimensions than echocardiography.^{84,85} The improved accuracy of aortic annular sizing by CCTA can influence patient outcomes. In a study of 133 patients who underwent CCTA before TAVI/TAVR, it was reported that, in comparison with TEE based sizing, the use of CCTA-based aortic annulus dimensions led to a significantly lower rate of 'worse-than-mild' paravalvular regurgitation after TAVI (7.5 vs. 21.9%).⁸⁶

Besides aortic annulus size, distance of the coronary ostium to the aortic valve plane, aortic cusp length, width of the aortic sinus, width of the sinotubular junction, and width

of the ascending aorta are important measures for TAVI planning.⁸⁵ Unlike surgery for aortic valve replacement, in TAVI the cusps are not resected but instead they are crushed by the endoprosthesis. This way, the distance of the coronary ostia to the aortic valve plane and aortic cusp length is important to evaluate the potential risk of coronary occlusion, a rare but menacing complication.⁸⁷ The width of the aortic sinus, the sinotubular junction, and the ascending aorta are also important measurements for the self-expandable TAVI, since it extends beyond the sinotubular junction into the ascending aorta. The evaluation of CAD in these patients might be challenging especially in the presence of advanced coronary calcification, although some authors have reported a good accuracy in this setting.⁸⁸

CTA also provides information on the suitability of access site, taking in consideration the minimum vessel lumen required for each TAVI system (Table 1). Small vessel diameter, severe atherosclerotic disease, bulky calcification, and tortuosity are the main determinants of vascular complications in TAVI procedures.^{89,90} Not only the iliac and femoral artery, but also the entire aorta should be examined by CTA, since it can identify tortuosity, dissections or thrombus, all increasing the risk of procedure-related complications, which can

be anticipated with CTA (Figure 8). In addition, the assessment of left ventricle and chest wall may influence the feasibility, safety, and effectiveness of the procedure. CTA data sets should be evaluated for the presence of LV thrombi as a source of embolic complications. The disposition of the LV apex relative to the chest wall and alignment of the LV-axis with LV outflow tract orientation may be useful information for transapical procedures. The optimal viewing projections for TAVI implantation can also be virtually simulated by CTA, with potential reductions in contrast dose and procedure time.

Percutaneous valvular interventions are not limited to TAVI, and mitral interventions are becoming a reality. CTA can be useful in this setting, especially for coronary sinus annuloplasty techniques, since CTA can provide information on the relation between the coronary sinus and the left circumflex and also between the coronary sinus and the level of the annulus and these anatomical relations have been linked to the success and safety of the procedure.⁹¹ The role of CTA for mitral interventions aimed at the leaflets, like edge-to-edge repair technologies, has yet to be defined, and presently echocardiography plays a central role in the selection and guidance of these procedures.

Table 1 Manufacturer-suggested anatomic evaluation for TAVI

	Aortic annulus. diameter,mm	Ascending aorta. diameter,mm	Sinus of Valsalva. width,mm	Sinus of Valsalva. height,mm	Distance aortic annulus. to left main ostium,mm	Minimal iliofemoral diameters, mm
CoreValve Evolut Bioprosthesis 23 mm	18–20	≤34	≥25	≥15	–	6
CoreValve Bioprosthesis 26 mm	20–23	≤40	≥27	≥15	–	6
CoreValve Bioprosthesis 29 mm	23–27	≤43	≥29	≥15	–	6
CoreValve Bioprosthesis 31 mm	26–29	≤43	≥29	≥15	–	6
Edwards SAPIEN XT 23	18–21	–	–	–	≥10	6
Edwards SAPIEN XT 26	22–24	–	–	–	≥10	6.5
Edwards SAPIEN XT 29	25–28	–	–	–	≥10	7

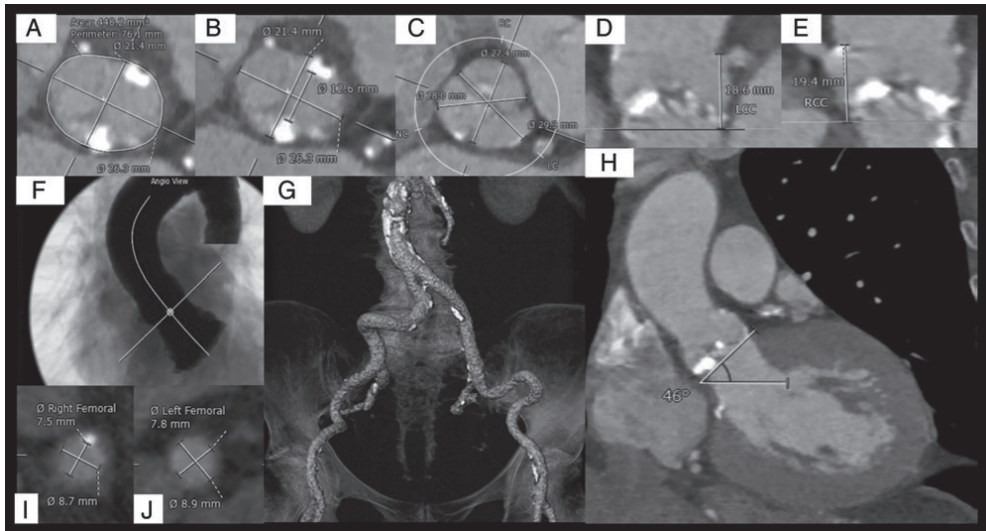


Figure 8: CTA evaluation for TAVI. (A) and (B) Aortic annulus measurements; (C) Aortic cusps lengths; (D) and (E) Aortic sinus heights for left coronary cusp (LCC) and right coronary cusp (RCC); (F) CTA simulation of an optimal viewing projection for valve implantation; (G) Three dimensional reconstruction of the abdominal aorta showing severe iliofemoral tortuosity; (H) aortic root angulation measurement; (I) and (J) right and left femoral mensuration.

Other structural heart interventions can benefit from the detailed anatomical evaluation prior to the procedure, like the evaluation of the left atrial appendage in patients candidate for closure devices.⁹² In addition, left atrial appendage morphology has been correlated with the risk of stroke in patients with atrial fibrillation, suggesting CTA as a potential tool for risk stratification regarding anticoagulation management in these patients.⁹³

The detailed morphological characterization of coronary anatomy and plaque distribution provided by CCTA might also be useful in the evaluation of bifurcation lesions, and can have some implications regarding selection of the PCI bifurcation technique.^{94,95} In a recent study, plaque distribution and morphology assessed by CCTA was associated with side branch compromise after left main PCI.⁹⁶ The development of some complications during

PCI has also been linked to CCTA plaque characteristics. In one study, the presence of low-attenuation plaque and napkin ring-like appearance of culprit lesions on CCTA were associated with the development of slow-flow or no-reflow phenomenon during PCI.⁹⁷

Another condition easily identified with CCTA is myocardial bridging, and this explains the higher prevalence in CCTA reports, in line with classic autopsy series and much higher than in ICA studies.⁹⁸ In most of the cases this is a benign finding, although it has been associated with the development of myocardial ischaemia and found to be more prevalent in patients with apical ballooning syndrome.⁹⁹ Additionally, bridging of the left anterior descending imposes a higher technical difficulty for bypass surgery and has been associated with higher rates of complications, including perforation of the right ventricle,

and therefore its preoperative identification can potentially help planning the revascularization procedure.⁹⁸

In summary,

- (1) CCTA is becoming an alternative for ICA in many purely diagnostic procedures that are becoming less often referred to the cathlab.
- (2) The performance of CCTA as a gatekeeper for ICA is expected to lead to an increase in the ratio of interventional to diagnostic procedures.
- (3) CCTA can potentially be useful in planning PCI especially more complex interventions like CTOs and bifurcations.
- (4) CTA is routinely used in the selection process of percutaneous valvular interventions as is the case of TAVI, especially for correct annular sizing.
- (5) Lastly, some CCTA plaque features can also be useful as predictors of potential complications during PCI and the operator can take advantage of this information in planning the procedure.

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Chapter 1.4

Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous

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ABSTRACT

Purpose: The pathophysiology of acute coronary syndromes (ACS) after noncardiac surgery is not established yet. Thrombosis over a vulnerable plaque or decreased oxygen supply secondary to anemia or hypotension may be involved. The purpose of this study was to investigate the pathophysiology of ACS complicating noncardiac surgery.

Methods: Clinical and angiographic data were prospectively recorded into a database for 120 consecutive patients that had an ACS after noncardiac surgery (PACS), for 120 patients with spontaneous ACS (SACS), and 240 patients with stable coronary artery disease (CAD). Coronary lesions with obstructions greater than 50% were classified based on two criteria: Ambrose's classification and complex morphology. The presence of Ambrose's type II or complex lesions were compared between the three groups.

Results: We analyzed 1470 lesions in 480 patients. In PACS group, 45% of patients had Ambrose's type II lesions vs. 56.7% in SACS group and 16.4% in stable CAD group ($P<0.001$). Both PACS and SACS patients had more complex lesions than patients in stable CAD group (56.7% vs. 79.2% vs. 31.8%, respectively; $P<0.001$). Overall, the independent predictors of plaque rupture were being in the group PACS ($P<0.001$, OR 2.86; CI, 1.82–4.52 for complex lesions and $P<0.001$, OR 3.43; CI, 2.1–5.6 for Ambrose's type II lesions) or SACS ($P<0.001$, OR 8.71; CI, 5.15–14.73 for complex lesions and $P<0.001$, OR 5.99; CI, 3.66–9.81 for Ambrose's type II lesions).

Conclusions: Nearly 50% of patients with perioperative ACS have evidence of coronary plaque rupture, characterizing a type 1 myocardial infarction.

INTRODUCTION

Annually, more than 230 million noncardiac surgeries are performed worldwide [1]. Despite improvements in surgical and anesthetic techniques, mortality and cost related to these procedures are raising [2]. Cardiac complications are a major cause of morbidity and mortality after noncardiac surgeries, and patients experiencing a perioperative myocardial infarction (MI) have a high mortality and prolonged hospital stay [3]. The etiology and pathophysiology of myocardial ischemia and infarction after noncardiac surgery is still subject of controversies [1,3–7]. In this setting, it may involve thrombosis over a vulnerable plaque or decreased oxygen supply secondary to anemia or hypotension, designated type 1 and type 2 by the universal definition of MI [8,9]. Depending on the predominant mechanism, prognosis and treatment may be different. Although two retrospective pathology studies reported that nearly 50% of patients with fatal perioperative MI have plaque disruption [10,11], it has been suggested that, in patients who survive a perioperative MI, the incidence of type 2 MI would be much higher than type 1 [1]. However, there are no studies designed to establish the pathophysiology in patients that survived a perioperative acute coronary syndrome (ACS).

The presence of coronary plaques with complex morphologic features in coronary angiography is the angiographic hallmark of unstable coronary syndromes and correlates with pathologic plaque rupture and thrombus, characterizing a type 1 MI [12–19]. Ambrose's type II eccentric lesions are strongly associated to disrupted plaques and their finding have 92% specificity [17–20]. In order to determine the pathophysiology of ACS complicating

noncardiac surgery we compared the presence of plaque rupture as a marker of type 1 MI in patients with ACS after noncardiac surgery (PACS), patients in the emergency room with spontaneous ACS (SACS), and patients with stable coronary artery disease (CAD). The present study was performed at the biggest University Hospital in Brazil where, roughly, 40,000 non-cardiac surgeries are performed annually.

METHODS

Between February 2006 and June 2010 clinical and angiographic data were prospectively recorded into a database for 120 consecutive patients that had PACS after noncardiac surgery, for 120 patients with SACS, and for 240 patients with stable CAD. The study protocol was approved by the hospital's ethics committee.

Inclusion criteria

Consecutive patients submitted to noncardiac surgery who presented with ACS within 30 days after the procedure were included in the PACS group. Patients with suspected perioperative ACS were evaluated by a cardiologist and were included if they had unstable angina with electrocardiographic ischemic signs (ST segment depression or T wave abnormalities) or MI, defined as follows: detection of a typical rise and fall of biochemical markers of myocardial necrosis (troponin) with at least one value above the 99th percentile of the upper reference limit together with: ischemic symptoms or development of pathological Q waves on the electrocardiogram (ECG) or ECG changes indicative of ischemia (ST segment elevation or depression) [21].

For the SACS group, patients that had arrived in the emergency room on random days and met the same criteria of ACS were included at admission.

For the stable CAD group, patients that were submitted to elective coronary angiography on random days were included before the procedure. Angiography was indicated by clinic's physician based on symptoms of stable angina or evidence of CAD on complementary tests.

Exclusion criteria

Patients in the PACS and SACS group were excluded if coronary angiography was not performed. Patients in the stable CAD group were excluded if they had had an ACS diagnosis in the previous 2 months.

Clinical data

Clinical data such as age, gender, presence of diabetes, hypertension, smoking status, history of prior MI, stable angina, heart failure, prior myocardial revascularization procedures, and cardiovascular medication use were collected for the three study groups.

Patients in the PACS and SACS groups were followed-up until hospital discharge, and information about recurrent unstable angina and myocardial infarction and death was obtained. The use of antiplatelet and anti-coagulant agents prescribed for ACS treatment and bleeding episodes were also recorded. Bleeding episodes were classified as major or minor based on TIMI's criteria [22].

Angiographic analysis

All angiographies were analyzed by a single experienced observer who was unaware of the patients' clinical diagnosis. The number and location of coronary lesions with obstructions greater than 50% were recorded. Each

lesion was classified based on Ambrose's classification [17–19]. This classification divides the lesions into 4 types: concentric (symmetric and smooth narrowing), type I eccentric (asymmetric stenosis with smooth borders and a broad neck), type II eccentric (asymmetric stenosis in the form of a convex intraluminal obstruction with a narrow neck due to one or more overhanging edges or irregular or scalloped borders, or both) and multiple irregularities (three or more serial, closely spaced narrowing or severe diffuse irregularities within a vessel) [17–19].

Lesions were also categorized as complex or not using a classification adapted from Goldstein et al. [12]. Lesions were considered complex if they caused at least 50% stenosis and had one or more of the following morphologic features:

- An intraluminal filling defect consistent with thrombus, defined as abrupt vessel cutoff with persistence of contrast, or an intraluminal filling defect in a vessel within or adjacent to a stenotic region with surrounding homogeneous contrast opacification;
- Plaque ulceration, defined by the presence of contrast and hazy contour beyond the vessel lumen;
- Plaque irregularity (haziness), defined by irregular margins or overhanging edges;
- Impaired flow (TIMI flow < 3, except lesions characteristic of chronic total occlusion, identified as tapering lesions with multiple fine collaterals).

The presence of at least one Ambrose's type II lesion or a complex lesion per patient was compared between the three study groups.

Statistical analysis

Base-line demographic characteristics, clinical and angiographic variables were compared between the three groups. Frequencies and percentages are given for categorical variables. These variables were compared by chi-square test when applicable and otherwise by Fisher's exact test. Numerical variables are reported as means±standard deviation (SD). For continuous variables, statistical comparisons were made with use of Student's t-test (normal distribution) or Mann-Whitney test (asymmetric distribution). Post hoc analysis for continuous variables was made by the Tukey-HSD (honest significant difference) test. Multivariate logistic regression analysis was performed to access independent clinical predictors for plaque rupture in patients from all three groups. All clinical variables with a value of $P < 0.25$ in univariate analysis were tested. Belonging to PACS or SACS group, presence of diabetes or anemia, age > 70 years old, and lack of use of aspirin, betablocker and statins were included in the multivariable model to test association with complex lesions. Belonging to PACS or SACS group, not having hypertension or history of prior MI, anemia, and lack of use of

aspirin, betablocker, and statins were included in the multivariable model to test association with Ambrose's type II lesions. Adjusted odds ratio (OR) is reported with corresponding 95% confidence intervals (CI). Model adequacy was measured by Hosmer & Lemeshow's goodness of fit test. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using the SPSS 15.0 software.

RESULTS

One hundred seventy patients with suspected PACS were evaluated. Nine patients were not included because they did not have ACS (eight had isolated troponin elevations and one had pulmonary thromboembolism). Forty patients were excluded because coronary angiography was not performed and one patient was excluded due to technical reasons in analyzing the angiography, leaving 120 patients that were included in the PACS group. In the SACS group, 145 patients were evaluated and 120 were included. Overall, 480 patients and 1470 lesions were analyzed.

Table 1 Baseline characteristics.

	PACS (n=120)	SACS (n=120)	CAD (n=240)	P
Male sex no. (%)	86(71.7)	81 (67.5)	157 (65.7)	0.52
Age (years; mean±SD)	67.82±10.02	64.53±12.41	61.95±9.72	<0.001*
History of				
Diabetes mellitus, n (%)	51 (42.5)	42 (35)	106(44.4)	0.23
Hypertension, n (%)	99 (82.5)	101 (84.2)	203 (84.9)	0.84
Prior MI, n (%)	22 (18.3)	50 (41.7)	84 (35.1)	<0.001
Stable angina, n (%)	20 (16.7)	19 (15.8)	197 (82.5)	<0.001
Heart failure, n (%)	18 (15)	7 (5.8)	59 (24.7)	<0.001
Smoking status, n (%)				
No	41 (34.2)	52 (43.3)	122 (51)	
Current	27 (22.5)	26 (21.7)	30 (12.6)	0.01
Previous	52 (43.3)	42 (35)	87 (36.4)	
Prior revascularization procedure, n (%)				
None	98 (81.7)	69 (57.5)	160 (66.9)	
PTCA	11 (9.2)	26 (21.7)	45 (18.8)	
CABG	10 (8.3)	17 (14.2)	24 (10)	0.004
PTCA and CABG	1 (8.0)	8 (6.7)	10 (4.2)	
Hemoglobin (g/dL; mean±SD)	12.48±2.21	13.73±1.72	14.08±1.57	<0.001†
Cr (mg/dL; mean±SD)	1.68±1.93	1.2±0.72	1.25±1.43	0.43

PACS: Perioperative acute coronary syndrome; SACS: Spontaneous acute coronary syndrome; CAD: coronary artery disease; n: number; SD: standard deviation; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; Cr: creatinine.

* PACS vs. SACS ($P=0.04$); PACS vs. stable CAD ($P < 0.001$); SACS vs. stable CAD ($P=0.08$).

† PACS vs. SACS ($P < 0.001$); PACS vs. stable CAD ($P < 0.001$); SACS vs. stable CAD ($P=0.21$).

Table 2. Medication at admission.

	PACS (n = 120)	SACS (n = 120)	CAD (n = 240)	P
Aspirin, n (%)	60 (50)	68 (56.7)	229 (95.8)	<0.001
β-Blockers, n (%)	47 (39.2)	60 (50)	195 (81.6)	<0.001
Statin, n (%)	36 (30)	59 (49.2)	201 (84.1)	<0.001
ACE inhibitor, n (%)	58 (48.3)	53 (44.2)	160 (70.5)	<0.001

PACS: perioperative acute coronary syndrome; SACS: spontaneous acute coronary syndrome; CAD: coronary artery disease; n: number; ACE: angiotensin-converting enzyme.

Baseline characteristics

Clinical and laboratory characteristics of the 480 patients and medications at the time of admission are listed in Tables 1 and 2, respectively. There were no differences between the three groups in the prevalence of male gender, hypertension or diabetes. Patients in PACS group were older and had lower hemoglobin levels than patients in SACS or stable CAD groups. Patients in PACS group also had less prior history of known CAD (history of MI or prior myocardial revascularization procedures) than patients of the other two groups.

Clinical data and outcome

In PACS group, the mean time between the procedure and the ACS was 2.2±3.3 days and 71.7% of patients had an ACS within the first 72 h after surgery. Regarding the type of operation, 46 patients (38.3%) were submitted to vascular surgery, 25 (20.8%) to general abdominal surgery, 12 (10%) to urologic surgery, 10 (8.3%) to orthopedic surgery, 7 (5.8%) to head and neck surgery, 7 (5.8%) to neurosurgery, 4 (3.3%) to kidney transplantation, and 9 (7.7%) to other procedures. Regarding anesthesia, 67 (60.4%) patients received general anesthesia, 20 (18%) regional anesthesia and 24 (21.6%) combined general plus regional anesthesia. Mean anesthesia duration was 363 ±

212 min (range from 60 to 1425 min). Only 48 (40.7%) patients presented with chest pain as the clinical manifestation of ACS. As

for ACS classification, 19 (15.8%) patients had unstable angina, 94 (78.3%) had non-ST elevation MI and 7 (5.8%) had ST elevation MI. In SACS group, 19 (5.8%) patients had unstable angina, 78 (65%) had non-ST elevation MI and 23 (19.2%) had ST elevation MI. Patients in the PACS group had a longer time from the ACS to angiography than patients in the SACS group (5.5 ± 8 days vs. 1.3 ± 1.4 days, respectively; P<0.001). During follow-up there was no difference between the PACS and SACS groups regarding recurrent angina (12.5% vs. 10%, respectively; P=0.54) or myocardial infarction (10% vs. 5%, respectively; P=0.14), but patients in PACS group were more frequently on Killip’s Classification III and IV than patients in SACS group (35% vs. 12.5%, respectively; P<0.001), and had higher mortality (15% vs. 4.2%; P=0.02).

The use of antiplatelet agents and anticoagulant therapy in both groups are shown in Table 3. Eleven (9.2%) patients in the PACS group had a bleeding episode (6 major bleeding, including 2 fatal, and 5 minor bleeding) whereas 10 (8.3%) patients in the SACS

Table 3. Acute coronary syndrome treatment medication.

Medication	PACS, n (%)	SACS, n (%)	P
Aspirin	119 (99.2)	118 (98.3)	1.00
Clopidogrel	78 (65)	82 (70.1)	0.40
Heparin	104 (86.7)	120 (100)	<0.001
Tirofiban	11 (9.2)	90 (75)	<0.001
β-Blockers	102 (85)	110 (91.7)	0.10
Statin	118 (98.3)	120 (100)	0.50
ACE inhibitor	94 (78.3)	108 (90)	0.01
Dobutamine	23 (19.2)	3 (2.5)	<0.001

PACS: perioperative acute coronary syndrome; SACS: spontaneous acute coronary syndrome; CAD: coronary artery disease; ACE: angiotensin-converting enzyme; n: number.

Table 4. Angiographic characteristics.

	PACS, n (%)	SACS, n (%)	Stable CAD, n (%)	P
Complex lesion	68 (56.7)	95 (79.2)	76 (31.8)	<0.001
Ambrose's type II lesions	54 (45)	68 (56.7)	44 (16.4)	<0.001
Thrombus	9 (7.5)	39 (32.5)	21 (8.8)	<0.001
Ulceration	15 (12.5)	18 (15)	16 (6.7)	0.03
Haziness	45 (37.5)	54 (45)	39 (16.3)	<0.001
TIMI flow <3	27 (22.5)	61 (50.8)	48 (20.1)	<0.001

PACS: perioperative acute coronary syndrome; SACS: spontaneous acute coronary syndrome; CAD: coronary artery disease; n: number; TIMI: thrombolysis in myocardial infarction.

group presented with bleeding (6 major and 4 minor but none fatal; $P=0.09$). Interestingly, only 3 patients on the PACS group presented with bleeding from the operative site and 5 patients had gastrointestinal bleeding despite the use of ulcer prophylaxis.

Angiographic results

Twenty-eight patients did not have obstructions above 50%: 7 (5.8%) in PACS group, 3 (2.5%) in SACS group and 18 (7.5%) in stable CAD group. Of the 1471 lesions analyzed, 349 were in patients of the PACS group (mean 2.86 ± 1.71 lesions per patient), 404 were in patients of the SACS group (mean 3.31 ± 1.71 lesions per patient), and 717 were in patients of the stable CAD group (mean 2.94 ± 1.86 lesions per patient; $P=0.10$). There was no difference between the three groups regarding the location of the lesions.

In PACS group, 45% of patients had Ambrose's type II lesions vs. 56.7% in SACS group and 16.4% in stable CAD group ($P<0.001$). Both PACS and SACS patients had more complex lesions than patients in stable CAD group (56.7% vs. 79.2% vs. 31.8%, respectively; $P<0.001$). Comparison between angiographic characteristics of patients is

shown in Table 4. After univariate analysis, applied to the entire cohort of 480 patients, the following variables were associated to the presence of complex lesions, and were included in the multivariable model: belong-

ing to PACS or SACS group ($P<0.001$), presence of diabetes ($P=0.153$), presence of anemia ($P=0.002$), age > 70 years old ($P=0.002$), and lack of medication use: aspirin ($P<0.001$), betablocker ($P<0.001$) and statins ($P=0.001$). The independent predictors of complex lesions were being in the group PACS ($P<0.001$; OR, 2.86; 95% CI, 1.82–4.52) or SACS ($P<0.001$; OR, 8.71; 95% CI, 5.15–14.73) and the presence of diabetes ($P=0.025$; OR, 1.58; 95% CI, 1.06–2.36; Table 5). The variables associated to Ambrose's type II lesions in the univariate model, that were included in the multivariable model, were: belonging to PACS or SACS group ($P<0.001$), not having hypertension ($P=0.221$) or history of prior MI ($P=0.148$), anemia ($P=0.004$), and lack of medication use: aspirin ($P<0.001$), betablocker ($P=0.004$), and statins ($P=0.002$). The independent predictors of Ambrose's type II lesions were being in the group PACS ($P<0.001$; OR, 3.43; 95% CI, 2.1–5.6) or SACS ($P<0.001$; OR, 5.99; 95% CI, 3.66–9.81; Table 5).

Table 5. Independent predictors of plaque rupture in the multivariate logistic regression model.

	Adjusted OR	95% CI	P
Predictors of complex lesions [†]			
PACS group	2.86	1.82–4.52	<0.001
SACS group	8.71	5.15–14.73	<0.001
Diabetes	1.58	1.06–2.36	0.025
Predictors of Ambrose's type II lesions [†]			
PACS group	3.43	2.10–5.60	<0.001
SACS group	5.99	3.66–9.81	<0.001

PACS: perioperative acute coronary syndrome; SACS: spontaneous acute coronary syndrome.

[†] Hosmer & Lemeshow goodness of fit: $P=0.647$.

[†] Hosmer & Lemeshow goodness of fit: $P=0.270$.

DISCUSSION

This was the first prospective study that evaluated the presence of plaque rupture in consecutive patients with ACS a noncardiac surgery. Regarding the clinical and outcome characteristics of patients with perioperative ACS, our study confirmed previous findings that perioperative ACS occurs mainly within the first 72 h of the procedure, most events are non-ST-elevation MI and only 40% of patients have thoracic pain [5,6,23–26]. As expected, inhospital mortality was higher in patients with perioperative ACS than spontaneous ACS. This finding could be attributed to baseline diseases (co-morbidities) that motivated surgery (malignant disease, vascular disease, trauma, etc.).

Our findings suggest that nearly 50% of patients with perioperative ACS have markers of plaque disruption, suggesting a type 1 MI. Our data is in line with the two retrospective autopsy studies that investigated coronary anatomy in patients with fatal perioperative MI. Dawood et al. [10] studied 42 patients with fatal perioperative MI and found out that 55% of patients had evidence of unstable plaques with disruption. Cohen et al. [11] also studied 26 patients with fatal perioperative MI and detected plaque rupture on autopsy in 45% of them. In a retrospective study that used a catheterization laboratory database, Berger et al. [27] identified 48 patients referred for emergency coronary angiography for acute MI within 7 days of noncardiac surgery. Only critically ill patients with postoperative

MI were included: 33 patients (68.8%) had ST-segment elevation, and 21 patients had cardiogenic shock. Although the purpose of their study was to determine the clinical course and outcome of patients undergoing

immediate angiography for perioperative MI and not to study the angiographic characteristics, they reported the presence of thrombus in 30 patients (62.5%).

Differently from Berger et al. [27], Dawood et al. (28%) [10] and Cohen et al. (35%) [11] we found a low percentage of thrombus in angiography of patients in PACS group (7.5%). This result may be related to the long time between MI and angiography in this group (5.5 days in average), consequently prolonged time under antiplatelet and anticoagulant agents, spontaneous lysis of some thrombi, and the small number of patients with ST-elevation MI (more prone to exhibit thrombus over culprit lesion). Indeed, patients with perioperative non-ST-elevation ACS usually are more severely ill than patients with spontaneous SCA, and before being referred to coronary angiography, physicians had to be sure that the patient could receive antiplatelet and anticoagulant therapy (considering the risk of bleeding) and that infections were under control. Reinforcing the presence of unstable coronary plaques in perioperative ACS, we found similar frequencies of haziness and ulceration on angiography in PACS and SACS groups, an unlikely finding in patients with stable CAD. Indeed, multivariate analysis indicated that belonging to PACS or SACS groups was associated to an increased risk of angiographic markers of plaque disruption.

Out of the perioperative setting and using intravascular ultrasound, Hong et al. also found that the only independent predictor of coronary plaque disruption among patients with stable angina and myocardial infarction was having the diagnosis of acute MI [28]. Conversely, previous authors have suggested that postoperative tachycardia, hypotension, hypertension, anemia, and hypoxemia are

common causes of prolonged ST-depression and type 2 infarction in patients with stable CAD undergoing noncardiac surgery [1]. The cornerstone of this hypothesis is the finding of prolonged ST depression in perioperative Holter monitoring preceding the ischemic event in previous studies [29]. In addition, the rare occurrence of ST elevation MI in PACS reinforces the theory that the incidence of type 2 MI could be higher than type 1 MI [1,29]. In spite of its theoretical biological plausibility, until now there was no clinical evidence about the true incidence of type 1 MI. The present study provided this missing evidence.

Our study has some limitations. Among the excluded patients, 18 (45%) died before the angiography could be done, reflecting their critical clinical status, and we missed their angiographic characteristics. We used coronary angiography for classifying lesions and determine the presence of plaque disruption. Although it is not the gold standard to diagnose plaque rupture, previous authors showed that complex angiographic lesion morphology and Ambrose's type II lesions are strongly correlated with plaque rupture [20,16]. In conclusion, nearly 50% of patients with perioperative myocardial infarction have evidence of coronary plaque rupture, characterizing a type 1 MI.

CLINICAL IMPLICATIONS

The present study indicates that, as well as in spontaneous ACS, plaque rupture plays

an important role in the pathophysiology of perioperative ACS. At the bed side, this information is very useful, as antiplatelet and anticoagulant therapies and invasive evaluation should be strongly considered. On the other hand, type 1 and type 2 MI mechanism are not mutually exclusive in the pathophysiology of perioperative ACS. In consequence, preventing hypotension, tachycardia, anemia and hypertension remain important in the care of patients with perioperative ACS. Therefore, prevention and treatment measures that act in both mechanisms are essential for reducing the occurrence and mortality of perioperative ACS.

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CONFLICT OF INTEREST

None declared.

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Chapter 1.5

Anatomic characteristics and clinical implications of angiographic coronary thrombus: insights from a patient-level pooled analysis of SYNTAX, RESOLUTE, and LEADERS Trials

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ABSTRACT

Background—The distribution of thrombus containing lesions in an all-comer population admitted with a heterogeneous clinical presentation (stable, unstable angina or an acute coronary syndrome) and treated with PCI is yet unclear and the long-term prognostic implications are still disputed. This study sought to assess the distribution and prognostic implications of coronary thrombus, detected by coronary angiography, in an all-comer population recruited in all-comer percutaneous coronary intervention (PCI) trials.

Methods and Results—Patient-level data from 3 contemporary coronary stent trials were pooled by an independent academic research organization (Cardialysis, Rotterdam, the Netherlands). Clinical outcomes in terms of major adverse cardiac events (MACE, a composite of death, myocardial infarction, and repeat revascularization), death, myocardial infarction (MI), and repeated revascularization were compared between patients with and without angiographic thrombus containing lesion (TCL). Pre-procedural TCL was present in 257 patients (5.8%) and absent in 4193 (94.2%). At 3-year follow-up, there was no difference for MACE (25.3 vs. 25.4%; $P=0.683$); all-cause death (7.4 vs. 6.8%; $P=0.683$); myocardial infarction (5.8 vs. 6.0%; $P=0.962$), and any revascularizations (17.5 vs. 17.7%; $P=0.822$), between patients with and without TCL. The comparison of outcomes in groups weighing the jeopardized myocardial by TCL also did not show a significant difference. TCL were seen more often in the first 2 segments of the right (43.6%) and left anterior descending (36.8%) coronary arteries. The association of TCL and bifurcation lesions was present in 40.1% of the pre-specified segments.

Conclusions—TCL involved mainly the proximal coronary segments and did not have any impact on clinical outcomes. A more detailed thrombus burden quantification is required to investigate its prognostic implications.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifiers: NCT00114972, NCT01443104, NCT00617084.

Key Words: thrombus, PCI, drug-eluting stent, outcome, vulnerable plaque

INTRODUCTION

Coronary thrombus has been associated with acute coronary syndromes and disease progression. The rupture of thin cap fibro-atheromas allows the blood to come in contact with the highly thrombogenic contents of the plaque (e.g. necrotic core/collagen) favoring the occurrence of most of acute coronary syndromes^{1,2}. In addition, invasive imaging studies have shown that coronary thrombosis can also be present in stable coronary artery disease (CAD) and has been associated with plaque progression^{3,4}.

Thrombus containing lesions (TCL) appears to be associated with an increased risk of distal embolization and no or poor distal flow and low myocardial blush grades after percutaneous coronary intervention (PCI)^{5,6}. However, the prognostic relevance of coronary thrombus as assessed by angiography is still unclear and the results presented in the literature are disputed⁷⁻⁹.

The aim of the present study is to examine the angiographic anatomic characteristics of TCL and their correlations with clinical events (all-cause death, myocardial infarction [MI] and all revascularizations) in the largest ever pooled all-comer population enrolled in contemporary PCI trials.

METHODS

Patient population: We analyzed patient-level data from 3 all-comer coronary drug-eluting stent (DES) trials: LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial, RESOLUTE (Resolute All Comers) trial and SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac

Surgery). Detailed individual study design and trial results are available elsewhere¹⁰⁻¹². In brief, all studies included patients with obstructive CAD that was amendable to coronary stent implantation (Supplementary Table 1). These trials had an all-comers design, but, in the SYNTAX trial, the enrolled patients must had complex (three-vessel or left main) CAD to be enrolled. All studies complied with the Declaration of Helsinki and were approved by the ethical review board in each institution. All patients provided written, informed consent for participation in the individual study. The angiographic images were reviewed by independent core lab analysts (Cardialysis, Rotterdam, The Netherlands) who identify the presence or not of thrombus. Aiming to evaluate the clinical characteristics and prognosis, the patients were divided in 2 groups according to the presence or not of at least one thrombus containing lesion as assessed by coronary angiography.

Clinical outcomes. Major adverse cardiac events (MACE) was defined as a composite of all-cause death, MI and any repeat revascularization. There was a wide variation in the definition of MI among studies. This is due to each study inclusion criteria, variations in study design, and the different periods during which studies were performed. Since all clinical events from each individual trial were adjudicated by independent clinical event committees, no attempt was made to readjudicate MI events in the different trials to compensate for the differences in individual definition of MI. Therefore, all MIs reported in the current study are as per individual study protocol definitions.

Angiographic Assessment. The angiographic assessment was performed by an independent corelab (Cardialysis, Rotterdam, The Nether-

lands) based on the SYNTAX score concept. The SYNTAX score for each patient was calculated by scoring all coronary lesions with a diameter stenosis $\geq 50\%$, in vessels ≥ 1.5 mm, using the SYNTAX score algorithm, which is described in full elsewhere¹³. All angiographic variables were recorded prospectively by a team of 2 core laboratory analysts.

A bifurcation was classified by a division of a main, parent, branch into two daughter branches of at least 1.5mm diameter according to the Medina classification¹⁴. The smaller of the two daughter branches was designated as the 'side branch'. Following the SYNTAX score recommendations, bifurcations were only

scored for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a, 3/4/16 and 13/14/15. Coronary thrombus was defined according to the Academic Research Consortium (ARC) definition as spheric, ovoid or irregular intraluminal filling defect or lucency surrounded on three sides by contrast medium seen just distal or within the coronary stenosis in multiple projections or a visible embolization of intraluminal material downstream¹⁵. To further evaluate the prognostic impact of thrombus, the summation of segment weighing factors (Table1) used in the SYNTAX score was used if TCL were present.

Table 1. Segment weighing factor

Segment No	Right dominance	Left dominance
1	1	0
2	1	0
3	1	0
4	1	n.a.
16	0.5	n.a.
16a	0.5	n.a.
16b	0.5	n.a.
16c	0.5	n.a.
5	5	6
6	3.5	3.5
7	2.5	2.5
8	1	1
9	1	1
9a	1	1
10	0.5	0.5
10a	0.5	0.5
11	1.5	2.5
12	1	1
12a	1	1
12b	1	1
13	0.5	1.5
14	0.5	1
14a	0.5	1
14b	0.5	1
15	n.a.	1

Data analysis. All patients with a calculated SYNTAX score were included in the analysis. Discrete data were summarized as percent (frequencies) and were compared using the chi-squared test. Continuous data were expressed as mean±SD and were compared using Student's t-test or Wilcoxon rank-sum test based on their distributions. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test. Comparison of events rates between groups were adjusted for confounding factors in a Cox-regression

model. All variables were stratified according to presence of at least one TCL using a Cox-regression model. The differences were regarded significant when $p < 0.05$ (two-tailed). The Breslow-Day chi-squared test was calculated to test the statistical evidence of heterogeneity across the studies ($p < 0.1$). The chi-squared test and I^2 statistic was calculated to test the statistical evidence of heterogeneity across the studies¹⁶ (Supplementary Table 2, supplementary Figures 1-5). SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used for all other statistical analyses.

Table 2. Baseline clinical characteristics

	Pts without thrombus containing lesions N=4193	Pts with thrombus containing lesions N=257	P
Age	64.6±10.7	62.7±10.7	0.006
Male,%	3127 (74.6)	208 (80.9)	0.022
Diabetes Mellitus,%	1032 (24.6)	50 (19.5)	0.061
Body mass index, kg/m ²	27.7±4.5	27.8±4.5	0.831
Hypertension,%	3061 (73.0)	150 (58.4)	<0.001
Hyperlipidemia,%	2842 (67.8)	136 (52.9)	<0.001
Current smoker,%	1279 (30.5)	132 (51.4)	<0.001
Peripheral vascular disease,%	317 (7.6)	16 (6.2)	0.446
Family history of premature CAD,%	1443 (27.3)	87 (33.9)	0.518
History of Stroke/TIA,%	222 (5.3)	13 (5.1)	0.849
Creatinine>200 micromol/L	1.3	0.4	0.530
Creatinine clearance; ml/min	90.6±37.4	98.7±33.9	0.001
Previous myocardial infarction,%	1225 (29.2)	55 (21.4)	0.006
Previous PCI, %	1027 (24.5)	32 (12.5)	<0.001
Presentation			<0.001
NSTEMI,%	558 (13.3)	62 (24.1)	
Stable CAD,%	2131 (50.8)	50 (14.0)	
STEMI,%	539 (12.9)	112 (43.6)	
Unstable angina,%	965 (23.0)	33 (12.8)	
LVEF,%	56.8±11.9	54.7±11.9	0.052

Pts=patients; TIA= Transient Ischemic Attack; MI=myocardial infarction; PCI=percutaneous coronary intervention; NSTEMI= Non-ST-Segment Elevation Myocardial Infarction; STEMI= ST-Segment Elevation Myocardial Infarction; LVEF=left ventricular ejection fraction

RESULTS

Baseline characteristics. Table 2 depicts patients' baseline demographics. Pre-procedural thrombus was present in 257 patients (5.8%) and absent in 4193 (94.2%). Patients with at least one TCL were younger (62.7 ± 10.7 vs. 64.6 ± 10.7 ; $P=0.006$), more frequently male (80.9% vs. 74.6%; $P=0.022$) and current smokers (51.4% vs. 30.5%; $P<0.001$), less likely to suffer from hypertension (58.4% vs. 73.0%; $P<0.001$) and hyperlipidemia (52.9 vs. 67.8%; $P<0.001$). The left ventricular ejection fraction

tended to be higher in patients without TCL (56.8 ± 11.9 vs. 54.7 ± 11.9 ; $P=0.052$). Presence of thrombus at baseline was more frequently related with an acute presentation ($P<0.001$).

Angiographic characteristics. Patients with and without TCL had similar angiographic characteristics (Table 3). There were differences for higher prevalence of total occlusions (0.37 ± 0.56 vs. 0.27 ± 0.49 total occlusions/patient; $P=0.010$) and more frequent involvement of the proximal right coronary artery (0.33 ± 0.47 vs. 0.27 ± 0.45 lesions/patient; $P=0.045$) in the thrombus group.

Table 3. Baseline angiographic characteristics

	Pts without thrombus containing lesions N=4193	Pts with thrombus containing lesions N=257	P
Baseline SYNTAX score \pm SD	17.7 \pm 11.6	18.6 \pm 10.7	0.239
Number of total occlusions/patient \pm SD	0.27 \pm 0.49	0.37 \pm 0.56	0.010
Number of aorto-ostial lesions/patient \pm SD	0.06 \pm 0.25	0.07 \pm 0.27	0.714
Number of lesions with severe tortuosity/patient \pm SD	0.81 \pm 1.09	0.73 \pm 1.07	0.265
Number of lesions with length>20mm/patient \pm SD	0.51 \pm 0.76	0.51 \pm 0.65	0.884
Number of lesions with heavy calcification/patient \pm SD	0.40 \pm 0.87	0.35 \pm 0.82	0.367
Number segments with diffuse disease/patient \pm SD	0.04 \pm 0.19	0.04 \pm 0.18	0.877
Lesions in left main/patient	0.10 \pm 0.31	0.07 \pm 0.26	0.086
Lesions in LAD proximal/patient	0.33 \pm 0.50	0.34 \pm 0.50	0.820
Lesions in LAD mid/patient	0.58 \pm 0.58	0.54 \pm 0.58	0.243
Lesions in LAD apical/patient	0.15 \pm 0.38	0.13 \pm 0.36	0.275
Lesions in 1 st diagonal/patient	0.25 \pm 0.45	0.28 \pm 0.48	0.247
Lesions in 2 nd diagonal/patient	0.01 \pm 0.11	0.02 \pm 0.12	0.722
Lesions in proximal circumflex/patient	0.19 \pm 0.40	0.17 \pm 0.37	0.481
Lesions in distal circumflex/patient	0.35 \pm 0.52	0.30 \pm 0.49	0.116
Lesions in intermediate/patient	0.08 \pm 0.27	0.09 \pm 0.31	0.416
Lesions in first obtuse marginal/patient	0.13 \pm 0.34	0.13 \pm 0.34	0.686
Lesions in second obtuse marginal/patient	0.12 \pm 0.34	0.09 \pm 0.29	0.107
Lesions in RCA proximal/patient	0.27 \pm 0.45	0.33 \pm 0.47	0.045
Lesions in RCA mid/patient	0.34 \pm 0.49	0.34 \pm 0.48	0.983
Lesions in RCA distal/patient	0.25 \pm 0.46	0.27 \pm 0.48	0.447
Lesions in Posterolateral/patient	0.07 \pm 0.25	0.05 \pm 0.23	0.21
Lesions in Posterior descending /patient	0.01 \pm 0.09	0.00 \pm 0.00	0.17

Pts=patients; TO=total occlusion; LM=left main coronary artery; LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; Mg=marginal; RCA=right coronary artery; Pl=posterolateral branch; PD=Posterior descending branch.

Table 4. Kaplan-Meier Events Rate Comparison Between Groups

	Pts without thrombus containing lesions N=4193	Pts with thrombus containing lesions N=257	P
30 days, n(%)			
MACE	254 (6.1)	17 (6.6)	0.714
All-cause death	47 (1.1)	3 (1.2)	0.937
All MI	163 (3.9)	9 (3.5)	0.754
All Revascularization	114 (2.7)	11 (4.3)	0.131
1-year			
MACE	669 (16.0)	48 (18.7)	0.229
All-cause death	127 (3.0)	10 (3.9)	0.423
All MI	196 (4.7)	11 (4.3)	0.778
All Revascularization	480 (11.5)	35 (13.7)	0.217
3-year			
MACE	1067 (25.4)	65 (25.3)	0.874
All-cause death	287 (6.8)	19 (7.4)	0.683
All MI	250 (6.0)	15 (5.8)	0.962
All Revascularization	742 (17.7)	45 (17.5)	0.822

MACE= major adverse cardiac events (composite of all-cause death, myocardial infarction and all revascularization); MI=myocardial infarction

Clinical Outcomes. There was no difference between the groups (Table 4 and Figure 1) for any of the studied outcomes up to 3-year follow-up. MACE occurred in 1067 patients (25.4%) in the group without thrombus at baseline and 65 (25.3%) in the group with thrombus ($P=0.874$). Consistently, all-cause death ($P=0.683$), MI ($P=0.962$) and any revascularization ($P=0.822$) was not significantly different in the two groups.

Subgroup analysis. In the stratified analysis, the occurrence of MACE was homogeneously distributed across the clinical and angiographic covariates with the only exception of clinical presentation (Figure 2). There was a significant interaction between the patients presenting with acute coronary syndrome (HR 0.881, CI 0.65-1.19) and stable CAD (HR 1.637, 95% CI 1.04-2.59) with respect to the presence of thrombus at baseline ($P=0.028$).

A more detailed analysis of the subgroup with stable CAD can be found in the Supplementary Table 3. The thrombus at baseline was related to a higher rate of MACE (38% vs 26%, $P=0.03$), mainly due to an increased rate of repeated revascularization (30% vs 18%, $P=0.01$). However, after adjustment for confounders (i.e. age, creatinine clearance, previous myocardial infarction, LVEF and number of total occlusions/patient) this effect was no longer present (supplementary Figures 6 [A-D] and 7 [A-D]).

Anatomic characteristics of thrombus containing lesions. In the subgroup of patients with TCL ($n=257$), 261 lesions had angiographic thrombus. As shown in Figure 3, the presence of TCL occurred preferentially in proximal segments. More specifically 43.6% of these complex lesions were seen in the first 2 segments of the right coronary artery and

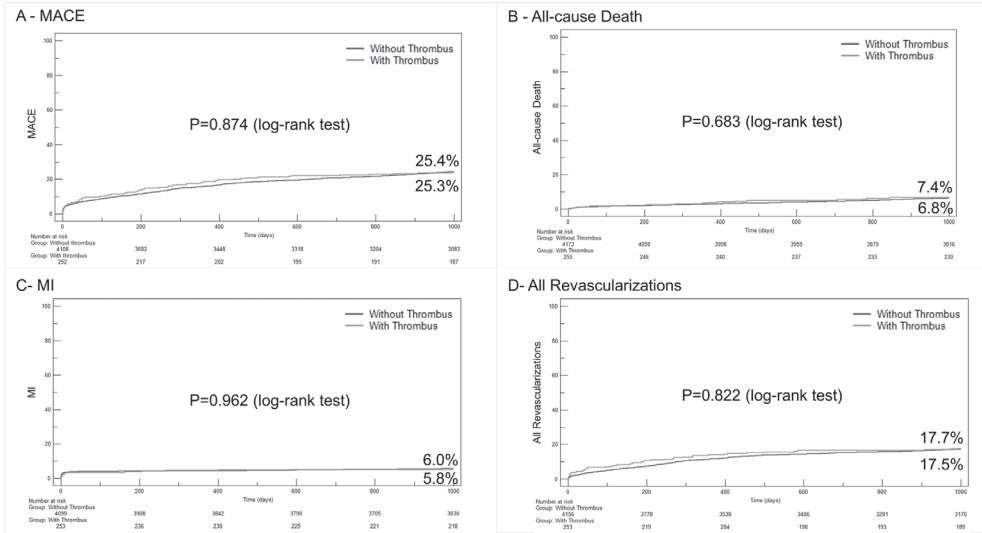


Figure 1. Kaplan-Meier cumulative curves for (A) MACE (composite of all-cause death, myocardial infarction and all revascularizations), (B) all-cause death, (C) myocardial infarction (MI) and (D) all revascularizations.

	Patients with Thrombus	Patients without Thrombus	HR (95% CI)	P	P _{interaction}	
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.299 (0.785 - 2.150)	0.385	0.31	
Male	49/208 (23.6%)	779/3127 (24.9%)	0.962 (0.721 - 1.284)	0.791		
Female	16/49 (32.7%)	287/1066 (24.9%)	1.291 (0.780 - 2.135)	0.321		
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.087 (0.771 - 1.532)	0.635	0.691	
Age<65	35/143 (24.5%)	469/2023 (23.2%)	1.088 (0.772 - 1.534)	0.631		
Age>65	30/114 (26.3%)	598/2170 (27.6%)	0.981 (0.680 - 1.416)	0.919		
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.075 (0.807 - 1.431)	0.777	0.706	
DM	15/50 (30.0%)	339/1032 (32.8%)	0.961 (0.573 - 1.611)	0.879		
Non-DM	50/207 (24.2%)	728/3161 (23.0%)	1.073 (0.806 - 1.430)	0.628		
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.070 (0.736 - 1.554)	0.724	0.796	
CrCl<90	36/107 (33.6%)	508/2100 (24.2%)	1.070 (0.736 - 1.554)	0.997		
CrCl≥90	29/150 (19.3%)	559/2093 (26.7%)	0.999 (0.713 - 1.401)	0.724		
MACE	36/138 (26.1%)	672/2642 (25.4%)	1.060 (0.684 - 1.643)	0.793	0.824	
LVEF<50	15/53 (28.3%)	235/815 (28.8%)	0.981 (0.582 - 1.653)	0.941		
LVEF≥50	21/85 (24.7%)	437/1827 (23.9%)	1.061 (0.685 - 1.644)	0.791		
MACE	65/257 (25.3%)	1067/4193 (25.4%)	2.098 (0.984 - 4.471)	0.055	0.028	
ACS	46/207 (22.2%)	522/2062 (25.3%)	0.881 (0.652 - 1.191)	0.410		
Stable CAD	19/50 (38.0%)	545/2131 (25.6%)	1.637 (1.036 - 2.587)	0.035		
MACE	65/257 (25.3%)	1067/4193 (25.4%)	1.054 (0.732 - 1.517)	0.778	0.862	
SS 0-11	10/61 (16.4%)	255/1412 (18.1%)	0.905 (0.481 - 1.703)	0.757		
SS 12-22	24/101 (23.8%)	367/1412 (26.0%)	0.920 (0.609 - 1.391)	0.694		
SS>22	31/95 (32.6%)	445/1369 (32.5%)	1.055 (0.733 - 1.518)	0.775		

Figure 2. Stratified analysis for MACE (composite of all-cause death, all myocardial infarction and all revascularizations) according to the presence or absence of thrombus containing lesions. DM=diabetes mellitus, CrCl=creatinine clearance, LVEF=left ventricular ejection fraction, ACS=acute coronary syndromes, CAD=coronary artery disease; SS=anatomical SYNTAX score.

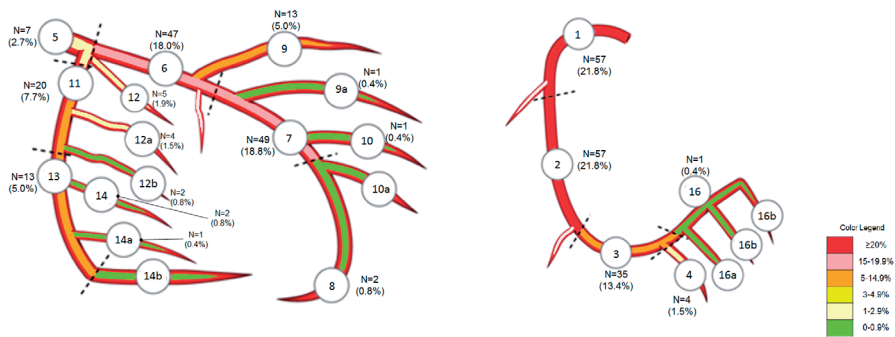


Figure 3. Distribution of angiographic thrombus containing lesions

36.8% in the first two segments of the left anterior descending coronary artery.

As demonstrated in Figure 4, TCL were seen quite often in coronary bifurcations. The association of thrombus containing and bifurcation lesions was present in 40.1% of the aforementioned pre-specified segments. In the left anterior descending coronary

artery, there was appreciable coexistence of thrombus and bifurcation lesions (45.9% of the lesions). On the other hand, the combination thrombus-bifurcation was not frequent in the distal right coronary artery (8.6% of the lesions).

Clinical outcomes according to myocardium at risk. We divided the subgroup of patients

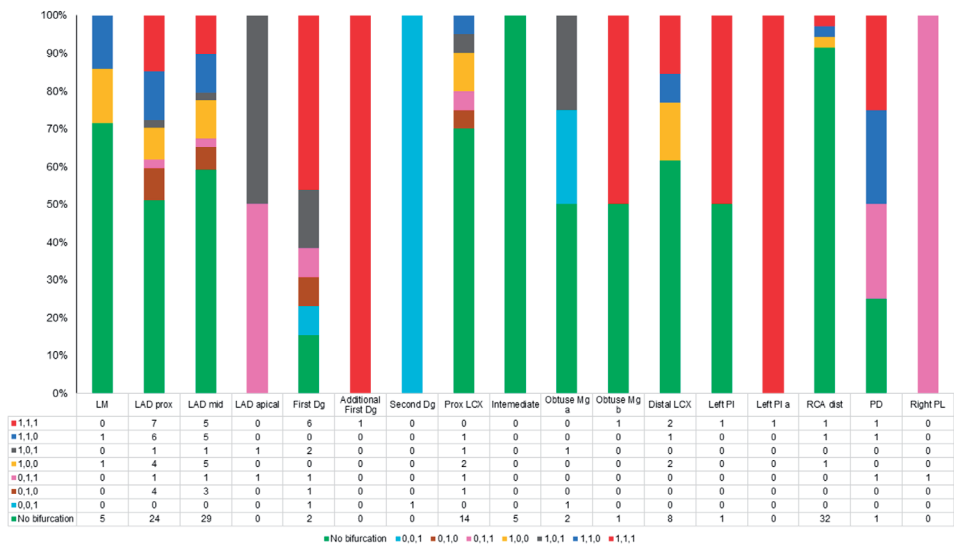


Figure 4. Per-segment association of thrombus and bifurcation lesions according to Medina¹⁴ classification. LM=left main coronary artery; LAD=left anterior descending coronary artery; Dg=diagonal branch; LCX=left circumflex coronary artery; Mg=marginal; RCA=right coronary artery; Pl=posterolateral branch; PD=Posterior descending branch

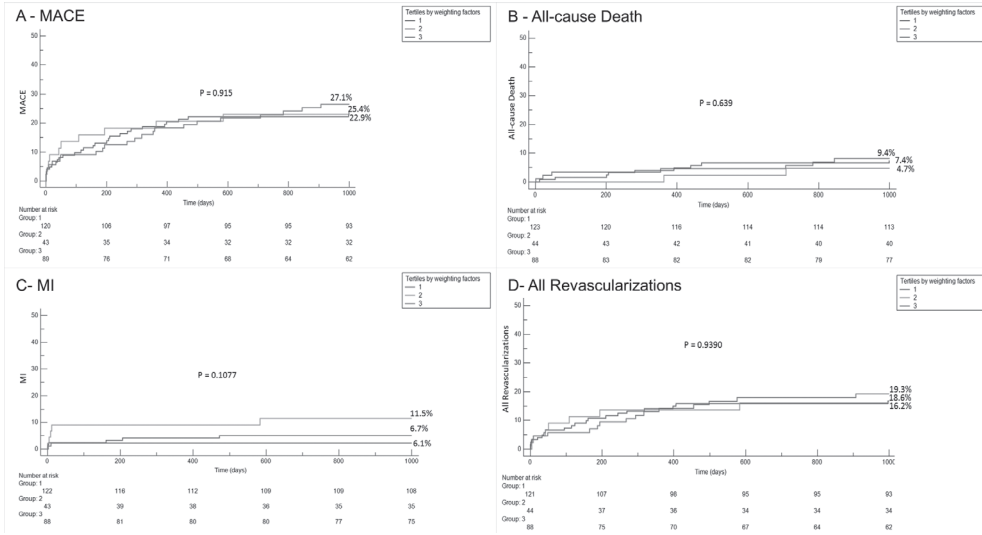


Figure 5. Kaplan-Meier cumulative curves for (A) MACE (composite of all-cause death, myocardial infarction and all revascularizations), (B) all-cause death, (C) myocardial infarction (MI) and (D) all revascularizations according to tertiles of the sum of segment weighing factors in patients with thrombus containing lesions

with TCL into tertiles of the sum of segment weighing factors (Table1). As shown in Figure5, the weighting for myocardium at risk, did not produce significant difference in outcomes (MACE, all-cause death, MI or all revascularizations) for patients with TCL.

DISCUSSION

The findings of our study can be summarized as follows: (i) TCL were seen more often in the proximal segments; (ii) there was a considerable coexistence of bifurcation and thrombus containing lesions; (iii) the presence of thrombus at baseline was not related to any additional risk of MACE, even after weighing for myocardium at risk.

Anatomy of angiographic coronary thrombus. Coronary thrombus is mostly formed following rupture of atherosclerotic lesions

containing a large necrotic core and a thin fibrous cap^{1,2}. In the present study we found that thrombus was angiographically detected in the proximal coronary segments and mainly in the right and left anterior descending coronary arteries. Our results are similar to those reported by Wang et al. who analyzed coronary angiograms from 208 consecutive patients presented with ST-elevation MI¹⁷. However, in their methodology they were evaluating the site of coronary occlusion. Although they used a slightly different coronary segmentation (BARI classification) they also have found that the two most proximal segments of right coronary artery and left anterior descending coronary artery were also responsible for the absolute majority (65.4%) of acute coronary occlusion¹⁷. In the present analysis, it was studied a 25-fold larger population and included a population with a broader spectrum of the disease (also stable CAD and

NSTEMI); the vessel occlusion is not mandatory for thrombus diagnosis. Importantly, all angiographic assessments were performed by an experienced independent core laboratory which has proven to have a higher consistency and better prognostic discrimination than investigator reported angiographic findings¹⁸.

Interestingly, distribution of TCFA, as assessed by VH-IVUS and OCT, resembles the distribution of thrombus found in the present study; this may indicate that TCFA are the

underlying substrate of coronary thrombus found in this study^{19,20} (Table 5). These invasive imaging findings are also in line with previous anatomopathological studies^{2,4,21}.

It has to be highlighted however that angiography, due to its limited resolution, is far from being the gold standard tool for coronary thrombus diagnosis. For instance, in the present analysis there was a low percentage (9.2%) of patients with acute coronary syndromes that were classified as

Table 5. Distribution of complex coronary lesions

	% in Proximal Segment	% in Mid Segment	% Total
Wang et al. ¹⁷			
Observation:			
Site of coronary occlusion Distribution, %			
RCA	12.5	14.4	26.9
LAD	14.5	24.0	38.5
LCX	8.6	4.3	13.0
LM	-	-	0.5
Present Study			
Observation:			
Thrombus containing lesions Distribution, %			
RCA	21.8	21.8	43.7
LAD	18.0	18.8	36.8
LCX	7.7	5.0	12.6
LM	-	-	2.7
PROSPECT sub study ¹⁹			
Observation:			
VH-TCFA-Containing Lesion Distribution, %			
RCA	17.1	15.1	32.2
LAD	24.2	10.8	35
LCX	15.2	11.8	27
LM	-	-	n.a.
Tian et al. ²⁰			
Observation:			
OCT-TCFA-Containing Lesion Distribution,%			
RCA	n.a.	n.a.	45.0
LAD	n.a.	n.a.	35.9
LCX	n.a.	n.a.	19.1
LM	-	-	n.a.

LM=left main coronary artery; LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; RCA=right coronary artery; VH= virtual histology intravascular ultrasound; OCT=optical coherence tomography, TCFA=thin cap fibroatheroma

having TCL. Similarly, Goto et al. detected angiographic thrombus in only 14.6% of patients in a population of exclusively acute coronary syndromes⁷. Importantly, while Goto et al. defined thrombus as “an intraluminal filling defect or an area of contrast staining noted within the target stenosis”⁷ and we used the definition recommended by the Academic Research Consortium¹⁵.

Another interesting aspect of our findings is the relatively frequent association between thrombus and bifurcation. In the LAD, a bifurcation lesion was present in almost half of the TCL. The most plausible explanations for this association are: 1. The most frequent location of TCFA is in bifurcation²² and 2. The endothelial shear stress in coronary bifurcations has a particular distribution. In relatively straight segments, the endothelial shear stress is pulsatile and unidirectional²³. Conversely, in coronary bifurcations, disturbed laminar flow occurs, and pulsatile flow generates low and/or oscillatory endothelial shear stress²³. The role of endothelial shear stress in more advanced atherosclerosis was demonstrated 45 years ago²⁴ and have been reproduced in autopsy-based coronary models, human in vivo studies in arterial models derived from intravascular ultrasound or magnetic resonance and in vivo animal experiments^{23,25}.

Thrombus and clinical events. In the present study, the presence of thrombus did not have any impact on clinical events, even when it was adjusted for the amount of myocardial at risk. Corroborating our findings, Singh et al. have shown that the introduction of the coronary stents and the use of more contemporary anti-platelet therapy made the presence of thrombus irrelevant for long-term death and myocardial infarction⁸. On the other hand, Sianos et al. have demonstrated that large

thrombus burden is an independent predictor major adverse events (defined as death, repeat myocardial infarction infarct-related artery infarct-related artery) in patients treated with drug eluting stents for STEMI⁹. Additionally, large thrombus burden has been related to larger myocardial damage as detected by contrast-enhanced cardiac magnetic resonance²⁶. The aforementioned findings suggest that, for clinical prognostic discrimination, the angiographic thrombus assessment should be no longer classified as a binary variable but as a more detailed thrombotic burden quantification.

Limitations

The present study has all inherent limitations of a post-hoc analysis. In addition, the number of stable patients with TCL was limited and may have hindered an accurate risk estimation in this subset. The classification of bifurcation lesions was restricted to those defined by the SYNTAX score and we could not establish whether TCL could be associated with smaller side branches. However, the use of the SYNTAX score concepts have demonstrated consistent prognostic impact for PCI treated patients^{12,27-29}. Information on thrombus aspiration was not available in this study. Nevertheless, the recent Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial showed that routine thrombus aspiration exclusively in a context of primary PCI did not reduce the rate of death from any cause or the composite of death from any cause, rehospitalization for myocardial infarction, or stent thrombosis at 1 year³⁰.

Conclusion

In this patient-level pooled analysis of three contemporary, all-comers stent trials, coronary

TCL involved mainly the proximal coronary segments and frequently bifurcations. Angiographic thrombus did not have any impact on 3-year MACE demonstrating that a more detailed thrombus burden quantification is

required to investigate its prognostic implications.

Disclosures

None.

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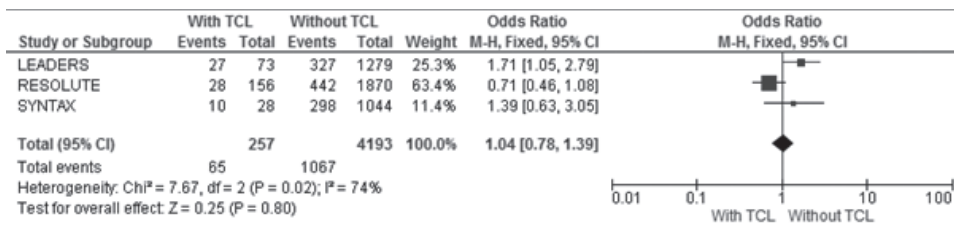
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SUPPLEMENTAL MATERIAL

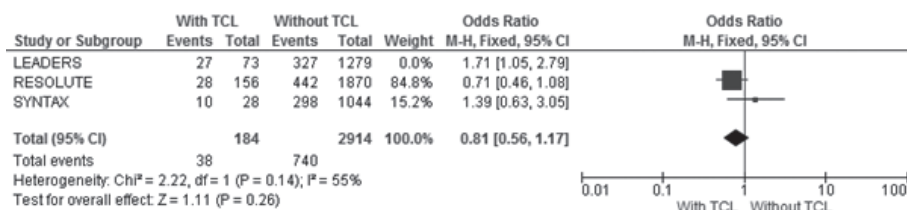
Supplemental Methods:

Discrete data were summarized as percent (frequencies) and were compared using the chi-squared test. Continuous data were expressed as mean±SD and were compared using Student's t-test or Wilcoxon rank-sum test based on their distributions. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test. Comparison of events rates between groups were adjusted for confounding factors in a Cox-regression

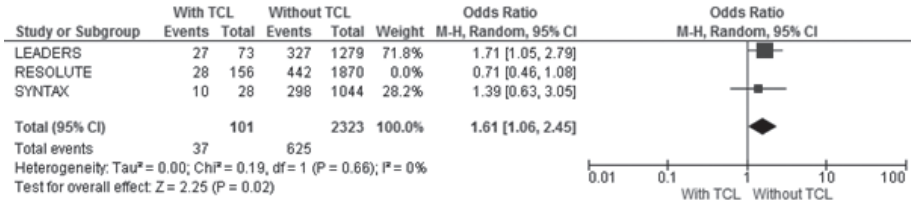
model. All variables were stratified according to presence of at least one TCL using a Cox-regression model. The differences were regarded significant when $p < 0.05$ (two-tailed). The Breslow-Day chi-squared test was calculated to test the statistical evidence of heterogeneity across the studies ($p < 0.1$). The chi-squared test and I^2 statistic was calculated to test the statistical evidence of heterogeneity across the studies¹ (Supplementary Table2, supplementary Figures1-5). SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used for all other statistical analyses.



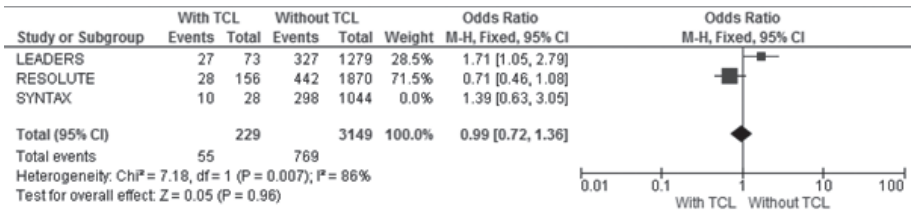
Supplemental Figure 1. Combined OR using the 3 trials using fixed effects for patients with thrombus containing lesions (TCL)



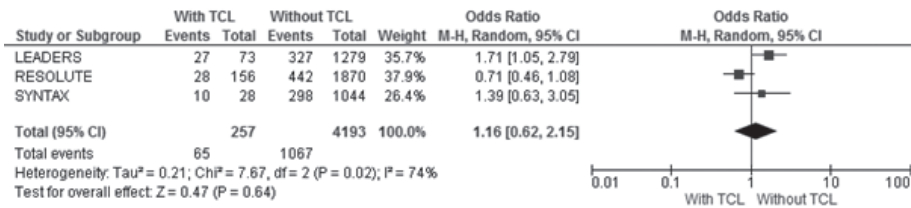
Supplemental Figure 2. When the LEADERS Trial was removed from the pooled analysis there was no longer heterogeneity:



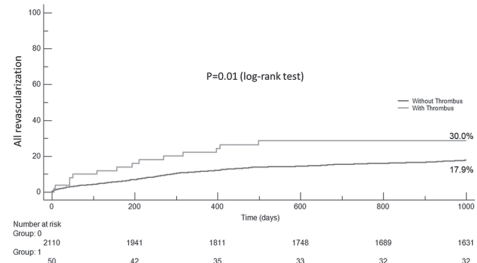
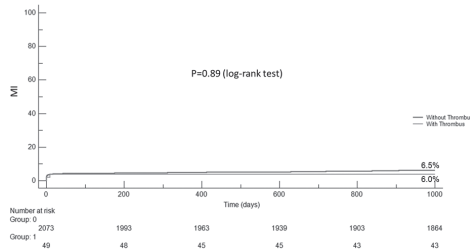
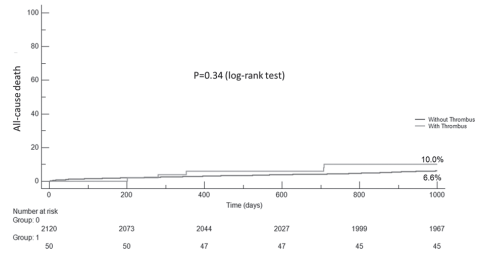
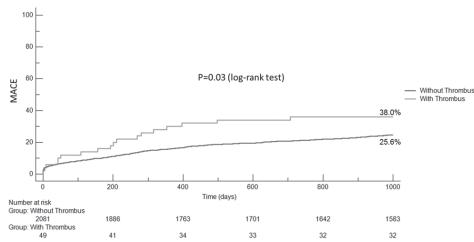
Supplemental Figure 3. Also when the RESOLUTE trial was removed from the pooling there was no significant heterogeneity:



Supplemental Figure 4. However, when we pool RESOLUTE and LEADERS and remove from the analysis the SYNTAX trial, the heterogeneity became even more evident:



Supplemental Figure 5. Pooled trial results using Bayesian random effects in which TCL did not have impact on long-term occurrence of MACE:

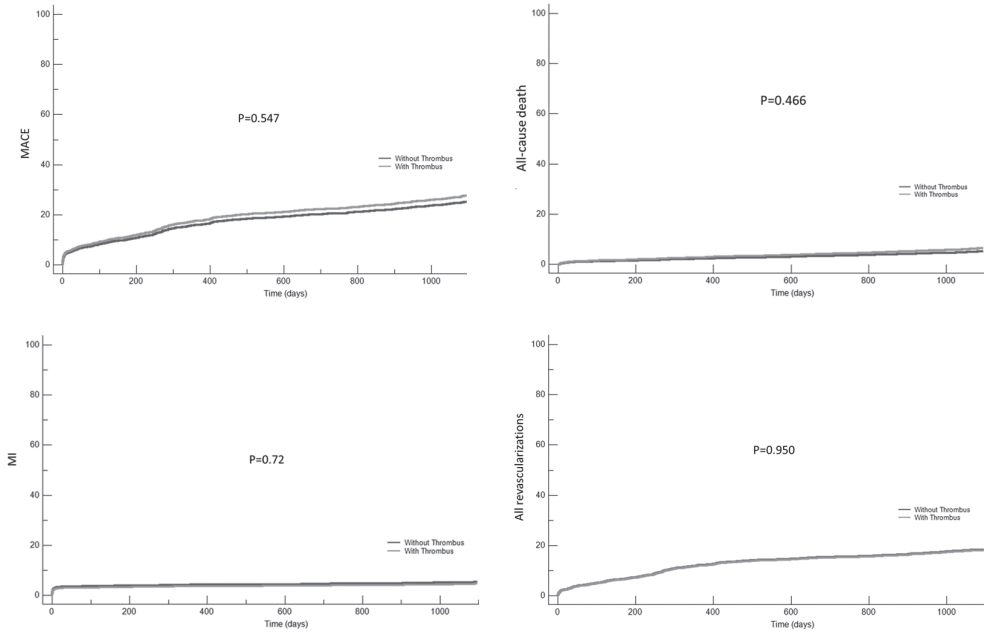


Supplemental Figure 6A. Kaplan-Meier curve comparison for MACE (composite of all-cause death, all myocardial infarctions and all revascularizations) according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Figure 6B. Kaplan-Meier curve comparison for all-cause death according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Figure 6C. Kaplan-Meier curve comparison for myocardial infarction according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Figure 6D. Kaplan-Meier curve comparison for all revascularizations according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease



Supplemental Figure 7A. Adjusted MACE (composite of all-cause death, all myocardial infarctions and all revascularizations) rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Figure 7B. Adjusted all-cause death rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Figure 7C. Adjusted all myocardial infarctions rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Figure 7D. Adjusted all revascularizations rate comparison according to presence/absence of thrombus containing lesions in patients with stable coronary artery disease

Supplemental Table 1. Summary of the trials included in the present analysis

	LEADERS ²	RESOLUTE ³	SYNTAX ⁴
Enrolment Period	11/2006-05/2007	04/2008-10/2008	03/2005-04/2007
Study Design	RCT	RCT	RCT
Number of Patients	1707	2292	1101
Number of Patients with SYNTAX score Total (acute†)	1352 (535)	2026 (736)	1072 (0)
Stents Used	SES, BES	EES, ZES	PES
Inclusion criteria	Patients aged ≥18 years old AND Presentation: Stable angina, ACS, STEMI AND ≥1 lesion ≥50% DS in vessel with RVD 2.25-4.00mm* No restriction on total number of treated lesions, treated vessels, lesion length or number of stents implanted.		Presentation: stable angina, unstable angina or silent ischaemia, AND >50% DS in three major epicardial coronary arteries and/or LMS No restriction on the total implanted stent length.
Exclusion criteria	Inability to take dual anti-platelet therapy Allergy to study medicines Terminal illness <6 months life expectancy Pregnancy Participation in another trial		Previous PCI or CABG Acute MI Need for concomitant cardiac surgery
Study Procedure	Stenting procedure at operator's discretion; Direct stenting was allowed Aim for complete revascularisation		
DAPT	Aspirin†	100mg	≥75mg
	Clopidogrel (duration)	75mg (12 months)	75 mg (≥ 6 months)

*2.25-3.50mm in LEADERS

†Acute- ST-elevation and Non-ST elevation myocardial infarction

Supplemental Table 2. Assessment of heterogeneity among the trials:

Endpoint	Chi-square P value	I ²
All-cause death	0.13	51%
All revascularizations	0.20	38%
Myocardial Infarction	0.69	0%
MACE (composite by death, myocardial infarction and all revascularizations)	0.02	74%

There was a significant heterogeneity for MACE (Supplemental Figure 1) but interestingly was not caused by the SYNTAX trial (Supplemental Figures 2-4). The Supplemental Figure 5 shows the combined OR using Bayesian random effects in which thrombus containing lesion (TCL) did not have impact on long-term occurrence of MACE

Supplemental Table 3. Baseline clinical and angiographic characteristics according the presence/absence of thrombus in patients with stable coronary artery disease

	Without thrombus N=2131	With thrombus N=50	P
Age	63.6±11.2	61.8±11.9	0.031
Male,%	1610 (75.6)	39 (78.0)	0.868
Diabetes Mellitus,%	595 (27.9)	18 (36.0)	0.206
Body mass index, kg/m ²	27.7±4.5	27.5±4.6	0.527
Hypertension,%	1613 (75.7)	40 (80.0)	0.616
Hyperlipidemia,%	1578 (74.0)	35 (70.0)	0.517
Current smoker,%	524 (24.6)	13 (26.0)	0.794
Peripheral vascular disease,%	190 (8.9)	4 (8.0)	0.767
Family history of premature CAD,%	1394 (65.4)	34 (68.0)	0.756
History of Stroke/TIA,%	128 (6.0)	5 (10.0)	0.209
Creatinine>200 micromol/L	32 (1.5)	0 (0.0)	1.000
Creatinine clearance; ml/min	93.2±41.4	100.1±34.6	0.012
Previous myocardial infarction,%	637 (29.9)	13 (26.0)	0.639
Previous PCI, %	583 (27.4)	10 (20.0)	0.334
LVEF,%	54.8±11.6	52.0±10.9	0.01
Anatomical Characteristics			
Baseline SYNTAX score ±SD	17.1±11.3	18.0±10.2	0.276
Number of total occlusions/patient±SD	0.33±0.51	0.41±0.56	0.04
Number of aorto-ostial lesions/patient±SD	0.05±0.23	0.06±0.56	0.566
Number of lesions with severe tortuosity/patient±SD	0.74±1.07	0.68±1.02	0.425
Number of lesions with length>20mm/patient±SD	0.51±0.71	0.53±0.62	0.750
Number of lesions with heavy calcification/patient±SD	0.33±0.77	0.25±0.68	0.158
Number segments with diffuse disease/patient±SD	0.04±0.20	0.03±0.17	0.531
Lesions in left main/patient	0.08±0.29	0.06±0.26	0.246
Lesions in LAD proximal/patient	0.31±0.48	0.33±0.51	0.491
Lesions in LAD mid/patient	0.56±0.58	0.54±0.60	0.579
Lesions in LAD apical/patient	0.16±0.39	0.11±0.34	0.08
Lesions in 1 st diagonal/patient	0.24±0.45	0.26±0.46	0.549
Lesions in 2 nd diagonal/patient	0.01±0.12	0.01±0.12	0.875
Lesions in proximal circumflex/patient	0.18±0.40	0.16±0.37	0.587

Supplemental Table 3. Baseline clinical and angiographic characteristics according the presence/absence of thrombus in patients with stable coronary artery disease (continued)

	Without thrombus N=2131	With thrombus N=50	P
Lesions in distal circumflex/patient	0.32±0.50	0.27±0.47	0.178
Lesions in intermediate/patient	0.10±0.31	0.07±0.26	0.155
Lesions in first obtuse marginal/patient	0.13±0.34	0.10±0.32	0.319
Lesions in second obtuse marginal/patient	0.11±0.33	0.10±0.31	0.559
Lesions in RCA proximal/patient	0.25±0.44	0.32±0.48	0.026
Lesions in RCA mid/patient	0.33±0.48	0.32±0.47	0.734
Lesions in RCA distal/patient	0.23±0.45	0.26±0.46	0.333
Lesions in Posterolateral/patient	0.03±0.18	0.02±0.14	0.787
Lesions in Posterior descending /patient	0.11±0.32	0.12±0.33	0.351

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Chapter 1.6

Serial Volumetric Assessment of Coronary Fibroatheroma by Optical Frequency Domain Imaging: Insights From the TROFI Trial

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Submitted

ABSTRACT

Background

Coronary lesions precursors of acute events remain elusive, since they undergo continuous changes and their temporal changes are not very well characterized. In natural history studies, optical frequency domain imaging (OFDI) has been used only to assess fibroatheromas as a two-dimensional structure and sometimes in a single frame fashion.

Aim

We aim at describing the serial volumetric modifications of the fibrous cap (FC) of the fibroatheromas as determined by OFDI over a 6-month follow-up period.

Methods

In 49 patients, OFDI investigation was performed following treatment of culprit lesion and at 6-month follow-up in patients with ST-segment elevation myocardial infarction (STEMI). A fully automatic volumetric quantification of FC was done in all lipid-containing frames of non-culprit lesions in the infarct related artery. These lesions were matched at baseline and 6-month follow-up.

Results

A total of 58 non-culprit lipid rich lesions (34 TCFAs and 24 thick-cap fibroatheroma [ThCFA]) were found in 34 patients at baseline. Overall, there was a FC volume decrease of 1.57 (Interquartile Range [IQR] -4.13 to 0.54) mm³ at 6-months. 27% of the lesions changed their phenotype over time (TCFA or thick-cap fibroatheroma ThCFA). TCFAs that became ThCFAs at follow-up had smaller mean and maximal FC as compared with lesions that remained TCFAs (P=0.01 for both).

Conclusions

Non-culprit fibroatheromas located in the infarct related artery of patients with STEMI had a volumetric reduction of the FC after 6-month follow-up. Quantitative FC assessment was able to differentiate high-risk lesions that became ThCFAs. There was a considerable change of plaque phenotype (TCFAs or ThCFAs) over time.

INTRODUCTION

The characterization of culprit lesions and even more the identification of coronary lesions precursors of acute events remain the holy grail of intracoronary imaging (1). It has been shown that in patients receiving optimal pharmacological treatment, the presentation of acute coronary syndromes or death may be associated with the total number of segments with significant disease rather than the ischemic burden (2). This suggests that plaque disruption might be the main cause of major cardiac outcomes rather than the ischemia induced by obstructive plaques.

Coronary plaques have been scrutinized to understand characteristics related to the hazard of subsequent cardiovascular events (3-5). Traditionally, a plaque with a fibrous cap (FC) thickness $<65 \mu\text{m}$ on top of a necrotic core is nominated thin cap fibroatheroma (TCFA) and is considered as a high risk plaque. More recently, a threshold for FC of $53.5 \mu\text{m}$ has also been correlated also to plaque rupture or TCFA (3, 4).

Optical coherence tomography (OCT) is an intravascular light-based imaging method with a near-histological resolution of $10\text{-}20 \mu\text{m}$. Currently, OCT is the only technology available in the clinical setting that provides spatial resolution sufficient to assess FC thickness accurately (FCT) (6, 7). Consequently, OCT has been used to study the ability of pharmacological or interventional therapies to promote FC thickening (i.e. plaque stabilization) (8, 9). However, in natural history studies, OCT has been used only to assess coronary fibroatheromas as a two-dimensional structure and sometimes the assessment is only performed in a single frame (8, 9). This approach is very limited and is not able to pick up changes that

may occur in other dimensions in the FC. The recently developed optical frequency domain imaging (OFDI) technique, an analogue of the Fourier-domain OCT, is the state-of-the-art of this technology.

Accordingly, we sought to describe the changes of coronary fibroatheromas over a 6-month follow-up period, describing the serial volumetric modifications of the FC as determined by OCT.

METHODS

Study population

The TROFI (Thrombus Aspiration on Flow Area in Patients With ST-Elevation Myocardial Infarction; ClinicalTrials.gov Identifier: NCT01271361) trial has been described in details previously (10, 11). In brief, the TROFI trial prospectively randomized STEMI patients to receive either primary percutaneous coronary intervention (PCI) with thrombectomy ($n=71$) or without thrombectomy ($n=70$) prior to biolimus-A9 eluting metallic stent (Nobori®, Terumo Europe N.V., Leuven, Belgium) implantation. STEMI patients having an angiographically visible stenosis ($>30\%$) or pre-procedural TIMI flow grade ≤ 2 in a single de-novo, native, unstented vessel were considered for enrollment. The study protocol was approved by the local ethics committees at each of the five European participating centers, and written informed consent was obtained from all enrolled patients.

Optical frequency domain imaging (OFDI) acquisition

The present study included OFDI data regardless of the randomization arm. After the post-procedural angiography, OFDI image acquisition

tion was performed with the TERUMO OFDI system (Terumo Europe N.V., Leuven, Belgium) with imaging element rotating at 9600 rpm allowing imaging at 160 frames/s. Intracoronary nitroglycerin (0.2 mg) was administered before the OFDI acquisition. An automated OFDI pullback with a speed of 20 mm/s was performed during continuous intracoronary injection of 100% contrast medium using an injection pump at a pressure of 300 p.s.i with a flow rate of 3 to 4 ml/s for a maximum of 4 seconds or manually. Imaging calibration was performed as previously described (12). At 6-month follow-up the same OFDI console and acquisition methodology was used in the infarct related coronary artery.

Off-line OFDI analysis

The OFDI raw data were transformed from the original 16 bits polar image to an 8 bits Cartesian image of 1024 by 1024 pixels. The off-line analysis was performed using the QCU-CMS software (LKEB, Leiden University, The Netherlands). Four experienced image analysts were involved in the present evaluation (HG, JI, TM, SN). The first step was the delimitation of regions of interest (ROIs) by identifying lipid rich non-culprit lesions in the infarct related artery at the index procedure. The fibrous cap was identified as a signal-rich band overlying the lipid core. Serial OFDI images at baseline and 6-month follow-up were reviewed side by side on the screen, and ROIs were matched based on the distance from landmarks, such as branches, calcifications, and stents.

The quantification of FC was done in all corresponding frames for volumetric analysis of cap thickness. After the lumen border detection in the transversal image, the operator delineated the lipid-rich sector laterally using the two rays which emanate from vertex localize in

the center of the imaging catheter. (Figure1). In case the guide-wire shadow was located within the defined sector, the shadow area was marked out and excluded from the analysis. Next the fully automatic fibrous cap segmentation was applied on (transversal OCT images), and the luminal- and abluminal boundaries of the fibrous cap within the manually defined sector were extracted automatically. (Figure1). The detection of the fibrous cap was done using the largest gradient in pixel intensity (1st derivative) between the fibrous cap tissue and the lipid region (i.e. where the slope on the sigmoid curve changes fastest). To avoid false edge information, the pixels in front of the maximum intensity in the fibrous cap region (i.e. pixels originating from the lumen), were discarded. After segmentation, the distances between the lumen and fibrous cap borders were determined allowing the computation of the minimal, maximum, and mean fibrous cap thickness within the sector. The distance was calculated by dividing the lumen contour in 1 degree intervals and next determine the shortest distance from each lumen point to the fibrous cap contours. This assessment for the minimal FCT has shown perfect agreement for both inter- and intra-observer assessments ($\kappa=1.00$) (In press report). An example is presented in Figure1.

The presence of TCFA was defined as a minimal FCT $<65 \mu\text{m}$ in at least one frame of the longitudinal region of interest. Lesions with minimal FCT $>65 \mu\text{m}$ were named thick-cap fibroatheromas (ThCFA). Lesions that were TCFA at baseline and had FCT $>65 \mu\text{m}$ at follow-up were named Pacified TCFA. ThCFAs that became TCFA at follow-up were Newly developed TCFA.

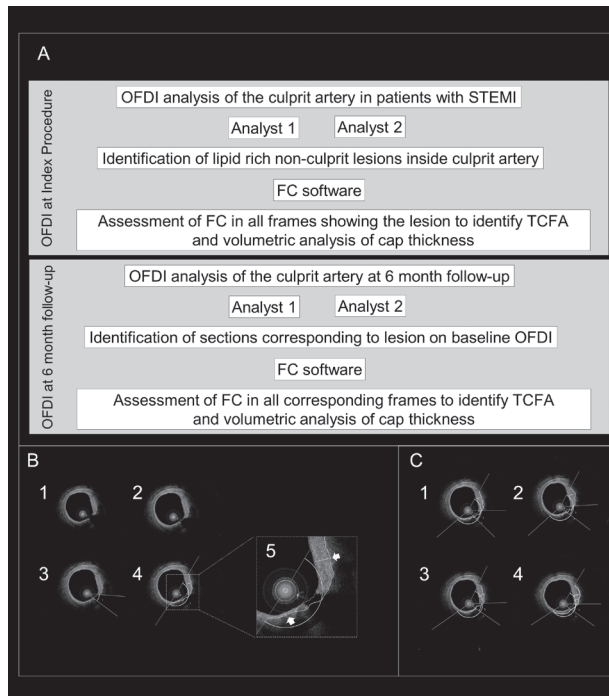


Figure 1. Representation of fibrous cap (FC) measurement. (A) Two analysts identified non-culprit, lipid-rich plaques at baseline. Thereafter, using anatomic landmarks, the two analysts found correspondent lesions at follow-up. (B) (1 and 2) the first step is lumen border detection; (3) Secondly the guidewire artefact is masked to avoid interference; (4) the software detects the FC by using the largest gradient in pixel intensity; (5) identification of minimal FC thickness (white arrow); mean FC thickness (green line); maximal FC thickness (yellow arrow); (C) The same steps are repeated in all frames involved in that region of interest. OFDI: optical frequency domain imaging; STEMI: ST elevation myocardial infarction; TCFA: thin-cap fibroatheroma

Data Analysis

Discrete data were summarized as percent (frequencies) and were compared using the chi-squared test. Continuous data were expressed as mean \pm SD or median [interquartile range (IQR)] and were compared using Student's t-test or Wilcoxon rank-sum test based on their distributions. The distribution was tested using the Kolmogorov-Smirnov test. $P < 0.05$ was considered statistically significant. SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

RESULTS

Between November 24th, 2010 and October 11th, 2011, 141 patients (71 patients in the thrombectomy arm and 70 patients in the non-thrombectomy arm) were enrolled at 5 European sites. In 3 predefined centers, the enrolled patients ($n=51$) were followed-up angiographically and with OFDI at 6 months. Paired (post-procedure and follow-up) OFDI recordings were available in 49 patients. The baseline clinical characteristics are depicted in the Table 1.

Table 1. Baseline and procedure characteristics

Demographics	Thrombectomy N=26	Non thrombectomy	
		N=25	p
Age	59 ± 10	57 ± 13	0.42
Male, %	77	76	0.94
Heart Rate	73.77± 21.59	71.76 ± 14.68	0.7
Risk factors, %			
Diabetes mellitus	7.7	8.0	0.97
Insulin	0.0	0.0	
Current Smoking	58	52	0.49
Hypercholesterolemia	42	20	0.08
Hypertension	38	28	0.43
Family history of CAD	50	56	0.66
Procedural details			
Stents implanted per lesion	1.23±0.6	1.36±0.8	0.5
Mean total stent length / lesion (mm)	23.2±10.5	25.4±13.1	0.52
Mean stent diameter (mm, nominal)	3.1±0.39	3.1±0.37	0.64
Number of aspiration / lesion	1.81± 0.40		
Device successfully reached, %	100		
Device successfully crossed, %	100		
Thrombus successfully removed, %	100		

OFDI Results

In 34 patients (69%), a total of 58 non-culprit lipid rich lesions were found in the infarct related artery. The table 2 presents the overall changes in these regions. 1624 frames were analyzed at baseline and 1596 at 6-month follow-up. It was found an overall stabilization in these lipid-rich regions (Table 2). The

minimal FCT increased significantly from 0.07 (Interquartile Range [IQR] 0.018-0.096) mm at baseline to 0.12 (IQR 0.09-0.17) mm at 6-month follow-up ($P<0.01$). The number of frames with FCT smaller than 65 μm also decrease significantly ($P<0.01$). The mean FCT increased $0.03\pm 0.07\text{mm}$ ($P<0.01$) and the lesion length decreased by $0.98\pm 1.92\text{mm}$

Table 2. Overall changes in lipid-rich non-culprit lesions (n=58) as assessed by optical frequency domain imaging. Values are mean ± standard or median (Interquartile Range)

	Baseline	Follow-up	Delta	P
Minimal cap thickness, mm	0.07(0.02-0.10)	0.12 (0.09-0.17)	0.06±0.06	<0.01
Number of Frames with Cap thickness <65 μm	1 (0-8.0)	1 (0-3)	-2.91±6.7	<0.01
Maximal cap thickness, mm	0.511 (0.45-0.59)	0.529 (0.47-0.61)	0.01 (-0.03 to 0.07)	0.13
Mean cap thickness, mm	0.29±0.07	0.32±0.09	0.03±0.07	<0.01
Mean FC Angle, degrees	254.04±55.67	235.72±69.24	-18.31±54.78	0.03
Length, mm	7.47±2.84	6.48±2.75	-0.98±1.92	<0.01
Cap Volume, mm ³	18.26 (8.23-40.21)	14.02(7.21-36.53)	-1.57 (-4.13 to 0.54)	<0.01

after 6 months ($P < 0.01$). Consequently, it was found a FC volume decrease of $1.57 (-4.13$ to $0.54)$ mm^3 at follow-up mostly driven by the shortening of the lipid-rich regions at follow-up (Figure 2).

Out of 58 lesions, 34 lesions were TCFA at baseline and 30 at 6-month follow-up. Ten

lesions that were TCFA at baseline became ThCFAs at follow-up. Out of 24 lesions that were ThCFAs at baseline, 6 became TCFA at follow-up. Therefore, 28 lesions were ThCFA at 6-month follow-up (Figure 3). An example of the natural history of fibroatheromas is given in Figure 4.

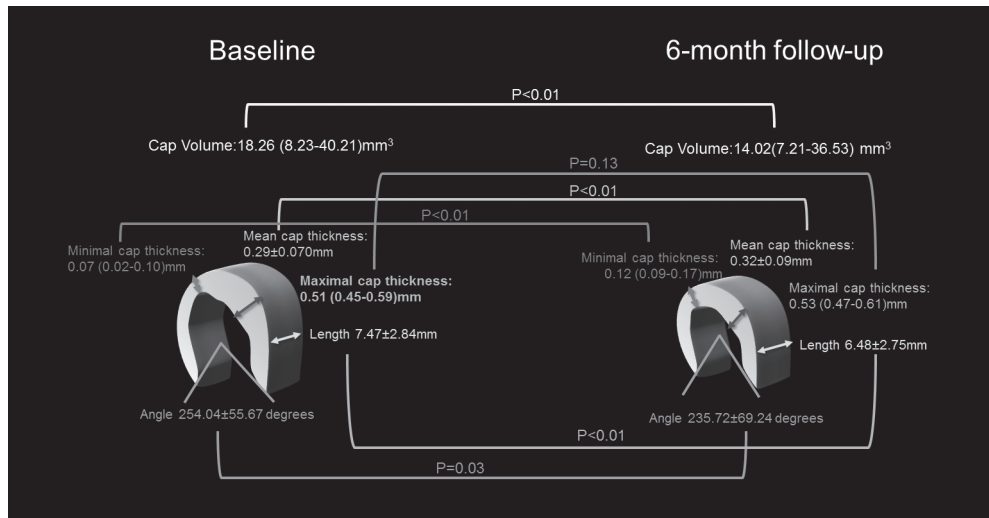


Figure 2. Schematic representation of the volumetric temporal change in the fibrous cap (FC). There was a significant decrease in the FC volume due to an reduction in FC angle, length, mean and minimal thicknesses. The maximal FC thickness did not change significantly

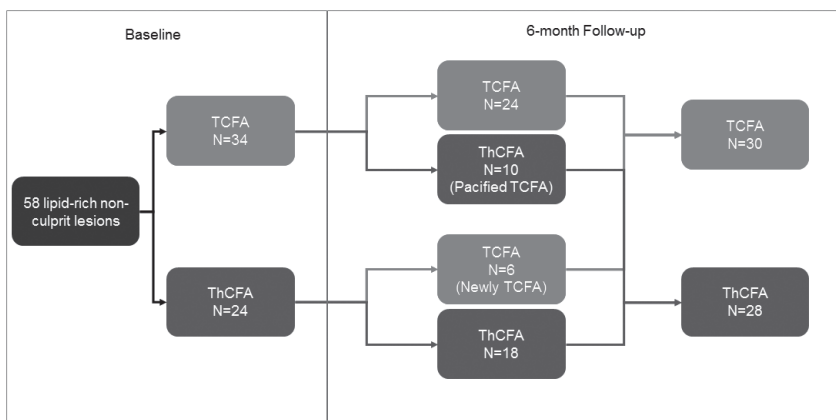


Figure 3. Schematic representation of the natural history of lipid-rich; non-culprit lesions of the present study

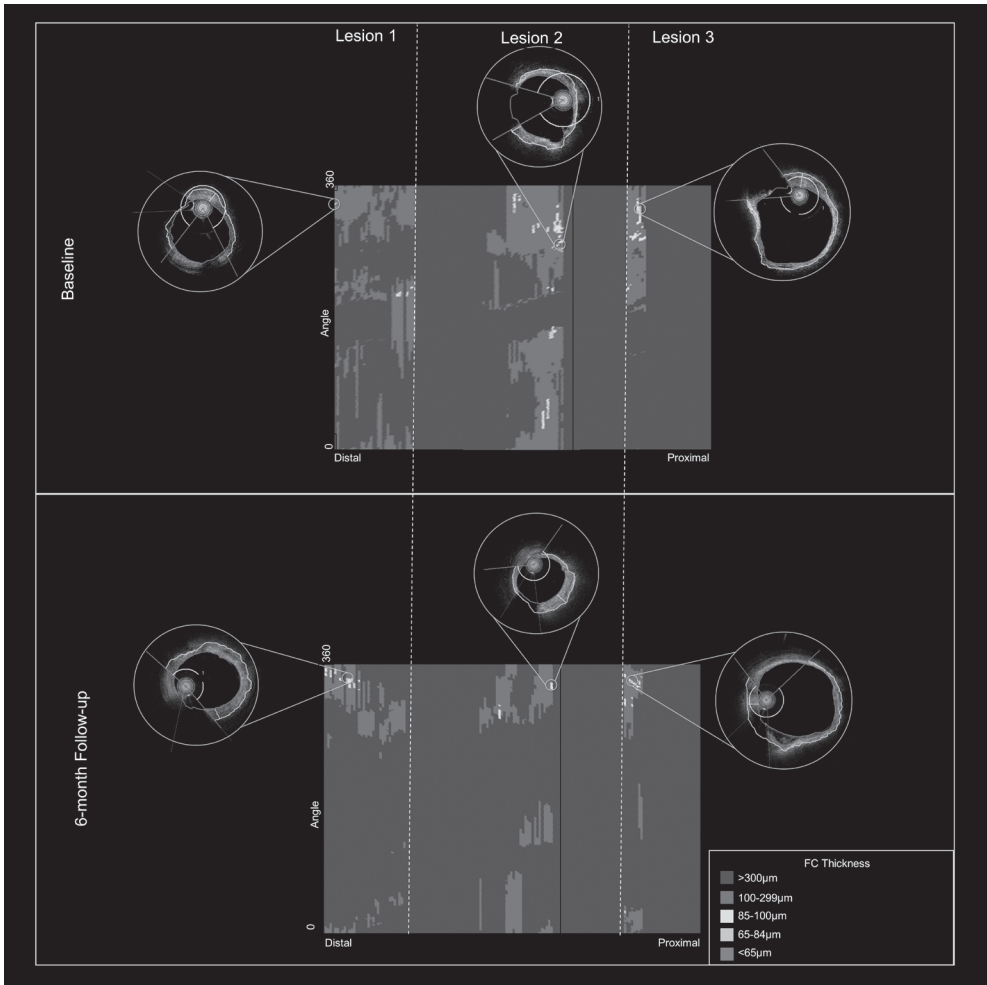


Figure 4. Temporal changes of 3 fibroatheromas in the same patient matched for the index procedure and 6-month follow-up. A two-dimensional map, color-coded by the fibrous cap thickness is given. There is better OFDI characteristics in all lesions. The X axis represents the distance from the distal to proximal segment of the coronary artery, while the Y axis represents the circumferential segment (angle). The Lesion 1 and Lesion 2 were thin-cap fibroatheromas (TCFA) that became a Pacified TCFA 6 months later. The lesion 3 was found to be ThCFA in the two acquisitions. It has to be highlighted that the frames where the minimal thickness were located were different between the two time points.

The TCFA at 6-month (n=30) had similar FC volume at baseline and follow-up (P=0.37) (Table 3). There was however a significant increase in the mean FCT (P=0.03) and a 0.85 ± 2.10 mm decrease in the lesion length (P=0.03). There was also a trend to reduction

in the number of frames with FCT <65 µm (P=0.06).

At baseline, Pacified TCFA had different OFDI findings as compared with lesions that remained TCFA (Table 4; Figure 5). The maximal and the mean FCT were significantly larger

Table 3. Optical frequency domain imaging findings of TCFAs at follow-up (n=30). Values are mean ± standard or median (Interquartile Range)

	Baseline	Follow-up	Delta	P
Minimal cap thickness,mm	0.05±0.043	0.05 ±0.034	0.01±0.04	0.99
Maximal cap thickness, mm	0.50 (0.44 to 0.54)	0.52 (0.47 to 0.60)	0.02 (-0.02 to 0.06)	0.18
Mean cap thickness	0.25 (0.22 to 0.30)	0.28 (0.24 to 0.32)	0.02 (-0.02 to 0.06)	0.03
Angle, degrees	274.88±42.04	266.53±54.68	-8.35±44.04	0.31
Lesion Length,mm	8.17±2.82	7.32±2.71	-0.85±2.10	0.03
Number of frames with FCT <65 µm	4 (1 to 17)	3 (1 to 11)	-1.5 (-7.25 to 1.25)	0.06
FC volume , mm ³	29.05 (11.33 to 43.72)	27.88 (9.51 to 51.47)	-1.72±8.65	0.37

Table 4. Baseline comparison of optical frequency domain imaging findings of lesions that remained thin-cap fibroatheromas (TCFA) versus lesions that became pacified TCFAs

	Remained TCFA (n=24)	Pacified TCFA (n=10)	P
Minimal cap thickness ,mm	0.03 (0.00 to 0.06)	0.05 (0.00 to 0.09)	0.38
Number of Frames with Cap thickness <65 µm	8 (2 to 21)	5 (1 to 13)	0.11
Maximal cap thickness, mm	0.49±0.07	0.56±0.10	0.01
Mean cap thickness, mm	0.25±0.05	0.30±0.06	0.01
Mean FC Angle, degrees	278.60±34.71	264.42±27.45	0.26
Lesion Length, mm	8.10±2.56	7.84±2.37	0.79
Cap Volume, mm ³	40.65±36.66	35.43±30.97	0.69

in Pacified TCFAs (P=0.01 for both). Pacified TCFAs has also a trend to have less frames with Cap thickness<65 µm. The cap volume was not different (P=0.69).

The lesions that were ThCFAs at follow-up demonstrated an increase of 0.03±0.06mm in the mean FCT (P=0.01), a decrease of 0.89 (IQR -1.53 to -0.08)mm in the lesion length and a median decrease of 16.9% of the FC volume (P<0.01 for all) (Table5).

Newly TCFAs and lesions that remained ThCFAs did not have any significant difference in the OFDI findings at baseline. Newly TCFAs had however a trend to have longer lesions (P=0.16), with wider angle (P=0.17) and with a larger cap volume (P=0.17) (Table6).

DISCUSSION

The main findings of the present study can be summarized as follows: (1) Lipid-rich, non-culprit lesions were frequently found in infarct related coronary arteries in STEMI patients; (2) there was an overall reduction in fibrous-cap volume after 6 months mostly driven by shortening of the lesion length; (3) 27% of lesions changed their phenotype (TCFAs or ThCFAs) over time; (4) Pacified TCFAs had different plaque characteristics at baseline as compared with lesions that remained TCFAs.

The precise identification of plaques that are prone to rupture and cause a major coronary event is a field of major clinical relevance. In this regard OCT is the only clinically available method with enough resolution to measure the FCT *in vivo* accurately. Although TCFAs as

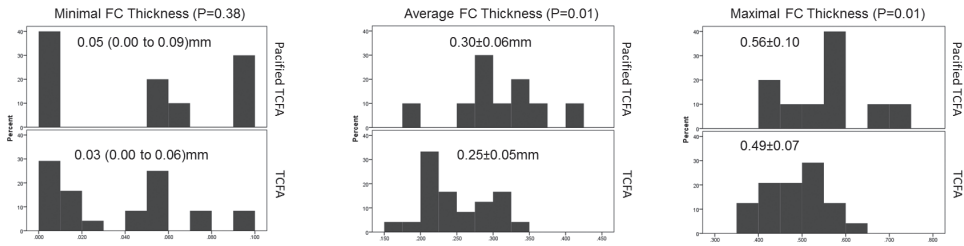


Figure 5. Distribution of fibrous cap thickness at baseline between lesions that remained thin-cap fibroatheromas (TCFAs) versus lesions that became pacified TCFAs

Table 5. Optical frequency domain imaging findings of thick-cap fibroatheromas at baseline and 6-month follow-up (n=28)

	Baseline	Follow-up	Delta	P
Minimal cap thickness,mm	0.09 (0.07 to 0.11)	0.09 (0.08 to 0.14)	0.04±0.05	0.07
Maximal cap thickness, mm	0.54±0.11	0.56±0.10	0.02±0.09	0.20
Mean cap thickness	0.31±0.07	0.34±0.08	0.03±0.06	0.01
Angle, degrees	231.70±60.37	202.72±68.75	-28.98±63.44	0.02
Lesion Length,mm	5.98 (4.75 to 8.96)	5.14 (3.60 to 7.06)	-0.89 (-1.53 to -0.082)	<0.01
FC volume , mm ³	10.98 (4.82 to 20.58)	9.02 (3.89 to 17.78)	-1.85 (-3.61 to -0.39)	<0.01

Table 6. Baseline comparison of optical frequency domain imaging findings of lesions that remained thick-cap fibroatheromas (ThCFA) versus Newly TCFAs

	Remained ThCFA (n=18)	Newly TCFAs (n=6)	P
Minimal cap thickness ,mm	0.10 (0.08 to 0.13)	0.10 (0.07 to 0.12)	0.58
Maximal cap thickness, mm	0.53 (0.45 to 0.60)	0.51 (0.49 to 0.66)	0.58
Mean cap thickness, mm	0.31 (0.26 to 0.39)	0.31 (0.24 to 0.36)	0.87
Mean FC Angle, degrees	197.88 (162.20 to 250.87)	288.76 (183.17 to 309.24)	0.17
Lesion Length, mm	5.12 (4.18 to 8.20)	8.17 (5.15 to 12.21)	0.16
Cap Volume, mm ³	9.29±7.54	14.41±9.25	0.17

visualised by OCT are often diagnosed with confidence, some factors may preclude a correct diagnosis: those involving the qualitative classification (identification of FAs) and those concerning the measurement of the FC with the aim to distinguish TCFAs from ThCFAs (13, 14). The present work used a fully automatic FC volumetric assessment by OCT, a method that has shown to have a much more robust

measurement than the manual assessment done by experienced analysts (In press report).

Another important aspect of imaging of coronary fibroatheromas is to assess their temporal changes and correlations with clinical factors, laboratory findings and therapeutic agents. Factors such as high circulating neopterin (a pteridine derivative secreted by activated macrophages), low eicosapentaenoic

acid/arachidonic acid ratio, current smoking, low-density lipoprotein and presentation with acute coronary syndrome have been correlated with thinner fibrous cap thickness by OCT or the presence of TCFAs (15-17). Conversely, high intensity atorvastatin therapy (20 mg/day) has shown to increase the fibrous cap thickness in coronary plaques as compared with 5 mg/day (9). In addition, percutaneous coronary interventions with bioresorbable scaffolds or metallic stents have been tested to passivate vulnerable plaques over time with promising results (8, 18, 19). However, these invasive strategies still do not have evidence strong enough to be implemented in the clinical practice. The present work describes, for the first time, the volumetric temporal changes of FC by OFDI and can be used in future investigations of natural history of coronary atherosclerosis.

It has to be highlighted that it was found 58 non-culprit fibroatheromas in the target vessel of 34 STEMI patients (1.7 lesions/patients). Moreover, 34 fibroatheromas were quantified as TCFAs at baseline (1.0/patient). Galon et al., using a similar automatic algorithm for FC assessment, have also found a considerable number of non-culprit fibroatheromas in the target vessel of 10 STEMI patients (2.11 lesions/patient)(20). In their work however the overall minimal and mean cap thickness were about the half of the value we found in the present work (0.03 ± 0.02 mm vs. 0.07 and 0.14 ± 0.03 vs. 0.29 ± 0.07 ; respectively). Besides the relatively small sample sizes, as abovementioned, patients' individual characteristics may have influenced these discrepancies.

Another important finding of the present study is the dynamic nature of the fibroatheromas. There was an overall improvement

of these non-culprit plaques with significant increase of the minimal and mean FCT with reduction of the FC angle, lesion length and cap volume ($P<0.01$ for all). However, when these lesions were classified qualitatively (TCFAs or ThCFAs) 27% changed their phenotype over time and TCFAs still were present in a sizeable proportion (58% at baseline and 51% at 6-month follow-up (Figure 3). However the remaining TCFAs at 6-month also had signals of improvement with shorter lesion length and larger mean cap thickness (Table 3). Importantly, it was shown that the regions where the minimal FC was found in each lesion may change over time (Figure 4). Interestingly, pacified TCFAs had larger mean and maximum FC as compared with plaques that remained TCFAs over time (Table 4). The clinical explanation and prognostic implications of these quantitative measurements still have to be investigated.

LIMITATIONS

The TROFI trial was design to investigate the role of thrombectomy on improving the flow area in STEMI patients. Therefore the clinical variables (ex. lipid control, pharmacological adherence, etc) for plaque phenotype modifications over time could not be explored. As abovementioned, the relatively small sample size does not allow for explore the prognostic implications of FC volume change still have to be established. Additionally, the present methodology does not takes into account the presence of OCT signal intensity that may be correlated with the presence of macrophages which may be a contributor to atherosclerotic plaque instability (21). Nonetheless, we demonstrated for the first time a serial description

of a volumetric quantification of FC which allows for investigation of the natural history of high-risk coronary plaques.

CONCLUSION

Non-culprit fibroatheromas located in the infarct related artery of patients with STEMI had

a volumetric reduction of the FC after 6-month follow-up. Quantitative FC assessment was able to differentiate high-risk lesions that became ThCFAs. There was a considerable change of plaque phenotype (TCFAs or ThCFAs) over time.

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PART 2

INTERPLAY BETWEEN CORONARY ATHEROSCLEROSIS AND
PATIENTS' CLINICAL PROFILE

Chapter 2.1

Women Are From SATURN and Men Are From an ASTEROID: Deciphering the REVERSAL of Coronary Atheroma

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Women are under-represented (range from 8% to 68%) in most lipid-lowering randomized clinical trials. Meta-analysis data from 170,000 participants showed that women had a significant proportional risk reduction of 16% (99% confidence interval: 3% to 27%; $p = 0.002$ per 1.0 mmol/l decrease in low-density lipoprotein cholesterol [LDL-C]) of the combined endpoint of coronary death, nonfatal myocardial infarction coronary revascularization, and stroke (1). Is this because women had a greater change in intravascular ultrasound (IVUS) percentage atheroma volume (PAV) in progression/regression trials, as shown in this substudy of the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) study (2)? This observation has

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not been proven to be a consistent one. In the ASTEROID (A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) study, in which high dose rosuvastatin was administered, the findings were at variance with the current report (Table 1). Men had slightly larger regression than women. Of note, the IVUS analyses were performed under the same standard operating procedures in the same analysis core laboratory in both studies. Why did the differential impact of rosuvastatin and atorvastatin on plaque regression in women was not reproduced?

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In the SATURN trial subgroup analysis, overall (taking both groups together: rosuvastatin- and atorvastatin-treated patients) women had a greater reduction in PAV ($-1.52 \pm 0.18\%$ vs. $-1.07 \pm 0.10\%$, $p = 0.03$) (2), but only in cases with LDL-C levels <70 mg/dl. Interestingly, the percentage of women that achieved LDL-C levels <70 mg/dl was smaller compared to men (61.7% vs. 65.0%, respectively). Thus, women showed more regression despite that they were fewer achieving the target of LCL-C. Taken all together, it is interesting to see that even in the best-case scenario, namely in the context of a large randomized clinical trial, less than two-thirds of patients achieved the per protocol target (LDL-C levels <70 mg/dl).

Is percentage atheroma volume the best parameter to compare women versus men? The percent atheroma volume with as numerator atheroma volume and as denominator vessel volume, may mask the specific directional changes in its numerator and denominator (3) when used as primary endpoint to compare 2 pharmacological agents or 2 groups; it has, though, a lower variation (smaller SD) than atheroma volume and therefore has been used as a primary endpoint in many IVUS studies. In Table 2, it can be seen that, looking purely at the actual atheroma size changes without normalizing for the vessel volume, in all studies with the exception of the ASTEROID

TABLE 1 Sex-Related Changes in Percentage Atheroma Volume at 24 Months in Different Progression/Regression Trials

	SATURN	SATURN	ASTEROID
	Rosuvastatin 40 mg	Atorvastatin 80 mg	Rosuvastatin 40 mg
Male	-1.09	-1.03	-0.8
Female	-1.76	-0.71	-0.7

ASTEROID = A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; SATURN = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin.

TABLE 2 Atheroma Volume Changes by Sex

	SATURN		SATURN		ASTEROID		REVERSAL	
	24 Months		24 Months		24 Months		18 Months	
	40 mg Rosuvastatin*	80 mg Atorvastatin*	80 mg Atorvastatin*	40 mg Rosuvastatin†	40 mg Rosuvastatin†	80 mg Atorvastatin‡	80 mg Atorvastatin‡	
Male	-7.21	-5.62	-5.62	-6.1	-6.1	0.7	0.7	
Female	-9.68	-7.70	-7.70	-4.2	-4.2	-2.3	-2.3	

*Adjusted change from baseline in atheroma volume. †Atheroma volume in most diseased 10-mm subsegments. ‡Median percentage change in atheroma volume.
REVERSAL = Reversing Atherosclerosis with Aggressive Lipid Lowering; other abbreviations as in Table 1.

trial, women showed more atheroma volume regression than men.

Additional lessons learned from previous progression/regression trials, in general:

1. The larger the PAV at baseline is, the larger the regression in PAV is (4).
2. The larger the reduction in LDL-C is, the larger the regression in PAV is (5).
3. The higher the increase in high-density lipoprotein cholesterol (HDL-C) is, the larger the regression in PAV is (5).
4. The larger the reduction in C-reactive protein (CRP) levels is, the larger the regression in PAV is (6).

Yet, in this substudy from the SATURN trial, women had a larger regression in PAV compared to men, despite the fact that women had smaller plaques at baseline and they had on average higher levels of CRP. As mentioned previously, women, in lipid-lowering trials, had a reduction of the combined endpoint of coronary death, nonfatal myocardial infarction coronary revascularization and stroke. Moreover, in another substudy of the SATURN trial, the CRP levels were associated with major adverse

cardiac events (MACE) (7), which makes it harder to dissect this complex interplay between women and CRP and their association with MACE.

Is it then the greater reduction in PAV in women related to the fact that they had on treatment lower LDL-C and higher HDL-C values? In this report (SATURN trial gender analysis), compared with men, women had higher HDL-C at baseline and follow-up. In the REVERSAL (Reversing Atherosclerosis with Aggressive Lipid Lowering) trial (8), the patients with HDL-C above the mean who were treated with atorvastatin had a regression of -1.5% (p = 0.97 for the comparison with baseline), but not their counterparts. At variance, in this SATURN trial gender analysis, irrespective of the baseline HDL-C (above or below the mean), there was a significant reduction in PAV. Thus, the association of atheroma changes and HDL-C need to be further elucidated.

Many of the lessons learned in previous progression/regression trials have been challenged in this gender report of the SATURN study. In order to get clarity on whether there is a differential impact of gender on coronary atheroma size or these changes in plaque size are due to other potential confounding factors, we would like to encourage the authors to pool the data of the SATURN, ASTEROID, and REVERSAL studies to further elucidate these observations.

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KEY WORDS atherosclerosis, atorvastatin, IVUS, rosuvastatin, statins

Chapter 2.2

Correlation of Cardiovascular Risk Factors, Angina Patterns and Intravascular Ultrasound Findings: Largest Contemporary Characterization of Target Lesions in ABSORB II trial

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Submitted

ABSTRACT

Background: Patients and plaque's characteristics have been scrutinized to understand how risk factors relate to the hazard of subsequent cardiovascular events. However, the clinical and health outcomes measures assessed by the Seattle Angina Questionnaire (SAQ) have never been correlated with the characteristics of obstructive plaque determined by intravascular ultrasound (IVUS).

Objectives: To describe the pre-treatment intravascular ultrasound (IVUS grey scale and backscatter tissue data) findings of obstructive lesions according to patient demographics and health outcome measures in the ABSORB II trial (ClinicalTrials.gov, number NCT0142528).

Methods: An independent corelab (Cardialysis, Rotterdam, The Netherlands) analysed IVUS segments flanked by the presence of side branches beyond 5mm distally and 5mm proximally to the to be treated regions. Patient demographics, anthropometric measures, cardiovascular risk factors and baseline SAQ were correlated with IVUS findings.

Results: 464 patients had pre-procedural IVUS grey-scale and 438 patients had IVUS radio-frequency assessment before device implantation. The mean age was 61.5 ± 10.0 years old, 23.3% were female and 25.0% were diabetics. Clinical characteristics were able to differentiate plaque features by IVUS and VH IVUS. Patients with abdominal obesity ($P < 0.01$) and increase in body mass had more negative remodeling ($P = 0.01$), a finding that was related to worse angina frequency scores by SAQ ($P < 0.01$). Reduction in HDL-C ($P = 0.01$), lesion in RCA ($P < 0.01$), lesion in proximal LAD ($P < 0.01$) and worse angina stability by SAQ ($P = 0.03$) were independently correlated with plaque burden. Smaller lumen area ($P < 0.01$), larger vessel area ($P < 0.01$) and more physical limitation by SAQ ($P = 0.03$) were independently correlated with the maximum necrotic core area.

Conclusions: IVUS assessment of obstructive lesions showed that clinical characteristics still were able to differentiate the manifestation of coronary artery disease. Negative remodelling was associated with worse angina frequency by the SAQ. Patient reported physical limitation and angina stability were, respectively, associated with necrotic core size and plaque burden.

Key words: intravascular ultrasound; virtual histology; atherosclerosis, clinical characteristics; angina; Seattle Angina Questionnaire.

INTRODUCTION

Despite medical advances, coronary artery disease (CAD) remains a major public health problem as it has been the leading cause of death in the world in the last decade (1). As a consequence, the care of patients with CAD is costly since it implies careful ascertainment of the diagnosis and risk, control of symptoms, and therapies to improve survival (2).

Patients' and plaque characteristics have been scrutinized to understand how risk factors relate to the hazard of subsequent cardiovascular events (3-5) and response to therapeutic agents in atherosclerosis progression/regression trials (6-9). In this regard, intravascular ultrasound (IVUS)—and its derived parameters - is the best invasive method for assessing the plaque burden, being able to study plaque temporal changes and features related to high risk plaques (5). The rationale for IVUS studies is based on the fact that the atherosclerotic plaque represents the pathological substrate for the occurrence of ischemic cardiovascular events. Plaque burden and necrotic core areas have been described in pathologic studies of vulnerable patients (10). However, so far, plaque characterization by IVUS findings is mostly related to non-culprit lesions (3,6,7).

Regarding patient's risk stratification, health status assessment has proven to be a valuable tool, being independently associated with 1-year mortality and acute coronary syndromes among outpatients with CAD (1). Nevertheless, health status scores have never been correlated with IVUS (grey scale and backscatter tissue characteristics) plaque features. Thus, it is not known whether Seattle Angina Questionnaire (SAQ) parameters are correlated with the extent of the disease as

assessed by IVUS characteristics of obstructive lesions.

Accordingly, we sought to describe the pre-treatment IVUS (grey scale and backscatter tissue characteristics) findings of to be intervened lesions according to patient demographics, anthropometric measures, cardiovascular risk factors and SAQ in the ABSORB II trial (ClinicalTrials.gov, number NCT01425281). In addition, we aimed to identify the clinical characteristics independently related to plaque burden and the largest necrotic core area in these obstructive lesions.

METHODS

Patient Population and Definitions: The design of the ABSORB II trial (ClinicalTrials.gov ID: NCT01425281) has been described previously (11,12). In brief it is a randomised, active-controlled, single-blinded, multicentre clinical trial comparing the second-generation Absorb BVS with the XIENCE everolimus-eluting metallic stent (12). The trial was sponsored by Abbott Vascular and enrolled 501 subjects on a basis of 2:1 (Absorb: XIENCE) randomization in 46 centres across Europe and New Zealand. The trial protocol allowed the treatment of up to two de-novo native coronary artery lesions, each located in different major epicardial vessels, with a maximum lumen diameter between 2.25mm and 3.8 mm and a maximum lesion length of 48 mm as assessed by online quantitative coronary angiography. All lesions had to have a visually estimated diameter stenosis of $\geq 50\%$ and $< 100\%$ with a TIMI flow of ≥ 1 .

Low-density lipoprotein cholesterol (LDL-C) was considered high when $\geq 70\text{mg/dL}$. HDL-C was considered low when $\leq 40\text{mg/dL}$. Triglyceride

erides was defined as high when ≥ 150 mg/dL (13). Patients were considered as having abdominal obesity when waist circumference > 102 cm for men and > 88 cm for women. Abnormal renal function when creatinine clearance < 90 mL/min. Metabolic syndrome was identified by the presence of three or more of the components: abdominal obesity, HDL-C (Men < 40 mg/dL and Women < 50 mg/dL); blood pressure $\geq 130/85$ mmHg; fasting glucose ≥ 110 mg/dL or triglycerides ≥ 150 mg/dL (14).

Patient reported angina severity was assessed at baseline (before IVUS) by the SAQ. The SAQ is a disease-specific measure for patients with CAD that represents assessment of a 4-week window (recall period). SAQ has demonstrated to be reproducible and related to clinical events (1,15). The SAQ quantifies patients' physical limitations caused by angina, symptom frequency, recent changes in symptoms, treatment satisfaction, and the degree to which the disease affects their quality of life. Each scale has a score from 0 to 100, where higher scores indicate better function (eg, less physical limitation, less angina, and better quality of life).

Laboratory tests. Blood samples were taken from all patients at baseline and were analysed at an independent core laboratory (ICON Plc, Dublin Ireland). Lipid profile (including total cholesterol, LDL-C calculated, HDL-C, and Triglycerides [TG]) was checked. The Friedewald formula was used for calculation of LDL-C concentration (16). If plasma TG levels were above 400 mg/dL the measured LDL-C concentration was then reported.

IVUS imaging. The present study reports as regions of interest the target lesion of the ABSORB II trial before the device implantation. All lesions were imaged for IVUS and

IVUS radiofrequency (VH[®]- IVUS, Volcano Corporation, San Diego, California, USA) with the 45 MHz Revolution[®] catheter (Volcano Corporation, San Diego, California, USA)(17). The IVUS acquisition was performed at a pullback speed of 0.5 mm/sec following the administration of anticoagulation and intracoronary nitroglycerine. During the catheter pullback, the radiofrequency data was captured at the peak of the R-wave, enabling the reconstruction of a colour-coded map of coronary plaque composition, via the VH-IVUS algorithm: red (indicating necrotic core), white (dense calcium), light green (fibro-fatty), and dark green (fibrous).

The quantitative IVUS analysis was performed by a Core Imaging Laboratory (Cardialysis, Rotterdam, The Netherlands) using customized software (qIVUS[®] 3.0, Medis, Leiden, The Netherlands). The analyst selected the region of interest flanked by the presence of side branches beyond 5mm distally and 5mm proximally to the stented/scaffolding regions. External elastic membrane (EEM) and lumen area data were obtained for every cross-section. Plaque area was determined as the area between the leading edges of the 2 contours. The present study used previously described IVUS greyscale and VH-IVUS parameters that are shown in Figure 1.(18-20). Data analysis. Discrete data were summarized as percent (frequencies) and were compared using the chi-squared test. Continuous data were expressed as mean \pm SD or median [interquartile range (IQR)] and were compared using Student's t-test or Wilcoxon rank-sum test based on their distributions. Largest plaque burden (%) and largest necrotic core area (mm^2) were the dependent variables explored in a lesion level linear regression analyses. The set of variables with a p value ≤ 0.10 in the uni-

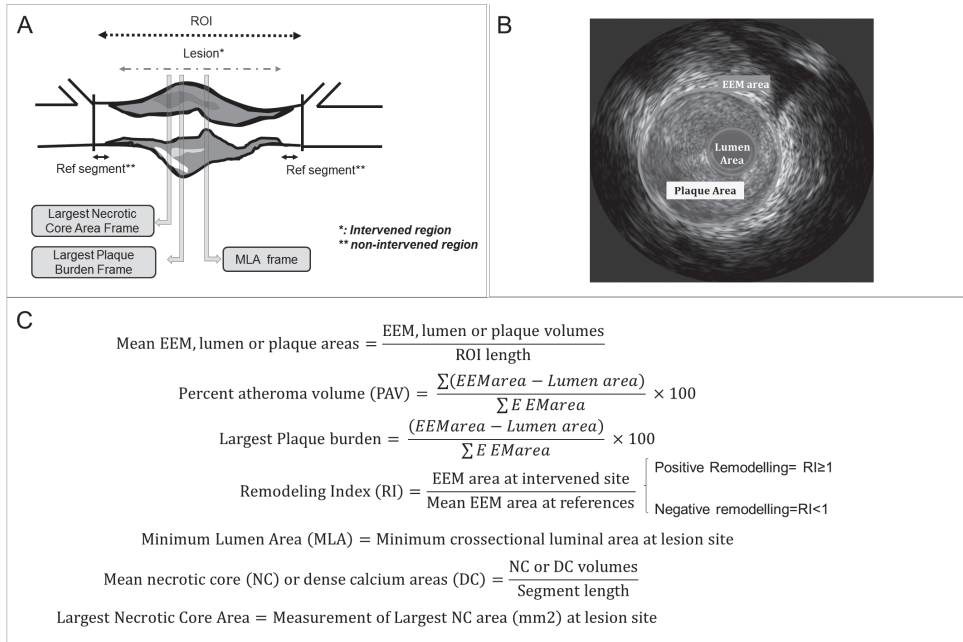


Figure 1. (A) The analyst selected the region of interest flanked by the presence of side branches beyond 5mm distally and 5mm proximally to the stented/scaffolded regions. (B) External elastic membrane (EEM) and lumen area data were obtained for every cross-section. Plaque area was determined as the area between the leading edges of the 2 contours. The parameters assessed in the present study are summarized in (C).

variate regression analyses were included in the multivariate regression analyses. Forward selection was used, and the entry criterion and stay criterion were set to 0.05. SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. Sensitivity and specificity curves were used to identify the optimal threshold for defined as the cut-off that separated patients with necrotic core area $\geq 3.45 \text{ mm}^2$ and plaque burden $\geq 75\%$ previously validated in histologic studies (10). For patient level analysis, when patient had more than one lesion, the average value of IVUS parameters were used for subgroup analysis except for Total Plaque Volume (in which the sum of patient atheroma volume values were used); largest necrotic core area and largest

plaque burden (in which the highest absolute value was used).

RESULTS.

Out of 501 enrolled patients, 464 (498 lesions) had imaging of obstructive lesions (pre-procedure), the IVUS study being the focus of the present study. In addition, 438 patients (471 lesions) had IVUS radiofrequency data analysis assessment before device implantation and are also herewith described. Table 1 shows the baseline characteristics of patients enrolled in the present study. The mean age was 61.5 ± 10.0 years old, 23.3% were female, 67.9% had history of treated hypertension

and 25.0% were diabetics. The median fasting HDL-C was 42.9 (Interquartile Range [IQR] 36.7-51.8) mg/dL, the median fasting LDL-C was 92.8 (IQR 69.6-119.9) mg/dL.

Patient Level Grey Scale IVUS Findings and Clinical Characteristics. Figure 2 summarizes the main grey scale IVUS findings and details of these findings can be found in the supplementary material (Table 1 and Figure 1). Of note, 90% of patients/lesions imaged in this study had a larger plaque burden compared to the classical previous IVUS studies, which included non-obstructive/non-intervened le-

sions. The percent atheroma volume (PAV) was higher in patients with low HDL-C (60.8 ± 8.3 vs $57.0 \pm 9.2\%$; $P < 0.01$) and in patients with metabolic syndrome (59.5 ± 8.7 vs $57.7 \pm 9.2\%$; $P = 0.05$). Patients with diabetes had significantly smaller PAV (56.8 ± 9.1 vs $58.8 \pm 8.8\%$; $P = 0.04$) (Figure 2A). Analysis of the frame with the largest plaque burden showed it to be significantly larger in patients with medically treated hypertension [82.6 (IQR 77.7 - 86.1) vs. 80.9 (74.9 - 84.7)%; $P = 0.02$] (Figure 2B).

The MLA was significantly smaller in male patients [2.0 (IQR 1.7 - 2.4) vs. 1.8 (IQR 1.5 - 2.4)

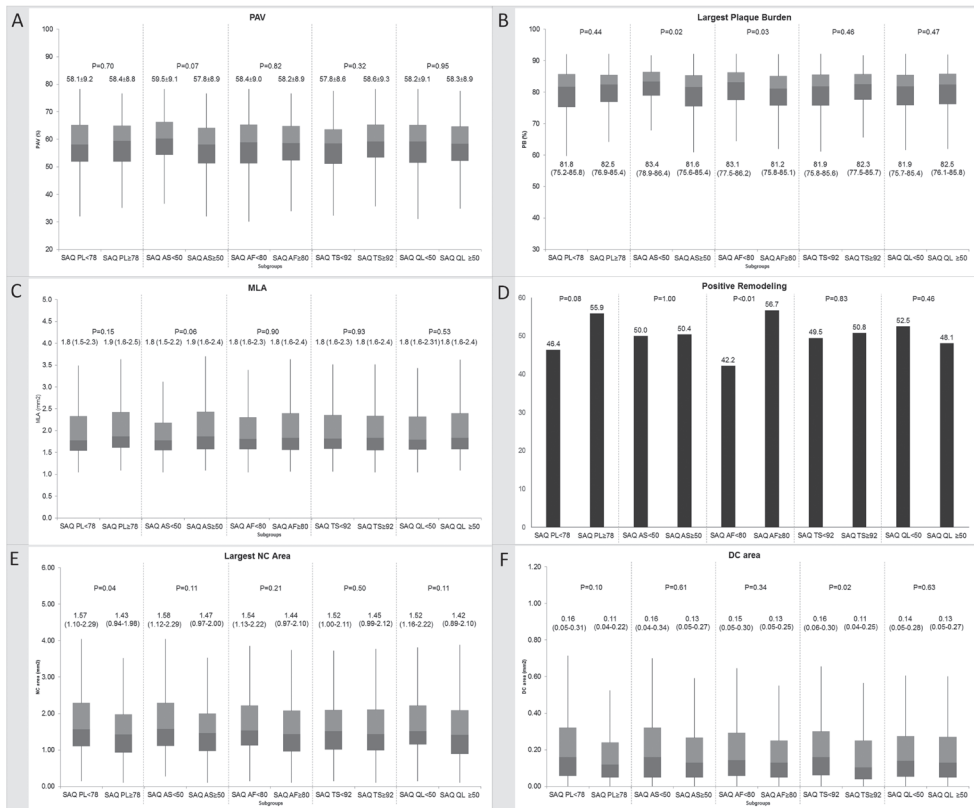


Figure 2. Patient level subgroups comparison of the main grey scale intravascular ultrasound findings. (A) Percent atheroma volume (PAV); (B) Largest plaque burden (PB); (C) Minimum lumen area (MLA) and (D) Positive remodelling. NAO= no abdominal obesity; AO=abdominal obesity; BMI= body mass index; DM= diabetes mellitus; HDL-C=high-density lipoprotein cholesterol; LDL-C= Low-density lipoprotein cholesterol; Tg= triglycerides; ACS=acute coronary syndrome; CAD=coronary artery disease.

Table 1. Baseline demographics and clinical characteristics of IVUS patients (n=464)

Female gender, n (%)	108 (23.3)
Age; mean±SD	61.5±10.0
Waist circumference, cm; median (IQR)	100 (92-108)
BMI, kg/m ² ; median (IQR)	27.5 (25.3-30.10)
Know family history of premature CAD	162 (34.9)
Current smokers	103 (22.2)
Diabetes Mellitus	116 (25.0)
Treated hypertension	315 (67.9)
Systolic pressure at rest, mmHg; median (IQR)	132 (120-145)
Diastolic pressure at rest, mmHg; median (IQR)	76 (70-82)
Previous PCI, n (%)	161 (34.7)
Previous CABG, n (%)	11 (2.4)
Diagnosis, n (%)	
MI with normalized cardiac enzymes	12 (2.6)
Unstable angina	99 (21.3)
Silent ischemia	56 (12.1)
Stable angina	297 (64.0)
Total cholesterol, mg/dL; median (IQR)	158.5 (131.5-189.5)
Fasting HDL-C, mg/dL; median (IQR)	42.9 (36.7-51.8)
Fasting LDL-C, mg/dL; median (IQR)	92.8 (69.6-119.9)
Fasting TG, mg/dL; median (IQR)	91.7 (51.6-135.3)
Creatinine clearance, mL/min; median (IQR)	93.8 (78.7-113.6)
Fasting glucose, mg/dL; median (IQR)	100.9 (91.9-115.3)
SAQ PL; median (IQR)	78.5 (58.3-94.4)
SAQ AS; median (IQR)	50.0 (25.0-75.0)
SAQ AF; median (IQR)	80.0 (60.0-100.0)
SAQ TS; median (IQR)	94.0 (81.0-100.0)
SAQ QL; median (IQR)	50 (33.3-66.7)
Lipid lowering therapy use, n (%)*	
Atorvastatin	187 (40.3)
Dose (mg) ±SD	42.2±21.3
Simvastatin	150 (32.3)
Dose (mg) ±SD	33.6±9.5
Rosuvastatin	55 (11.8)
Dose (mg) ±SD	15.0±12.6
Pravastatin	13 (2.8)
Dose (mg) ±SD	26.9±19.3
Other statin	4 (0.9%)
Ezetimibe	19 (4.1)
Dose (mg) ±SD	10.7±2.7
Polyunsaturated fatty acid	10 (2.16)

*Medication started before index procedure or at index procedure date, some of the medication may be combined. . SD=standard deviation; IQR=interquartile range; BMI=body mass index; CAD=coronary artery disease; PCI=percutaneous coronary intervention; CABG= coronary artery bypass graft; MI=myocardial infarction; SAQ= Seattle Angina Questionnaire; PL=physical limitation; AS=angina stability; AF=angina frequency; TS=treatment satisfaction; QL=quality of life.

mm²; P=0.02); in patients with low HDL-C [1.9 (IQR 1.6-2.5) vs. 1.8 (1.5-2.1) mm²; P<0.01]; and in patients with high triglycerides [1.8 (IQR1.6-2.4) vs. 1.7 (1.5-2.3) mm²; P=0.05]. Patients with high LDL-C had significantly larger MLA [1.7 (1.5-2.1) vs.1.9 (1.6-2.4); P=0.03] (Figure2C).

Coronary remodelling reflects to which extent the vessel was able to accommodate the plaque and cause reduction in lumen dimensions (Figure 2D). The prevalence of positive remodelling was significantly reduced in patients with abdominal obesity (P<0.01), decreased progressively with the increase in body mass index (P=0.01) and tended to be lower in patients with metabolic syndrome (P=0.10), abnormal renal function (P=0.09), males (P=0.12) and diabetes mellitus (P=.013). Specifically, in diabetics, although the negative remodelling did not reach the statistically significance margin, a significantly smaller PAV caused similar lumen reduction assessed by both MLA (P=0.56) (Figure2C) and mean lumen area (P=0.96) (supplementary Table1).

Patient Level VH IVUS findings and baseline characteristics. Figure3 summarizes the main VH IVUS findings and supplementary Table2 details these findings. The maximum necrotic core area tended to be higher in males (P=0.06) and in patients with metabolic syndrome (P=0.08) (Figure 3A). The % necrotic core was higher in patients without treatment for hypertension (17.4±7.5 vs. 15.5±6.4; P<0.01). The mean dense calcium area was significantly larger in males (P=0.03) (Figure 3B). The % dense calcium was significantly larger in patients not treated for hypertension [4.1 (1.8-7.8) vs. 3.2 (1.4-6.3); P=0.04]. Current smokers had lower % necrotic core (14.4±6.2% vs.16.6±6.9; P<0.01); smaller dense calcium areas [0.09 (0.03-0.23) vs. 0.13 (0.05-0.28)

Table 2. Patient Level correlation coefficients between Seattle Angina Questionnaire domains and IVUS/VH findings

	Total Plaque Volume, mm ³		PAV (%)		Largest PB (%)		MLA mm ²		Mean LA, mm ²		RI		Largest NC area, mm ²		Mean DC area, mm ²	
	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P
SAQ PL	-0.039	0.41	0.04	0.87	0.03	0.55	0.06	0.18	-0.061	0.20	0.095	0.07	-0.14	<0.01	-0.13	0.01
SAQ AS	-0.049	0.31	-0.04	0.40	-0.09	0.06	0.08	0.08	0.025	0.61	-0.012	0.81	-0.08	0.09	-0.02	0.65
SAQ AF	-0.072	0.13	0.03	0.53	-0.09	0.06	-0.03	0.59	-0.125	<0.01	0.131	0.01	-0.07	0.13	-0.04	0.38
SAQ TS	0.036	0.44	0.03	0.58	0.02	0.67	0.02	0.62	0.037	0.43	-0.013	0.80	-0.01	0.83	-0.06	0.19
SAQ QL	-0.003	0.95	-0.02	0.74	0.02	0.90	0.00	0.90	-0.077	0.10	0.056	0.29	-0.08	0.09	-0.05	0.33

SAQ= Seattle Angina Questionnaire; PL= physical limitation; AS=angina stability; AF=angina frequency; TS= treatment satisfaction; QL= quality of life; CC=correlation coefficient; PAV=percent atheroma volume; PB=plaque burden; MLA=minimum lumen area; LA=lumen area; RI=remodelling index; NC=necrotic core; DC=dense calcium

mm²; P=0.02) and lower % dense calcium [3.6 (IQR 1.6-6.9) vs. 2.1 (1.2-5.0); P<0.01] but a higher necrotic core/dense calcium

ratio [5.0 (3.3-8.7) vs. 4.1 (2.7-6.7); P=0.03] (supplementary Table2).

Patient Level IVUS Grey Scale, VH IVUS and Health Status Assessment. Table 2 depicts

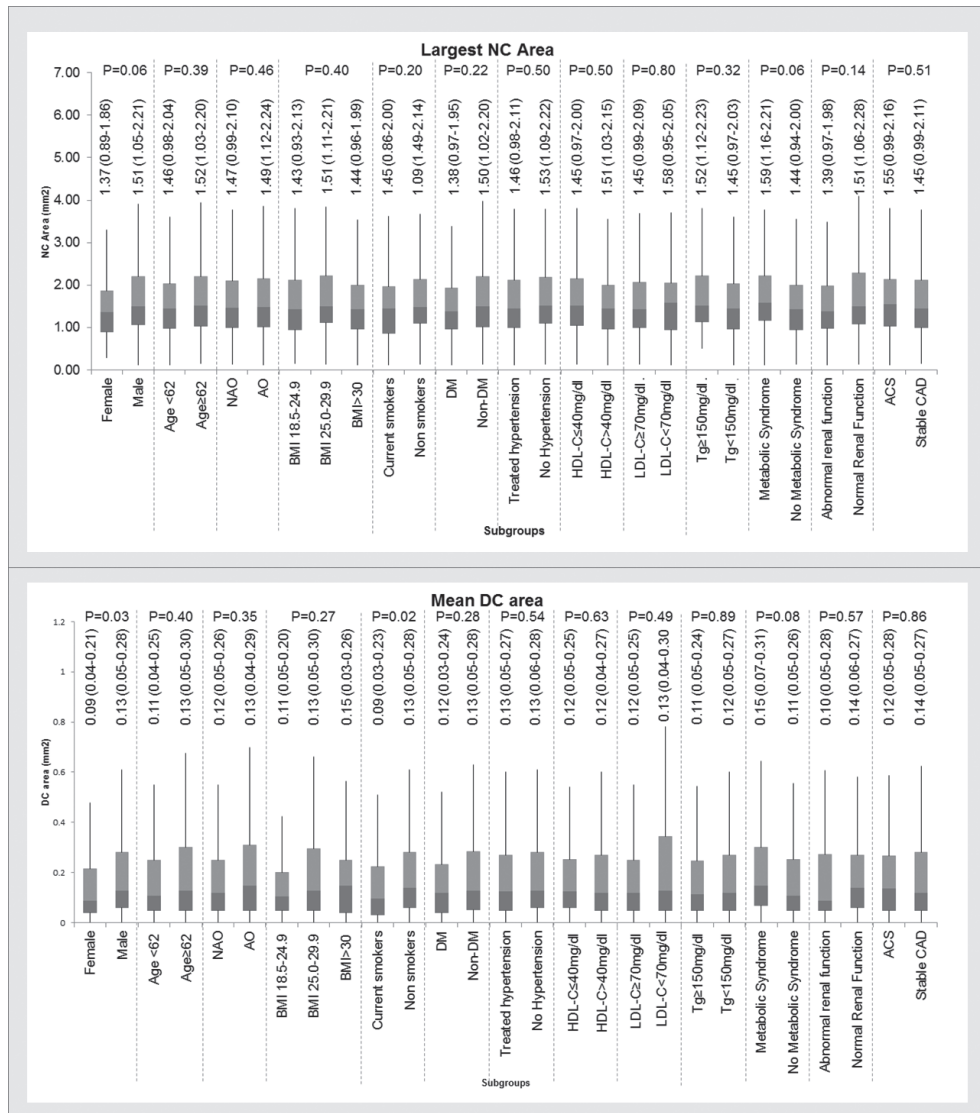


Figure 3. Patient level subgroups comparison of the main intravascular ultrasound radiofrequency findings. (Upper panel) Largest necrotic core (NC) area. (Lower Panel) Mean dense calcium (DC) area. NAO= no abdominal obesity; AO=abdominal obesity; BMI= body mass index; DM= diabetes mellitus; HDL-C=high-density lipoprotein cholesterol; LDL-C= Low-density lipoprotein cholesterol; Tg= triglycerides; ACS=acute coronary syndrome; CAD=coronary artery disease.

the correlation coefficients between IVUS findings and SAQ domains. The mean lumen area had a significant correlation with SAQ angina frequency ($P<0.01$). The largest plaque burden trended to be correlated with the largest plaque burden and angina frequency ($P=0.06$ for both). The remodelling index had a positive and significant correlation with angina frequency ($P=0.01$) and trended to be correlated with physical limitation ($P=0.07$); i.e. the bigger the vessel remodelling, the better was the patient's symptomatology. Interestingly, the total plaque volume did not have any significant correlation with angina severity. The largest necrotic core area and the mean dense calcium area were significantly correlated with SAQ physical limitation ($P<0.01$ and $P=0.01$; respectively). Interestingly, the total plaque volume did not have a significant correlation with any SAQ domain.

Lesion level predictors of the largest plaque burden and maximum necrotic core area. The list of variables (only those with a

p value <0.10) and their univariate association with maximum necrotic area and largest plaque burden is shown in Table 3. In the multivariate analysis (Table 4), lesions in the right coronary artery (RCA) and in the proximal left descending anterior artery (LAD) had a positive independent association with plaque burden. Fasting HDL-C and SAQ angina stability had a negative independent association with plaque burden.

Regarding maximum necrotic core area, mean vessel area and lesions in the proximal LAD had a positive independent association. Mean lumen area and SAQ physical limitation had a negative independent association with maximum necrotic core area.

The assessment of receiver-operating characteristic (ROC) for plaque burden higher than 75% found SAQ angina stability score ≤ 25 as the best cut-off [area under the curve [AUC] 0.59 (95% CI 0.55-0.64). For a necrotic core area $>3.45\text{mm}^2$ the best cut-off point for SAQ

Table 3. Variables (only with a p value <0.10) and their univariate association with largest plaque burden and maximum necrotic core area

	Largest Plaque Burden (%)		Maximum Necrotic Core Area	
	Parameter estimate (95%CI)	P	Parameter estimate (95%CI)	P
Male Gender	2.094 (0.598 to 3.590)	<0.01	0.155 (-0.24 to 0.33)	0.09
Treatment for Hypertension	2.055 (0.723 to 3.386)	<0.01	-	-
Fasting HDL (md/dl)	-0.089 (-0.137 to -0.041)	<0.01	-	-
Fasting Triglycerides (mg/dl)	0.009 (0.001 to 0.016)	0.03	-	-
Fasting Glucose (mg/dl)	0.016 (-0.002 to 0.033)	0.07	-	-
Metabolic Syndrome	1.322 (-0.075 to 2.719)	0.06	0.143 (-0.012 to 0.298)	0.07
Lesion in RCA	1.450 (0.052 to 2.848)	0.04	0.281 (-0.041 to 0.603)	0.09
Lesion in Proximal LAD	2.395 (0.739 to 4.051)	<0.01	0.466 (0.274 to 0.658)	<0.01
Known family history of CAD	-	-	-0.147 (-0.306 to 0.11)	0.07
Mean Lumen Area (mm^2)	-	-	0.077 (0.025 to 0.129)	<0.01
Mean Vessel Area	-	-	0.117 (0.099 to 0.136)	<0.01
PAV	-	-	0.046 (0.038-0.053)	<0.01
SAQ AS	-0.027 (-0.049 to -0.005)	0.01	-	-
SAQ PL			-0.004 (-0.007 to 0.000)	0.03

Table 4. Variables (with P <0.05) and their multivariate association with largest plaque burden and maximum necrotic core area

	Largest Plaque Burden (%)		Maximum Necrotic Core Area	
	Parameter estimate (95%CI)	P	Parameter estimate (95%CI)	P
Fasting HDL (md/dl)	-0.082 (-0.132 to -0.33)	0.01	-	-
Lesion in RCA	2.278 (0.723 to 3.833)	<0.01	-	-
Lesion in Proximal LAD	3.511 (1.619 to 5.402)	<0.01	0.184 (0.015 to 0.354)	<0.01
Mean Lumen Area (mm ²)	-	-	-0.269 (-0.334 to -0.203)	<0.01
Mean Vessel Area (mm ²)	-	-	0.194 (0.168 to 0.221)	<0.01
SAQ AS	-1.762 (-3.309 to -0.215)	0.03	-	-
SAQ PL	-	-	-0.004 (-0.006 to -0.001)	<0.01

physical limitation was ≤ 60 points [AUC 0.58 (95% CI 0.53-0.63)] (Figure 4).

DISCUSSION.

The main findings of the present IVUS study, dedicated exclusively to obstructive lesions, can be summarized as follows: (1) clinical characteristics were able to differentiate the manifestation of CAD assessed by PAV, largest plaque burden, minimal luminal area and vessel wall remodelling; (2) SAQ was able to identify plaque characteristics by IVUS grey scale and IVUS VH; (3) SAQ physical limitation and SAQ angina stability were found to have an independent association with necrotic core area and plaque burden, respectively.

Previous studies have mainly either correlated non-culprit -and non-obstructive lesions- to clinical characteristics in a transversal approach or explored the natural history of atherosclerosis by IVUS and its correlation with coronary events (3-5). The present study however, is unique in the sense that it explored exclusively obstructive plaques. Additionally, for the first time, we validated angina severity with plaque features. For instance, in the landmark PROSPECT (Providing Regional

Observations to Study Predictors of Events in the Coronary Tree) trial (3) the prevalence of coronary lesions with plaque burden >70% was only 9% (n=283 lesions). Interestingly, demographic factors of PROSPECT's patients had poor discrimination in detecting high-risk plaques (21). Herewith we report a population in which more than 90% of patients/lesions imaged had a larger plaque burden compared to the classical previous IVUS studies (supplementary Table 1, supplementary Figure 1) which resulted in 498 lesions with a median plaque burden of 82.4% (IQR 76.2-85.7%) and a median MLA of 1.8 mm² (IQR 1.6-2.4 mm²).

Patient level IVUS findings and their correlation with clinical characteristics and angina patterns. In the present study abdominal obesity and increase in body mass index had less positive remodeling. In our sub-group analysis, we found that male patients had a trend to higher PAV and a significant smaller MLA. In the present study the male gender did not emerge as an independent variable related to plaque burden. Similarly, in non-obstructive coronary lesions, male gender emerged as a factor related to higher PAV (22). Lipid disorders had a marked relevance in our findings. In addition to being independently

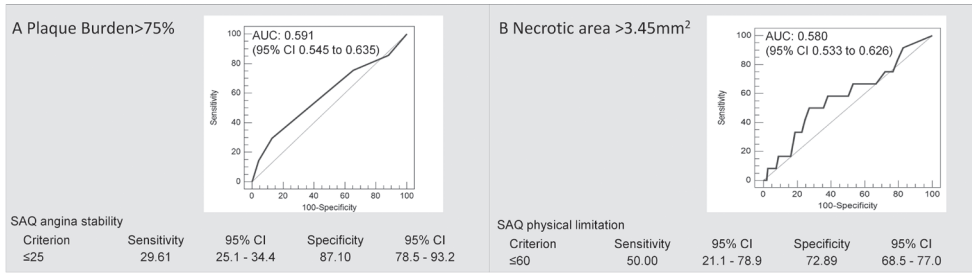


Figure 4. Receiver-operating characteristic (ROC) for (A) plaque burden higher than 75% using SAQ angina stability score found ≤ 25 as best cut-off. (B) For a necrotic core area $>3.45\text{mm}^2$ the best cut-off point for SAQ physical limitation was ≤ 60 points [AUC 0.58 (95% CI 0.53-0.63)]

correlated to a large plaque burden, a HDL-C lower than 40mg/dL produced larger PAV and smaller lumen dimensions. On the other hand, a high LDL-C was found to be associated only with a larger MLA but not with PAV or the largest plaque burden. Both lipids have been demonstrated to have an impact in the natural history of atherosclerosis. The higher the increase in HDL-C, the larger the regression in PAV and the larger the reduction in LDL-C is, the larger the regression in PAV (23). However, for comparison of absolute atheroma burden, a sub study of the SATURN trial showed also that HDL-C, but not LDL-C, was able to discriminate PAVs larger or smaller than 36.2% (24). In addition, the present study showed that metabolic syndrome was also related to higher PAV and to a larger absolute plaque burden. Compared with IVUS studies of non-obstructive lesions, the impact of metabolic syndrome on atherosclerotic burden has been disputed (22,25). These findings reinforce the interest on HDL-targeted therapies in which the clinical role of drugs such as cholesteryl ester transfer protein inhibitors still need to be established (26).

It is worth mentioning that the necrotic core/dense calcium ratio has been shown to be related to known risk factors of sudden death

in a study of male patients and was higher in smokers(27). In the present study we also found correlation between necrotic core/dense calcium ratio and current tobacco use.

The presence of systemic hypertension had a marked impact on our findings, being correlated with a larger plaque burden, smaller MLA and trends to reduced prevalence of positive remodeling ($P=0.12$) and larger PAV ($P=0.06$).

Figure5 summarizes the patient level characteristics and the IVUS variables in this study. Regarding patient reported angina patterns, we found that mean lumen area, remodelling index, maximum necrotic core area and mean dense calcium area were associated with worse angina symptoms. Thus, the interplay between plaque and remodelling was responsible for patient symptoms. As expansive enlargement prevents luminal narrowing we found that a lack of positive remodeling reflected in lower SAQ angina frequency scores. Importantly the mean LA and not the MLA had correlation with angina.

Lesion level high risk IVUS findings and their correlation with clinical subgroups and angina patterns. Recently, Narula et al. (10) studied the histologic characteristics of 295 coronary atherosclerotic plaques, including stable, vulnerable and disrupted plaques.

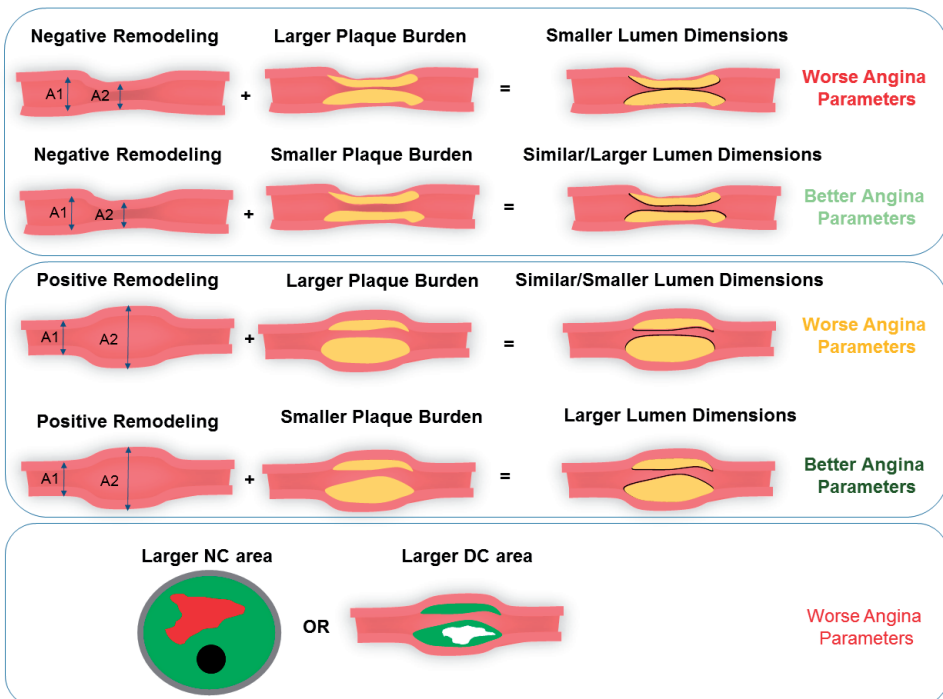
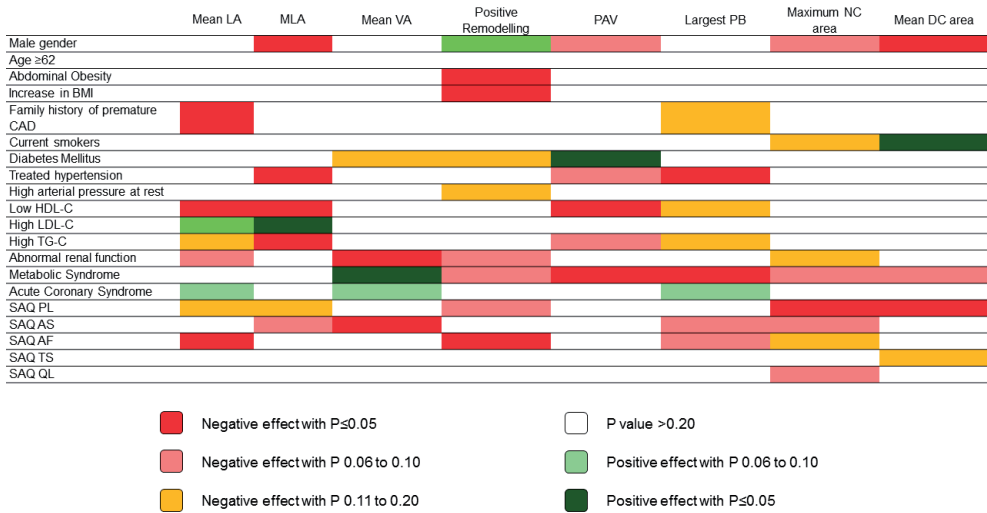


Figure 5. Schematic representation of the interplay among grey scale findings and clinical characteristics (upper panels). The lower panel shows a schematic representation of IVUS and VH IVUS findings and their impact on angina patterns assessed by the Seattle Angina Questionnaire (SAQ). LA=lumen area; MLA= minimum lumen area; VA=vessel area; PAV=percent atheroma volume; PB= Plaque Burden; NC=necrotic core; DC=dense calcium; SAQ=Seattle Angina Questionnaire; PL=physical limitation; AS=angina stability; AF=angina frequency; TS=treatment satisfaction; QL=quality of life

Thickness of the fibrous cap, plaque burden (>73.67%), macrophage infiltration and necrotic core area (>3.45mm²) were used in two multivariate models for identification of complex lesions. Their conclusion confirmed the results of PROSPECT (3) where a plaque burden higher than 70-75% -combined with thin fibrous plaque- should alert the clinicians (10). The aforementioned facts explain why we used as the object of our multivariate analysis the maximum cross-sectional luminal area stenosis and the largest necrotic core areas. Reduction in HDL-C, lesion in RCA, lesion in proximal LAD and worse angina stability by SAQ were independently correlated with plaque burden. These findings are in line with previous invasive investigations of coronary atheroma. In non-obstructive lesions, low HDL-C has also been found to be independently related to larger PAV, and consequently to clinical events (24). In addition, it has been shown that the two most proximal segments of the right coronary artery and the left anterior descending coronary artery were also responsible for the majority (65.4%) of acute coronary occlusions(28) and resembles the distribution of optical coherence tomography thin cap fibroatheromas (29). However, for the first time, we demonstrated a strong correlation between patient reported functional status and higher risk plaques. The best cut-off for a plaque burden>75% was SAQ angina stability scores≤25. This finding reinforces the results of Spertus et al. where outpatients with CAD had progressively worse outcomes with lower SAQ score (1). Specifically, a SAQ angina stability scores≤25 had a 2.9 fold higher 1-year mortality and a 2.3 fold higher ACS admission rate compared with patients with improved symptoms(1).

Smaller lumen area, larger vessel area and lower SAQ physical limitation were correlated with the maximum necrotic core area. Ruptured plaques of patients with ACSs also have smaller lumens, greater plaque burden and positive remodeling (30). Additionally, in the PROSPECT trial, the model with the best C-statistic for event prediction used minimum lumen area as a continuous variable. It was found that every 1mm² reduction in lumen area increased the event rate by 44% (3). The reason for a larger vessel area being correlated with necrotic core area is that in vulnerable plaques, matrix metalloproteinases (MMPs), that are secreted by macrophages do not digest only the matrix components within the fibrous cap (5) but an increased MMP activity in atherosclerotic arteries with extreme expansive remodeling was also demonstrated (31). Regarding the SAQ physical limitation score, our unprecedented findings are further supported by the work of Spertus et al. (1). In their study, the physical limitation score was the one with the best prognostic discrimination. Interestingly, Spertus et al. showed that quality of life had the worst prognostic discrimination among the SAQ scores. In the present study this score was not able to differentiate any IVUS or VH IVUS findings.

The main message of our findings on SAQ is that worse physical limitation and worse angina stability are continuously and strongly related to necrotic core area and plaque burden. However, in addition, we explored the best cutoff in identifying plaques at highest risk. Both cutoffs for SAQ angina stability and physical limitation had low sensitivity and high specificity for detection of a large plaque burden and a large necrotic core, respectively. In other words, they may not serve to detect positive cases but help to identify patients

with a lower chance of high risk plaques. Despite the advances in imaging methods, features related to vulnerable plaque did not improve the risk predictions compared to clinical approaches. Therefore, the identification and treatment of vulnerable plaque to avoid clinical events is so challenging that it has started to be considered a "myth"(32). In this regard, the correlations herewith demonstrated between high risk plaque features and a consistent and reproducible patient report health status measure adds to the medical literature since they can be easily used in clinical practice(32).

Limitations. The present study limited the inclusion of myocardial infarction for patients with normalized enzymes. As consequence, the sub group of acute coronary syndromes herewith reported had mainly patients with unstable angina. Therefore, we were not able to reproduce previously reported differences of IVUS findings comparisons between subjects with stable CAD and ACS. Nevertheless, the prevailing literature lacks an analysis dedicated to obstructive lesions and their clinical correlations. In addition, as aforementioned,

for the first time we validated patient reported health measures to an invasive assessment of coronary atherosclerosis.

As all studied lesions underwent percutaneous treatment, we could not explore their evolution. However, as in the inclusion criteria patients needed to have ischemic symptoms, in the context of a controlled randomized trial we assume that their clinicians interpreted that the revascularization was performed at the right time.

CONCLUSION.

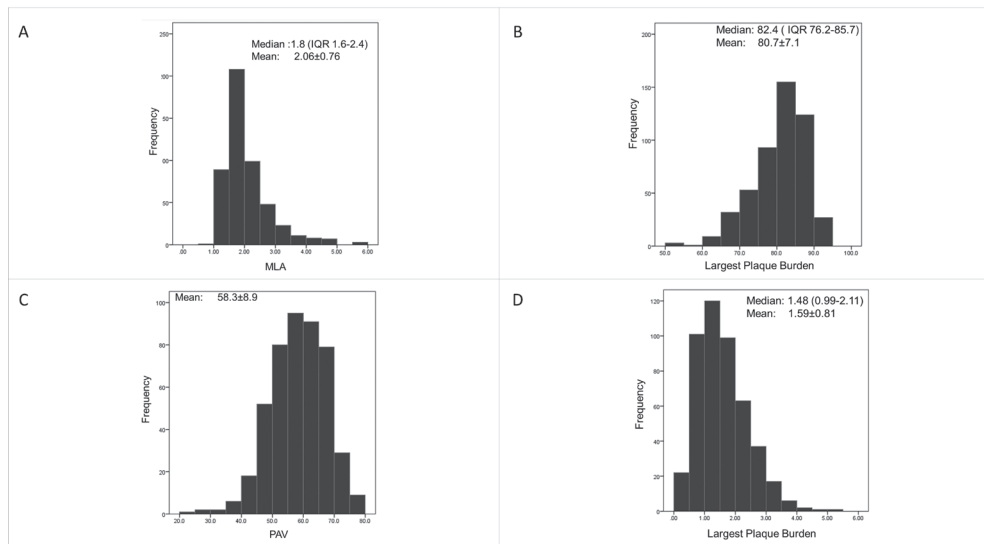
In the present IVUS study dedicated to obstructive lesions, clinical characteristics were able to differentiate the manifestation of CAD assessed by PAV, largest plaque burden, luminal area and remodelling. Negative remodelling was associated with worse angina frequency by the SAQ. Patient reported physical limitation and angina stability were, respectively, associated with necrotic core size and plaque burden.

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SUPPLEMENTAL MATERIAL



Supplemental Figure 1. Distribution of (A) minimum lumen area (MLA); (B) Largest plaque burden; (C) Percent Atheroma Volume (PAV) and (D) Largest necrotic core area

Supplemental Table 1. IVUS grey scale results according to patient's clinical characteristics and health outcomes measures

	Mean LA		MLA		Mean VA		Positive remodelling		PAV		Largest PB	
	P		P		P		%	P	P		P	
Overall (n=464)	4.8 (3.9-5.7)	-	1.8 (1.6-2.4)	-	11.5 (9.4-14.2)	-	50.7	-	58.4±8.9	-	82.4 (76.2-85.7)	-
Gender	0.89		0.02		0.21		0.12		0.06		0.19	
Female (n=108)	4.8 (4.1-5.4)		2.0 (1.7-2.4)		11.1 (9.3-13.3)		43.5		56.8±9.6		82.9 (77.6-86.1)	
Male (n=356)	4.8 (3.9-5.7)		1.8 (1.5-2.4)		11.7 (9.5-14.6)		53.0		58.7±8.7		81.9 (75.9-85.4)	
Age [§]	0.70		0.84		0.68		0.61		0.77		0.49	
<62 (n=231)	4.9 (3.9-5.7)		1.8 (1.5-2.4)		11.7 (9.6-14.2)		49.2		58.2±9.2		82.4 (75.9-85.4)	
≥62 (n=233)	4.8 (4.0-5.6)		1.8 (1.6-2.3)		11.4 (9.2-14.3)		52.1		58.4±8.7		82.4 (76.7-86.0)	
Abdominal Obesity ¶	0.15		0.17		0.11		<0.01		0.79		0.26	
No (n=187)	4.9 (3.7-5.6)		1.8 (1.5-2.3)		11.1 (9.2-14.1)		58.3		58.5±8.9		81.9 (76.5-84.8)	
Yes (n=167)	4.8 (4.1-5.7)		1.9 (1.6-2.4)		11.7 (9.7-14.4)		41.0		58.3±8.9		83.0 (75.6-86.6)	
Weight	0.86		0.55		0.67		0.01		0.29		0.77	
BMI 18.5 to 24.9 (n=98)	4.8 (3.8-5.4)		1.8 (1.6-2.2)		11.4 (8.9-13.4)		62.0		57.4±9.0		82.2 (77.1-85.4)	
BMI 25.0 to 29.9 (n=245)	4.8 (3.8-5.7)		1.8 (1.6-2.4)		11.7 (9.4-11.7)		51.3		58.5±8.9		82.6 (75.9-85.4)	
BMI>30 (n=120)	4.8 (4.1-5.5)		1.8 (1.5-2.4)		11.3 (9.5-14.1)		40.2		58.3±9.0		82.1 (76.1-86.8)	
Known family history of premature CAD	0.05		0.35		0.21		0.38		0.42		0.12	
No (n=263)	5.0 (3.9-5.8)		1.8 (1.6-2.4)		11.5 (9.4-14.6)		49.5		58.3±9.1		82.4 (76.2-85.4)	
Yes (n=162)	4.7 (3.8-5.4)		1.8 (1.6-2.3)		11.5 (9.1-13.8)		54.9		59.0±8.8		82.9 (77.7-86.6)	
Current smokers	0.66		0.56		0.61		1.00		0.58		0.31	
No (n=361)	4.9 (3.9-5.6)		1.8 (1.5-2.3)		11.5 (9.3-14.2)		50.5		58.4±9.0		82.2 (76.2-85.4)	
Yes (n=103)	4.8 (4.0-5.6)		1.8 (1.6-2.5)		11.8 (9.7-14.3)		51.2		57.9±8.8		82.8 (76.1-86.0)	
Diabetes Mellitus	0.96		0.82		0.11		0.13		0.04		0.88	
No (n=348)	4.8 (3.9-5.6)		1.8 (1.6-2.3)		11.6 (9.5-14.2)		53.0		58.8±8.8		82.4 (76.7-85.4)	
Yes (n=116)	5.0 (3.9-5.7)		1.8 (1.5-2.5)		11.0 (9.2-14.1)		43.9		56.8±9.1		82.4 (75.7-86.0)	

Supplemental Table 1. IVUS grey scale results according to patient's clinical characteristics and health outcomes measures (continued)

	Mean LA		MLA	P	Mean VA		Positive remodeling		PAV	Largest PB	
	P						%	P		P	
Treated hypertension	0.78			0.04		0.23		0.83		0.06	
No (n=149)	4.9 (3.9-5.7)	1.9 (1.6-2.5)			11.5 (9.2-13.3)	49.6			57.2±9.5		80.9 (74.9-84.7)
Yes (n=315)	4.8 (3.9-5.6)	1.8 (1.6-2.3)			11.5 (9.4-14.6)	51.2			58.8±8.7		82.6 (77.7-86.1)
High arterial pressure at rest †	0.74			0.98		0.89		0.11		0.52	
No (n=179)	4.8 (3.8-5.6)	1.8 (1.6-2.4)			11.5 (9.5-14.1)	55.9			58.6±8.9		82.4 (76.4-84.8)
Yes (n=285)	4.9 (3.9-5.7)	1.8 (1.6-2.4)			11.5 (9.3-14.4)	47.4			58.1±9.0		82.4 (76.0-86.1)
Low HDL-C**	<0.01			<0.01		0.98		0.64		<0.01	
No (n=234)	5.0 (3.9-5.8)	1.9 (1.6-2.5)			11.5 (9.3-14.2)	51.1			57.0±9.2		82.6 (76.1-86.0)
Yes (n=105)	4.6 (3.7-5.3)	1.8 (1.5-2.1)			11.6 (9.4-14.3)	47.6			60.8±8.3		81.4 (75.4-84.3)
High LDL-C†	0.08			0.03		0.52		0.24		0.31	
No (n=77)	4.5 (3.6-5.4)	1.7 (1.5-2.1)			11.7 (9.2-13.5)	43.4			59.1±10.5		81.2 (76.9-85.1)
Yes (n=262)	4.9 (4.0-5.7)	1.9 (1.6-2.4)			11.5 (9.4-14.6)	51.9			58.0±8.6		82.6 (75.7-85.6)
High TG-C††	0.12			0.05		0.91		1.00		0.06	
No (n=266)	4.8 (3.9-5.7)	1.8 (1.6-2.4)			11.5 (9.4-14.2)	49.8			57.8±9.0		81.9 (75.7-85.4)
Yes (n=73)	3.8 (4.4-5.4)	1.7 (1.5-2.3)			11.6 (9.0-14.3)	50.7			59.9±9.1		82.9 (77.3-86.5)
Abnormal renal function##	0.09			0.65		0.05		0.09		0.56	
No (n=262)	4.9 (4.0-5.7)	1.8 (1.6-2.4)			11.8 (9.6-1.5)	55.1			58.0±9.5		81.9 (76.0-85.3)
Yes (n=189)	4.7 (3.8-5.4)	1.8 (1.5-2.4)			11.1 (8.9-14.0)	45.7			58.5±8.6		82.6 (76.7-86.1)

*separated by median; † waist circumference >102 cm for men and >88cm for women, **HDL-C<40mg/dl; †LDL-C>70mg/dl; ††TG>150mg/dl; † Blood pressure≥130/85 mmHg; ## Creatinine Clearance<90mL/min. SAQ=Seattle Angina Questionnaire; PL=physical limitation; AS=angina stability; AF= angina frequency; TS= treatment satisfaction; QL=quality of life

Supplemental Table 2. VH IVUS results according to patient's clinical characteristics and health outcomes measures

	NC area		P	Maximum NC area		DC area	DC %		NC/DC ratio			
	NC %	P		DC %	P							
Overall (n=436)	0.57 (0.33-0.87)	-	16.1±6.8	-	1.48 (0.99-2.11)	-	0.13 (0.05-0.27)	-	3.5 (1.5-6.7)	-	4.2 (2.8-6.9)	-
Gender	0.11	0.96	0.06	0.03	0.25	0.07						
Female (n=99)	0.53 (0.30-0.73)		16.1±6.8		1.37 (0.89-1.86)		0.09 (0.04-0.21)		3.0 (1.3-5.7)		4.7 (3.0-7.6)	
Male (n=336)	0.57 (0.34-0.89)		16.1±6.8		1.51 (1.05-2.21)		0.13 (0.05-0.28)		3.6 (1.5-6.8)		4.1 (2.7-6.8)	
Age*	0.40	0.17	0.39	0.40	0.41	0.34						
<62 (n=217)	0.54 (0.30-0.85)		15.7±6.8		1.46 (0.98-2.04)		0.11 (0.04-0.25)		3.0 (1.5-6.0)		4.4 (2.9-6.6)	
≥62 (n=219)	0.58 (0.36-0.89)		16.5±6.8		1.52 (1.03-2.20)		0.13 (0.05-0.30)		3.6 (1.4-6.9)		3.9 (2.7-7.1)	
Abdominal Obesity †	0.42	0.53	0.46	0.35	0.67	0.63						
No (n=216)	0.56 (0.33-0.87)		16.4±6.9		1.47 (0.99-2.10)		0.12 (0.05-0.26)		3.5 (1.6-6.2)		4.3 (2.9-6.6)	
Yes (n=196)	0.55 (0.33-0.90)		16.0±6.9		1.49 (1.12-2.24)		0.13 (0.04-0.29)		3.6 (1.4-7.0)		4.0 (2.6-7.0)	
Weight	0.18	0.88	0.40	0.27	0.59	0.51						
BMI 18.5 to 24.9 (n=98)	0.54 (0.31-0.83)		16.0±6.9		1.43 (0.93-2.13)		0.11 (0.05-0.20)		3.2 (1.6-5.3)		4.6 (3.2-6.4)	
BMI 25.0 to 29.9 (n=245)	0.58 (0.37-0.91)		16.1±6.8		1.51 (1.11-2.21)		0.13 (0.05-0.30)		3.2 (1.6-6.8)		4.3 (2.7-7.0)	
BMI>30 (n=120)	0.55 (0.29-0.81)		16.1±6.8		1.44 (0.96-1.99)		0.15 (0.03-0.26)		4.0 (1.4-7.0)		3.7 (2.7-7.3)	
Know family history of premature CAD	0.68	0.63	0.37	0.74	0.81	0.91						
No (n=247)	0.57 (0.34-0.91)		15.9±6.7		1.49 (1.02-2.20)		0.13 (0.05-0.28)		3.3 (1.5-6.6)		4.2 (2.8-7.3)	
Yes (n=153)	0.57 (0.33-0.84)		16.2±6.8		1.47 (0.94-2.12)		0.11 (0.05-0.26)		3.4 (1.6-6.5)		4.4 (2.9-6.2)	
Current smokers	0.12	<0.01	0.20	0.02	<0.01	0.03						
No (n=361)	0.57 (0.35-0.88)		16.6±6.9		1.09 (1.49-2.14)		0.13 (0.05-0.28)		3.6 (1.6-6.9)		4.1 (2.7-6.7)	
Yes (n=103)	0.51 (0.27-0.80)		14.4±6.2		1.45 (0.86-2.00)		0.09 (0.03-0.23)		2.1 (1.2-5.0)		5.0 (3.3-8.7)	
Diabetes Mellitus	0.28	0.45	0.22	0.28	0.93	0.62						
No (n=325)	0.57 (0.35-0.87)		16.0±6.8		1.50 (1.02-2.20)		0.13 (0.05-0.28)		3.2 (1.5-6.8)		4.3 (2.8-6.7)	
Yes (n=111)	0.52 (0.30-0.89)		16.5±6.8		1.38 (0.97-1.95)		0.12 (0.03-0.24)		3.6 (1.3-6.5)		4.2 (2.8-8.0)	
Treated hypertension	0.99	<0.01	0.50	0.54	0.04	0.17						
No (n=149)	0.58 (0.33-0.86)		17.4±7.5		1.53 (1.09-2.22)		0.13 (0.06-0.28)		4.1 (1.8-7.8)		4.0 (2.7-6.4)	
Yes (n=315)	0.55 (0.33-0.88)		15.5±6.4		1.46 (0.98-2.11)		0.13 (0.05-0.27)		3.2 (1.4-6.3)		4.3 (2.8-7.1)	

Supplemental Table 2. VHI IVUS results according to patient's clinical characteristics and health outcomes measures (continued)

	NC area		Maximum NC area		DC area		DC %		NC/DC ratio	
	P	NC %	P	NC area	P	DC area	P	DC %	P	NC/DC ratio
High arterial pressure at rest ‡	0.59	0.33	0.70	0.70	0.21	0.16	0.18			
No (n=164)	0.58 (0.32-0.90)	16.5±7.1	1.52 (1.09-2.04)	0.14 (0.07-0.29)	3.7 (1.8-6.9)	4.0 (2.7-6.3)				
Yes (n=272)	0.54 (0.33-0.86)	15.9±6.7	1.46 (0.97-2.14)	0.12 (0.05-0.26)	3.2 (1.4-6.5)	4.3 (2.8-7.5)				
Low HDL-C**	0.22	0.49	0.50	0.63	0.80	0.96				
No (n=234)	0.55 (0.32-0.81)	16.2±7.0	1.45 (0.97-2.00)	0.12 (0.04-0.27)	3.6 (1.4-6.8)	4.2 (2.8-7.2)				
Yes (n=105)	0.60 (0.34-0.92)	15.7±6.4	1.51 (1.03-2.15)	0.12 (0.05-0.25)	3.2 (1.5-5.7)	4.3 (2.8-6.9)				
High LDL-C†	0.38	0.80	0.80	0.49	0.71	0.27				
No (n=77)	0.63 (0.31-0.94)	16.2±6.7	1.58 (0.95-2.05)	0.13 (0.04-0.30)	3.6 (1.4-6.5)	3.9 (2.5-7.3)				
Yes (n=262)	0.54 (0.33-0.84)	16.0±6.9	1.45 (0.99-2.09)	0.12 (0.05-0.25)	3.2 (1.5-6.3)	4.3 (2.8-7.0)				
High TG-C††	0.88	0.43	0.32	0.89	0.51	0.29				
No (n=266)	0.57 (0.32-0.84)	16.1±7.1	1.45 (0.97-2.03)	0.12 (0.05-0.27)	3.3 (1.4-6.9)	4.3 (2.7-6.8)				
Yes (n=73)	0.54 (0.37-0.89)	15.5±5.6	1.52 (1.12-2.23)	0.11 (0.05-0.24)	3.1 (1.6-5.4)	4.3 (3.0-7.6)				
Abnormal renal function	0.26	0.91	0.14	0.57	0.12	0.42				
No	0.59 (0.34-0.89)	16.2±6.7	1.51 (1.06-2.28)	0.14 (0.06-0.27)	3.5 (1.6-6.8)	4.0 (2.8-6.5)				
Yes	0.54 (0.32-0.84)	16.2±6.9	1.39 (0.97-1.98)	0.10 (0.05-0.28)	3.3 (1.5-6.8)	4.4 (2.7-7.3)				
Metabolic Syndrome	0.09	0.54	0.06	0.08	0.65	0.49				
No (n=223)	0.55 (0.32-0.82)	16.3±6.9	1.44 (0.94-2.00)	0.11 (0.05-0.26)	3.3 (1.6-6.7)	4.2 (2.8-6.9)				
Yes (148)	0.62 (0.38-0.93)	15.8±6.8	1.59 (1.16-2.21)	0.15 (0.07-0.31)	3.7 (1.5-6.8)	3.9 (2.7-6.8)				
Diagnosis	0.23	0.96	0.51	0.86	0.71	0.49				
Stable CAD (n=330)	0.54 (0.33-0.87)	16.1±6.9	1.45 (0.99-2.11)	0.12 (0.05-0.28)	3.5 (1.5-6.8)	4.2 (2.7-6.8)				
ACS (n=106)	0.63 (0.31-0.97)	16.1±6.7	1.55 (0.99-2.16)	0.14 (0.05-0.27)	3.2 (1.7-6.3)	4.7 (3.0-7.1)				

**separated by median; † waist circumference >102 cm for men and >88cm for women, **HDL-C<40mg/dl; †LDL-C>70mg/dl; ††TG>150mg/dl; ‡ Blood pressure≥130/85 mmHg; ‡‡ Creatinine Clearance<90mL/min. SAQ=Seattle Angina Questionnaire; PL=physical limitation; AS=angina stability; AF= angina frequency; TS= treatment

Chapter 2.3

Prognostic Value of Site SYNTAX Score and Rationale for Combining Anatomic and Clinical Factors in Decision Making : Insights From the SYNTAX Trial

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ABSTRACT

BACKGROUND The results of SYNTAX trial have been reported based on "corelab" calculated SS (cSS). It has been shown that reproducibility of SS is better among the core laboratory technicians than interventional cardiologists. Thus, the prognostic value and clinical implication of the "site" SYNTAX SS (sSS) remain unknown.

OBJECTIVES The study sought to evaluate the prognostic value and clinical implication of the sSS after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in the randomized SYNTAX trial.

METHODS The sSS was calculated by the site investigators before randomization in the SYNTAX trial. New tertiles based on the sSS were defined with low (0 to 19), intermediate (20 to 27), and high (≥ 28) scores. The clinical endpoints were compared between PCI and CABG by Kaplan-Meier estimates, log-rank comparison, and Cox regression analyses using the new tertiles. The sSS-based SS II was calculated and its predictive performance was evaluated.

RESULTS The mean difference in cSS and sSS is 3.8 ± 11.2 , with a mean absolute difference of 8.9 ± 7.8 . In the overall cohort, using sSS there was a higher incidence of major adverse cardiac and cerebrovascular events (MACCE) at 5-year follow-up in the PCI group for low (31.9% vs. 24.5%; $p = 0.054$), intermediate (39.5% vs. 29.5%; $p = 0.019$), and high (43.0% vs. 31.4%; $p = 0.003$) tertiles, compared with the CABG group. Similarly, in the 3-vessel disease subgroup, 5-year MACCE rates were higher in PCI group in all tertiles. Conversely, in the left main subgroup, MACCE rates were similar for PCI and CABG groups in all tertiles. The sSS-based SS II (c-index: 0.736) had predictive performance similar to the cSS-based SS II (c-index: 0.744), with net reclassification index of -0.0062 ($p = 0.79$).

CONCLUSIONS Appropriate training and unbiased assessment are needed when using SS in clinical decision making. sSS and tertiles based on sSS showed poor discrimination among low, intermediate, and high-risk groups. However, combining clinical factors with sSS retained the predictive performance of SS II. (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries; NCT00114972) (J Am Coll Cardiol 2014;64:423-32) © 2014 by the American College of Cardiology Foundation.

ABBREVIATIONS
AND ACRONYMSAUC = area under the receiver
operating characteristic curvesCABG = coronary artery bypass
grafting

CI = confidence interval

cSS = 'corelab' SYNTAX score

HR = hazard ratio

MI = myocardial infarction

MACCE = major adverse
cardiac or cerebrovascular
event(s)

NRI = net reclassification index

PCI = percutaneous coronary
intervention

SS = SYNTAX score

sSS = 'site' SYNTAX score

SYNTAX = SYnergy Between
PCI With TAXUS and Cardiac
SurgeryULMCA = unprotected left
main coronary artery

3VD = 3-vessel disease

Interventional cardiologists and surgeons in the SYNTAX (SYnergy Between PCI With TAXUS and Cardiac Surgery) trial originally used the SYNTAX score (SS) to extract objective information from the coronary angiogram on the technical challenges posed by coronary anatomy to percutaneous coronary intervention (PCI) and to facilitate discussions made by the heart team (1). Subsequently, it became apparent that the SS had a prognostic value to predict short- and long-term outcomes (2-4). The European and American revascularization guidelines currently recommend the SS to guide the heart team in decision making (5-7). Moreover, high-risk SS category is a key inclusion/exclusion criterion, imposed by the U.S. Food and Drug Administration, in several ongoing randomized controlled trials, including EXCEL (Evaluation of Xience Prime or Xience V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), PARTNER-II (Placement of Aortic Transcatheter Valves), and SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation).

SEE PAGE 433

Knowledge of variability in calculating SS is of paramount importance at a time of its widespread use as a clinical decision-making tool. Risk stratification of patients in the SYNTAX trial was based on "corelab" SS (cSS), which was calculated by the core laboratory technicians blinded to the treatment group. However, all sites participating in SYNTAX also had a "site" SS (sSS) calculated by the site investigators, who at that time had no knowledge of the prognostic significance of the SS. The discrepancy between cSS and sSS has been previously highlighted in the SYNTAX trial (8). Recently, Génèreux et al. (9) have demonstrated that interventional cardiologists underestimate the number of lesions, bifurcation, and the presence of small-vessel disease, resulting in a lower SS than that reported by the core laboratory technicians. The significance

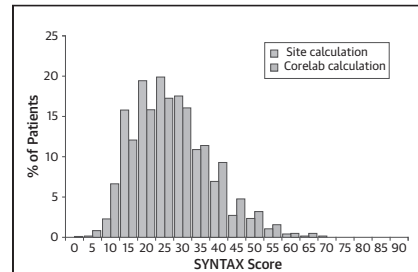


FIGURE 1 Distribution and Individual Difference of the cSS and the sSS

The mean SS was 28.7 ± 11.4 for the corelab and 24.9 ± 10.2 for the site. cSS = corelab SYNTAX score; SS = SYNTAX score; sSS = site SYNTAX score.

and prognostic value of the sSS in the SYNTAX trial have not been evaluated.

This study aimed to examine the difference between the cSS and sSS in the randomized SYNTAX trial and the prognostic performance of the sSS in assessing outcomes among patients undergoing PCI or coronary artery bypass grafting (CABG). We also investigated the predictive performance of the SYNTAX II score, a recently developed risk score that combines the anatomic SS with clinical variables to predict long-term outcome of PCI and CABG when calculated using either cSS or sSS.

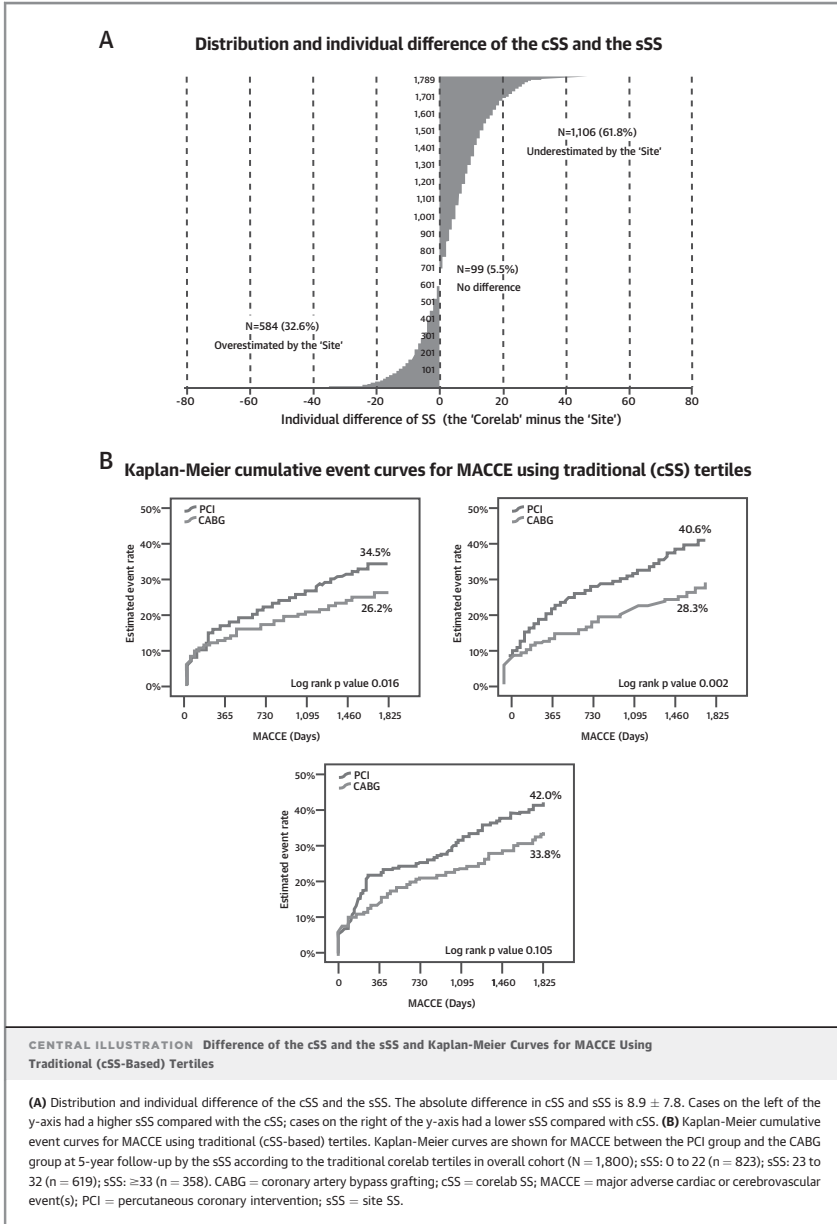
METHODS

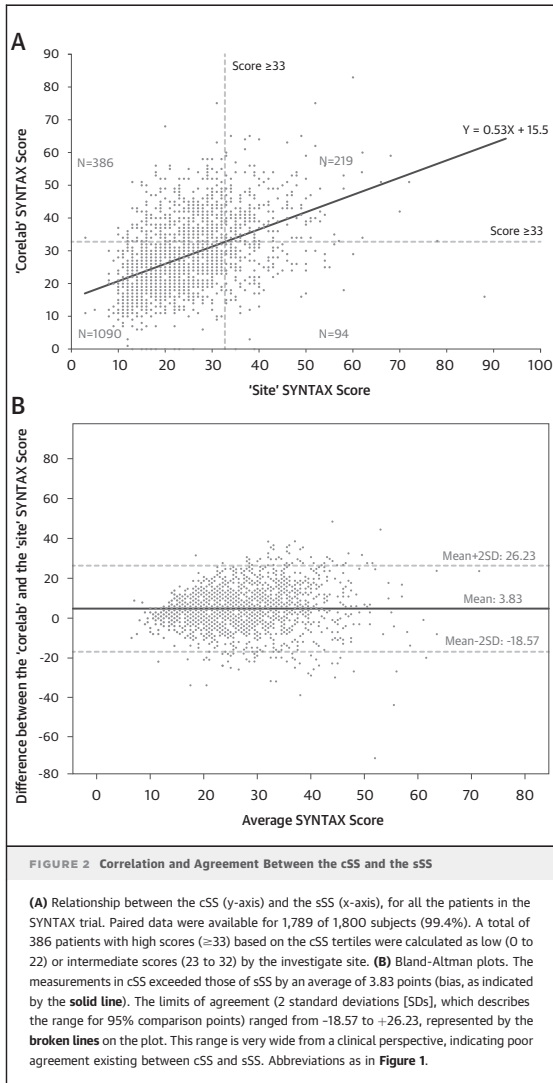
THE SYNTAX RANDOMIZED TRIAL. The SYNTAX trial (NCT00114972) was a prospective, multicenter, randomized trial to investigate subjects with unprotected left main coronary artery (ULMCA) disease (isolated or associated with 1-vessel, 2-vessel, or 3-vessel disease), or de novo 3-vessel disease (3VD) (10). Eligible patients were randomized on a 1:1 ratio to CABG ($n = 897$) or PCI with Taxus Express paclitaxel-eluting stent (Boston Scientific Corporation, Natick, Massachusetts; $n = 903$) and followed up for 5 years. The primary clinical endpoint of the SYNTAX trial was a composite

and the Imperial College London, London, United Kingdom. The SYNTAX trial was funded by Boston Scientific. Dr. Banning has received speaker and advisory honoraria from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Dawkins is a full-time employee and holds stock in Boston Scientific. Dr. Stone has served as consultant for Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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of major adverse cardiac or cerebrovascular events (MACCE) (e.g., death from any cause, stroke, myocardial infarction [MI], or repeat revascularization) at 1-year follow-up. Secondary endpoints included the incidence of MACCE and its components at 1-month, 6-month, 3-year, and 5-year follow-up. An independent clinical event committee comprising interventional

cardiologists, cardiac surgeons, and a neurologist adjudicated all events.

THE SS CALCULATION. During the local heart team meeting, the cardiac surgeon and interventional cardiologist systematically reviewed the coronary angiogram and specified the number of coronary lesions, along with their angiographic location and characteristics. Diagnostic angiograms were scored according to the SS algorithm (1). Each significant lesion (defined as a diameter stenosis of $\geq 50\%$ in ≥ 1.5 -mm vessels) is visually assessed and awarded a score related to location and severity of the coronary lesion. Additional points are given for total occlusion, bifurcation or trifurcation lesion, aorto-ostial lesion, severe tortuosity, heavy calcification, thrombus, and diffusely diseased segment. The sSS was calculated during the local heart team meeting before randomization. Calculation of the cSS was done by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands), blinded to treatment assignment.

THE SS II CALCULATION. The SS II has been previously generated by a combination of anatomic cSS and clinical factors (age, creatinine clearance, left ventricular ejection fraction, presence of ULMCA disease, peripheral vascular disease, sex, and chronic obstructive pulmonary disease) to predict 4-year mortality risk after PCI or CABG (11). Using the same model, we also have calculated SS II using the sSS and using the sSS-based SS II to predict 4-year mortality and make a treatment recommendation.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean \pm SD and categorical variables are shown as counts and percentages of the total. Bland-Altman plots were used to compare the cSS and sSS. The predictive values of anatomic cSS and sSS were compared by evaluating differences in the area under the receiver operating characteristic curves (AUC) and standard errors using the Delong method. The agreement between observed and predicted risks for cSS and sSS was assessed with the Hosmer-Lemeshow test. Comparisons of 5-year clinical outcomes between CABG and PCI were conducted with the Kaplan-Meier method and the log-rank tests. By Cox regression analyses, the relative risks were shown as hazard ratios (HRs) and 95% confidence interval (CI). Two patient subsets were predefined in this study: patients with ULMCA (with or without additional vessel involvement), and those with 3VD in the absence of left main coronary disease. To calculate the SS II, multiple imputations (5 \times) of missing values was performed with an advanced imputation strategy, which takes into account the correlation between all potential predictors (11,12). The performance of the

sSS-based SS II was evaluated using c-statistics (Harrell's c-index) (13), calibration plots (14), reclassification table, and net reclassification index (NRI) (15,16). A probability value of less than 0.05 was considered statistically significant. All analyses were undertaken using SPSS 20.0 (IBM Corporation, Armonk, New York).

RESULTS

SS BY THE CORE LABORATORY AND SITE. The cSS was calculated in 99.4% (n = 1,789) of patients, missed in 0.6% (n = 11) of patients. The sSS was available in 100% (n = 1,800). The cSS and sSS distributions are shown in **Figure 1**. The mean SS was 28.7 ± 11.4 (range: 0 to 83) for the corelab and 24.9 ± 10.2 (range: 3 to 88) for the site. The mean difference between cSS and sSS is 3.8 ± 11.2, with an absolute difference of 8.9 ± 7.8 (**Central Illustration**). The sSS was numerically identical to the cSS in 99 patients (5.5%), underestimated in 1,106 (61.8%), and overestimated in 584 (32.7%). A significant correlation (r = 0.49; p < 0.05) was found between the cSS and sSS as shown in **Figure 2A**. However, Bland-Altman

		Corelab SYNTAX Score			In Total
		Low (≤22)	Median (>22-≤32)	High (>32)	
Site SYNTAX score	Low (≤22)	409	262	145	816
	Median (>22-≤32)	122	254	241	617
	High (>32)	43	94	219	356
In total		574	610	605	1,789

Values in bold represent concordant scores.

plots showed that the limits of agreement (2 SDs that describe the range for 95% comparison points) were very wide (-18.57 to +26.23 score), indicating a poor agreement between the corelab and site calculated SS (**Fig. 2B**). Only 882 (49.3%) patients have concordant scores according to the corelab SS-defined tertiles (**Table 1**).

CLINICAL ENDPOINTS USING sSS AND ESTABLISHED SS TERTILES. Using the sSS, patients were grouped into traditional SYNTAX tertiles of low (≤22 score,

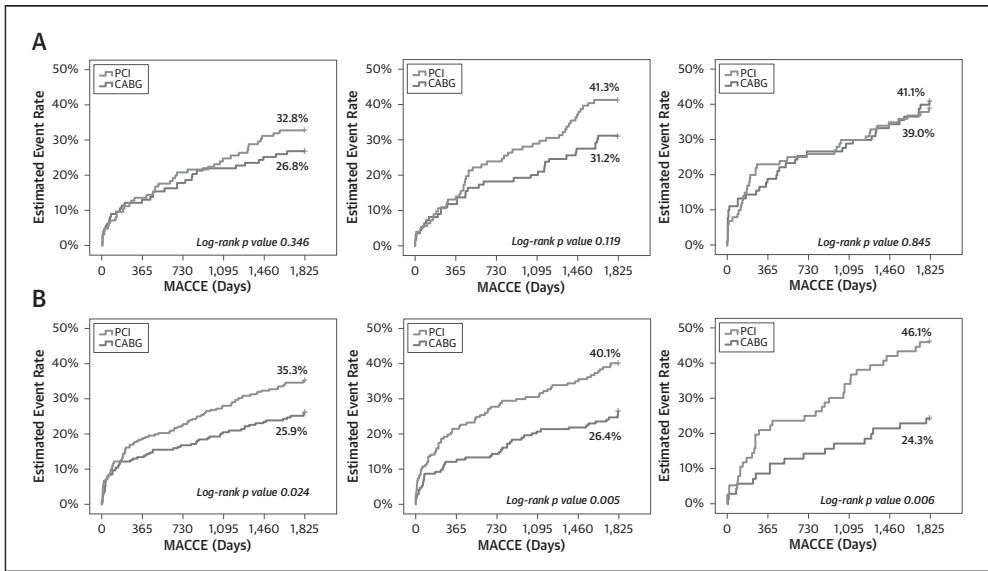
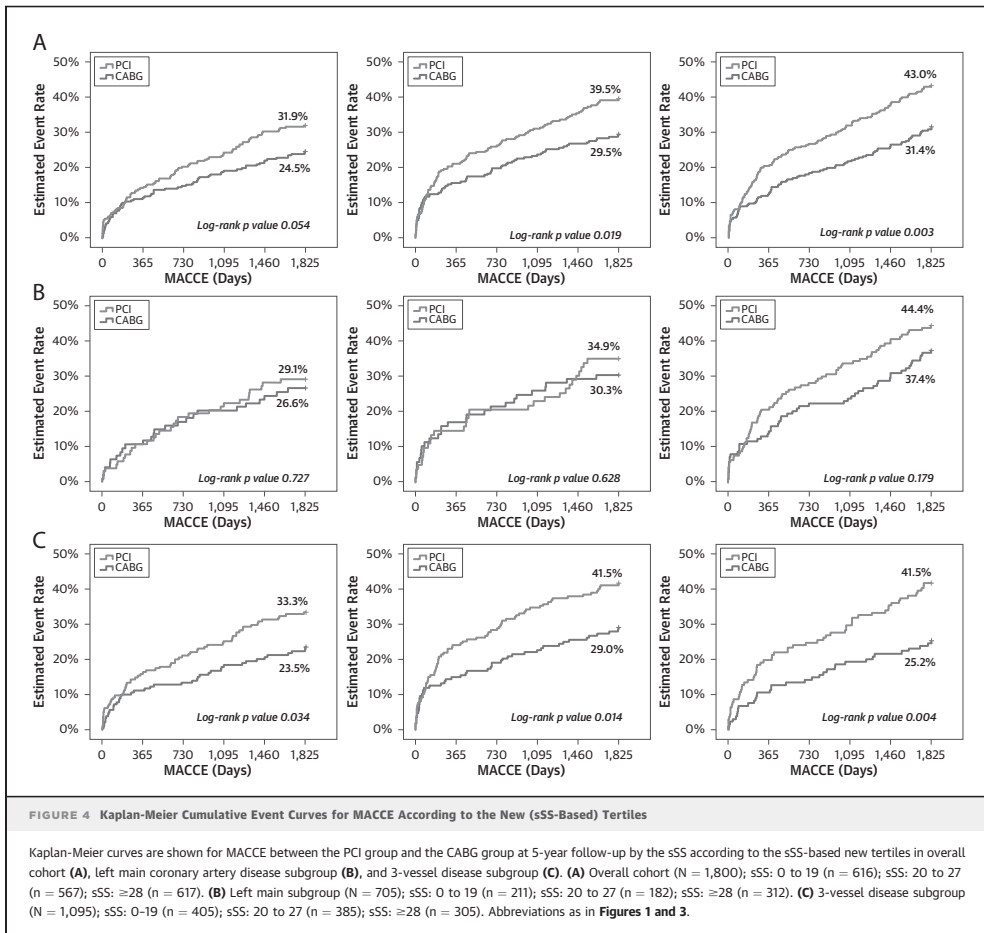


FIGURE 3 Kaplan-Meier Cumulative Event Curves for MACCE Using Traditional (cSS-Based) Tertiles

Kaplan-Meier curves are shown for MACCE between the PCI group and the CABG group at 5-year follow-up by the sSS according to the traditional corelab tertiles in the left main coronary artery disease subgroup (**A**) and the 3-vessel disease subgroup (**B**). (**A**) Left main subgroup (N = 705); sSS: 0 to 22 (n = 266); sSS: 23 to 32 (n = 245); sSS: ≥33 (n = 194). (**B**) Three-vessel disease subgroup (N = 1,095); sSS: 0 to 22 (n = 557); sSS: 23 to 32 (n = 374); sSS: ≥33 (n = 164). CABG = coronary artery bypass grafting; MACCE = major adverse cardiac or cerebrovascular event(s); PCI = percutaneous coronary intervention; other abbreviations as in **Figure 1**.



n = 823), intermediate (23 to 32 score, n = 619), and high (≥ 33 score, n = 358) scores (Central Illustration).

In the overall cohort, using the sSS, MACCE rates in the low and intermediate tertiles were significantly higher in the PCI group than in the CABG group ($p = 0.016$, $p = 0.002$, respectively); MACCE rate in the high-score tertile was numerically but not statistically higher with PCI compared with CABG (42.0% vs. 33.8%; $p = 0.105$) (Central Illustration). In the ULMCA subgroup, the 2 revascularization strategies had similar MACCE rates during the 5-year follow-up period (Fig. 3A). In the 3VD subgroup, the incidence of MACCE was significantly higher in the PCI group

than in the CABG group in all tertiles (low, 35.3% vs. 25.9%; $p = 0.024$; intermediate, 40.1% vs. 26.4%; $p = 0.005$; high, 46.1% vs. 24.3%; $p = 0.006$) (Fig. 3B).

CLINICAL ENDPOINTS USING sSS AND NEW TERTILES BASED ON sSS. The actual tertiles according to the sSS were low (≤ 19 score, n = 616), intermediate (20 to 27 score, n = 567), and high (≥ 28 score, n = 617).

In the overall cohort, there was a trend toward higher incidence of MACCE in the PCI group for low scores, compared with the CABG group, but this difference was not statistically significant (31.9% vs. 24.5%; $p = 0.054$) (Fig. 4A). Risk of MACCE for intermediate and high scores was significantly increased

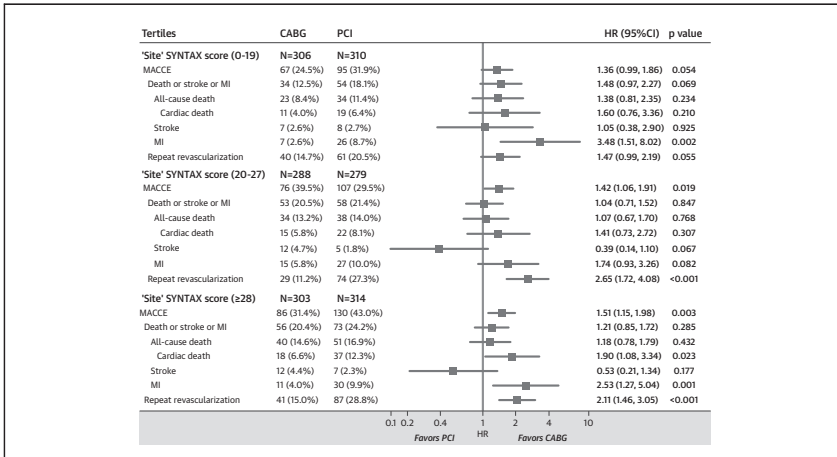


FIGURE 5 Clinical Outcomes at 5-Year Follow-Up According to the New Tertiles

HR was calculated for CABG versus PCI at 5-year follow-up for each clinical endpoint according to the sSS-based new tertiles. CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; other abbreviations as in Figures 1 and 3.

with PCI versus CABG (39.5% vs. 29.5%; $p = 0.019$; 43.0% vs. 31.4%; $p = 0.003$, respectively) (Fig. 4A).

In the ULCMA disease subgroup ($n = 705$), MACCE rates were comparable and did not differ significantly between the 2 groups in each tertile (Fig. 4B). In the 3VD subgroup ($n = 1,095$), all groups of low, intermediate, and high scores showed a significantly higher incidence of MACCE in the PCI group than those in the CABG group at 5-year follow-up (Fig. 4C).

There was no significant difference in death, stroke, and repeat revascularization between PCI and CABG in the low tertiles, but a higher risk of MI in the PCI group ($p = 0.002$) (Fig. 5). In the intermediate tertiles, a significantly higher proportion of patients had repeat revascularization after PCI than after CABG (HR, 2.65; 95% CI: 1.72 to 4.08; $p < 0.001$). In the high tertiles, there was a significantly higher risk of death, MI, and repeat revascularization in the PCI group, but an insignificantly lower risk of stroke ($p = 0.177$) (Fig. 5).

SUBSTANTIAL CHANGES IN TREATMENT DECISION USING sSS. The predictive accuracy for 4-year mortality was modest with cSS (AUC, 0.57; 95% CI: 0.54 to 0.59) and dropped further with sSS (AUC, 0.55; 95% CI: 0.53 to 0.57). There was a poor agreement between predicted and observed MACCE for the sSS and cSS, using Hosmer-Lemeshow test ($p = 0.51$, $p = 0.31$,

respectively). Furthermore, the treatment decision based on SS tertile changed in more than one-third of patients depending on whether cSS or sSS is used (Table 2). For 9.4% of patients, the treatment decision changed from PCI or CABG to CABG and for 25.7% the treatment recommendation changed from CABG to PCI or CABG.

MINIMAL CHANGES IN TREATMENT DECISION USING sSS-BASED SS II. The sSS-based SS II had predictive power similar to the cSS-based SS II (Harrell's c-index: 0.736, 0.744, respectively). The calibration plots of the sSS-based SS II showed a good agreement between the observed and predicted risk of mortality (Fig. 6). The recommendations according to the

Recommendations	sSS		Total
	CABG or PCI	CABG	
cSS CABG or PCI	601 (33.6%)	168 (9.4%)	769 (43.0%)
CABG	459 (25.7%)	561 (31.3%)	1,020 (57.0%)
Total	1,060 (59.3%)	729 (40.7%)	1,789 (100%)

*Based on following recommendation: 3VD and SS ≤ 22 -PCI or CABG; 3VD and SS > 22 -CABG; ULMCA and ≤ 32 -PCI or CABG; ULMCA and SS > 32 -CABG.
 CABG = coronary artery bypass grafting; cSS = corelab SYNTAX score; PCI = percutaneous coronary intervention; sSS = site SYNTAX score; ULMCA = unprotected left main coronary artery; 3VD = three-vessel disease.

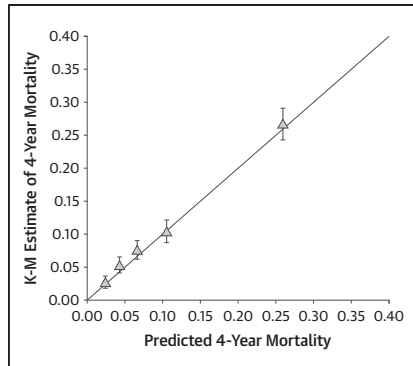


FIGURE 6 Calibration Plots for the sSS-Based SS II

Calibration plots are shown for the sSS-based SS II model predicting 4-year risk of mortality. The triangles indicate the observed frequencies by quintile of predicted probabilities. Good agreement was found between the observed and predicted mortality for each group. K-M = Kaplan-Meier; other abbreviations as in Figures 1 and 3.

original cSS- and the sSS-based SS II models did not warrant a change in revascularization strategy (from PCI to CABG or CABG to PCI) in a large majority of patients (Table 3). A large majority (83%) of patients had the same recommendation: only eligible for CABG (n = 346; 19.2%); only eligible for PCI (n = 76; 4.2%); or potentially amenable to both types of revascularization (n = 1,070; 59.4%). Patients with or without events are reclassified by the sSS-based SS II model, and their results are presented in Table 4 (NRI, -0.0062; p = 0.79).

DISCUSSION

This post-hoc study of the SYNTAX randomized trial has highlighted a significant difference in the

anatomic SS calculated by the site and corelab and the calculation of tertiles based on the sSS, which compromised the ability of the SS to distinguish the low-, intermediate-, and high-risk patients, especially in the subgroup of 3VD. However, the prognostic performance of SS II, which combines clinical variables with the SS, remained largely unaffected whether the cSS or the sSS was used.

DIFFERENCES IN SITE AND CORELAB SS. There is a significant absolute difference in the SS calculated by the site investigators and the core laboratory analysts in the SYNTAX trial. Lack of advanced training at each site is a plausible underlying reason for this difference (9,17). Appropriate training can significantly reduce intraobserver and interobserver variability of the SS calculation by interventional cardiologists (9). A study comparing SS calculation by interventional cardiologists and angiographic core laboratory technicians has shown that inter-observer agreement was initially poor among interventional cardiologists ($\kappa = 0.33$), but improved substantially after advanced training ($\kappa = 0.76$).

Although SS is a continuous variable, in practice it is used as a categorical variable, with 3 categories determined by cSS cutoff values of 22 and 33. These SS categories are being extensively used in clinical practice and the guidelines to decide revascularization strategy and in the ongoing randomized trials (e.g., EXCEL, PARTNER-II, and SURTAVI) as inclusion/exclusion criteria (18). However, our data highlight the variability in calculating SS, which may have a significant impact on decision making and potential consequences on patient outcomes based on the choice of revascularization strategy.

OUTCOMES BASED ON sSS TERTILES. Using the new tertiles (based on sSS) in the ULMCA disease subgroup, there were no statistical differences in MACCE rates between CABG and PCI in all tertiles. These findings are consistent with studies demonstrating comparable clinical outcomes for patients with left main disease undergoing either PCI or CABG, especially in low-risk patients (19,20). Park et al. (19) have reported that PCI with sirolimus-eluting stents was noninferior to CABG with respect to MACCE at 2 years in the treatment of patients with unprotected left main coronary artery stenosis. Because the newer-generation drug-eluting stents have been shown to significantly reduce the stent-related adverse events (21,22), we speculate that the ongoing EXCEL trial will show noninferiority of PCI for treating the majority of patients with ULMCA disease.

It is noteworthy that for new site-based tertiles, not only was a comparable MACCE in the low tertile

TABLE 3 Recommendations According to the cSS- and the sSS-Based SS II Models

Recommendations	sSS-Based SS II			Total
	CABG	CABG or PCI	PCI	
cSS-based SS II				
CABG	346 (19.2%)	173 (9.6%)	0 (0)	519 (28.8%)
CABG or PCI	71 (3.9%)	1,070 (59.4%)	42 (2.3%)	1,183 (65.7%)
PCI	0 (0)	22 (1.2%)	76 (4.2%)	98 (5.4%)
Total	417 (23.2%)	1,265 (70.3%)	118 (6.6%)	1,800 (100%)

A total of 82.8% of patients (bold) had same recommendations. No recommendation was completely shifted from PCI to CABG or vice versa.

Abbreviations as in Table 2.

but also the lowest incidence of MACCE was in the intermediate tertile for both CABG and PCI groups. This is somewhat similar to the findings in the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, which suggested no differential treatment effect according to the category of the SS (≤ 22 and ≥ 33) in patients with diabetes and complex coronary artery disease (23). Indeed, SS as an anatomic tool without taking into consideration the clinical risk profile of an individual patient is suboptimal in predicting all the clinical outcomes. Therefore, attempts have been made to combine anatomic SS with clinical factors (e.g., Logistic Clinical SS) to accurately predict individual patients' risk (24).

sSS-BASED SS II. Recently proposed SS II, using anatomic and clinical variables, has been shown to significantly improve decision making between CABG and PCI compared with using anatomic SS alone (11). In the present study, although the site investigators frequently underestimated the sSS and using it changed treatment decisions, its influence on the overall capability of the SS II to predict prognosis and guide decision making was limited. This suggests that clinical variables were more powerful and counteracted any variability in calculating SS. It is plausible that this superiority of SS II stems from the fact that it used SS as a continuous variable and not as a categorical variable. This may circumvent the limitation, outlined above, of the dependence of classification agreement in categorical variables on variability in repeated measurements and frequency distribution of the studied population.

CLINICAL IMPLICATION AND FUTURE PERSPECTIVE. This study has many potential implications on clinical practice. Revascularization guidelines strongly recommend that heart teams use SS for decision making. However, it is essential to highlight that adequate training of the staff calculating SS is vital. It also may be possible in the near future to develop automated algorithms and software to calculate SS from coronary angiography or noninvasive multislice computed tomography (25). Furthermore, it is noteworthy that the uptake of anatomic SS in clinical practice has been modest, despite recommendation by the guidelines. It is probably attributable to variability in calculating SS and lack of clinical risk factors, which physicians generally believe to be equal or more important. Finally, it is appropriate to suggest that the heart teams use SS II, instead of anatomic SS, for decision making to refer the patients for either surgery or PCI.

TABLE 4 Reclassification Table Comparing 4-Year Mortality Risk Strata for Original cSS- and the sSS-Based SS II

SS II Model Using the cSS	SS II Model Using the sSS			Total
	0% to 5%	5% to 10%	$\geq 10\%$	
0% to <5%				
Persons included	600.0 (93.8)	40.0 (6.3)	0.0 (0.0)	640.0 (35.6)
Case patients	18.0 (77.9)	5.1 (22.1)	0.0 (0.0)	23.1 (12.2)
Control participants	582.0 (94.3)	34.9 (5.7)	0.0 (0.0)	616.9 (38.3)
Observed risk, %*	3.0	12.8	0.0	
5% to <10%				
Persons included	58.0 (10.2)	476.0 (83.4)	37.0 (6.5)	571.0 (31.7)
Case patients	5.0 (12.1)	35.2 (85.3)	1.1 (2.6)	41.3 (21.8)
Control participants	53.0 (10.0)	440.8 (83.2)	35.9 (6.8)	529.7 (32.9)
Observed risk, %*	8.6	7.4	2.9	
$\geq 10\%$				
Persons included	1.0 (0.2)	64.0 (10.9)	524.0 (89.0)	589.0 (32.7)
Case patients	0.0 (0.0)	7.1 (5.7)	117.9 (94.3)	125.0 (66.0)
Control participants	1.0 (0.2)	56.9 (12.3)	406.1 (87.5)	464.0 (28.8)
Observed risk, %*	0.0	11.1	22.5	
Total				
Persons included	659.0 (36.6)	580.0 (32.2)	561.0 (31.2)	1,800.0 (100.0)
Case patients	23.0 (12.1)	47.5 (25.1)	119.0 (62.8)	189.4 (100.0)
Control participants	636.0 (39.5)	532.6 (33.1)	442.0 (27.4)	1,610.6 (100.0)
Observed risk, %*	3.5	8.2	21.2	10.5

Values are n (%). In patients who died, the SS II model using the sSS reclassification declined by 3.11%, whereas in nonevent patients the reclassification improved by 2.49%. The net reclassification index was -0.0062 ($p = 0.79$). *Observed risk at 4 years is estimated from the Kaplan-Meier curve by using observations in each cell. Abbreviations as in Table 2.

STUDY LIMITATIONS. This is a post-hoc study from the SYNTAX randomized trial. At the time of the trial, an online calculator for SS was not available, and the trial sites may have had limited or varying experience in calculating SS, which may have potential influence on the observed variability.

CONCLUSIONS

The anatomic SS was frequently underestimated by the site. Advanced training and unbiased assessment is mandatory in clinical use of the SS. The sSS and tertiles based on sSS showed poor discrimination between low-, intermediate-, and high-risk groups. However, combining clinical factors with sSS retained the predictive performance of SS II.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Training and unbiased assessment are needed to apply the coronary anatomic SYNTAX score in clinical decision making. Combining clinical factors with the SYNTAX score (referred to as the SYNTAX-II score) reduces variability.

TRANSLATIONAL OUTLOOK: The ongoing SYNTAX-II study will prospectively evaluate the predictive value of the SYNTAX-II score with regard to both short- and long-term clinical outcomes as a guide to referral of patients with coronary artery disease for either surgical or percutaneous revascularization.

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KEY WORDS corelab SS, MACCE, site SS, SYNTAX score, SYNTAX score II

Chapter 2.4

Impact of diabetes on stent thrombosis and major clinical events at 4 years after zotarolimus-eluting vs sirolimus-eluting coronary stent implantation: an analysis from the PROTECT randomized trial

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Submitted

ABSTRACT

Objectives

We compared diabetic vs non diabetic patients with regards to definite or probable stent thrombosis (primary endpoint) and major clinical coronary events at 5 years. Diabetes was a pre-specified subgroup analysis within the PROTECT Trial.

Background

Stent thrombosis is a potential catastrophic complication, which could be prevented by tailoring antiplatelet treatment.

Methods

The PROTECT randomized trial compared the Endeavor zotarolimus-eluting stent (E-ZES) and the Cypher sirolimus-eluting stent (C-SES). A total of 8709 patients were enrolled, including 2411 diabetics of whom 1174 were allocated to the E-ZES group and 1237 patients to the C-SES group.

Results

At 5 years, the primary endpoint, definite or probable stent thrombosis, was higher among patients with diabetes mellitus (DM) than those without DM (non DM) (3.0% vs 1.9%, $p=0.004$). The rate of cardiac death was 7.3% vs 2.6%, $p<0.001$, all myocardial infarction was 6.5% vs. 5.5%, $p=0.104$, for diabetics and non diabetics respectively.

Definite or probable stent thrombosis rate was lower among non DM than non insulin-dependent DM (NIDDM) (1.9% vs. 2.7%, $p=0.035$) and insulin-dependent DM (IDDM) (1.9% vs. 4.0%, $p<0.001$). Cardiac death rates were also different in these 3 groups, in non DM was 2.5%, in NIDDM was 6.0% (vs. non DM, $p<0.001$) and in IDDM 11.2% (vs. non DM, $p<0.001$).

Conclusions

At 5-year, stent thrombosis rates and cardiac death / large non-fatal MI rates were much higher among diabetics than non diabetics. These events appeared to be especially higher in patients with insulin-dependent diabetes.

INTRODUCTION

About a quarter of patients treated with percutaneous coronary interventions are diabetics.¹ These patients have a greater likelihood of follow-up events such as restenosis and the fast-developing new lesions in non-treated coronary segments. These subsequent events result in an increased long-term mortality of diabetic patients compared with their counterparts.² Therefore, many guidelines recommend an intensive treatment of patients with diabetes since they are considered to be at a higher risk of cardiovascular events^{3,4}. Specifically, in patients treated with percutaneous coronary interventions, diabetes mellitus has been associated with an increase rate of death, non-fatal myocardial infarction (MI) and stent thrombosis⁵. Current guidelines for myocardial revascularization mentioned that diabetics may require a longer duration of DAPT.⁶ Is there enough evidence to support this practice?

The PROTECT study which randomised 8709 to either the Endeavor zotarolimus-eluting stent (E-ZES; Medtronic, Inc) group and to the Cypher sirolimus-eluting stent (C-SES; Cordis, Johnson & Johnson) group concluded that no evidence of superiority of E-ZES compared with C-SES in definite or probable stent thrombosis rates was noted at 3 years.⁷ The PROTECT study brings an opportunity to investigate whether stent thrombosis rate is different between diabetic patients and their counterparts since it is the largest contemporary well controlled trial in which the central point was stent thrombosis.

METHODS

Study design

The PROTECT study design has been previously reported⁸. Briefly, this was a randomised, open-label, two-arm, multinational superiority trial, with the hypothesis being that E-ZES was superior to C-SES in respect of definite or probable stent thrombosis at 3 years, with a prospective randomised open-label blinded-endpoints design. Patients were randomly assigned to a stent type (1:1 ratio) after signed patient informed consent was obtained and all protocol inclusion and exclusion criteria were confirmed. Patients aged 18 years or older undergoing elective, unplanned, or emergency procedures in native coronary arteries were eligible for enrolment. Patients who had had bare-metal stent implantation in the preceding 12 months, a previous drug-eluting stent, or brachytherapy were excluded. The protocol was approved by the institutional ethical committee and/or centralised national ethical board in accordance with local regulations.

Patients and investigators were aware of treatment assignment. Assignment was concealed to the clinical event committee, core lab staff responsible for ECG and angiogram analyses, data management, and statistical analysis, and sponsor staff, excluding a small number responsible for vigilance reporting.

Procedures

Treatment of coronary lesions was done in accordance with the manufacturer's instructions and local or national guidelines. Antiplatelet therapy with aspirin and clopidogrel (75 mg) or another thienopyridine derivative was either started 3 days before the procedure or through a loading dose (clopidogrel 300–600 mg or its equivalent for other thienopyridine) for

patients not yet taking these medications. Post procedure, aspirin was prescribed indefinitely and thienopyridine therapy for a minimum of 3 months up to 12 months, according to guidelines, or for longer as per the physician's decision. Prolongation or reinstatement of thienopyridine therapy was allowed where clinically indicated.

Data collection, source document verification of all reported events, and on-site monitoring were performed by three independent clinical contract research organisations (CROMSOURCE, Kraainem, Belgium; Pacific Clinical Research Group, Mosman, NSW, Australia; Vibgyor Scientific Research, Ahmedabad, India)

Sites in the USA and Canada were monitored by Medtronic monitors. Patient informed consent and source documentation of all reported events were monitored in all patients. Other data monitoring was done in 30% of randomly selected patients at all participating centres.

All deaths and all triggers for suspected myocardial infarction, stent thrombosis, or bleeding were adjudicated by an independent clinical events committee. Revascularisations and strokes (not related to a bleeding) were not adjudicated.

Cardiac biomarker data (creatinine kinase, creatine kinase myocardial-band if creatine kinase was outside of the normal range, and troponin) were to be obtained within 72 h of the procedure and at least once after the procedure. Centres were instructed to report all obtained biomarker values for event adjudication. At 3-year follow-up visit with electrocardiograph was mandatory.

Statistical analysis

The primary outcome was the composite of definite or probable stent thrombosis, ac-

ording to the Academic Research Consortium definition, (22) at 3 years in the intention-to-treat population. Diabetes was a pre-specified subgroup analysis within the PROTECT Trial.

The main secondary outcomes were chosen to identify sequelae of stent thrombosis: (1) total death and large non-fatal myocardial infarction, (2) total death and nonfatal myocardial infarction, (3) cardiac death and large non-fatal myocardial infarction, and (4) cardiac death and non-fatal myocardial infarction. Cardiac death was defined according to the Academic Research Consortium definition as any death unless an unequivocal non-cardiac cause could be established. Myocardial infarctions are reported according to the historical WHO and the Academic Research Consortium definitions. The WHO definition was used for the related composite endpoints to be consistent with other contemporary studies comparing drug-eluting stents. A large myocardial infarction was defined as acute ST-elevation myocardial infarction, new pathological Q-waves not present on the baseline electrocardiograph, or creatine kinase more than five times the upper limits of normal. We obtained prospective data on bleeding complications, according to the Thrombolysis In Myocardial Infarction criteria. Lesion success was defined as the attainment of less than 50% residual stenosis of the target lesion with any percutaneous method; device success as the attainment of less than 50% residual stenosis of the target lesion with only the assigned device; and procedure success as the attainment of less than 50% residual stenosis of all the target lesions and no in hospital major adverse cardiac events.

The sample size assumptions were previously published in the main report of the study. Dichotomous and categorical variables

are reported as counts and percentages; between-group differences were assessed with Fisher's exact test for dichotomous variables and Cochran-Mantel-Haenszel Modified Ridit Scores for categorical variables. Continuous variables are reported as means (SD) and were compared with the use of a two-sample t test. We did the analysis according to the intention-to-treat principle in the entire enrolled study population. We used the Kaplan-Meier method to study the time to clinical outcomes and applied the logrank test to time-to-event between groups. For all outcomes, a two-sided p value lower than 0.05 represented statistical significance.

All significant variables in the univariable analysis ($p < 0.20$) were put into the multivariable Cox proportional hazard regression models: Gender; Age ≥ 75 ; diabetes; Prior MI; Prior Stroke; Smoked cigarette within 90 days; Serum Creatinine ($\mu\text{mol/l}$); Time dependent covariate for DAPT; Assigned Treatment Code; Total stent length per patient (mm); At least 1 stent ≤ 2.75 mm in diameter; At least 1 lesion overlapping stent; At least 1 lesion with thrombus; At least 1 lesion calcification (moderate/severe); At least 1 lesion tortuosity (moderate/severe); At least 1 lesion pre procedure TIMI 0-1-2.

We did the analyses with SAS, version 9.3 (SAS Institute Inc, Cary, NC, USA). This trial is registered with Clinicaltrials.gov, number NCT00476957.

RESULTS

Between May 21, 2007 and Dec 22, 2008, 8791 patients from 36 countries were recruited, but only 8709 patients provided a valid signed consent and were eligible for inclusion in

the analysis. Out of these patients, 2411 had diabetes and 6298 non diabetes.

The baseline clinical characteristics were very dissimilar between diabetes and non diabetes groups (table 1). Patients with diabetes were older, mean age 63.5 ± 10.1 vs. 61.7 ± 10.8 , $p < 0.001$, more hypertensive 78.3 vs. 58.5%, $p < 0.001$, more dyslipidemic 66.3 vs. 60.8%, $p < 0.001$ and also had more peripheral vascular disease 7.0 vs. 4.0%, $p < 0.001$ compared to their counterparts. On the other hand, patients with diabetes were less frequently male 73.3 vs. 77.5%, $p < 0.001$ and presented also less frequently with acute MI 22.6 vs. 27.1%, $p < 0.001$, than the non diabetes patients.

The most common treated vessel was the left anterior descending in both groups. Lesion characteristics were similar between groups with the exception of severe calcification, which was more common in patients with diabetes (table 2). Procedure characteristics were also similar between groups, with the exception of number of lesions per patient, stents per patient, multilesion/vessel stenting and longer stented segment per lesion/patient which was greater in patients with diabetes. Interestingly, diabetic patients stayed longer period in hospital compared to non diabetics (2.11 ± 4.34 vs. 1.82 ± 2.06 days, $p < 0.001$)

The use of antiplatelet drugs at 30 days and up to 360 days was similar in both DM and non DM groups (table 3, figure 1). At 1800 days, this was different; patients using DAPT were 33.9% and 20.7% in non diabetics ($p < 0.001$) (Figure 1).

At 5 years, the primary endpoint, definite or probable stent thrombosis, was higher among diabetics than non diabetics (3.0% vs 1.9%, $p < 0.004$). (table 4 and figure 1). The rate of definite or probable stent thrombosis was

Table 1. Baseline Demographics and Clinical Characteristics

Patient Characteristics	Diabetes N=2411	Non Diabetes N=6298	P-value
Age (Years)	63.5±10.1	61.7±10.8	< 0.001
BMI (kg/m ²)	29.1±4.9	27.3±4.2	< 0.001
Male	73.3 (1767/2411)	77.5 (4881/6298)	<0.001
History of smoking	51.9 (1251/2411)	59.8 (3764/6298)	<0.001
Current smoker	19.0 (458/2411)	27.4 (1724/6298)	<0.001
Diabetes Mellitus	100.0 (2411/2411)	0.0 (0/6298)	<0.001
Insulin Dependent	25.1 (606/2411)	0.0 (0/6298)	<0.001
Hypertension	78.3 (1889/2411)	58.5 (3686/6298)	<0.001
Hyperlipidemia	66.3 (1598/2411)	60.8 (3831/6298)	<0.001
Prior MI	23.6 (570/2411)	19.4 (1222/6298)	<0.001
Prior CABG	7.2 (173/2411)	4.0 (250/6298)	<0.001
Prior PCI	15.8 (382/2411)	11.2 (708/6298)	<0.001
Prior Stroke	4.8 (116/2411)	2.4 (154/6298)	<0.001
Current Cardiac Status			
Silent Ischemia	9.5 (228/2411)	5.3 (333/6298)	<0.001
Stable Angina	47.0 (1132/2411)	49.6 (3125/6298)	0.026
Unstable Angina	20.9 (505/2411)	18.0 (1133/6298)	0.002
(Acute) MI	22.6 (546/2411)	27.1 (1707/6298)	<0.001
ST elevation (STEMI)	7.0 (169/2411)	9.1 (571/6298)	0.002
Non ST elevation (NON STEMI)	15.6 (377/2411)	18.0 (1136/6298)	0.008
Left Ventricular Ejection Fraction			<0.001
< 30	2.2 (31/1383)	0.9 (28/3106)	
30-50	32.6 (451/1383)	24.7 (768/3106)	
> 50	65.1 (901/1383)	74.4 (2310/3106)	
Serum Creatinine (µmol/l)	90.8±45.4	86.9±30.2	< 0.001
Renal Function ¹			0.213
Stage 0/1	46.4 (1061/2286)	46.2 (2707/5865)	
Stage 2	36.1 (826/2286)	39.6 (2325/5865)	
Stage 3	16.2 (371/2286)	13.8 (807/5865)	
Stage 4	0.9 (21/2286)	0.3 (18/5865)	
Stage 5	0.3 (7/2286)	0.1 (8/5865)	

¹GFR according to Cockcroft-Gault formula: estimated GFR, without RACE

also higher for diabetics over the first 30 days and between 31 and 360 days, but thereafter (between 1 and 5 years), it was not statistically different between diabetics and non diabetics (table4 and figure1).

The rate of cardiac death was 7.3% vs 2.6%, $p < 0.001$; all myocardial infarction rate was 6.5% vs. 5.5%, $p = 0.104$ (and large, non-fatal

MI was 3.1% vs 2.3%, $p = 0.042$), for diabetics and non diabetics respectively (Table5 and Figure3).

By insulin-dependent status, at 5 years, the primary endpoint, definite or probable stent thrombosis, was lower among non diabetics (non DM) than non insulin-dependent diabetics (NIDDM) (1.9% vs. 2.7%, $p = 0.035$)

Table 2. Procedural Characteristics

Measures	Diabetes (N=2411 Patients, 3627 Lesions)	Non Diabetes (N=6298 Patients, 8663 Lesions)	P-value
Lesions with Pre-Dilatation	68.5 (2486/3627)	68.4 (5927/8663)	0.898
Number of lesions treated per patient	1.49±0.79	1.36±0.67	< 0.001
No Lesions/Vessels Treated	0.7 (17/2409)	0.7 (45/6297)	1.000
Multiple Lesions Treated	35.8 (862/2409)	28.2 (1773/6297)	<0.001
Number of vessels treated per patient	1.26±0.51	1.18±0.44	< 0.001
Multiple Vessels Treated	23.7 (572/2409)	17.0 (1072/6297)	<0.001
Number of stents per patient	1.70±1.04	1.58±0.95	< 0.001
Number of stents per lesion	1.13±0.46	1.15±0.48	0.080
Total Stent Length per patient (mm)	32.95±22.19	30.58±20.17	< 0.001
Total Stent Length per lesion (mm)	21.89±11.42	22.23±11.61	0.133

and than insulin-dependent diabetics (IDDM) (1.9% vs. 4.0%, $p<0.001$). Cardiac death rates were also different in these 3 groups, in non DM was 2.6%, in NIDDM was 6.0% (vs. non DM, $p<0.001$) and in IDDM 11.3% (vs. non DM, $p<0.001$) (Figures 2, 4 and 5).

Within the group of patients with diabetes, the population was divided according to the stent type (E-ZES vs. C-SES). The baseline, procedure and lesion (with the exception of calcification that was higher in E-ZES group) characteristics were similar between the E-ZES and C-SES. Among diabetics, the primary endpoint did not differ between groups (2.5% for E-ZES vs 3.5% for C-SES; $p=0.214$).

After adjustment for all significant univariate predictors, in the COX multivariate analysis, insulin dependent diabetes mellitus (HR 1.96, 95%CI [1.2,3.1], $p=0.0037$), smoking (HR 1.86, 95%CI [1.35,2.54], $p=0.0001$) and total stent length (HR 1.01, 95%CI [1.00,1.02], $p=0.0008$) among others were associated with an increase rate of definite/probable stent thrombosis at 5 years. Table 6. Conversely, DAPT in patients randomized to C-SES (HR 0.37, 95%CI [0.22,0.60], $p<0.0001$) was associated with less stent thrombosis events.

DISCUSSION

The main findings in this post-hoc analysis of the PROTECT study are: 1. Patients with diabetes mellitus have an increased risk of stent thrombosis after adjusting for baseline, procedural and lesion characteristics; 2. Diabetics have also higher rates of death, MI, TVF and TLF compared to their counterparts; 3. Insulin dependent DM showed the highest rates of death, MI, TVF and TLF compared to non-insulin dependent diabetes and non diabetes patients.

The trial (PROTECT trial) and stent thrombosis

The PROTECT trial has been the largest ever contemporary trial powered to explore differences in stent thrombosis using drug-eluting stents. This study included a “nearly” all comers population. Patient with diabetes mellitus were 27.7%, which is higher than that enrolled in other all-comer trials (LEADERS and RESOLUTE trials).^{9,10} In the PROTECT study also a higher percentage of patients with acute myocardial infarction, compared with LEADERS trial, were included. Although the number of

Table 3. Medication use

Drug	Diabetes (N=2411)	Non Diabetes (N=6298)	P-value
Procedure Medication			
GP IIb/IIIa	20.9 (503/2409)	17.1 (1076/6298)	<0.001
Heparin or LMWH	95.4 (2298/2409)	96.0 (6049/6298)	0.185
LMWH	5.8 (139/2409)	4.9 (311/6298)	0.117
Bivalirudin or other direct thrombin inhibitor	4.3 (104/2409)	3.9 (245/6298)	0.360
Aspirin	95.8 (2308/2409)	97.0 (6110/6298)	0.006
Clopidogrel	95.5 (2301/2409)	97.3 (6125/6298)	<0.001
Ticlopidine	0.6 (14/2409)	0.3 (16/6298)	0.025
Other anti-platelet/anti-thrombin drug	7.1 (172/2409)	5.2 (326/6298)	<0.001
At Discharge			
Aspirin	97.9 (2359/2409)	97.6 (6147/6297)	0.424
Clopidogrel	98.0 (2362/2409)	98.3 (6188/6297)	0.472
Ticlopidine	0.3 (7/2409)	0.2 (12/6297)	0.440
Other anti-platelet/anti-thrombin drug	4.5 (109/2409)	3.0 (186/6297)	<0.001
Aspirin and (Clopidogrel or Ticlopidine)	96.5 (2324/2409)	96.4 (6070/6297)	0.898
Aspirin and (Clop, Ticl or other AP/AT)	96.6 (2326/2409)	96.5 (6076/6297)	0.948
At 30 Days			
Aspirin	97.7 (2332/2386)	97.5 (6114/6268)	0.638
Clopidogrel	98.1 (2342/2387)	98.3 (6162/6269)	0.583
Aspirin and (Clopidogrel or Ticlopidine)	96.6 (2304/2386)	96.3 (6037/6268)	0.607
Aspirin and (Clop, Ticl or other AP/AT)	96.6 (2306/2386)	96.4 (6044/6268)	0.648
At 180 Day			
Aspirin	97.8 (2304/2357)	97.1 (6043/6224)	0.102
Clopidogrel	97.0 (2289/2360)	96.9 (6036/6226)	0.944
Aspirin and (Clopidogrel or Ticlopidine)	95.6 (2253/2357)	94.8 (5898/6224)	0.121
Aspirin and (Clop, Ticl or other AP/AT)	95.7 (2256/2357)	94.9 (5905/6224)	0.116
At 360 Day			
Aspirin	96.6 (2245/2324)	96.6 (5975/6184)	0.946
Clopidogrel	90.0 (2094/2327)	89.9 (5562/6188)	0.904
Aspirin and (Clopidogrel or Ticlopidine)	87.8 (2040/2323)	87.4 (5402/6184)	0.581
Aspirin and (Clop, Ticl or other AP/AT)	88.1 (2046/2323)	87.6 (5417/6184)	0.578
At 1800 Day			
Aspirin	89.4 (1776/1987)	90.6 (5134/5667)	0.123
Clopidogrel	39.9 (793/1988)	25.6 (1448/5667)	<0.001
Aspirin and (Clopidogrel or Ticlopidine)	33.9 (673/1987)	20.7 (1173/5666)	<0.001
Aspirin and (Clop, Ticl or other AP/AT)	35.6 (707/1987)	22.7 (1286/5666)	<0.001
Average Duration (days)			
Aspirin	1528.0±517.3	1604.7±454.0	< 0.001
Anti-Platelet (Clopidogrel or Ticlopidin)	925.9±637.2	767.1±581.5	< 0.001

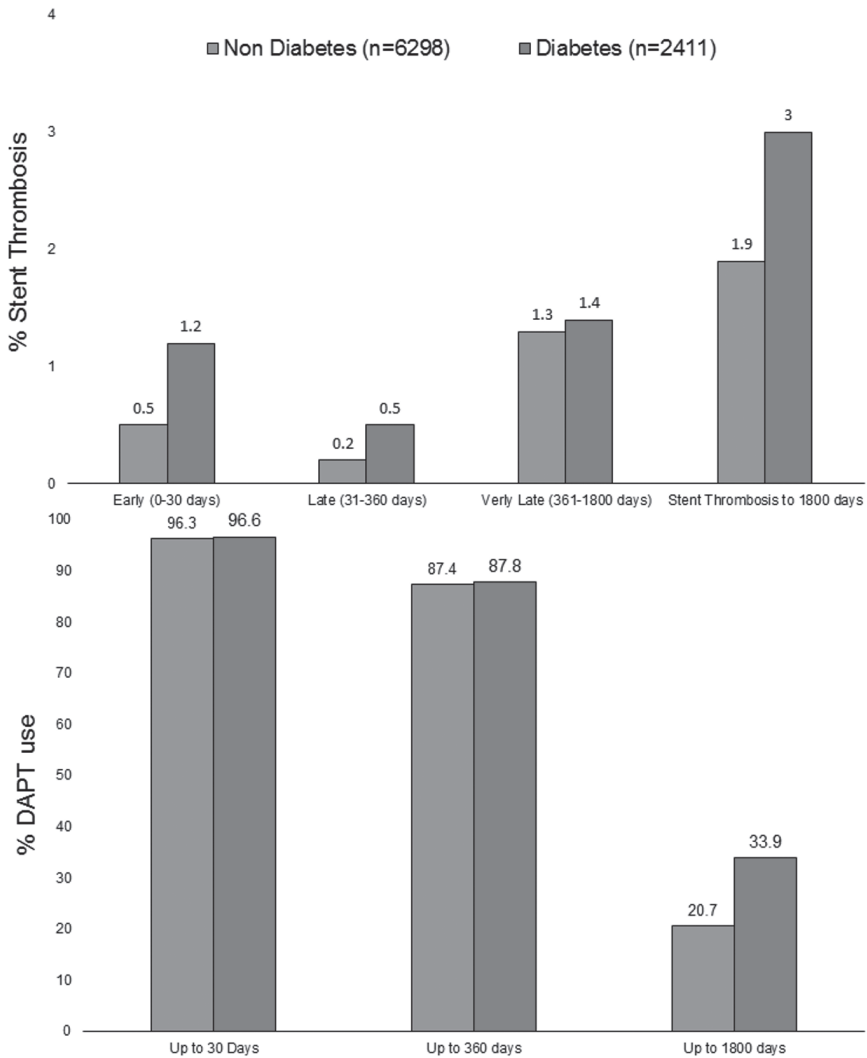


Figure 1. Incidence of stent thrombosis (ST) and dual antiplatelet therapy (DAPT). At the top, the incidence of stent thrombosis at different time points (at all time points for the comparison diabetes vs. non diabetes, there is a significant p value <0.05, except for the period between 360 and 1800 days). At the bottom, the DAPT therapy which was statically significant less used for non diabetes patients until 1800 days.

Table 4. Stent Thrombosis According to Academic Research Consortium Definition

Complications	Diabetes (N=2411)	Non Diabetes (N=6298)	P-value
Stent Thrombosis to 1800 Days			
ARC Definite ST	1.7 (40/2300)	1.4 (83/6068)	0.222
ARC Definite + Probable ST	3.0 (70/2300)	1.9 (118/6068)	0.004
ARC Definite + Probable + Possible ST	7.7 (178/2300)	3.6 (218/6068)	<0.001
Acute (0 to 1 Days)			
ARC Definite ST	0.1 (3/2300)	0.1 (4/6068)	0.402
ARC Definite + Probable ST	0.1 (3/2300)	0.1 (6/6068)	0.713
ARC Definite + Probable + Possible ST	0.1 (3/2300)	0.1 (6/6068)	0.713
Sub-Acute (2 to 30 Days)			
ARC Definite ST	0.6 (13/2300)	0.2 (14/6068)	0.028
ARC Definite + Probable ST	1.1 (25/2300)	0.4 (23/6068)	<0.001
ARC Definite + Probable + Possible ST	1.1 (25/2300)	0.4 (23/6068)	<0.001
Early (0 to 30 Days)			
ARC Definite ST	0.7 (16/2300)	0.3 (18/6068)	0.019
ARC Definite + Probable ST	1.2 (28/2300)	0.5 (29/6068)	<0.001
ARC Definite + Probable + Possible ST	1.2 (28/2300)	0.5 (29/6068)	<0.001
Late (31 to 360 Days)			
ARC Definite ST	0.3 (6/2300)	0.1 (6/6068)	0.103
ARC Definite + Probable ST	0.5 (11/2300)	0.2 (12/6068)	0.036
ARC Definite + Probable + Possible ST	1.4 (33/2300)	0.5 (30/6068)	<0.001
Very Late (361 to 1800 days)			
ARC Definite ST	0.8 (19/2300)	1.0 (59/6068)	0.611
ARC Definite + Probable ST	1.4 (32/2300)	1.3 (77/6068)	0.666
ARC Definite + Probable + Possible ST	5.2 (119/2300)	2.6 (160/6068)	<0.001

Table 5. Cumulative events rate at 5-year follow-up

	Diabetes (N=2411)	Non Diabetes (N=6298 Patients)	P-value
TLF ²	16.4 (377/2300)	10.5 (638/6068)	<0.001
TVF ³	20.4 (470/2300)	13.6 (824/6068)	<0.001
MACE ⁴	21.9 (503/2300)	14.0 (850/6068)	<0.001
MACCE ⁵	23.7 (546/2300)	15.5 (942/6068)	<0.001
Death	12.4 (285/2300)	5.3 (324/6068)	<0.001
Cardiac Death	7.3 (168/2300)	2.6 (155/6068)	<0.001
Non Cardiac Death	5.1 (117/2300)	2.8 (169/6068)	<0.001
Vascular Death	1.0 (22/2300)	0.5 (29/6068)	0.017
Non Cardiovascular Death	4.1 (95/2300)	2.3 (140/6068)	<0.001
All MI ⁶ (Extended historical definition)	6.5 (149/2300)	5.5 (336/6068)	0.104
Q Wave	2.2 (51/2300)	1.5 (89/6068)	0.022
TV MI	5.5 (127/2300)	4.6 (277/6068)	0.076
Q Wave	1.8 (42/2300)	1.1 (67/6068)	0.013
Non TV MI	1.0 (23/2300)	1.0 (63/6068)	1.000
Q Wave	0.4 (9/2300)	0.4 (23/6068)	1.000

	Diabetes (N=2411)	Non Diabetes (N=6298 Patients)	P-value
Large MI	2.9 (67/2300)	2.2 (135/6068)	0.079
Q Wave	2.2 (50/2300)	1.4 (87/6068)	0.020
All MI ⁶ (ARC Definition)	18.0 (413/2300)	15.9 (967/6068)	0.027
Q Wave	2.0 (47/2300)	1.4 (85/6068)	0.039
Sudden Death	0.1 (2/2300)	0.1 (7/6068)	1.000
Target Vessel MI ⁷	16.7 (384/2300)	14.8 (897/6068)	0.032
Q Wave	1.7 (39/2300)	1.1 (64/6068)	0.020
Sudden Death	0.1 (2/2300)	0.1 (6/6068)	1.000
Non TV MI	1.6 (36/2300)	1.4 (85/6068)	0.608
Q Wave	0.3 (8/2300)	0.4 (22/6068)	1.000
Sudden Death	0.0 (0/2300)	0.0 (1/6068)	1.000
Large MI ⁸	3.1 (71/2300)	2.3 (139/6068)	0.042
Q Wave	2.0 (47/2300)	1.3 (81/6068)	0.022
Sudden Death	0.1 (2/2300)	0.1 (7/6068)	1.000
All Revascularizations ⁹	20.5 (472/2300)	16.2 (985/6068)	<0.001
Emergent CABG	0.7 (15/2300)	0.4 (22/6068)	0.095
TLR	7.7 (177/2300)	5.2 (318/6068)	<0.001
Clinically Driven TLR	7.3 (167/2300)	5.0 (306/6068)	<0.001
CABG	1.5 (35/2300)	0.7 (45/6068)	0.002
RePCI	6.0 (139/2300)	4.4 (270/6068)	0.003
Non Clinically Driven TLR	0.5 (12/2300)	0.2 (14/6068)	0.045
CABG	0.0 (1/2300)	0.0 (0/6068)	0.275
RePCI	0.5 (11/2300)	0.2 (14/6068)	0.073
TVR	12.9 (296/2300)	9.2 (556/6068)	<0.001
Clinically Driven TVR	12.3 (282/2300)	8.8 (536/6068)	<0.001
CABG	2.3 (54/2300)	1.3 (77/6068)	<0.001
RePCI	10.4 (240/2300)	7.8 (474/6068)	<0.001
Non Clinically Driven TVR	0.9 (20/2300)	0.6 (34/6068)	0.126
CABG	0.1 (3/2300)	0.1 (6/6068)	0.713
RePCI	0.7 (17/2300)	0.5 (28/6068)	0.132
Non-TV Revascularization	12.0 (277/2300)	10.0 (609/6068)	0.009
CABG	1.8 (42/2300)	1.4 (83/6068)	0.130
RePCI	10.4 (240/2300)	8.9 (543/6068)	0.039
Death/MI/Revascularization	32.3 (742/2300)	23.1 (1400/6068)	<0.001
Hemorrhagic Stroke on Clopidogrel	0.5 (11/2300)	0.3 (17/6068)	0.201
Bleeding (GUSTO)	6.4 (148/2300)	5.7 (346/6068)	0.212
Bleeding (TIMI)	6.3 (145/2300)	5.6 (339/6068)	0.208
Bleeding (CURE)	5.4 (125/2300)	4.3 (258/6068)	0.022

¹ All composite endpoints containing MI are based upon extended historical definition. ² TLF= cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. ³ TVF= cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target vessel revascularization (TVR) by percutaneous or surgical methods. ⁴ MACE= Major Adverse Cardiac Events defined as death, MI, emergent cardiac bypass surgery, or clinically driven target lesion revascularization (repeat PTCA or CABG). ⁵ MACCE= Major Adverse Cardiac and Cerebral Events defined as death, MI, emergent cardiac bypass surgery, or clinically driven target lesion revascularization (repeat PTCA or CABG) and stroke. ⁶ MI= Myocardial Infarction (Target Vessel and Non-target Vessel). ⁷ TV MI= MI not clearly attributable to a non target vessel. Non TV MI = MI clearly attributable to a non target vessel. ⁸ Large MI= Myocardial Infarction with ST elevation ACS, or discharged with a new Q-waves on the ECG or a CPK >5 ULN. ⁹ TLR= Target Lesion Revascularization Per Site Reported, TVR= Target Vessel Revascularization Per Site Reported.

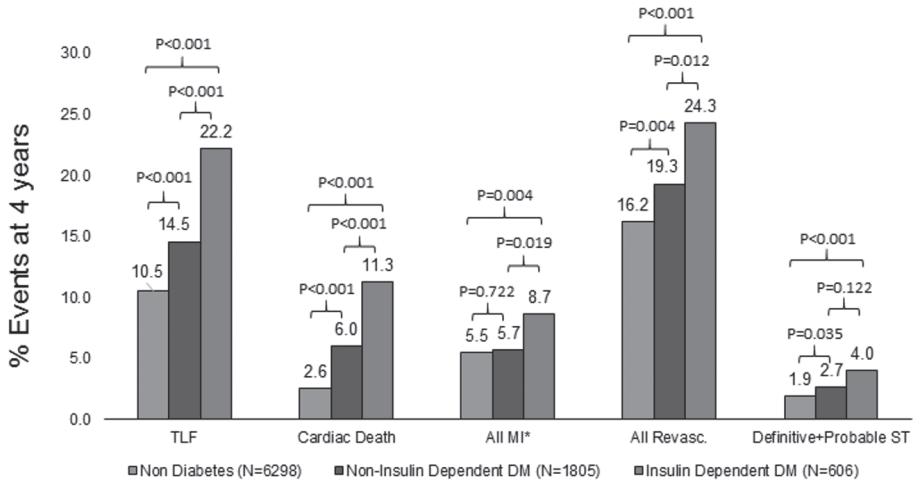


Figure 2. Clinical outcomes up to 5 years by diabetes status.

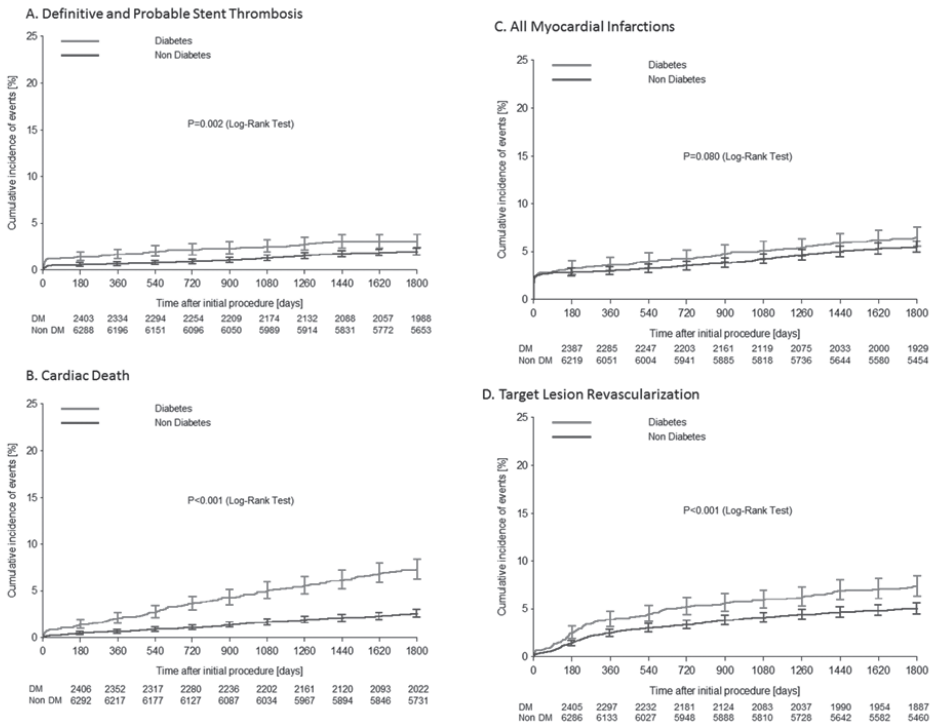


Figure 3. Kaplan-Meier curves showing stent thrombosis (A), cardiac death (B), All myocardial infarctions (C) and all revascularizations (D)

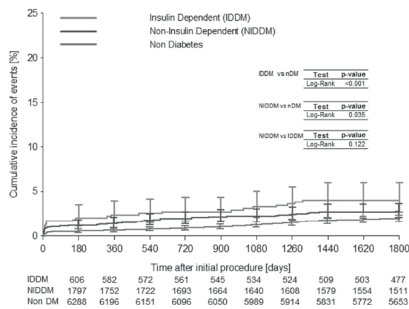


Figure 4. Kaplan-Meier curves showing stent thrombosis (definite and probable) rates in diabetics (by insulin status) and non diabetics

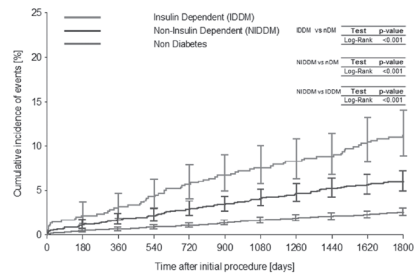


Figure 5. Kaplan-Meier curves showing cardiac death rate in diabetics (by insulin status) and non diabetics

Table 6. Predictors of definite/probable stent thrombosis at 5 years

Covariates	HR (95% CI)	P value
DAPT in patients randomized to E-ZES	1.12 [0.60;2.08]	0.7238
DAPT in patients randomized to C-SES	0.37 [0.22;0.60]	<.0001
At least 1 stent <=2.75 mm in diameter	1.86 [1.36;2.55]	0.0001
Smoked cigarette within 90 days	1.86 [1.35;2.54]	0.0001
Total stent length per patient (mm)	1.01 [1.00;1.02]	0.0008
Diabetes Dummy: IDDM vs rest	1.96 [1.24;3.10]	0.0037
At least 1 lesion with thrombus	1.60 [1.07;2.40]	0.0213
Serum Creatinine ($\mu\text{mol/L}$)	1.00 [1.00;1.01]	0.0308
Prior MI	1.42 [1.03;1.95]	0.0337
Age ≥ 75	1.49 [1.00;2.22]	0.0497
Prior Stroke	1.67 [0.88;3.18]	0.1153

lesions per patient was comparable in the 3 studies, total stent length per lesion was longer in the PROTECT trial than in the other 2 all-comer trials. Thus, we could claim that the PROTECT population represents our current clinical practice. This is one of the reasons why the overall incidence of stent thrombosis is not much different than the observed in the other 2 all-comer trials.

In the PROTECT study, a higher rate of stent thrombosis was observed in the diabetic population compared to their counterparts. The reasons for these differences could partly be

attributed to the fact that known predictors of stent thrombosis (more calcified lesions and longer stented regions) were present in the diabetes group, despite the higher use of DAPT in diabetics at nearly all time points. After adjustment for all the significant univariate variables, insulin dependent diabetes mellitus was associated with an increased risk of stent thrombosis in this report. It could be, therefore, speculated that prolonged DAPT in diabetic patients (especially insulin dependent DM) may be desirable to prevent stent thrombosis. Supportive evidence for

prolonged DAPT comes from the DAPT study in which dual antiplatelet therapy beyond 1 year was associated with reduction in stent thrombosis.¹¹

The disease (diabetes mellitus) and stent thrombosis

Patients with diabetes mellitus treated with percutaneous coronary interventions have a higher likelihood to experience stent thrombosis (>30d)¹². Diabetic patients commonly present a prothrombotic state (increased plasminogen activator inhibitor-1, factor VII and XII, fibrinogen and reduced tissue plasminogen activator levels). Further, intense platelet reactivity in diabetic patients has been associated with an increased risk of major coronary events.¹³ The two main reasons for platelet hyperreactivity are the presence insulin resistance and hyperglycaemia.¹⁴ Specifically, hyperglycaemia alters platelet calcium homeostasis, leading to cytoskeleton abnormalities and increased secretion of pro-aggregant factors. Moreover, hyperglycaemia-induced up-regulation of glycoproteins (Ib and IIb/IIIa), P-selectin and enhanced P2Y₁₂ signalling which are known contributors of atherothrombotic events. Having said this, currently, only aspirin daily is recommended as a secondary prevention in diabetic patients. It is only in patients that were treated with PCI for ACS that prasugrel and ticagrelor are recommended for 1 year.¹⁵

Diabetics with nephropathy who received clopidogrel experienced significantly increased cardiovascular and overall mortality compared with their counterparts.¹⁶ In this report, the stages of chronic kidney disease \geq 2 were in more than 50% of the diabetic population. Whether this contributed to the increased

rate of outcomes in diabetics was in this report not explored.

The antiplatelet medication (clopidogrel vs. others) and stent thrombosis

At 5 years, in the diabetes group roughly 35% of patients are taking clopidogrel (compared to 22.5% in the non diabetic group, $p < 0.001$), which means either that the diabetic patients have got more CV events over the follow-up time that required restarting of clopidogrel or that treating physicians considered this population at a higher risk of events. There is, however, no evidence to support this latter attitude, so this is a gap in knowledge. In the multivariate analysis we have introduced DAPT as a time dependent covariate, which after adjustment for other variables, showed that the continue use of DAPT was associated with a HR 0.51. This means that if the diabetic group was not taking for longer time DAPT, the ST event rate would have been even higher.

Nevertheless, the increased rate of stent thrombosis could be also then partly attributed to the fact that a less potent drug (clopidogrel) has been mostly given and to the fact that clopidogrel-induced antiplatelet effects have a wide interindividual variability.¹⁷ Prasugrel was superior to clopidogrel in the subgroup diabetes mellitus analysis of TRITON-TIMI 38 study. The stent thrombosis rate in clopidogrel group was 3.6% vs. 2.0 in the prasugrel group (HR 0.52, 95%CI: 0.33–0.84).¹⁸ Also in the diabetes analysis of the PLATO study, ticagrelor showed superiority to clopidogrel, stent thrombosis rate was 1.3% vs. 2.0% (HR: 0.62, 95% CI: 0.39–1.00), particularly in patient with HbA_{1c} \geq 6.0%.¹⁹

In diabetics patients, there is no a head-to-head comparison in terms of effectiveness to

reduce stent thrombosis between clopidogrel, ticagrelor and prasugrel. There is, however, an adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor in a broader population.²⁰ These authors showed that there was a 36% reduction of stent thrombosis in patients treated with prasugrel compared to ticagrelor (OR= 0.64 [0.43–0.93], $p= 0.020$). One report considered that this might have attributed to the fact that a considerably number of patients received double doses of clopidogrel before PCI in the clopidogrel arm of the PLATO study;²¹ double-dose of clopidogrel has been proved to reduce stent thrombosis (HR 0.68; 95% CI, 0.55 to 0.85; $P=0.001$).²² This might have avoided observing a greater difference between clopidogrel and ticagrelor. In turn, in the stent thrombosis PLATO study dedicated report, ticagrelor reduced stent thrombosis events across a broad list of subgroups, including diabetes mellitus.²³

The time course and stent thrombosis

At 5 years, the primary endpoint, definite or probable stent thrombosis, was higher among diabetics than non diabetics. This difference is due to an increased rate of definite or probable stent thrombosis in diabetics over the first 30 days and between 31 and 360 days, because thereafter (between 1 and 5 years), there was no a statistically significant difference between diabetics and non diabetics. In this regard, there are in the literature contrasting reports, on one hand, in the HORIZONS-AMI study, insulin-dependent DM was a independent predictor of ST within 30 days, but not in period between 31 and 360 days, and again independent predictor of ST between 1-2 years.²⁴ While in the Dutch stent thrombosis registry, diabetes mellitus

was associated with late (>30d) but not with early stent thrombosis.¹²

Study limitations

There are a number of limitations worth considering; firstly, C-SES is no longer available. Secondly, due to the nature of this predefined post hoc analysis, the baseline characteristics of the two compared groups are rather different. Therefore, we have performed a multivariable analysis to adjust for potential confounders.

Patients were not randomized to different durations of DAPT according to the diabetic status. The differences of DAPT duration (longer for diabetic patients) might have masked the real incidence of clinical adverse outcomes in such population.

CONCLUSIONS

In this large trial, so far the only powered for stent thrombosis, 5-year stent thrombosis rates and cardiac death / large non-fatal MI rates were much higher among diabetics than non diabetics. These events appeared to be especially higher in patients with insulin-dependent diabetes. This report may indicate the need for customizing antiplatelet treatment in the diabetic population.

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PART 3

RISK STRATIFICATION IN COMPLEX CORONARY ARTERY DISEASE

Chapter 3.1

Risk Stratification in 3-Vessel Coronary Artery Disease: Applying the SYNTAX score II in the Heart Team Discussion of the SYNTAX II trial

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Risk Stratification in 3-Vessel Coronary Artery Disease: Applying the SYNTAX Score II in the Heart Team Discussion of the SYNTAX II Trial

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Background: Heart Team (HT) and the SYNTAX Score II (SSII) have been integrated to the contemporary guidelines with the aim to provide a multidisciplinary decision-making process between coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI). **Aims:** To prospectively assess the agreement between the HT decision and the SSII recommendation regarding the revascularization strategy in patients with 3-vessel coronary artery disease (CAD) of the SYNTAX II trial. **Methods:** The SSII predicts the 4-year mortality of an individual patient both after PCI and after CABG. Patients were treated by PCI when the SSII predicted a mortality risk favoring PCI or when risk predictions were equipoise between PCI and CABG. However, the HT could overrule the SSII and recommend either CABG or PCI. **Results:** A total of 202 patients have been screened and 24 did not fulfill inclusion criteria. The median age was 67.0 (IQR 59.0–73.3), and 167 (82.7%) were male. The HT endorsed SSII treatment recommendation, for CABG or PCI, in 152 patients (85.4%). Three patients had preference for PCI, irrespective of the HT decision. The main reason for the HT to overrule the SSII and recommend CABG was the prospect of a more complete revascularization (21 of 25 patients). Patients recommended for CABG by the HT had significantly higher anatomical SYNTAX score ($P = 0.03$) and higher predicted mortality risk for PCI ($P = 0.04$) when compared with patients that were enrolled in the trial. **Conclusion:** The SYNTAX score II showed to be a suitable tool for guiding treatment decisions of patients with 3-vessel coronary artery disease being endorsed by the HT in the vast

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Additional Supporting Information may be found in the online version of this article.

Conflict of interest: Nothing to report.

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INTRODUCTION

In a non-emergency setting, an accurate risk estimation of patients with multivessel coronary artery disease (CAD) is fundamental to determine whether the patient should be treated either by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) [1]. This decision has to balance risk–benefit ratios of these therapeutic strategies, weighting the risks of death, myocardial infarction and stroke against improvements in health-related quality of life, and the need for repeat revascularization. Currently, for patients with complex CAD, international guidelines recommend a multidisciplinary approach referred to as the Heart Team (HT) [2–4]. The HT has become an integral part of the contemporary practice of cardiovascular medicine with the aim to provide an evidence-based, unbiased, multidisciplinary, decision-making process.

Aiming to help the HT to decide between CABG and PCI in patients with complex CAD, the SYNTAX Score II (SSII) combines anatomic and clinical factors and predicts long-term mortality. The SSII was developed in the landmark, all-comers, randomized SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Trial [5,6], being externally applied in more than 10,000 patients and implemented in the most recent international guidelines [3,7–10].

The ongoing single-arm SYNTAX II Trial (NCT02015832) uses the SSII to prospectively screen the patients who can potentially be revascularized by PCI with an equiproised prognosis of survival at 4-years when compared to CABG.

However, the SSII does not contemplate all variables that may influence the final choice of revascularization strategy such as frailty, bleeding risk, or the preference of the patient. The aim of the present interim report is to assess the applicability of the SSII recommendations in conjunction with the HT decision-making process regarding the revascularization strategy in patients with 3-vessel CAD screened for the SYNTAX II trial, a concept that has not yet been tested previously.

METHODS

The ongoing SYNTAX II Trial is a multicenter, all-comers, open-label, single-arm trial that will recruit 450 patients with 3-vessel CAD in ~25 European interventional cardiology centers. All patients will be

selected and treated following the SYNTAX II strategy described as follows: All patients will be treated with the everolimus-eluting stent with biodegradable abluminal coating (SYNERGY, Boston Scientific); the lesions will be treated only after interrogation of ischemia with the use of pressure wire; intravascular ultrasound (IVUS) guidance to optimize drug-eluting stent deployment, and the treatment of (chronic) total occlusion lesions with contemporary techniques, and will be compared with the PCI outcome of the original SYNTAX trial. The primary endpoint is the composite of all-cause death; cerebrovascular event (stroke); documented myocardial infarction or all-cause revascularization at 1-year follow-up. Secondary endpoints includes: (1) composite of all-cause death, cerebrovascular event (stroke), documented myocardial infarction (MI) at 1-year follow-up compared to the PCI arm of SYNTAX I; (safety endpoint); (2) composite of cardiovascular death, documented target-vessel MI and repeat target lesion revascularization at 1-year follow-up compared to the PCI arm of SYNTAX I; (device oriented clinical endpoint); (3) rates of individual components of Major Adverse Cardiac and cerebrovascular event (MACCE) (all-cause death, cerebrovascular event (stroke), documented MI, and repeat revascularization) at 1 year; (4) composite of MACCE rate and its individual components at 2–5 years follow-up (patient reported); (5) MI—according to Universal MI definition 2012 at all timepoints; (6) stent thrombosis—according to ARC definitions at all timepoints; and (7) retrospective validation of the residual SYNTAX score.

Patients were excluded, if: (1) Under the age of 21 years; (2) Known pregnancy at time of enrolment, (3) Female of childbearing potential, and last menstruation within the last 12 months, who are not taking adequate contraceptives; (4) Female who is breastfeeding at time of enrolment; (5) Prior PCI or CABG; (6) Ongoing acute MI and enzymes (CKMB) more than 2× upper limit of normal; (7) Concomitant cardiac valve disease requiring surgical therapy, reconstruction, or replacement; (8) Single or two-vessel disease at time of HT consensus; (9) Participation or planned participation in another cardiovascular clinical study before 1-year follow-up is completed; (10) Mental condition, psychiatric or organ cerebral disease, rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language

barrier such that the patient is unable to give informed consent and potential for non-compliance toward the requirement in the study protocol.

The SYNTAX Score II and the Heart Team Decision-Making Process

The SSII has been described in detail previously [8]. Briefly, SSII score uses two anatomical (anatomical SYNTAX score and presence of unprotected left main CAD) and six clinical variables (age, creatinine clearance, left ventricular ejection fraction, gender, chronic obstructive pulmonary disease, and peripheral vascular disease) to predict 4-year mortality after revascularization with CABG or PCI. The Cockcroft–Gault formula was used to estimate the creatinine clearance [11]. The presence of COPD was determined according to the EuroSCORE definition, as the long-term use of bronchodilators or steroids for lung disease [12]. PVD was defined as one or more of the following: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease or/and previous or planned intervention on the abdominal aorta, limb arteries, or carotids [13]. To mimic conventional clinical practice, investigator reported anatomical SYNTAX Scores were used in the analysis [14].

Using the actual baseline clinical and angiographic data from every screened patient in the trial, SSII was calculated for each patient using an electronic calculator available only to the investigators. In the assessment of a single, individual patient, the SSII generates different scores and distinct predicted mortalities according to the potentially applied mode of revascularization, percutaneous or surgical (Fig. 1). The SSII recommends CABG if the difference in the predicted mortality risk was in favor of CABG with 95% confidence. The SSII recommends PCI if the difference in mortality risk predictions was in favor of PCI with 95% confidence. Conversely, the SSII recommends PCI or CABG if mortality risk predictions are within the 95% confidence interval of the difference in mortality risk predictions.

Aiming to quantify and compare the predicted mortality risk between CABG and PCI, we calculated the delta predicted 4-year mortality and the delta SSII as follows:

$$\begin{aligned} \text{Delta SYNTAX score II} &= \text{SYNTAX score II PCI} \\ &- \text{SYNTAX score II CABG} \\ \text{Delta Predicted 4-year mortality (\%)} \\ &= \text{Predicted 4-year mortality PCI (\%)} \\ &- \text{Predicted 4-year mortality CABG (\%)} \end{aligned}$$

In the SYNTAX II trial, patients can be enrolled only when the SSII shows an equiposed long-term

mortality risk prediction between CABG and PCI or favors PCI. Having the SSII recommendation, each patient is assessed by the HT as to whether “equivalent anatomical revascularization” could be potentially achieved between CABG and PCI. However, the HT can overrule the SSII recommendation and preclude the enrollment in the trial (Fig. 1).

Statistical Analysis

Categorical variables are presented as numbers and percentages and are compared with the Chi-square test. Continuous variables are expressed as mean \pm SD or median with interquartile range (IQR), and are compared using the Student’s *t*-test or Wilcoxon rank-sum test based on their distributions. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corporation; Armonk, NY).

RESULTS

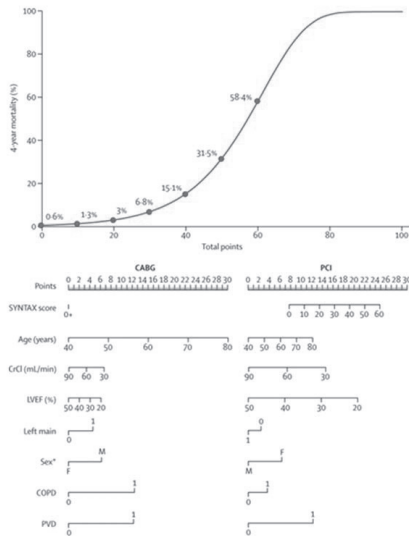
Table I depicts the SSII baseline demographics in the SYNTAX II trial. From February 2014 to November 2014, 202 patients were screened in the SYNTAX II trial. Overall the median age was 67 (interquartile range [IQR] 59.0–73.3) years, 82.7% were male, 7.9% had peripheral vascular disease, and 9.9% chronic obstructive pulmonary disease. Twenty-four patients (11.9%) had exclusion criteria as listed in the Fig. 2 and were not enrolled in the study.

The SSII and the Heart Team Discussion

Figure 2 shows the current screening process of the SYNTAX II trial. One hundred and seventy-eight patients met the inclusion criteria of the SYNTAX II trial and went through the HT assessment. The HT endorsed the SSII recommendations in 152 patients (85.4%). The HT decided for CABG in 25 patients (14.1%) and these patients could not be enrolled in the trial. A HT consensus could not be achieved in one subject (0.5%) and the patient decided for PCI. In 43 patients, the SSII recommendation was CABG, the HT agreed, but 2 subjects denied CABG and ultimately underwent PCI. However, as the SYNTAX II trial aims to recruit patients with 3-vessel disease based on patient safety, the inclusion of these two patients was retrospectively considered protocol violation. One patient was considered as adequate for PCI by the SSII, but allocated to CABG by the HT, but the patient denied surgery and was ultimately enrolled in the trial. There was a consensus to perform PCI in 109 (80.7%) patients.

The reasons for the HT to choose CABG were: CABG would provide a more complete revascularization

SYNTAX Score II normogram



SYNTAX Score II questions and calculator outputs:

(A)

Anatomical SYNTAX (points): 48

Age (years): 74

CrCl (ml/min): 49

LVEF (%): 50

Left Main: No

Sex: Female

COPD: No

PVD: No

SSII PCI (points): 51

SSII CABG (points): 28

4-year predicted mortality PCI (%): 33

4-year predicted mortality CABG (%): 6

Treatment recommendation: CABG

(B)

Anatomical SYNTAX (points): 16

Age (years): 75

CrCl (ml/min): 62

LVEF (%): 70

Left Main: No

Sex: Male

COPD: Yes

PVD: Yes

SSII PCI (points): 48

SSII CABG (points): 60

4-year predicted mortality P PCI (%): 28

4-year predicted mortality CABG (%): 57

Treatment recommendation: PCI

(C)

Anatomical SYNTAX (points): 20

Age (years): 49

CrCl (ml/min): 99

LVEF (%): 55

Left Main: No

Sex: Male

COPD: No

PVD: No

SSII PCI (points): 19

SSII CABG (points): 12

4-year predicted mortality PCI (%): 3

4-year predicted mortality CABG (%): 2

Treatment recommendation: CABG or PCI

Fig. 1. SYNTAX Score II calculator. In the SYNTAX II trial, the HT uses an online electronic calculator to predict the risk of each patient if they are submitted to coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). After entering the angiographic and clinical characteristics the calculator provides four outputs: SYNTAX score II PCI (points), 4-year predicted mortality if the patient is submitted to PCI; SYNTAX score II CABG (points), and 4-year predicted mortality if the patient is submitted to CABG. The SYNTAX Score II treatment recommendation is based on the difference in

these mortality predictions: CABG (right panel; A), PCI (right panel; B), or CABG or PCI (right panel; C). The HT can overrule the SYNTAX score II calculator but patients with CABG recommended by the SYNTAX score II cannot be enrolled in the SYNTAX II trial. CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; SSII = SYNTAX Score II; MP = mortality prediction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in 21 patients (83.3%); there was association of complex coronary anatomy and diabetes in two patients (8.3%); one patient had poor ventricular function (4.2%), and one followed the advice of his clinical cardiologist (4.2%).

Patients recommended to CABG by the SSII were mostly female, had a significantly higher anatomical complexity, and a higher predicted risk for PCI (delta 4-year predicted mortality = PCI 4-year predicted mortality - CABG 4-year predicted mortality) (8.0% [5.5–13.5]; $P < 0.01$) (Table I).

The comparison between the group of patients that was enrolled in the trial and those who were excluded by the HT is shown in Table I. Patients recommended to CABG had significantly higher anatomical SYN-

TAX score (22, IQR: 18–27 versus 20, IQR: 16–24), delta SYNTAX score II (SYNTAX score II PCI - SYNTAX score II CABG; 2.1 ± 5.2 vs. 1.6 ± 5.2 ; $P = 0.04$) and a higher delta in the predicted mortality favoring CABG in the overruled patients (1.0%, IQR: 0.0–2.8% vs. 0.0, IQR: -1 to 2.0%; $P = 0.04$).

DISCUSSION

The main findings of the present study can be summarized as follows: (i) the SSII risk stratification demonstrated to be an useful decision-making tool for patients with complex coronary artery disease; (ii) the SSII treatment recommendation was endorsed by the

TABLE I. SYNTAX Score II Based Patient Baseline Characteristics

	Total	Enrolled N = 113	Overruled by the Heart Team N = 24	SSII recommended CABG N = 41	Not enrolled for other reasons N = 24	P value (overall)	P value (enrolled and overruled by the Heart Team groups)
Male, %	167 (82.7)	107 (94.7)	23 (95.8)	15 (36.6)	22 (91.7)	<0.01	1.00
Age, years (Q1-3)	67.0 (59-73.3)	67.0 (59.0-71.5)	69.0 (59.0-76.3)	65.0 (53.5-73.5)	70.0 (62.3-73.5)	0.18	0.32
COPD, %	20 (9.9)	15 (13.3)	2 (8.3)	0 (0)	3 (12.5)	0.10	0.74
PVD, %	16 (7.9)	12 (10.6)	2 (8.3)	2 (4.9)	0 (0)	0.29	1.00
Creatinine Cl, ml/min±SD	72.0 (60.0-95.0)	72.6 (60.0-96.0)	88.8 (61.3-101.4)	63.6 (60.0-84.0)	70 (56.0-96.4)	0.16	0.55
LVEF, % ±SD	60.0 (55.0-65.0)	60 (55-65)	60 (51.3-65.0)	60 (50-65)	60 (55-63.8)	0.77	0.77
ULMCA, n (%)	2 (1)	0 (0)	1 (4.2%)	0 (0)	1 (4.2%)	0.09	0.17
SYNTAX score (Q1-3)	22.0 (16.8-26.0)	20 (16-24)	22 (18-27)	26 (17-34)	22 (15-24)	<0.01	0.03
SYNTAX Score II PCI (SD)	32.1 (8.7)	30.6 (8.6)	31.8 (8.4)	37.2 (8.6)	31.0 (7.0)	<0.01	0.91
SYNTAX Score II CABG (SD)	28.0 (10.3)	29.0 (10.9)	29.8 (8.3)	22.4 (8.2)	30.4 (9.0)	<0.01	0.20
Delta SYNTAX Score II	4.2 (7.3)	1.6 (5.2)	2.1 (5.2)	14.8 (4.3)	0.62 (5.4)	<0.01	0.04
[SYNTAX Score II PCI- SYNTAX Score II CABG] (SD)	8.0 (5.0-12.0)	7.0 (4.0-10.0)	7.5 (5.0-12.0)	12.0 (7.0-20.0)	7.0 (5.0-11.8)	<0.01	0.49
Predicted 4-year mortality PCI % (Q1-3)	6.0 (3.0-10.0)	6.0 (4.0-11.5)	7.5 (4.0-11.0)	4.0 (2.0-6.0)	7.0 (5.3-10.8)	<0.01	0.80
Delta Predicted mortality [Predicted 4-year mortality PCI - Predicted 4-year mortality CABG], % (Q1-3)	1.0 (-1.0 to 3.0)	0.0 (-1.0 to 2.0)	1.0 (0.0-2.8)	8.0 (5.5-13.5)	0.0 (-1.0 to 1.8)	<0.01	0.04a

COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; Q1-3 = quartile 1 and 3.

^aThe predicted mortality is a transformation of the SYNTAX score II. SSII on log hazard scale and is closest to normal and a t-test was done to compare.

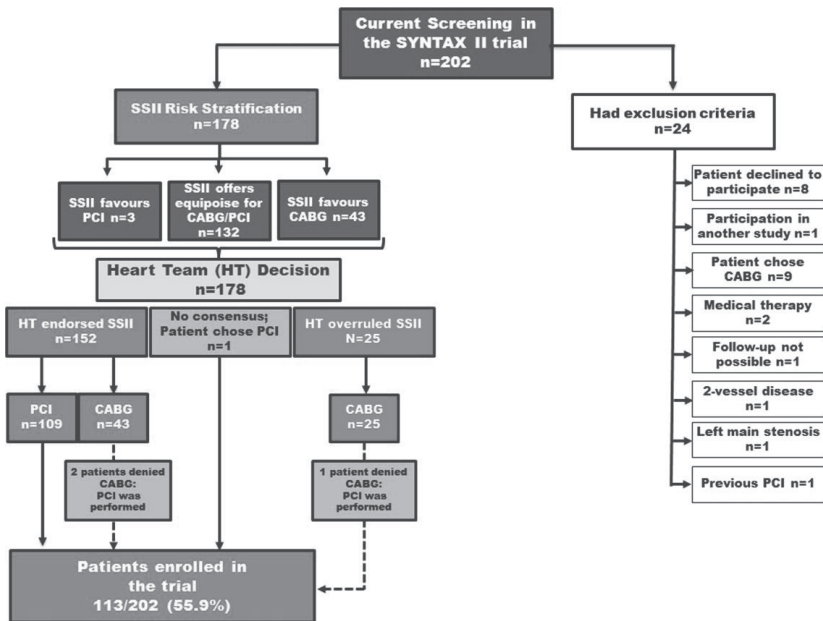


Fig. 2. Current screening of patients with complex coronary artery disease in the SYNTAX II trial. PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; SSII = SYNTAX score II; HT = Heart Team. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

HT discussion in the large majority of the cases; (iii) the main reason for the HT to overrule the SSII was high anatomical complexity that would have preclude more complete revascularization with CABG.

The Heart Team and the SSII

The concept of multidisciplinary teams is not new in medicine and has been practiced in oncology, palliative care, transplant medicine, and geriatric medicine [15,16]. In cardiovascular medicine, multidisciplinary teams are also established for heart failure and congenital heart diseases. Initially, this concept of multidisciplinary “Heart-Team” was extended to coronary artery disease in randomized trials comparing CABG with medical therapy for stable CAD, to select patients eligible for randomization [17,18]. With the advances of PCI techniques, interventional cardiologists and surgeons started to increasingly target the same patients. This new scenario has prompted them to work in close collaboration to ensure the best evidence-based patient selection, assuming clinical equipoise between treatments. The importance of this multidisciplinary approach lies in the

fact that non-compliance to guidelines may result in inappropriate revascularization [4,19].

Our study is the first report of the SSII implementation in the HT decision-making process, for stratification of complex CAD [3]. We showed a high agreement between the SSII treatment recommendation and the HT final decision: only 18.5% of the patients for whom the SSII considered PCI as reasonable revascularization treatment underwent CABG and out of 43 patients recommended to CABG by the SSII only 2 (4.7%) underwent PCI (Fig. 2). These findings highlight the importance of the SSII that provides objective individual risk stratification in the decision making (Fig. 3). Currently, the online calculator of the SSII is available only to the investigators of the SYNTAX II trial. However, it will be available soon for other physicians that may want to use it, as the online tool of the anatomical SYNTAX score (www.syntaxscore.com).

The main reason for the HT to overrule the SSII was a high anatomical complexity only amenable to CABG. The complete revascularization takes into account the operators experience and individual judicious judgment. Indeed, in patients with complex CAD, the completeness

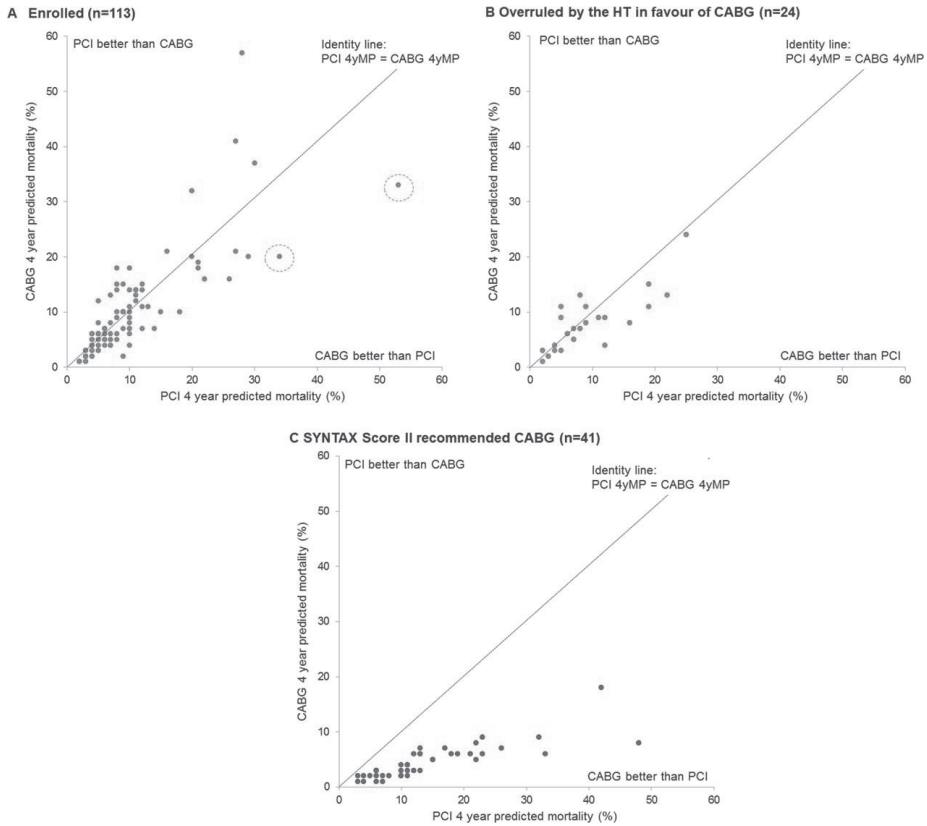


Fig. 3. Scatter plots showing SYNTAX Score II mortality predictions between (A) patients enrolled in the trial; (B) patients in whom the HT overruled SYNTAX Score II treatment recommendation; (C) patients who had SYNTAX Score II treatment recommendation CABG. The dashed circles in (A) represent patient that were recommended to CABG by the SYNTAX

score II but denied surgery. PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; 4yMP = 4-year mortality prediction; HT = Heart Team; SSII = SYNTAX Score II. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of revascularization has proven to reduce late all-cause mortality [20–23]. Specifically, total occlusion may play an important role in this regard. Although, it did not reach the statistical significance margin we could notice a progressive increase in the number of total occlusions in patients recommended to CABG by the Heart-Team or the SSII (Table I).

Patient Information and the Decision Making Process

Another key step in the process of decision-making is adequate patient information. The process of medical

decision-making and patient information is guided by the “four principles”: autonomy, beneficence, non-maleficence, and justice [24]. Therefore, the information provided needs to be unbiased, evidence-based, up-to-date, reliable, accessible, relevant, and consistent with legal requirements [3]. In our series, three patients (4.4%) denied CABG when it was recommended by the HT ($n = 25$) or the SSII ($n = 43$) (Fig. 2). The second condition constituted a protocol violation since patients recommended to CABG by the SSII can be overruled (by the HT or patient will) and treated by PCI, but not enrolled in the SYNTAX II trial. The investigators were notified accordingly on this matter.

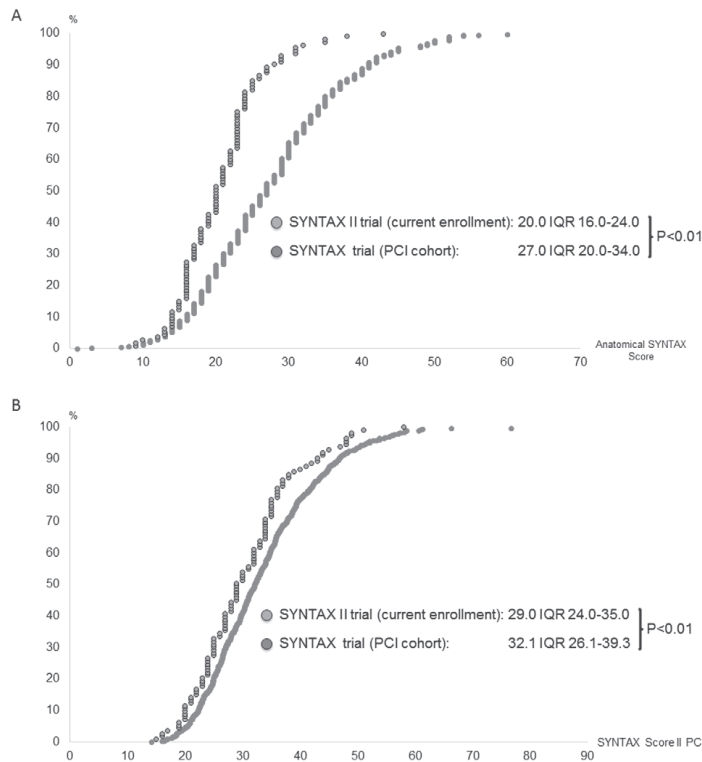


Fig. 4. Distribution and comparison of (A) anatomical SYNTAX Score and (B) SYNTAX score II PCI, between the current enrolment in the SYNTAX II trial and the previous SYNTAX trial (PCI 3-vessel disease cohort) [5]. Patients that have been included in the SYNTAX II trial have lower risk to percutaneous coronary intervention as assessed by the SSII as well as anatomical SYNTAX score. IQR = interquartile range. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

It has been shown that up to 68% of patients are not aware of an alternative revascularization strategy [25] and the SSII represents an advance in this matter as well. Instead of a simplistic description of prognosis according to an anatomical SYNTAX score tertile, the SSII provides an individual estimation of long-term prognosis for each revascularization strategy, helping to better enlighten the patient [26,27].

Innovations of the SYNTAX II Trial

The SYNTAX II trial has been enrolling patients with 3-vessel coronary artery disease in the light of the most recent evidence-based medical practices: (a) establishment of revascularization appropriateness on the grounds of HT discussion using the SYNTAX II

score; (b) ischemia-driven revascularization based on pressure guidewire interrogation; (c) use of a second generation drug-eluting stent (DES) with thin struts and biodegradable matrix; (d) DES deployment guided by intracoronary imaging; and (e) treatment at centers with expertise in chronic total occlusion (CTO) recanalization. As shown in Fig. 4, although the SYNTAX II trial has been enrolling only 3-vessel CAD, the selection of the patient for appropriate PCI based on SSII generates a population with a combined lower anatomical and clinical risk profile than in the original SYNTAX trial. In other words, there exists a 3-vessel patient population—to be carefully identified—that could benefit at long-term from percutaneous revascularization. Beyond the anatomical and clinical selection of the patients, the ischemic driven treatment optimized

by intravascular ultrasound is expected to further improve the patient outcomes. Needless to say that the 3rd generation DES used in this trial will abrogate many of the drawbacks of the first generation.

Limitations

The SSII, as all other risk scores implemented in medical guidelines [3], does not contemplate all individual procedural outcomes such as relief of angina, quality of life, stroke, and potential need for late re-intervention. Therefore, it is important to inform these long-term risks and benefits to the patient. However, the use of long-term all-cause mortality as goal permits a reproducible endpoint not subject to adjudication bias or definitional variation.

CONCLUSION

The SYNTAX score II showed to be a suitable tool for guiding treatment decisions of patients with 3-vessel coronary artery disease being endorsed by the HT in the vast majority of the patients that have been enrolled in the SYNTAX II trial.

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Chapter 3.2

Predictive Performance of SYNTAX Score II in Patients With Left Main and Multivessel Coronary Artery Disease.

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Background: SYNTAX score II (SSII) provides individualized estimates of 4-year mortality after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in order to facilitate decision-making between these revascularization methods. The purpose of the present study was to assess SSII in a real-world multicenter registry with distinct regional and epidemiological characteristics.

Methods and Results: Long-term mortality was analyzed in 3,896 patients undergoing PCI (n=2,190) or CABG (n=1,796) from the Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry cohort-2. SSII discriminated well in both CABG and PCI patient groups (concordance index [c-index], 0.70; 95% CI: 0.68–0.72; and 0.75, 95% CI: 0.72–0.78) surpassing anatomical SYNTAX score (SS; c-index, 0.50; 95% CI: 0.47–0.53; and 0.59, 95% CI: 0.57–0.61). SSII had the best discriminative ability to separate low-, medium- and high-risk tertiles, and calibration plots showed good predictive performance for CABG and PCI groups. Use of anatomical SS as a reference improved the overall reclassification provided by SSII, with a net reclassification index of 0.5 (P<0.01).

Conclusions: SSII has robust prognostic accuracy, both in CABG and in PCI patient groups and, compared with the anatomical SS alone, was more accurate in stratifying patients for late mortality in a real-world complex coronary artery disease Eastern population.

Key Words: Coronary artery bypass grafting; Percutaneous coronary intervention; Risk stratification; SYNTAX score; SYNTAX score II

Percutaneous coronary intervention (PCI), until recently, has been considered a class III indication (ie, potentially harmful) for patients with unprotected left main (ULMCA) and 3-vessel coronary artery disease (CAD).^{1,2} Coronary artery bypass grafting (CABG) has been the standard treatment for these patients with complex CAD for more than 50 years. Over the last decade, PCI has undergone a number of technical and technological advancements and hence has challenged the superiority of CABG.³ Consequently, every ad-

vance in PCI technology has been scrutinized and compared against CABG, generating debate as to whether a patient should be referred to CABG or PCI, with advantages for one or the other depending on context.⁴⁻¹⁰ Therefore, the accurate risk estimation of multivessel CAD remains a fundamental step in the decision-making process.¹¹

Presently, for patients with ULMCA or complex CAD, the prevailing guidelines recommend a multidisciplinary approach referred to as the heart team.^{12,13} These guidelines also advise

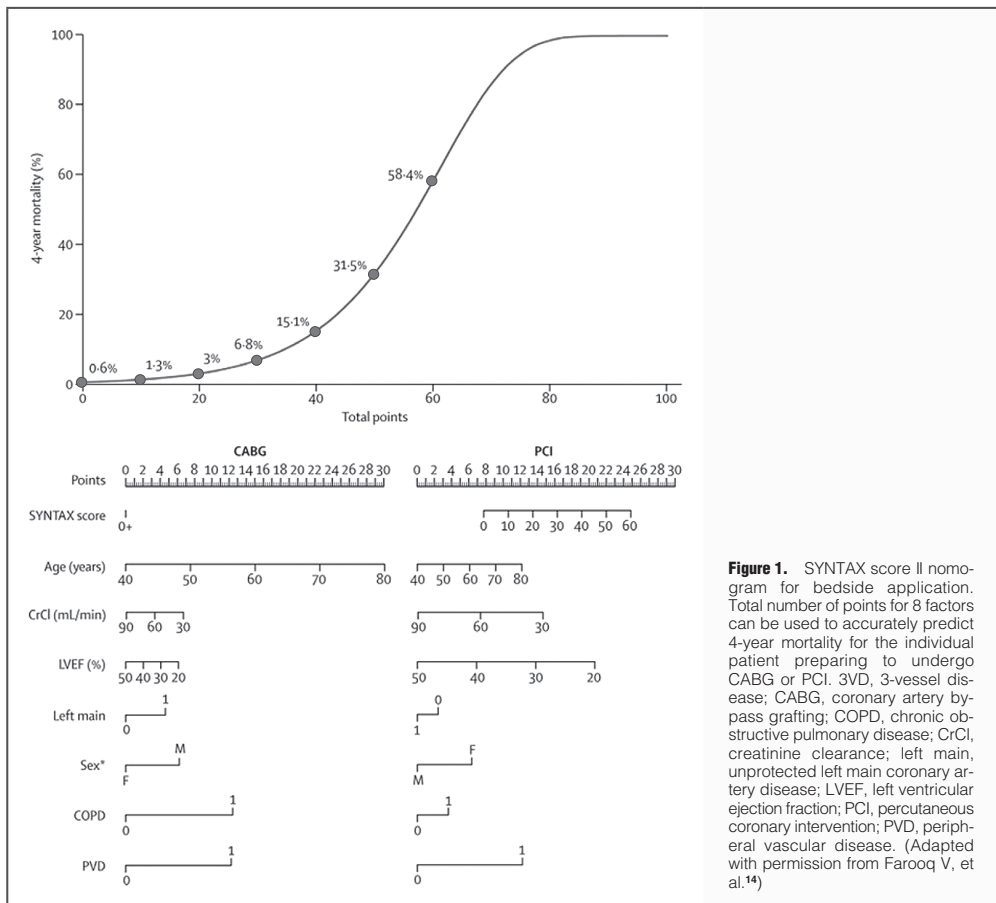


Figure 1. SYNTAX score II nomogram for bedside application. Total number of points for 8 factors can be used to accurately predict 4-year mortality for the individual patient preparing to undergo CABG or PCI. 3VD, 3-vessel disease; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; left main, unprotected left main coronary artery disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease. (Adapted with permission from Farooq V, et al.¹⁴)

the heart team to use synergy between PCI with taxus and cardiac surgery (SYNTAX) score alone or combined with the Society of Thoracic Surgeons (STS) score as a tool to make an objective risk stratification.^{12,13} The SYNTAX score II (SSII) has been recently developed by applying a Cox proportional hazards model to the results of the SYNTAX trial, obtaining a combination of clinical and anatomical predictors.^{9,14} Given that the SSII has been derived from an all-comers randomized trial of PCI vs. CABG, it has the potential to assess individual risk estimation between these revascularization strategies and facilitate multidisciplinary decision-making.

SSII has been shown to provide reliable predictions of 4-year mortality for complex CAD in an external validation of the Drug Eluting stent for Left main coronary Artery disease (DELTA) registry.^{14,15} The DELTA registry consisted of predominantly Western patients with ULMCA disease. In patients with 3-vessel disease and no left main involvement, however, SYNTAX score (SS) would represent more complex downstream coronary anatomical disease. This may be a signal of a more adverse risk profile, in patients who have evidence of

systemic atherosclerosis and therefore are at greater longer-term cardiovascular risk.¹⁶ This score has not been assessed in an Eastern population with complex 3-vessel CAD.

The purpose of the present study was therefore to assess SSII in patients with 3-vessel and/or ULMCA disease in a real-world multicenter registry with distinct regional and epidemiological characteristics.

Methods

Subjects

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry cohort-2 has been previously described in detail.¹⁷ Briefly, this was a physician-initiated non-industry-sponsored multicenter registry enrolling consecutive patients undergoing first coronary revascularization among 26 centers in Japan between January 2005 and December 2007. The relevant ethics committees in all participating centers approved the research protocol. Because of retrospective enrolment, written informed consent from the

Table 1. Subject Baseline Characteristics			
	PCI (n=2,190)	CABG (n=1,796)	P-value
Clinical characteristics			
Age (years)	71 (63–77)	70 (63–75)	<0.01
Male	1,554 (71)	1,336 (74.4)	0.02
BMI	23.7 (21.5–25.8)	23.3 (21.1–25.8)	<0.01
Diabetes	1,066 (48.7)	935 (52.1)	0.03
On insulin therapy	287 (13.1)	309 (17.2)	<0.01
Hypertension	1,907 (87.1)	1,514 (84.3)	0.01
Current smoking	541 (24.7)	437 (24.3)	0.79
Heart failure	454 (20.7)	387 (21.5)	0.53
Prior MI	415 (18.9)	396 (22)	0.02
Prior symptomatic stroke	346 (15.8)	248 (13.8)	0.08
Hemodialysis	124 (5.7)	119 (6.6)	0.21
COPD	70 (3.2)	60 (3.3)	1
PVD	227 (12.6)	256 (11.7)	0.36
Ejection fraction (%)	60 (50–67)	60 (49–68)	0.85
Creatinine clearance (mg/dl)	61.7 (44.2–80.9)	61.4 (43.7–78.9)	0.22
Procedural characteristics			
CAD extension			<0.01
3-vessel disease	1,825 (83.3)	1,156 (64.4)	
LM isolated	57 (3.2)	31 (1.4)	
LM and 1-vessel disease	89 (4.1)	108 (6)	
LM and 2-vessel disease	132 (6)	182 (10.1)	
LM and 3-vessel disease	113 (5.2)	293 (16.3)	
SYNTAX score	24 (17–30)	29 (23–37)	<0.01

Data given as median (IQR) or n (%).

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

patients was waived, excluding those patients who refused participation in the study when contacted for follow-up.

Among 15,939 patients enrolled in the registry, 3,986 participants had 3-vessel and/or ULMCA and were included in current analyses.

SSII

The SSII has been described in detail previously.¹⁴ Briefly, SSII uses the 2 anatomical variables (anatomical SS and ULMCA disease) and 6 clinical variables (age, creatinine clearance, left ventricular ejection fraction [LVEF], sex, chronic obstructive pulmonary disease, and peripheral vascular disease) to predict 4-year mortality after revascularization with CABG or PCI.

For the present study, SSII was calculated using a nomogram, with scores assigned for the presence and magnitude of each predictor directly based on the Cox proportional hazards model coefficients (**Figure 1**), generating different scores for PCI and CABG.¹⁴ The 4-year mortality estimates were obtained in accordance with the revascularization procedure that each patient underwent: PCI or CABG.

Statistical Analysis

Categorical variables are presented as numbers and percentages and were compared using the chi-squared test. Continuous variables are expressed as mean±SD or median with interquartile range (IQR), and were compared using Student's t-test or Wilcoxon rank-sum test based on their distributions.

SSII predictor data were all present in at least 90% of the patients. Multiple imputation (5×) of missing data was under-

taken using an imputation strategy that takes into account the correlation between all potential predictors. To obtain 4-year mortality predictions based on anatomical SS alone, Cox logistic regression analysis was used with anatomical SS as a sole linear predictor.

SSII for PCI (in patients undergoing PCI) and for CABG (in patients undergoing CABG) was evaluated using 4 metrics: c-statistics; calibration plots; reclassification tables; and net reclassification index (NRI). Outcome was analyzed using Kaplan-Meier curves with a 4-year time horizon. Discrimination was studied with the concordance index (c-index).¹⁸ Calibration was assessed by plotting the observed 4-year mortality by quintiles of the predicted 4-year mortality.¹⁹ Comparison between the anatomical and II SYNTAX scores was further quantified using a reclassification table and its NRI.^{20,21} The NRI uses reclassification tables constructed separately for participants with and without events, and quantifies the correct movement in categories: upwards for events and downwards for non-events as follows: NRI=[(percentage of events moved to higher risk category in event group)–(percentage of events moved to lower risk category in event group)]–[(percentage of non-events moved to higher risk category in non-event group)–(percentage of non-events moved to lower risk category in non-event group)]. Given that not all persons had follow-up completed to 4 years, the present reclassification was based on the expected number of case and control patients calculated using the Kaplan-Meier estimator.²¹ All statistical analysis was done using IBM SPSS Statistics for Windows, version 21.0 (IBM, Armonk, NY, USA).

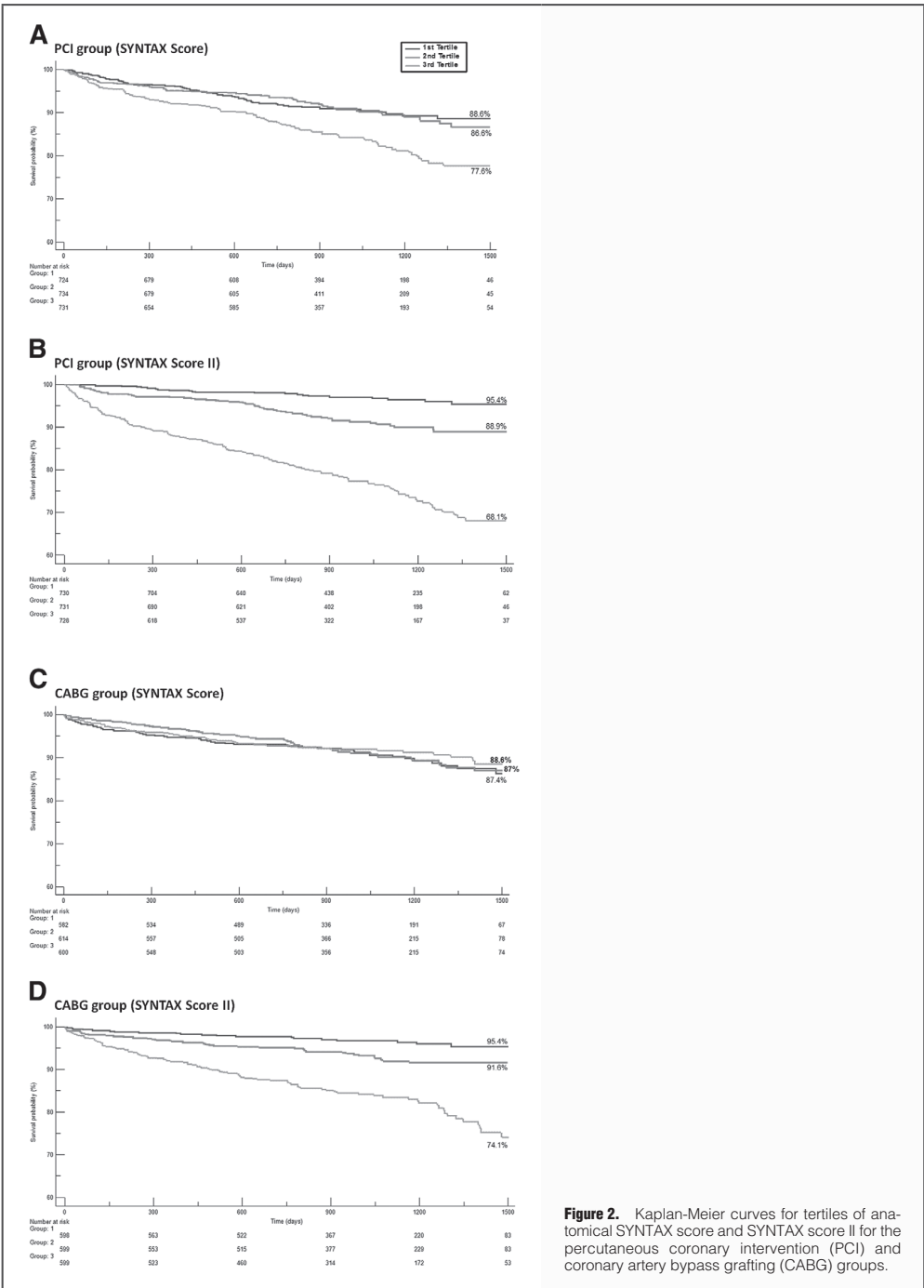


Figure 2. Kaplan-Meier curves for tertiles of anatomical SYNTAX score and SYNTAX score II for the percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) groups.

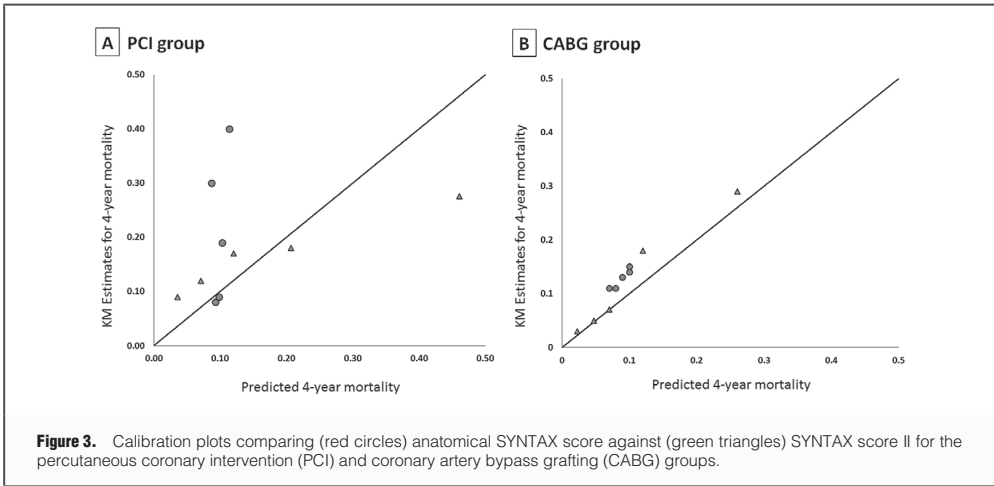


Figure 3. Calibration plots comparing (red circles) anatomical SYNTAX score against (green triangles) SYNTAX score II for the percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) groups.

Table 2. Reclassification Table: 4-Year Mortality Risk Strata^a				
PCI and CABG cohorts Predicted mortality by SS	Predicted mortality by SSII			Total
	<5%	>5–10%	>10%	
0–5%				
Persons included	0*	0	0	0
Death	0*	0	0	0
Survival	0*	0	0	0
Observed risk (%) ^{††}	0*	0	0	0
>5–10%				
Persons included	778	678*	1,128	2,584
Death	28.0 ^{††}	57.0*	270.7 [†]	355.7
Survival	750.0 [§]	621.0*	857.3**	2,228.3
Observed risk (%) ^{††}	3.6	8.4*	24.0	13.8
>10%				
Persons included	359	365	678*	1,402
Death	19.0 ^{††}	29.2 ^{††}	183.7*	232.0
Survival	340.0 [§]	335.8 [§]	494.3*	1,170.0
Observed risk (%) ^{††}	5.3	8.0	27.1*	16.5
Total				
Persons included	1,137	1,043	1,806	3,986
Death	47.0	86.2	454.5	587.6
Survival	1,090.0	956.8	1,351.5	3,398.4
Observed risk (%) ^{††}	4.1	8.3	25.2	14.7

*Patients classified as having the same risk by both scores; **patients classified as having higher risk by SSII who survived; [†]patients classified as having higher risk by SSII who died; ^{††}patients classified as having lower risk by SSII who died; [§]patients classified as having lower risk by SSII who died survived.

^{††}For patients who died the SSII reclassification improved by 33% whereas in non-event patients the reclassification improved by 16.7%. The net reclassification index was 0.5 (P<0.01). [‡]Estimated from the Kaplan-Meier curve using observations in each cell.

SS, SYNTAX score; SSII, SYNTAX score II. Other abbreviations as in Table 1.

Results

Patient Characteristics

Out of 3,986 patients included in the current study, 2,190 patients received PCI and 1,796 patients underwent CABG. Baseline characteristics of these patients are listed in **Table 1**.

Patients in the PCI group were older, and more often had hypertension, while patients in the CABG group more often had smaller body mass index, diabetes and prior myocardial infarction. Participants treated with CABG had more complex anatomical characteristics and a higher prevalence of associated ULMCA-triple vessel disease and higher anatomical SS.

Overall Kaplan-Meier estimated mortality at 4-year follow-up was 14.7% (15.9% for PCI and 12.6% for CABG).

Predictive Performance of SSII

Discrimination The c-index of SSII was 0.70 (95% CI: 0.68–0.72) in the CABG group and 0.75 (95% CI: 0.72–0.78) in the PCI group. On comparison of discrimination, anatomical SYNTAX showed a significant improvement for CABG and PCI groups (c-index, 0.50; 95% CI: 0.47–0.53 and 0.59, 95% CI: 0.57–0.61; respectively). Additionally, the SSII model was able to separate low-, medium- and high-risk tertiles better than anatomical SS for both groups (Figure 2).

Calibration The validation plots (Figure 3) of SSII indicated a reasonably good agreement between the observed and predicted risks for both the CABG and PCI groups. The anatomical SS showed disparity between predicted and observed mortality.

Reclassification Reclassification for all patients (both PCI and CABG patient groups), with and without events is summarized in Table 2. SSII showed a significant improvement in risk stratification (NRI, 0.5; $P < 0.01$). This was also observed when analyzing the PCI and CABG groups separately (Table S1).

Discussion

In this study, SSII was assessed in a large all-comers registry of Eastern patients with predominantly high-risk CAD. The findings can be summarized as follows: (1) SSII showed agreement between observed outcomes and predictions; (2) the metrics used showed similar risk stratification for both treatment cohorts (PCI and CABG); and (3) SSII substantially improved the predictive accuracy of long-term mortality predictions if compared with the anatomical SS alone.

SSII was developed from comparison between CABG and PCI in the SYNTAX trial.¹⁴ Its concept permits the composition of 1 single score to predict – based on randomized data – mortality if a patient is assigned to either CABG or PCI. Indeed, in the present study, SSII had similar and consistent predictive performance for both revascularization strategies in a real world population. In contrast, the current guidelines advise the heart team to use the anatomical SS alone or combined with the STS score as a tool to make objective risk stratification in the decision-making process between CABG and PCI.^{12,13} This concept, however, does not allow unified risk assessment. The anatomical SS has prognostic relevance only for patients assigned to PCI.^{9,19,22} Despite the fact that the STS score has been widely used for risk stratification in cardiac surgery,^{23–25} it was not formally validated as a predictive tool for PCI.

The metrics used to perform the present analysis reinforce the importance of comprehensive assessment with a combination of angiographic and key clinical characteristics for patients with complex CAD.²⁶ SSII had a significantly higher accuracy compared to anatomical SS for all-cause death measured by the c-statistic. It has been argued, however, that c-statistic is insensitive to systematic errors in calibration such as differences in average outcome.^{20,27} Therefore, we studied calibration using a graphical representation where predicted risk matched observed risk. In this comparison the SSII also had a more refined pattern (Figure 2). Indeed, a better discriminating model has more spread between quintiles of predicted risk than a poorly discriminating model.^{20,28}

Additionally, it is important for risk prediction as to whether a model can accurately stratify individuals into higher or lower risk categories. Therefore, we used the methodology described previously,^{20,21} which balances the reclassification of a new

score, subtracting, from a better risk grouping, a penalty if it lowers the estimated risk category of a patient with event or raises the estimated risk category of a patient without event. The overall NRI of 0.5 ($P < 0.01$) indicates that 50% of patients had a net better classification for higher and lower risk categories using the SSII vs. the anatomical SS. Also, when reclassified separately for type of revascularization – PCI or CABG – the reclassification of SSII was more accurate, indicating its potential as an integrated prediction tool (Table S1). Grouping patients in tertiles according to SSII, a separation of the Kaplan-Meier curves for the occurrence of deaths is evident (Figure 2). The same approach for anatomical SS showed a poor risk stratification (Figure 2).

Previously, SSII was predominantly evaluated in Western patients.¹⁵ Therefore, doubts may have existed over the utility of this tool in other populations. The present analysis confirms the potential to apply this model globally, given that we have now validated it in a population with unique epidemiological characteristics. Japan has the longest life expectancy at birth worldwide and a substantially lower proportion of mortality from cardiovascular diseases, compared with Western countries.^{29,30} Despite recent changes in the lifestyle and dietary habits of Japanese people, the incidence of myocardial infarction in Japan is still much lower than in other industrialized countries.^{31,32} Furthermore, even after revascularization – by either PCI or CABG – Japanese patients have been shown to have better long-term outcomes than US patients³³ and, regarding PCI, a significantly lower definite stent thrombosis than in Western countries.³⁴ All the aforementioned reasons could suggest that a score developed and validated mainly in Western populations may be less appropriate for global use. In the present cohort SSII discriminated well in both CABG and PCI patient groups (c-index, 0.70; 95% CI: 0.68–0.72 and 0.75, 95% CI: 0.72–0.78, respectively), a performance similar to its internal (c-index, 0.72) and external validations (DELTA registry; c-index, 0.71) in mainly Western patients.

Once more, the SSII predictions were consistent despite the fact that it does not include in its model diabetes mellitus. This could be questioned as a paradox because in the exclusively diabetic patients of the FREEDOM trial, CABG was superior to PCI by significantly reducing rates of death and myocardial infarction.¹⁰ Diabetes, however, was not a useful variable in the SSII, despite medically treated diabetes being stratified at randomization in the SYNTAX trial and reported in 26% of patients. Numerous arguments might explain this apparent divergence. First, diabetes was not an independent predictor of mortality in the SYNTAX trial.³⁵ Second, diabetes did not have an interaction effect ($P = 0.67$) with CABG or PCI for long-term mortality.¹⁴ Diabetes is a systemic disease, the severity and duration of which have a specific effect on organs such as the heart (detected on complex coronary anatomy and LVEF); peripheral vascular disease (a sign of systemic atherosclerosis); kidney (detected on creatinine clearance); and age (older patients are representative of a longer diabetes multi-organ effect). These arguments may be exemplified by a large population-based cohort study and meta-analysis involving 128,505 individuals with diabetes in which patients without diabetes but with chronic kidney disease and proteinuria had a stronger association with risk of myocardial infarction, and a higher rate of mortality, compared with those with diabetes.³⁶

Finally, it must be acknowledged that no risk-scoring system is perfect and that careful multidisciplinary clinical reasoning remains vital for decision-making.¹¹ SSII, however, can be a useful instrument in this process.

Study Limitations

This study has the inherent limitations of a retrospective analysis. The ultimate goal of SSII is to assist the heart team in the decision-making process between CABG and PCI.³⁷ Thus, a prospective study would be needed to achieve true validation of SSII, where the decision between CABG and PCI is randomized. The present analysis, being retrospective, cannot assess the treatment recommendation based on SSII for the simple fact that the decision was likely made based on a combination of measured variables (as included in SSII) and unmeasured variables (eg, bleeding risk, duration of dual antiplatelet therapy, frailty etc). Presently, validation of SSII is a pre-specified endpoint in the ongoing randomized EXCEL trial (NCT01205776), and SYNTAX trial II, which will use SSII to recruit participants based on patient safety. In the latest trial, functional lesion assessment was added to improve late PCI outcomes and it is plausible that this approach may improve the discrimination of anatomical SS.³⁸

In the PCI cohort of the CREDO-Kyoto registry patients were treated mainly with first-generation drug-eluting stent (DES). It is possible that its performance will be affected by the use of newer generation DES. SSII, however, focuses on 4-year overall mortality, an outcome that, apparently, is not affected by the type of stent used. For instance, in a recent meta-analysis of 20 clinical trials that included 20,005 patients, stent type did not alter the overall mortality, unlike late-lumen loss and stent thrombosis rate.³⁹ Therefore, we do not expect that the type of DES prescribed will affect the predictions made by the PCI model of SSII.

Conclusions

SSII has robust prognostic accuracy, both in CABG and PCI patient groups and – compared with the anatomical SS alone – was able to stratify patients for late mortality in a real-world complex CAD Eastern population.

Acknowledgments

H.M.G.-G. and M.-A.M. are employees of Cardialysis (an academic Clinical Research Organization). The other authors report no conflicts of interest.

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Supplementary Files

Supplementary File 1

Table S1. Reclassification table: 4-year risk strata for PCI vs. CABG

Please find supplementary file(s):
<http://dx.doi.org/10.1253/circj.CJ-14-0204>

Chapter 3.3

Validity of SYNTAX Score II for Risk Stratification of Percutaneous Coronary Interventions: A Patient-Level Pooled Analysis of 5,433 Patients Enrolled in Contemporary Coronary Stent Trials

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Validity of SYNTAX score II for risk stratification of percutaneous coronary interventions: A patient-level pooled analysis of 5433 patients enrolled in contemporary coronary stent trials

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ABSTRACT

Objectives: To assess the clinical profile and long-term mortality in SYNTAX score II based strata of patients who received percutaneous coronary interventions (PCI) in contemporary randomized trials.

Background: The SYNTAX score II was developed in the randomized, all-comers SYNTAX trial population and is composed by 2 anatomical and 6 clinical variables. The interaction of these variables with the treatment provides individual long-term mortality predictions if a patient undergoes coronary artery bypass grafting (CABG) or PCI.

Methods: Patient-level (n = 5433) data from 7 contemporary coronary drug-eluting stent (DES) trials were pooled. The mortality for CABG or PCI was estimated for every patient. The difference in mortality estimates for these two revascularization strategies was used to divide the patients into three groups of theoretical treatment recommendations: PCI, CABG or PCI/CABG (the latter means equipoise between CABG and PCI for long term mortality).

Results: The three groups had marked differences in their baseline characteristics. According to the predicted risk differences, 5115 patients could be treated either by PCI or CABG, 271 should be treated only by PCI and, rarely, CABG (n = 47) was recommended. At 3-year follow-up, according to the SYNTAX score II recommendations, patients recommended for CABG had higher mortality compared to the PCI and PCI/CABG groups (17.4%; 6.1% and 5.3%, respectively; P < 0.01).

Conclusions: The SYNTAX score II demonstrated capability to help in stratifying PCI procedures.

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1. Introduction

The SYNTAX score [1–3] was developed for the randomized comparison of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in the Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial [2]. The SYNTAX score provides objective quantification on the diseased coronary artery segment in terms of its severity, anatomical location and importance

in supplying blood to the myocardium. Based on the results of the SYNTAX trial [2,4,5] the SYNTAX score has been implemented as a watershed between CABG and PCI in prevailing guidelines [6,7]. However, the SYNTAX score cannot account for the effect related to clinical factors which are widely acknowledged to impact on long-term outcomes, such as a patients' age, left ventricular ejection fraction, and renal function [8–10].

Recently, the SYNTAX score II was developed by applying a Cox proportional hazards model to the SYNTAX trial data. A combination of clinical and anatomical predictors [5,11], together with their interaction with the treatment modality (CABG or PCI), enables estimation of the absolute risk difference between CABG and PCI and has the potential to assist the multidisciplinary decision-making process between these

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two strategies. The SYNTAX score II has been shown to provide reliable predictions of 4-year mortality for complex coronary artery disease, being externally applied in more than 10,000 patients and implemented in the most recent international guidelines [11–14].

We aim to assess the stratification by the SYNTAX score II theoretical treatment recommendation in heterogeneous patients treated with PCI. Additionally, we intend to evaluate the predictive performance of the SYNTAX score II in recent randomized trials in different clinical scenarios using different types of stents.

2. Methods

2.1. Study population

We pooled 7 contemporary coronary drug-eluting stent (DES) trials for which the independent core lab analysis assessment of SYNTAX scores were available: ARTS II (Arterial Revascularization Therapies Study II) trial, STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent in Myocardial Infarction) trial, EXCELLA II (Elixir Medical Clinical Evaluation of the Novolimus-Eluting Coronary Stent System) trial, LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial, MULTISTRATEGY (Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction) trial, RESOLUTE (Resolute All Comers) trial, and SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) [15–21]. Detailed individual study design and trial results are available elsewhere. In brief, all studies included patients with obstructive coronary artery disease (CAD) that was amenable to coronary stent implantation. Study inclusion criteria were deliberately heterogeneous ranging from low risk PCI to studies with an all-comers' design (Supplementary Table 1).

2.2. SYNTAX score II

The recent SYNTAX score II has been described in detail previously [11]. Briefly, the SYNTAX score II consists of 2 anatomical (unprotected left main coronary artery disease and anatomical SYNTAX score) and six clinical variables (age, creatinine clearance, left ventricular ejection fraction, sex, chronic obstructive pulmonary disease, and peripheral vascular disease).

Using the actual baseline clinical and angiographic data from each enrolled patient the SYNTAX score II was calculated for each patient. The SYNTAX score II generates different scores and distinct estimated mortalities for PCI and CABG. Patients were theoretically recommended for CABG if the difference in the predicted mortality risk was in favour of

CABG with 95% confidence. Patients were theoretically recommended for PCI if the difference in mortality risk predictions was in favour of PCI with 95% confidence. In addition, patients were classified as PCI/CABG if zero (equal risk predictions) was within the 95% confidence interval of the difference in mortality risk predictions.

2.3. Data analysis

Categorical variables are presented as numbers and percentages and are compared with the Chi-square test. Continuous variables are expressed as mean \pm SD or median with interquartile range (IQR), and are compared using the Student's *t*-test or Wilcoxon rank-sum test based on their distributions. The long-term mortality was compared amongst the aforementioned three groups using the log rank test for Kaplan–Meier estimates. All statistical analyses were done with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corporation, Armonk, NY).

3. Results

As shown in Table 1, pooled data from the seven trials contained 5433 patients with a mean age 63.3 ± 10.8 years, 75.3% were male, 21.8% had diabetes mellitus, 56.8% presented acute coronary syndrome and the mean body mass index was 27.52 ± 4.1 . The mean creatinine clearance was 92.1 ± 36.2 mg/dl, ejection fraction $56 \pm 11.1\%$ and SYNTAX score 14.2 ± 9.1 . There were 399 deaths (6.3%) over 3-year follow-up.

3.1. Treatment recommendation and long term mortality

According to the SYNTAX score II recommendations, 5115 patients could have undergone either CABG or PCI, 271 should have been treated exclusively by PCI and 47 by CABG (Table 1). There was a substantial heterogeneity between groups. The PCI recommended group was older, with better ejection fraction, higher prevalence of COPD and lower anatomical SYNTAX score. On the contrary, patients theoretically recommended to CABG (but treated by PCI) were younger male patients with higher anatomical SYNTAX, lower ejection fraction and 17% had peripheral vascular disease. After 3 years of follow-up the mortality (Fig. 1) was significantly higher in the CABG recommended group treated with PCI and mortality curves were similar for PCI and CABG/PCI groups (17.4%; 5.3% and 6.1%, respectively $P < 0.01$). Fig. 2 shows the cumulative distribution of the anatomical SYNTAX score according to the treatment recommendation. Although there was clear impact on the treatment recommendations – since the anatomical SYNTAX score is one of the components of the SYNTAX score II – there were patients

Table 1
Baseline characteristics.

	Total N = 5433	PCI N = 271	CABG or PCI N = 5115	CABG N = 47	P
Male, %	75.3	70	79	100	<0.01
Age, years \pm SD	63.33 \pm 10.83	74.19 \pm 6.32	62.84 \pm 10.67	53.97 \pm 12.14	<0.01
Hypertension, %	68.5	84.1	67.9	51.1	<0.01
Diabetes, %	21.8	26.9	21.6	17	0.09
BMI \pm SD	27.52 \pm 4.1	28.72 \pm 5.08	27.47 \pm 4.04	25.58 \pm 3.38	<0.01
Acute coronary syndromes, %	56.8	41	57.5	72.3	<0.01
Family history premature CAD, %	33.2	32.5	33.2	40.4	0.55
Previous TIA/CVA, %	1.9	3	1.8	4.3	0.21
Hyperlipidemia, %	63.2	67.2	63.1	53.2	0.145
COPD, %	5.7	16.2	5.1	0	<0.01
PVD, %	4	7.7	3.7	17	<0.01
Current smokers, %	32.4	18.8	32.9	53.2	<0.01
Previous PCI, %	24.8	29.2	24.4	34	0.07
Previous MI, %	27.5	18.1	27.8	40.1	<0.01
Creatinine Cl, ml/min \pm SD	92.16 \pm 36.24	81.63 \pm 66.74	92.78 \pm 33.7	85.82 \pm 43.41	<0.01
LVEF, % \pm SD	56.07 \pm 11.1	61.29 \pm 7.85	55.99 \pm 10.99	34.09 \pm 9.66	<0.01
SYNTAX score \pm SD	14.21 \pm 9.12	7.68 \pm 5.10	14.42 \pm 9.03	29.28 \pm 10.84	<0.01

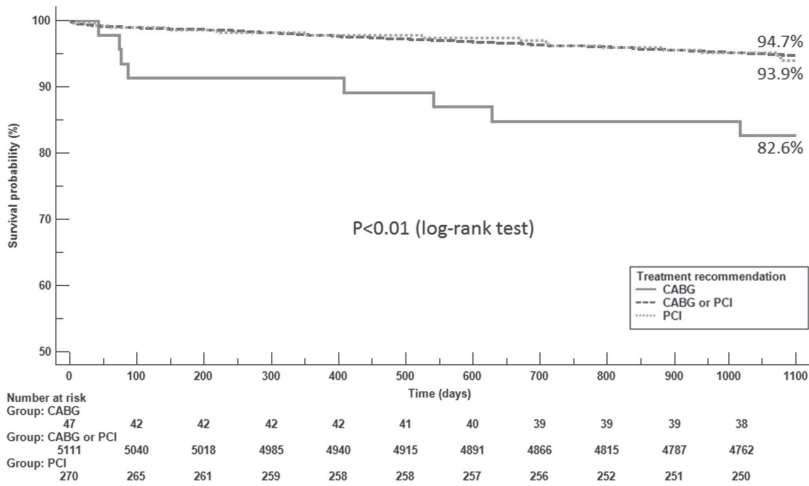


Fig. 1. Long-term survival probability according to SYNTAX score II treatment recommendations.

with low anatomical SYNTAX score (<22) recommended to CABG and patients with high (>33) where PCI could be considered.

4. Discussion

The data presented in this paper can be summarized as follows: (1) the SYNTAX score II based treatment recommendation for CABG was an uncommon finding in contemporary DES trials and (2) the SYNTAX score II showed clinical relevance through its ability to identify patients at higher risk for PCI.

4.1. PCI prescription based on SYNTAX score II

The ultimate goal of the SYNTAX score II is not only the isolated risk prediction for PCI or CABG [22]. As aforementioned, this score was developed in a randomized comparison between CABG and PCI to evaluate

the interactions of risk factors that could help in the decision making process between these revascularization strategies [11,22]. In these contemporary PCI trials the SYNTAX score II recommendation for CABG was present in only 47 patients (0.9% of total). The exclusively PCI suggestion was made in 271 (4.98%). Put into perspective with populations with complex CAD (Table 2), the treatment recommendations for CABG and PCI amongst the 3-vessel disease group in the SYNTAX trial were, respectively, 40.7% and 0.5% (the remaining 58.8% was in the CABG or PCI). For the left main cohort 11.5% was recommended to have CABG and 8.8% PCI [11]. The difference in these proportions of treatment recommendations confirms that the present group has a lower risk profile for PCI when compared to the SYNTAX trial.

The divergence of mortality curves, showing disadvantage for the CABG recommended group, was observed from onset of follow-up. It may be argued that these patients have higher mortality as they have worse left ventricular function and a higher SYNTAX score. On the

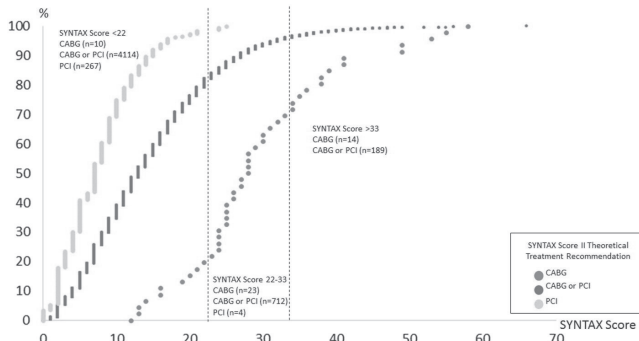


Fig. 2. Distribution of anatomical SYNTAX score according to the Theoretical Treatment Recommendation provided by the SYNTAX score II. Despite the SYNTAX score having a clear impact on recommendations, there were patients with low SYNTAX score (<22) recommended to CABG and patients with high (>33) SYNTAX score where PCI could be considered.

Table 2
SYNTAX score II based treatment recommendations in different populations.

	SYNTAX trial 3-Vessel disease cohort	SYNTAX trial Left main cohort	Present analysis
PCI, %	0.5	11.5	4.98
CABG or PCI, %	58.8	79.7	94.12
CABG, %	40.7	8.8	0.9

other hand these patients were, on average, almost 20 years younger than patients in the PCI recommended group. In fact, this is the argument that strengthens this analysis: to balance clinical and angiographic characteristics, identifying deltas of individual risk to distinguishing patients who could potentially have higher or lower benefit with PCI (Supplementary Figs. 1–3).

The SYNTAX score II interactions showed that some anatomical and clinical characteristics could have different impact in the type of treatment (CABG or PCI). This gives the clinician vital information for decision making: i.e., younger age favours CABG, older age favours PCI, COPD favours PCI, lower creatinine clearance favours CABG, unprotected left main coronary artery disease favours PCI, higher SYNTAX scores favours CABG, lower SYNTAX scores favours PCI and female gender favours CABG [11]. Interestingly, in the present paper all patients that theoretically selected for CABG were male. This can be explained by the high risk profile for PCI of this population that overruled gender: mean ejection fraction 34.09 ± 9.66 , age 53.97 ± 12.14 and anatomical SYNTAX score 29.28 ± 10.84 .

It must be acknowledged that no risk scoring system is perfect and careful multidisciplinary clinical reasoning remains vital for the decision-making process [23]. The heart team decision has to be sovereign over the SYNTAX score II since the latter does not assess numerous variables that are present in clinical practice as, for instance, frailty and emergency procedures. Although it would be tempting to assert that the CABG recommended patients treated by PCI should go to CABG, we cannot state that based only on the present findings. It has to be reinforced that we do not have a CABG control group to establish definitive comparisons. However, these findings highlight the importance of a comprehensive patient evaluation and not only a simplistic angiographic-based PCI prescription (Fig. 2). The higher clinical complexity of patients recommended to CABG may indicate individuals that deserve meticulous revascularization plan, using established strategies that may improve results and minimize the risks: e.g., intravascular ultrasound guided PCI [24,25], careful judgement of the chances to obtain complete revascularization [26], close monitoring of optimal medical treatment and adherence [27,28], and minimize the risk of bleeding [29]. On the other hand, the event rates for patients recommended to PCI and CABG/PCI were relatively low (6.1 and 5.3%, respectively).

5. Limitations

This study has the inherent limitations of a not pre-specified retrospective analysis. As previously discussed, the ultimate objective of the SYNTAX score II is to assist the heart team in the decision-making process between CABG and PCI [22]. Thus true validation of the SYNTAX score II would require a prospective study where the decision between CABG and PCI is done randomly. The present study, being retrospective, cannot assess the treatment recommendation based on the SYNTAX score II for the simple fact that the decision was made based on the inclusion criteria of each PCI trial, not having a CABG control group, which limits the complete interpretation of the outcomes. Presently, the validation of the SYNTAX score II has been prospectively applied in the ongoing randomized EXCEL trial (NCT01205776) [12], and the ongoing SYNTAX II trial which will use the SYNTAX score II to recruit participants based on patient safety (SYNTAX II trial lacks a CABG arm). However, we have shown consistently in a large controlled cohort that this tool can help to stratify PCI in clinical practice.

6. Conclusions

The SYNTAX score II demonstrated solid predictive performance and aptness to help in stratifying and prescribing PCI procedures.

Conflict of interest

All authors have no conflict of interest and did not receive grants or financial support from industry or from any other source to prepare this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2015.03.248>.

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Chapter 3.4

Appropriateness of Myocardial Revascularisation Assessed by the SYNTAX Score II in a Country Without Cardiac Surgery Facilities

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INTRODUCTION

Over the last few decades the optimal revascularisation modality of patients with complex coronary artery disease has been coronary artery bypass graft (CABG) surgery. However, percutaneous coronary intervention (PCI) has experienced a large number of technical and technological improvements, and hence, has challenged the superiority of CABG. Recent studies have shown that in certain groups of patients, PCI may be a safe and effective alternative (1-3).

The widespread adoption of PCI has led to the need for evidence-based clinical tools to aid decision-making on the most optimal revascularisation modality in patients with complex coronary artery disease (CAD). One of the first clinical tools to objectively determine which patients with complex CAD were suitable for PCI or CABG was the anatomical SYNTAX Score (4,5). The anatomical SYNTAX Score is an angiographic-based tool that allows for the objective quantification of the complexity of CAD (4,5,6,7). However, the anatomical SYNTAX Score does not incorporate clinical factors, which are widely confirmed to impact on mid- and long-term outcomes (8,9,10), and therefore influence on decision-making between CABG and PCI (11,12,13). In addition, the anatomical SYNTAX Score does not provide an individualised risk assessment due to the fact that patients are grouped into three risk groups.

Recently, the SYNTAX Score II was developed by applying a cox proportional hazards model to the results of all-comers, randomised SYNTAX Trial (10). This score unifies the anatomical SYNTAX Score with six clinical variables to form a single score for CABG and PCI, and gives long-term mortality predictions for

individual patient following CABG or PCI to aid decision-making by the Heart Team, composed of at least one interventional cardiologist, one cardiac surgeon and one clinical cardiologist, as recommended in the European Society of Cardiology (ESC) guidelines on myocardial revascularisation (14). However, recent literature suggests that the Heart Team concept is not systematically implemented in daily practice (15,16) or even inappropriately applied in patients with stable CAD (17,18).

Every cardiologist being interventional and clinical has dilemmas if CABG or PCI was the right decision, especially in case of complications that may strike their self-confidence on the knowledge and clinical skills. Very often asked by the patients, cardiologists today are struggling to find out the best myocardial revascularisation modality for their patients.

The purpose of the present study was to investigate whether indications for PCI or CABG based on the most educated intuitive judgment of PCI-operators without cardiac surgery on-site in routine clinical practice (without a Heart Team evaluation) in the era before the SYNTAX Score II approximate to the treatment recommendation of the recently published SYNTAX Score II. Our working hypothesis was that the SYNTAX Score II could help in better guiding myocardial revascularisation if it would have existed at the time of treatment, and is superior to the approach based on oculostenotic reflex which might be corrected by using a unique and organised system that SYNTAX Score II proposes.

METHODS

Database and study population

Between January 1, 2008, and May 30, 2010 patients from the University Hospital Clinical Centre Banja Luka, Bosnia and Herzegovina were retrospectively recruited using the hospital information system. The study group comprised consecutive, hemodynamically stable patients with angiographically proven 3-vessel CAD ($\geq 50\%$ diameter stenosis) or significant unprotected left main coronary artery (ULMCA) disease ($\geq 50\%$ diameter stenosis), who were treated locally with PCI or referred to other institutions abroad for CABG. The research protocol was approved by the relevant local ethics committee. Due to the retrospective nature of the study, written informed consent from the patients was waived, excluding those who refused participation in the study when contacted for follow-up.

Baseline angiographic and demographic characteristics were prospectively entered into a dedicated database. Patients with ST segment elevation myocardial infarction, previous CABG or PCI, terminal illnesses with projected life expectancy less than one year or patients with need for concomitant cardiac surgery were excluded from the study. All-cause mortality was ascertained by telephone contacts.

SYNTAX Score II

The SYNTAX Score II consists of eight variables, two anatomical (anatomical SYNTAX Score and ULMCA disease) and six clinical (age, creatinine clearance, left ventricular ejection fraction [LVEF]), gender, chronic obstructive pulmonary disease [COPD] and peripheral vascular disease [PVD]). The SYNTAX Score has been described in detail previously (4). In brief, the anatomical SYNTAX Score is derived from the summation

of the individual scorings for each separate lesion (defined as 50% diameter stenosis in vessel larger than 1.5 mm). For each patient, the anatomical SYNTAX Score calculation was based on the initial diagnostic angiogram and was calculated using the SYNTAX Score calculator available online (www.syntaxscore.com).

Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula (21). LVEF was assessed by transthoracic echocardiography. COPD was defined as the long-term use of bronchodilators or steroids for lung disease (EuroSCORE definition [22]). PVD was defined as one or more of the following: claudication, carotid occlusion or $>50\%$ diameter stenosis, amputation for arterial disease or/and previous or planned intervention on the abdominal aorta, limb arteries or carotids (Arterial Revascularisation Therapies Study Part I definition [23]).

Using the aforementioned data the SYNTAX Score II was calculated for each patient using an electronic calculator available only to the investigators of the SYNTAX II Trial. The SYNTAX Score II generates scores for PCI and CABG, and provides estimated all-cause mortality predictions following CABG or PCI to aid the Heart Team in decision-making on the most appropriate revascularisation modality. Patients were recommended for CABG if the difference in the predicted mortality risk was in favour of CABG with 95% confidence. Patients were recommended for PCI if the difference in mortality risk predictions was in favour of PCI with 95% confidence. In addition, patients were recommended for CABG or PCI if the predicted mortalities could not be separated with 95% confidence.

Statistical analysis

Categorical variables are presented as numbers and percentages and compared using the chi-

square test. Continuous variables are expressed as mean with standard deviation (SD) or median with inter-quartile range (IQR) and compared using a Student T test or Mann-Whitney U test according to the data distribution. The differences between revascularisation modality recommendations were analysed using a chi-square test. Differences in outcomes were analysed using Kaplan-Meier estimates at 4-year follow-up and compared with the log rank test. All statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 21.0 (IBM, Armonk, NY, USA).

RESULTS

Patients characteristics

Using the hospital information system, 3122 consecutive patients were screened and 2562 elected not to follow the inclusion criteria. Out of 560 patients included in this study, 362 (64.6%) patients underwent PCI and 198

(35.4%) patients were referred to other institutions abroad for CABG (Figure1). The mean age was 60.5 ± 9.1 years, 73.0% were men, 81.6% had 3-vessel CAD and 18.4% ULMCA disease. Baseline characteristics of the study population classified according to the performed treatment modality are listed in Table1. Patients in whom CABG was performed were more likely to be older, to have diabetes mellitus, arterial hypertension and more complex anatomical characteristics (higher anatomical SYNTAX scores) as well as a higher eGFR, compared to patients treated with PCI.

Comparison of clinical judgment and SYNTAX Score II treatment recommendation

Based on the SYNTAX Score II assessments, CABG was shown to be the treatment of choice in 232/560 (41.4%) patients, PCI in 3/560 (0.6%) patients and CABG or PCI in 325/560 (58.0%) patients (Table2).

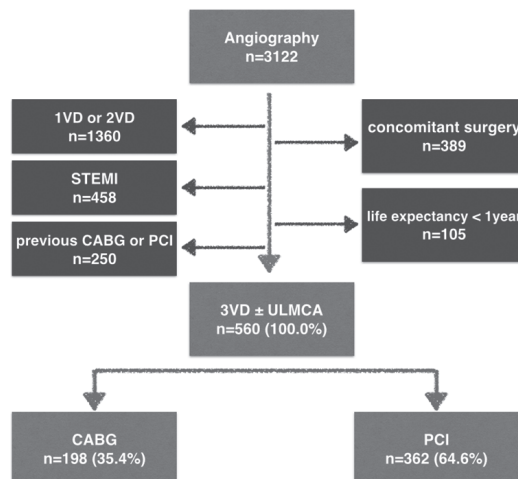


Figure 1. Study flow chart.

Table 1. Baseline characteristics according to the actual performed revascularisation modality (CABG or PCI) (n=560).

	Revascularisation performed according to the clinical judgment of the interventional cardiologists		
	CABG n=198	PCI n=362	P-value (2-tailed)
Age	62.3 ± 8.3	59.0 ± 9.6	< 0.001
Male	179 (90.4%)	296 (81.8%)	0.82
Diabetes on medical therapy	103 (52.0%)	108 (29.8%)	< 0.001
History of hypercholesterinemia	160 (80.8%)	261 (72.1%)	0.68
History of hypertension	192 (97.0%)	295 (81.5%)	0.011
Smoking history	95 (48.0%)	184 (50.8%)	0.12
Familiar history of CAD	116 (58.6%)	166 (45.9%)	0.087
History of heart failure	10 (5.1%)	14 (3.9%)	0.32
Previous MI	42 (21.2%)	85 (23.5%)	0.31
Previous stroke	14 (7.1%)	17 (4.7%)	0.16
COPD	9 (4.5%)	21 (5.8%)	0.39
PVD	31 (15.7%)	40 (11.1%)	0.25
LVEF	54.5 (45.0-60.0)	55.0 (45.0-60.0)	0.037
eGFR (ml/min)	89.5 (76.0-97.3)	83.0 (70.8-95.0)	0.006
LM	82 (41.4%)	21 (5.8%)	< 0.001
Anatomical SYNTAX Score	33.8 (26.0-43.1)	17.0 (10.0-24.0)	< 0.001

Data given as n (%) or mean ± SD or median (IQR). CAD, coronary artery disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; CrCl, creatinine clearance; LM, left main; SYNTAX, Synergy between percutaneous coronary intervention with Taxus and cardiac surgery; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

As shown in Table 2, 232 patients had treatment recommendations by the SYNTAX Score II for CABG, of which 99/232 (42.7%) patients had actually CABG, with the remainder (133/232, 57.3%) undergoing PCI. Three patients had SYNTAX Score II recommendations exclusively favouring PCI, 2/3 patients (66.7%) were treated with PCI and 1/3 patients (33.3%) underwent CABG. Further, 325 patients had SYNTAX Score II recommendations favouring CABG or PCI, 98/325 (30.2%) underwent CABG and 227/325 (69.8%) underwent PCI.

The discordance between clinical judgments and SYNTAX Score II recommendations was mainly evident in patients treated with PCI. Comparisons of baseline characteristics of patients treated with PCI stratified accord-

ing to treatment recommendation provided by the SYNTAX score II are listed in Table 3. The PCI recommended patients by the SYNTAX Score II were significantly older, had greater left ventricular function and eGFR, were more likely to be male, have COPD and less complex CAD expressed through anatomical SYNTAX score. In contrast, patients recommended by the SYNTAX Score II to CABG (but treated with PCI) were younger, more likely to be female patients with higher anatomical SYNTAX, lower ejection fraction and less likely to have COPD.

As shown in Figure 2, patients treated with PCI in whom the SYNTAX Score II recommendation was CABG, had a significantly higher SYNTAX Score II compared to patients with concordant recommendation (median [IQR]:

Table 2. Concordance or discordance between SYNTAX score II recommendation of revascularisation strategy (CABG or PCI) and the clinical judgment of the interventional cardiologists (chi square $P < 0.001$).

SYNTAX II recommendation	Revascularisation performed according to the clinical judgment of the interventional cardiologists		
	CABG	PCI	Total
CABG	99/560 (17.7%)	133/560 (23.8%)	232/560 (41.4%)
PCI	1/560 (0.2%)	2/560 (0.4%)	3/560 (0.6%)
CABG or PCI	98/560 (17.5%)	227/560 (40.5%)	325/560 (58.0%)
Total	198/560 (35.4%)	362/560 (64.6%)	560 (100%)

green: concordance between clinical judgment and SYNTAX score II recommendation;

red: discordance between clinical judgment and SYNTAX score II recommendation;

orange: equipoise of 4-year mortality between CABG and PCI (based on comparisons of mortality predictions not separated with 95% confidence).

Table 3. Comparisons of baseline characteristics of patients treated with PCI stratified according to treatment recommendation provided by the SYNTAX score II.

	Total N=362	CABG n=133	CABG or PCI n=227	PCI n=2	P-value
Age	59.0 ± 9.6	58.1 ± 9.3	59.4 ± 9.6	76.5 ± 2.1	0.02
Male, %	72.9	38.3	93.0	100.0	<0.01
Diabetes on medical therapy, %	26.5	28.6	25.6	0.0	0.57
History of hypercholesterinemia, %	61.3	65.4	59.0	50.0	0.46
History of hypertension, %	71.3	72.9	70.5	50.0	0.71
Smoking history, %	44.5	44.4	44.5	50.0	0.99
Familiar history of CAD, %	39.8	39.8	39.6	50.0	0.96
COPD, %	5.2	1.5	7.0	50.0	<0.01
PVD, %	9.7	7.5	11.0	0.0	0.50
LVEF	52.3 (45.0-60.0)	50.0 (40.0-60.0)	55.0 (50.0-60.0)	54.5 (54.0-)	< 0.01
eGFR (ml/min)	83.1 ± 20.3	76.7 ± 17.3	86.8 ± 21.0	93.5 ± 10.6	< 0.01
LM, %	5.2	3.8	5.7	50.0	0.01
SYNTAX Score	18.1 (10.0-24.0)	21.0 (14.0-30.0)	13.0 (11.0-20.0)	23.5 (23.0-)	< 0.01

Data given as mean ± standard deviation, % or median (IQR). CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; CrCl, creatinine clearance; LM, left main; SYNTAX, Synergy between percutaneous coronary intervention with Taxus and CABG.

33.4 [27.9-42.1], median [IQR]: 24.3 [19.0-30.2]), respectively, $P < 0.01$), suggesting a higher risk of death if PCI was performed.

SYNTAX Score II and Mortality Outcome

Overall mortality in the entire cohort of 560 patients at 4-year follow-up was 8.4%. Signifi-

cantly higher all-cause mortality was shown in the CABG recommended group treated with PCI compared with CABG/PCI and PCI recommended group treated with PCI (12.8% vs. 4.7% vs. 0.0%, respectively, log rank $P = 0.04$, Figure 3).

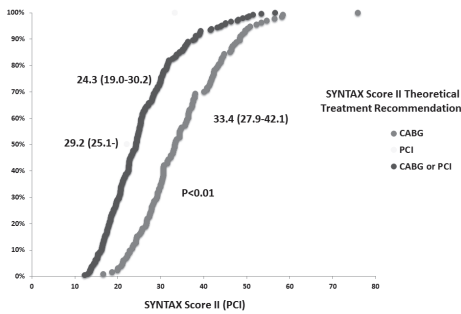


Figure 2. Cumulative percentage distribution of the SYNTAX Scores II (PCI) between SYNTAX Score II recommendation of revascularisation strategy in study population treated with PCI.

DISCUSSION

The main findings of the present study are: 1. The clinical judgment of PCI-operators without evaluation by the Heart Team deviated in 1/3 of the total population from the treatment modality recommended by the SYNTAX Score II; 2. The most striking deviation of 57% was noted in patients in whom SYNTAX Score II exclusively recommended CABG; 3. When stratified according to the SYNTAX Score II recommendation, patients treated with PCI in concordance with SYNTAX Score II treatment recommendation had different baseline characteristics from the patients with discordant treatment; 4. Within PCI group, patients in whom SYNTAX score II exclusively recommended CABG showed higher mortality at 4 years compared to patients with concordant decision-making.

Unilateral decision-making

In spite of the fact that almost every tertiary referral hospital in Europe is equipped with cardiac surgery, University Hospital Clinical Centre Banja Luka in Bosnia and Herzegovi-

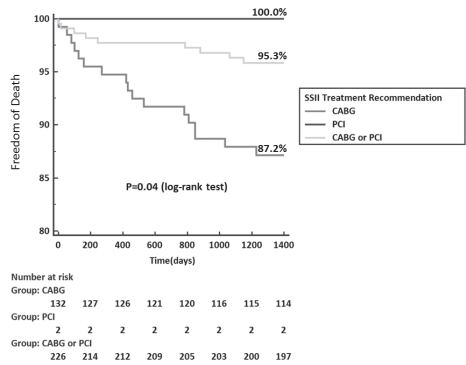


Figure 3. Comparisons of observed mortality at 4 years (Kaplan-Meier estimates and log-rank comparisons) in patients treated with PCI classified by SYNTAX Score II recommendation of revascularisation strategy (CABG; PCI; CABG or PCI).

na—the largest tertiary care institution in Republika Srpska, Bosnia and Herzegovina—has a high volume catheterisation laboratory (1500 procedures/year performing 400 PCIs/year) without cardiac surgery facilities being available in the country. Due to Republika Srpska’s political and economic conditions being a country in transition, and the fact that surgical myocardial revascularisation is not possible in the country, the choice of the method of revascularisation is left to the clinical judgment of the local PCI-operators without the consensus of a local Heart Team. The current study retrospectively reviewed in this hospital the revascularisation recommendations based on the SYNTAX Score II.

This is the first review of its kind to evaluate SYNTAX Score II treatment recommendation in “real world” population confronted with conditions which are far away from those in developed countries. Results of the present study demonstrated that only 42.7% of patients with estimated mortality predictions by the SYNTAX Score II clearly in favour of CABG were referred

to other institutions for CABG, whereas the remaining patients with CABG recommendation were treated locally with PCI. It is strongly comparable with findings of Hannan et al. (15) that interventional cardiologists in United States followed guideline recommendations regarding CABG in only 53% of patients (43% in our study with follow-up of 4 years despite the differences in size, economical strength and living standard between USA and Bosnia and Herzegovina). In the present study, patients with discordant decision-making not only had a higher mortality at 4 years, but also significantly higher SYNTAX Score II, thus demonstrating the robust predictive ability of the SYNTAX Score II. In addition, the present study highlights the need for a multidisciplinary Heart Team approach to prevent unilateral decision-making on the most appropriate revascularisation modality (14,16).

Multidisciplinary decision-making improved patients outcome and is recommended in selecting the most appropriate treatment strategy for individual patients with stable complex CAD (14,16). Despite the fact that the so-called "Heart Team" concept was introduced in 2010, it has not yet been widely implemented, leading to suboptimal decision-making as well as to inappropriate revascularisation (14-17). Recently published studies presented a large variability in PCI-to-CABG ratios between centres, which may predominantly be the consequence of physician-related factors (16, 27, 28). Our study investigated an ideal experimental population treated by strong independent interventional cardiologists without a Heart Team available. We believe that this study could encourage PCI-centres without cardiac surgery on-site to provide an evaluation of the Heart Team and to apply the SYNTAX Score II in patients with complex CAD.

Performance of the SYNTAX Score II

The SYNTAX Score II has been developed in the landmark, all-comers, randomised SYNTAX (Synergy between percutaneous coronary intervention with Taxus and cardiac surgery) trial (10) and externally validated in a total number of 8,405 patients from three large multicenter registries (10,19,20). The SYNTAX Score II showed a robust predictive performance with a high discriminatory ability. Moreover, the most recent ESC/EACTS guidelines on myocardial revascularisation (14) have endorsed the implementation of the SYNTAX Score II (Class IIa; Level of evidence B) in decision-making process between CABG and PCI. Therefore, our work represents an retrospective application of the SYNTAX score II in the clinical practice investigating whether the intuitive decision-making by interventional cardiologists is enough as good. The advantage of this approach is that all-cause mortality is not subject to any adjudication bias. Moreover, it is an endpoint hardly influenced by the recent advances in cardiology. As it was well summarised by Stephen S. Gottlieb "Dead is dead—artificial definitions are no substitute" (29).

Ultimate goal of the SYNTAX Score II

The SYNTAX score II provides not only the long-term mortality prediction after PCI or CABG, but also offers a unique treatment recommendation taking into account complexity of CAD and 6 clinical factors (10). As aforementioned, this score could assist the Heart Team in the decision-making process between two revascularization strategies (10,19,20). In the recently published pooled analysis from 7 contemporary PCI trials (n=5,433) authors stratified patients according to the SYNTAX score II recommendation, and concluded,

similarly to the present study, that patients with discordant treatment had significantly higher mortality at 3 years (CABG: 17.4%; PCI: 5.3% and CABG/PCI: 6.1% [24]).

Our findings are similar to the results from which the SYNTAX Score II was derived (10) and underline the concept that the decision between CABG and PCI in complex CAD should, in addition to anatomical characteristics, balance the clinical characteristics that may favour one therapy over the other. Using the SYNTAX Score II, younger age, female gender and reduced LVEF were shown to favour CABG compared to PCI on long-term mortality. Hence, in such patients a lower anatomical SYNTAX Score would be required in order for the long-term mortality risk to be similar between CABG and PCI. Nevertheless, older age, COPD or significant ULMCA disease favoured PCI compared to CABG. Thus, in this type of patient, a higher anatomical SYNTAX Score would be needed for the long-term mortality risks to be similar.

Finally, the present study, although limited due to small sample size, showed clearly benefit for patients treated with PCI in concordance with SYNTAX Score II recommendation. On the other hand, patients recommended for CABG (but treated with PCI) presented not only higher mortality at 4 years, but were younger making this analysis even more important.

Limitations

Firstly, the study has an unavoidable limitation on account of its retrospective nature. Currently the on-going EXCEL (Evaluation of XIENCE PRIME™ or XIENCE V® Everolimus Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation) trial (25) and SYNTAX II trial (26) will better quantify the performance of

the SYNTAX Score II. Our study, being retrospective and based on the metrics used in the SYNTAX Score II, cannot assess other reasons that PCI-operators without on-site cardiac surgery used in making decisions. There is no data regarding other variables that may guide clinicians in the decision-making process, such as bleeding risk, frailty or socioeconomic reasons including a total CABG-cost for patients in another country. The value of the study is also limited due to the small sample size and single-centre analysis.

CONCLUSION

The present study demonstrated that intuitive (most educated) decision-making process by interventional cardiologists for choosing optimal myocardial revascularisation method for individual patient (CABG or PCI) differed in 57% from the SYNTAX Score II recommendation for CABG only. Discordance between the SYNTAX Score II recommended revascularisation strategy and the clinical decision was met with a higher long-term 4-year mortality. Therefore, it appears that the SYNTAX Score II may potentially ameliorate traditional oculostenotic reflex triggering inappropriate PCI, and serve as a surrogate of objective Heart Team decision-making in PCI centres without cardiac surgery on-site.

Conflict of interest

All authors have no conflict of interest to disclose.

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Chapter 3.5

Cost-Effectiveness of Percutaneous Coronary Intervention vs. Bypass Surgery from a Dutch Perspective

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Heart *in press*

ABSTRACT

Aims. Recent cost-effectiveness analyses of percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) have been limited by a short time-horizon or were restricted to the U.S. healthcare perspective. We therefore used individual patient-level data from the SYNTAX trial to evaluate the cost-effectiveness of PCI vs. CABG from a European (Dutch) perspective.

Methods and results. Between 2005 and 2007, 1800 patients with three-vessel or left main CAD were randomized to either CABG (n=897) or PCI with drug-eluting stents (DES;n=903). Costs were estimated for all patients based on observed healthcare resource utilisation over 5 years of follow-up. Health state utilities were evaluated with the EuroQOL questionnaire. A patient-level microsimulation model based on Dutch life-tables was used to extrapolate the 5-year in-trial data to a lifetime horizon.

Although initial procedural costs were lower for CABG, total initial hospitalisation costs per patient were higher (€17506 vs. €14037, $p < 0.001$). PCI was more costly during the next 5 years of follow-up, due to more frequent hospitalisations, repeat revascularisation procedures, and higher medication costs. Nevertheless, total 5 year costs remained €2465/patient higher with CABG. When the in-trial results were extrapolated to a lifetime horizon, CABG was projected to be economically attractive relative to DES-PCI, with gains in both life expectancy and quality-adjusted life expectancy. The incremental cost-effectiveness ratio (€5390/QALY gained) was favourable and remained $< €80000/\text{QALY}$ in $> 90\%$ of the bootstrap replicates. Outcomes were similar when incorporating the prognostic impact of non-fatal MI and stroke, as well as across a broad range of assumptions regarding the effect of CABG on post-trial survival and costs. However, DES-PCI was economically dominant compared with CABG in patients with a SYNTAX Score ≤ 22 or in those with left main disease. In patients for whom the SYNTAX Score II favoured PCI based on lower predicted 4 year mortality, PCI was also economically dominant, whereas in those patients for whom the SYNTAX Score II favoured surgery, CABG was highly economically attractive (ICER range, €2967 to €3737/QALY gained).

Conclusions. For the broad population with three-vessel or left main disease who are candidates for either CABG or PCI, we found that CABG is a clinically and economically attractive revascularisation strategy compared with DES-PCI from a Dutch healthcare perspective. The cost-effectiveness of CABG vs. PCI differed according to several anatomic factors, however. The newly developed SYNTAX Score II provides enhanced prognostic discrimination in this population and may be a useful tool to guide resource allocation as well.

Trial registration: Clinical trial unique identifier: NCT00114972 (www.clinical-trials.gov)

Keywords: Coronary artery bypass grafting; drug-eluting stents; percutaneous coronary intervention; cost-benefit analysis; randomized clinical trial

INTRODUCTION

Approximately 2% of the total healthcare expenditure in the European Union is spent on the treatment of coronary artery disease (CAD). [1] Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for multivessel CAD have been compared in several studies. For patients without diabetes mellitus, these studies have demonstrated similar short- and long-term survival with either procedure, but CABG provided better angina relief and fewer repeat revascularisation procedures.[2, 3, 4, 5, 6, 7, 8] Long-term economic evaluations have found that while PCI is cost-saving in the short term, CABG is an economically attractive treatment option compared with balloon angioplasty or PCI using bare metal stents.[9]

The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial is the largest trial to date to compare PCI with CABG in a broad patient population. In contrast to earlier studies, the SYNTAX trial recruited patients with complex CAD (three-vessel or left main disease), used drug-eluting stents (DES), and applied an all-comers design. At 5-year follow-up, CABG had a lower rate of the composite endpoint of all-cause death, myocardial infarction, stroke or repeat revascularisation compared with DES-PCI- driven mainly by lower rates of non-fatal myocardial infarction (MI) and repeat revascularisation.

Although the U.S. and European healthcare systems differ significantly with respect to clinical practice patterns, availability of resources and prices, few economic evaluations of CABG vs. PCI have been performed from a European perspective.[7, 10, 11] Moreover, the available European economic substudies of randomized trials are >10 years old and have incorporated

only a brief time horizon. We therefore performed a prospective health economic study alongside the SYNTAX trial, adopting a Dutch perspective and using disease-simulation techniques to extrapolate the 5-year trial results to a lifetime horizon. In addition, we analysed the economic outcomes in subgroups defined on the basis of the new SYNTAX Score II[12]—a validated tool for combining clinical and anatomic factors to predict long-term survival after PCI or CABG. We hypothesized that this tool would be a good discriminator of economic outcomes and healthcare value.

METHODS

Between 2005 and 2007, 1800 patients with three-vessel or left main CAD were randomized to either CABG (n=897) or PCI with DES (n=903). Costs for the index hospitalisation and the five-year follow-up period were assessed by combining detailed resource-based and event-based methods. Quality of life was assessed directly from patients at baseline, 1, 6, 12, 36, and 60 months using the three-level EuroQOL (EQ-5D) health status instrument and converted to utility weights (range 0-1) using an algorithm developed for the Dutch population.[13]

Cost-effectiveness. The cost-effectiveness of CABG vs. PCI was assessed over a life-time horizon. Health benefits were expressed in QALYs in the primary analysis and as life-years in secondary analyses.[14, 15] Life-years and QALYs were discounted at 1.5% annually, and costs at 4% annually, as recommended by the Dutch Manual for Cost-analysis in Healthcare. [16] The analyses were based on a combination of (1) observed in-trial cost and quality of life data and (2) projections of post-trial

costs, life expectancy and quality-adjusted life expectancy obtained from a Markov disease-simulation model. As recommended by the Dutch Council for Public Health, a willingness-to-pay (WTP) threshold level of €80 000 per quality-adjusted life year (QALY) gained was used to assess cost effectiveness.[17]

RESULTS

Patient Population. In SYNTAX, 1800 patients with de novo three-vessel or left main CAD were randomized to either CABG (n=897) or PCI (n=903). Of the randomized patients, 27 assigned to CABG and 7 assigned to PCI did not undergo any revascularisation procedure and were excluded from the primary modified intention-to-treat (mITT) population (eFigure 1). There were no significant differences in any observed baseline characteristics between the CABG and PCI groups for the mITT population. Of the mITT patients, 148 (8.4%) were enrolled in The Netherlands, 39% had left main CAD, and the median follow-up was 60 months.

Initial Treatment Costs. Of the patients that were assigned to PCI, 885 (98.8%) underwent PCI and 11 (1.2%) underwent CABG. Among patients assigned to CABG, 854 (98.2%) underwent CABG, and 16 (1.8%) underwent PCI. Resource utilisation for the initial revascularisation procedures is summarised in eTable 2 (per protocol [PP] population). In the PCI group, 13.6% underwent staged procedures. On average, 2.1 guiding catheters, 3.5 guide-wires, 3.7 angioplasty balloons, and 4.5 drug-eluting stents were used during the initial PCI procedure. Although procedure duration was longer for CABG, initial procedure costs were €1351 lower with CABG as compared with PCI

(€6472 vs. €7823, $P<0.001$), owing to higher costs associated with disposable resources in the PCI group. For the mITT population, the difference in initial procedural costs was similar (€1354; €6444 vs. €7798, $P<0.001$) to the results in the PP population.

Clinical events, resource utilisation, and costs during the initial hospitalisation are summarized in Table 1. Post-procedural hospital costs were higher for the CABG group compared with the PCI group (€8725 vs. €3996, $P<0.001$), as were physician fees (€2264 vs. €2111, $P<0.001$). As a result, total initial hospitalisation costs were ~€3500/patient higher in the CABG group compared with the PCI group (€17506 vs. €14037, $P<0.001$).

Follow-up Resource Utilisation and Costs. Follow-up clinical outcomes, resource utilisation, and costs are summarised in eTable 3. During each year of follow-up, the annual rates of diagnostic catheterisation, repeat revascularisation, hospitalisation, and their associated costs were higher for patients assigned to initial PCI. In addition, costs for outpatient services and medications were consistently higher in the PCI group compared with the CABG group. Rehabilitation costs were greater in the first year after CABG and were similar between treatments in the subsequent years. Overall, the difference in cumulative medical care costs between the CABG and PCI narrowed from €3469 after the index hospitalisation to €2465 after 5 years of follow-up (Table 2 and Figure 1).

Utility Weights and QALYs. For both treatment groups, utility weights improved substantially over the course of the trial (eTable 5). At 1 month follow-up, utility weights were significantly lower after CABG than PCI (0.74 vs. 0.83, $P<0.001$), reflecting longer recovery after CABG. However, this early utility benefit

Table 1. Index Hospitalisation Events, Resource Utilisation, and Costs (mITT population)

	CABG (n=870)	PCI (n=896)	Difference (95% CI)	P value
Death, %	1.4(12))	1.8(16)	-0.4 (-1.6, 0.8)	0.49
MI, %	2.4(21))	2.7(24)	-0.3 (-1.7, 1.2)	0.72
Stroke, %	1.0(9))	0.1(1)	0.9 (0.2, 1.6)	0.01
Unplanned CABG, %	1.1(10))	0.8(7)	0.4 (-0.5, 1.3)	0.42
Unplanned PCI, %	0.5(4))	1.8(16)	-1.3 (-2.3, -0.3)	0.008
Complications, %				
Major bleeding	4.8(42)	4.5(40)	0.4 (-1.6, 2.3)	0.72
Respiratory failure	1.6(14)	0.0(0)	1.6 (0.8, 2.4)	< 0.001
Renal failure	2.4(21)	0.7(6)	1.7 (0.6, 2.9)	0.003
Wound infection	4.1 (36)	0 (0)	4.1 (2.8, 5.5)	< 0.001
Other infection	6.2(54)	0.4 (4)	5.8 (4.1, 7.4)	< 0.001
Atrial fibrillation	17.9 (156)	1.3 (12)	16.6 (13.9, 19.2)	< 0.001
Cardiac tamponade	0.8 (7)	0.3 (3)	0.5 (-0.2, 1.2)	0.22
Other procedures, %				
Permanent pacemaker	0.6(5)	0.2(2)	0.4 (-0.2, 0.9)	0.28
ICD implantation	0.2(2)	0.0(0)	0.2 (-0.1, 0.5)	0.24
Carotid endarterectomy	0.5(4)	0.0(0)	0.5 (0.0, 0.9)	0.06
Length of stay*				
ICU/CCU	3.0±5.2	1.6±2.9	1.5 (1.1, 1.9)	< 0.001
Total	13.9±10.1	6.7±7.7	7.2 (6.4, 8.0)	< 0.001
Initial hospitalisation costs, €				
Revascularisation procedures	6517±1691 [6347]	7930±4404 [7374]	-1413 (-1726, -1100)	< 0.001
Hospital stay + ancillary services	8725±4818 [7117]	3996±3816 [2143]	4729 (4324, 5134)	< 0.001
Physician fees	2264±370 [2126]	2111±587 [1887]	153 (107, 199)	< 0.001
Total	17506±5621 [16214]	14037±6850 [12597]	3469 (2883, 4054)	< 0.001

Values in brackets are medians. CCU, cardiac care unit; CI, confidence interval; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; mITT, modified intention-to-treat. * Length of stay in the different countries was converted to the Dutch perspective using a regression modelling approach (eTable 4).

Table 2. Cumulative In-Trial Costs, QALYs, and Life-Years, Adjusted for Censoring

Time Since Randomisation	Cumulative Costs, €			Cumulative QALYs			Cumulative Life-Years		
	CABG	PCI	Δ	CABG	PCI	Δ	CABG	PCI	Δ
1 year	20868	17495	3373	0.762	0.791	-0.029	0.975	0.965	0.009
2 years	22193	19156	3037	1.547	1.600	-0.022	1.933	1.912	0.022
3 years	23364	20507	2857	2.323	2.329	-0.005	2.877	2.832	0.045
4 years	24454	21879	2575	3.074	3.058	0.016	3.800	3.732	0.069
5 years	25680	23215	2465	3.802	3.762	0.040	4.701	4.601	0.100

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-years gained. Δ=difference between CABG and PCI group; , difference between CABG and PCI groups

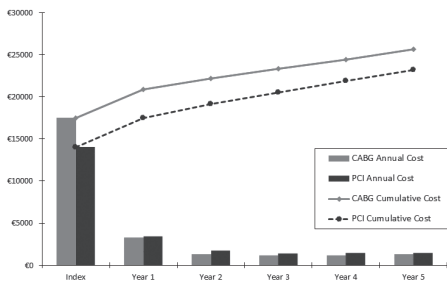


Figure 1. Mean cumulative medical costs (lines) and mean annual follow-up costs (bars) in 2012 euros, for the PCI and CABG groups. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. Note that the first set of bars represents the costs of the index hospitalisation.

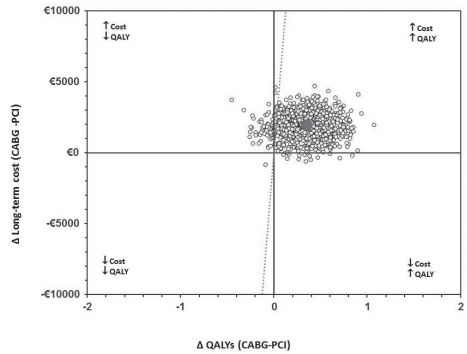


Figure 2. Joint distribution of projected lifetime incremental costs and quality-adjusted life expectancy for CABG vs. PCI based on bootstrap replication of the SYNTAX trial population, plotted on the cost-effectiveness plane. The red circle represents the estimated mean values (incremental cost=€1929, incremental QALYs=0.358). The green line represents the €80000/QALY cost-effectiveness threshold. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year.

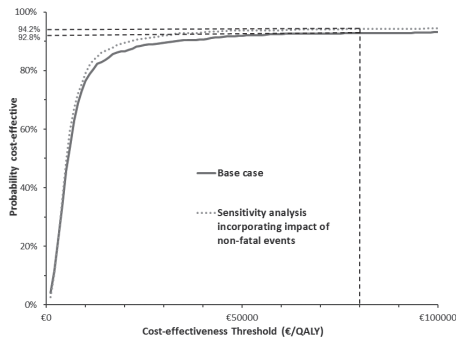


Figure 3. Cost effectiveness acceptability curve of CABG vs. PCI. The probability that CABG is cost-effective is calculated as the proportion of bootstrap-derived estimates falling below a given cost-effectiveness threshold and is plotted across a range of possible cost-effectiveness thresholds. The solid blue line represents the base-case analysis, while the dashed red line indicates the analysis in which the impact of MI and stroke were taken into account.

of PCI was no longer significant at 6 months and longer follow-up. As a result of the early utility benefit of PCI, cumulative quality-adjusted life-years were higher with PCI than with CABG through 3 years of follow-up (Table 2). At 5 years, however, life expectancy (4.70 vs. 4.60 years) and quality-adjusted life expectancy

(3.80 vs. 3.76 QALYs) were both greater with CABG than with PCI.

Lifetime Cost-Effectiveness- Overall Population. Results from lifetime cost-effectiveness analyses are shown in Table 3. Despite reductions in annual follow-up costs over the first 5 years of follow-up, patients in the CABG group were projected to incur €1929 higher overall healthcare costs over a lifetime horizon. Although CABG was only associated with a small gain in life expectancy (0.100 life-years) and quality-adjusted life expectancy (0.040 QALY) over the first 5 years of follow-up, extrapolation of the observed benefits over a lifetime horizon resulted in an increase in life expectancy of 0.488 years and an increase in quality-adjusted life expectancy of 0.358 QALYs with CABG as compared with PCI. The resulting incremental cost-effectiveness ratio (ICER) for CABG vs. PCI was €5390/QALY gained, with 92.8% of bootstrap replicates

Table 3. Lifetime Cost-Effectiveness Results for Base Case CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained. Costs are discounted at 4%, life-years and

	Cost, €		QALYs					% CABG <€80k ^{**}		
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)	ICER (€/QALY)		% Dominant	% Dominated
Tapered CABG effect between 5 and 10 years										
Base case lifetime analysis	38164	36235	1929 (252, 3591)	11.782	11.424	0.358 (-0.103, 0.783)	5390	1.3	5.1	92.8
Life-years instead of QALYs*	38164	36235	1929 (252, 3591)	14.359*	13.871*	0.488 (-0.052, 0.971)*	3953*	1.3	3.4	96.3
Undiscounted cost and QALYs	47053	45501	1552 (-617, 3655)	13.975	13.517	0.458 (0.098, 0.970)	3391	7.3	4.0	94.4
Incorporate prognostic effect of MI + /Stroke	37827	35796	2031 (357, 3499)	11.677	11.279	0.399 (-0.062, 0.800)	5092	0.8	4.6	94.2
Fixed CABG effect between 5 and 10 years										
Lifetime analysis	37823	36235	1588 (-118, 3296)	11.877	11.424	0.453 (-0.120, 0.975)	3505	3.7	4.9	94.3
Life-years instead of QALYs*	37823	36235	1588 (-118, 3296)	14.475	13.871	0.604 (-0.087, 1.208)	2629*	3.7	3.4	96.2
Undiscounted cost and QALYs	47053	45501	1552 (-1169, 3253)	13.975	13.517	0.458 (-0.126, 1.210)	3391	14.3	2.4	95.2
Incorporate prognostic effect of MI + /Stroke	37492	35796	1695 (-29, 3208)	11.773	11.279	0.494 (-0.077, 0.986)	3429	2.6	4.8	94.6
No effect of CABG beyond 5 years										
Lifetime analysis	38550	36235	2315 (641, 3975)	11.686	11.424	0.263 (-0.082, 0.594)	8815	0.3	6.3	90.7
Life-years instead of QALYs*	38550	36235	2315 (641, 3975)	14.242	13.871	0.371 (-0.032, 0.746)	6240*	0.3	3.2	96.6
Undiscounted cost and QALYs	47513	45501	2012 (-44, 4088)	13.858	13.517	0.341 (-0.016, 0.951)	5900	2.7	5.4	93.4
Incorporate prognostic effect of MI + /Stroke	38205	35796	2409 (779, 3854)	11.581	11.279	0.302 (-0.056, 0.624)	7971	0.8	3.2	95.3

* QALYs at 1.5% per year

Results in this row represent life-years (instead of QALYs) and cost per life-year gained (instead of cost per QALY gained)

**Probability that CABG is the preferred strategy at a societal ICER of €80000/QALY gained

and Sensitivity Analyses

Table 4. Lifetime Cost-Effectiveness Results for Subgroups

	Cost, €		QALYs		Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	ICER (€/QALY)	% CABG Dominant	% CABG Dominated	%CABG %CABG <€80k*
	CABG	PCI	CABG	PCI										
Age ≤60 (n=553)	39860	39162	697 (-2304, 4041)	16.864	16.560	0.303 (-0.411, 1.108)	2298	26.7	8.9	84.7				
Age 61-70 (n=586)	38220	36653	1567 (-1054, 4634)	11.447	11.270	0.178 (-0.459, 1.105)	8826	11.1	14.5	81.7				
Age >70 (n=627)	36502	33319	3182 (424, 6125)	7.361	7.163	0.198 (-0.554, 0.900)	16085	0.7	25.3	70.0				
Diabetes (n=1272)	39360	37875	1485 (-1500, 4742)	11.161	10.689	0.472 (0.164, 1.431)	3143	12.3	5.5	92.8				
No diabetes (n=494)	37675	35585	2090 (-29, 3965)	11.992	11.714	0.278 (-0.344, 0.690)	7509	2.0	23.8	72.9				
LM disease (n=694)	40269	37034	3235 (623, 6086)	11.025	11.471	-0.445 (-1.158, 0.359)	PCI dominant	0.1	80.8	15.6				
Three-vessel disease (n=1072)	36743	35725	1018 (-1076, 2884)	12.261	11.393	0.868 (0.215, 1.271)	1174	0.0	0.1	79.2				
SYNTAX Score ≤22 (n=562)	39230	37730	1500 (-1940, 4589)	12.498	12.502	-0.004 (-0.980, 0.537)	PCI dominant	6.6	51.6	28.7				
SYNTAX Score 23-32 (n=600)	36431	33935	2496 (101, 5270)	11.444	11.398	0.0458 (-0.625, 0.841)	54475	0.1	34.0	61.3				
SYNTAX Score ≥33 (n=595)	39017	37036	1982 (-1051, 4794)	11.480	10.371	1.109 (0.298, 1.740)	1787	10.3	0.5	99.4				
Difference in 4 year predicted mortality (SYNTAX score II)														
≥2% in favor of PCI (n=281)	36060	36359	-299 (-4950, 4572)	8.079	9.416	-1.336 (-2.531, 0.065)	PCI dominant	1.1	44.7	2.9				
0-2% in favor of PCI (n=235)	37637	34227	3409 (-1359, 8185)	11.593	12.473	-0.880 (-2.788, 0.599)	PCI dominant	0.6	78.4	15.2				
0-2% in favor of CABG (n=467)	34953	34425	527 (-1934, 3242)	14.014	13.873	0.141 (-0.748, 1.119)	3737	21.3	18.8	71.7				
2-5% in favor of CABG (n=320)	40205	37318	2887 (-1536, 6851)	13.613	12.840	0.773 (-0.413, 1.259)	3733	7.9	10.4	86.6				
≥5 in favor of CABG (n=463)	41158	38116	3041 (-240, 6969)	9.847	8.822	1.025 (0.358, 1.995)	2967	3.4	0.2	99.8				
Dutch patients (n=148)	36032	34996	1036 (-6570, 7168)	12.835	11.147	1.688 (-0.274, 2.409)	614	43.6	2.4	94.7				
Non-Dutch patients (n=1618)	38348	36346	2002 (294, 3694)	11.674	11.449	0.225 (-0.202, 0.715)	8898	1.2	13.0	85.2				

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio for CABG vs. PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained; LM, left main;

* Probability that CABG is the preferred strategy at a societal ICER of €80000/QALY gained

Costs are discounted at 4%, life-years and QALYs at 1.5% per year

falling below a societal willingness-to-pay threshold of €80000/QALY (Figures 2 and 3, and Table 3/row 1). When outcomes were expressed in life-years, CABG was associated an ICER of €3953/life-year gained (Table 3/row 2). In the analysis accounting for the prognostic impact of non-fatal MI and stroke, the benefit of CABG increased modestly to 0.399 QALYs, and the ICER was €5092/QALY gained with 94.2% of bootstrap replicates below a societal willingness-to-pay threshold of €80,000 (Figure 3, Table 3/row 4).

Results were robust across a wide range of alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI on both costs and survival beyond the 5 year timeframe observed in the trial. Assuming that the benefits of CABG would remain constant from year 5 to year 10, with no further benefit beyond 10 years, the ICER for CABG vs. PCI was €3505/QALY gained. When we conservatively assumed that there would be no benefit of CABG beyond the 5-year trial period, the ICER increased to €8815/QALY gained with 90.7% of the bootstrap replicates below the €80000/QALY threshold. Results were similar when the analysis incorporated the prognostic impact of non-fatal MI and stroke, or when effectiveness was expressed in life-years rather than QALYs (eTables 8 and 9).

Subgroup Analyses. Results from the pre-specified subgroup analyses are summarised in Table 4. For most subgroups, the results were similar to those of the overall trial population albeit with greater uncertainty due to the reduced sample sizes. However, the results in several subgroups differed substantially from those of the overall trial. For patients with less complex coronary anatomy (SYNTAX Score ≤ 22), PCI was projected to increase quality-adjusted life expectancy and to reduce

costs compared with CABG. Conversely, for patients with SYNTAX Scores of 23-32 and ≥ 33 , the ICERs for CABG vs. PCI were €54475/QALY gained and €1787/QALY gained, respectively.

PCI was an economically dominant strategy for patients with left main CAD, whereas CABG was highly economically attractive compared with PCI for patients with three-vessel disease (ICER €1174/QALY gained). For all other subgroups, CABG was economically attractive compared with PCI with ICERs $< \text{€}20,000/\text{QALY}$ gained. Importantly, results for the population of patients enrolled in the Netherlands ($n=148$) were consistent with those for the overall population as well. Results for subgroups were unchanged when we considered the impact of non-fatal MI and stroke on mortality (eTable 8).

When stratified according to differences in predicted 4-year mortality based on the SYNTAX score II, we found that the tool not only discriminates well for 4-year mortality but also for long-term economic outcomes (Figure 4). For patients for whom PCI was estimated to result in better 4-year survival, PCI was also economically dominant. For patients for whom CABG was predicted to result in better 4 year survival, CABG was also highly economically attractive (ICERs ranging from €2967 to €3737 per QALY gained).

Impact of Stent Pricing and Productivity Losses. We also performed a sensitivity analysis varying the acquisition cost of DES (eFigure 3). Although the ICER for CABG vs. PCI increased as the acquisition cost of DES decreased, even at a DES price of €0, the ICER for CABG remained $< \text{€}20,000/\text{QALY}$ gained in the overall trial population. When this analysis was repeated within strata according to SYNTAX Score, only the intermediate SYNTAX Score tertile was sensitive to stent price

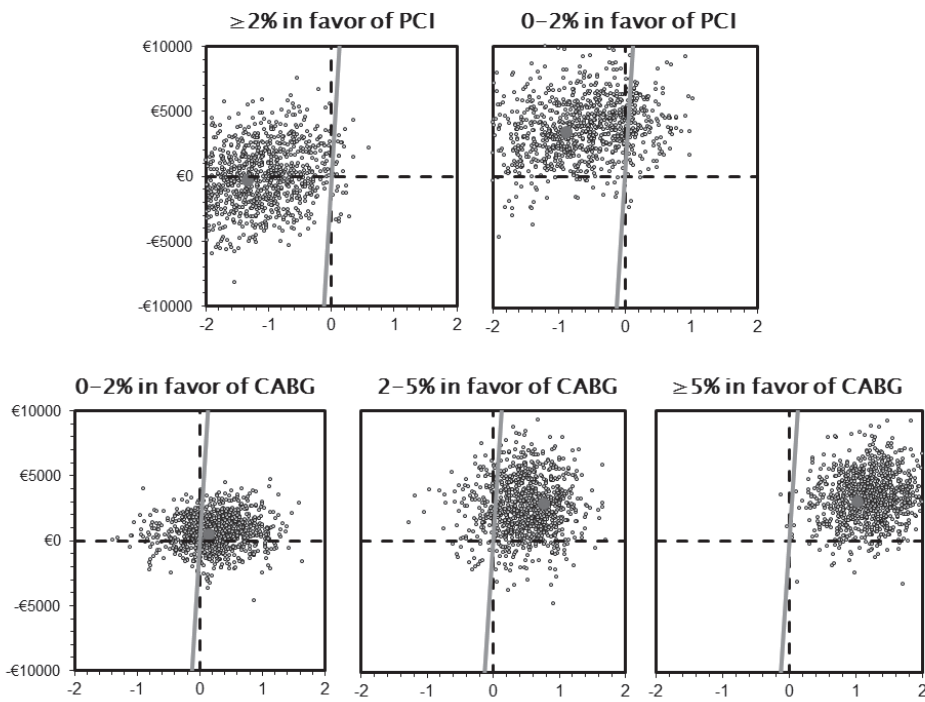


Figure 4.

Joint distribution of projected lifetime incremental costs and quality-adjusted life expectancy for CABG vs. PCI within subgroups stratified according to differences in predicted 4-year mortality based on the SYNTAX Score II. For each stratum, the red circle represents the estimated mean values. The green line represents the €80000/QALY cost-effectiveness threshold. Horizontal axes: difference in quality-adjusted life years (CABG-PCI). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

(eFigure 3 and eTable 10). For patients with a SYNTAX Score ≤ 22 , the PCI strategy remained economically attractive unless the stent price exceeded €1400/stent, while for patients with a SYNTAX Score ≥ 33 , CABG remained economically attractive at all stent acquisition costs. However, among patients with SYNTAX Scores between 23 and 32, the ICER for CABG vs. PCI remained $<€80,000/\text{QALY}$ gained only if the DES acquisition cost was $>€675/\text{stent}$.

Finally, we performed a sensitivity analysis to assess the impact of productivity loss on the cost-effectiveness of CABG vs. DES-PCI. Since no data on employment were collected from

the SYNTAX trial patients, we used several external sources to estimate the proportion of patients employed at baseline, the timing of return to work according to the type of revascularization procedure, and the average earning for a Dutch worker.[18, 19] After incorporating these factors in our analysis, the cost difference between the treatments increased by $\sim€400$ for the overall population, reflecting the greater productivity loss with CABG compared to PCI, but the ICER for CABG vs. PCI remained $<€7000/\text{QALY}$ gained (eTable 11). Also for subgroups according to SYNTAX Score tertile and LM or 3-vessel disease subgroups,

the results were similar to the main analyses that did not incorporate productivity losses.

DISCUSSION

This economic substudy of the SYNTAX trial is the first to directly compare long-term clinical and economic outcomes of DES-PCI vs. CABG among patients with three-vessel or left main CAD from a European (Dutch) healthcare perspective. Our results reveal that initial hospitalisation costs were higher with CABG, and these up-front costs were only partially offset by improved clinical outcomes and lower resource utilisation during follow-up. Over the first 5 years of follow-up, CABG improved life expectancy and quality-adjusted life expectancy (by 0.10 years and 0.040 QALYs, respectively) while increasing costs by ~€2500 compared with DES-PCI. These in-trial life expectancy results were magnified when extrapolated over a patient's lifetime (0.358 QALYs and 0.488 life years gained with CABG vs. DES-PCI), while the cost difference narrowed further (~€1900 higher costs with CABG vs. DES-PCI). In the base case analysis, the resulting lifetime cost-effectiveness ratios for CABG vs. DES-PCI were €5390/QALY gained and €3953/life year gained, values that are considered highly cost-effective from a Dutch perspective. These results were robust to a variety of alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI, stent pricing, and the prognostic impact of non-fatal myocardial infarction and stroke.

For most subgroups, the results were similar to those of the overall trial population albeit with more uncertainty due to the reduced sample sizes. In patients with

a SYNTAX Score ≤ 22 , however, DES-PCI was associated with a small lifetime gain of 0.004 QALY compared with CABG, resulting in an economically dominant position compared with CABG. These results suggest that for patients with relatively straightforward 3-vessel or left main CAD, DES-PCI might be the preferred revascularisation strategy on both clinical and economic grounds. A more definitive answer regarding the optimal treatment for left main CAD will be provided by the results of the ongoing EXCEL trial (NCT01205776 clinicaltrials.gov). In contrast, in the subgroup with highly complex CAD (SYNTAX Score ≥ 32), CABG was strongly favoured on clinical and economic grounds (1.109 QALY gain, €1982 higher costs compared with DES-PCI). In the intermediate SYNTAX Score group, CABG was associated with a small 0.049 QALY gain, surrounded by large uncertainty.

While device prices are often perceived to be an important driver of cost-effectiveness,[20] our results were not sensitive to the stent price. Indeed, the major determinant of cost-effectiveness in our DES-PCI vs. CABG comparison was the gain in (quality-adjusted) life expectancy rather than the cost difference. Therefore, we found no device cost at which DES-PCI would have been an economically attractive treatment option in the overall population, or in patients with a SYNTAX Score ≥ 32 . Only in the intermediate SYNTAX Score group did stent price affect the ICER materially. Indeed, for that subgroup, reducing the stent price by ~25% from current levels would make DES-PCI the preferred treatment option on economic grounds.

Role of the SYNTAX Score II. Our paper is the first to examine the economic implications of the SYNTAX Score II, which was recently developed in order to provide an objective,

evidence-based tool to enhance individualized decision making for patients with complex CAD.[12] This score predicts 4 year mortality with PCI or CABG and was constructed using both anatomical predictors (i.e. the anatomical SYNTAX Score) and clinical factors including age, gender, renal function, left ventricular ejection fraction, chronic obstructive pulmonary disease and peripheral vascular disease. Because of the small differences in costs between treatments and the resultant large impact of mortality differences on the ICER, we hypothesized that the SYNTAX Score II would also be a good discriminator of economic outcomes. In this analysis, we confirmed our hypothesis by showing that selecting patients for PCI vs. CABG based on 4-year mortality projections leads to treatment decisions that are both clinically and economically attractive.

Comparison with previous studies. Our results differ substantially from the cost-effectiveness of DES-PCI vs. CABG based on the 1-year SYNTAX data.[21] In that early analysis, DES-PCI was associated with a small QALY gain and ~\$3600 lower costs, suggesting that DES PCI was economically dominant compared with CABG. This discrepancy between the 1 year and lifetime cost-effectiveness of DES-PCI and CABG, emphasizes the importance of basing policy decisions on studies with long-term follow-up in order to capture benefits that emerge at later time points.

Few studies on the cost-effectiveness of CABG vs. PCI have been performed from a European country perspective.[9] The economic substudy of the Arterial Revascularisation Therapy Study (ARTS) trial found that after 3 year follow-up CABG was associated with €1798 higher costs than PCI using bare metal stents, but did not use QALYs to express benefits and did not project their findings

over a lifetime horizon.[22] Recently, a small (n=199) observational study examined the cost-effectiveness of CABG vs. DES-PCI from the perspective of the Austrian healthcare system. In that study, CABG was associated with €5400 higher costs at 5 years, leading to an ICER of €45615 per death, myocardial infarction, stroke or repeat revascularisation avoided.[11] The ICER was more favourable for CABG in those subgroups with a higher SYNTAX Scores—similar to the results of our study.

Limitations. Although the SYNTAX trial enrolled patients from 18 countries, the current analysis was performed from the perspective of a single country. We were careful to assign costs at levels of resource utilisation that were unlikely to differ by country, but this was not possible for length of stay. We therefore used regression modelling to adjust length of stay at the individual country level to Dutch norms. Following recommendations for economic analyses alongside multinational trials, all clinical outcomes were assumed to be similar across countries.[23] Restricting our analysis to Dutch patients only would have severely reduced our sample size and increased uncertainty in the results. Nonetheless, it is reassuring that our results were very similar when restricted to only Dutch trial participants.

In addition, our extrapolations necessitated assumptions on the impact of CABG on long-term survival, quality-of-life and healthcare costs. We used all possible data from the trial to inform these extrapolations and tested these assumptions in sensitivity analyses. Finally, DES-PCI was performed using first generation (paclitaxel-eluting) DES. Therefore, our results may not be generalisable to settings where second generation DES are used.

Conclusions. In this economic analysis based on the data from the SYNTAX trial, we

found that from a Dutch healthcare perspective, CABG is an economically attractive revascularisation strategy compared with DES-PCI. However, among patients with anatomically less complex disease, DES-PCI appears to be preferred on both clinical and economical grounds. Finally, we found that the newly developed SYNTAX Score II is a useful discriminator of economic value for revascularisation decisions, providing further support for its incorporation in clinical guidelines and economic policies.

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Chapter 3.6

The EXCEL & NOBLE Trials: similarities, contrasts and future perspectives for left main revascularization

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KEYWORDS

- coronary artery bypass graft
- drug-eluting stent
- left main
- percutaneous coronary intervention

Abstract

Unprotected left main coronary artery (ULMCA) stenosis has relatively high prevalence and exposes patients to a high risk for adverse cardiovascular events. The optimal revascularisation strategy (coronary artery bypass surgery [CABG] or percutaneous coronary intervention [PCI]) for patients with complex coronary artery disease is a topic of continuing debate. The introduction of the newer-generation drug-eluting stents (DES) – with documented improvements in both safety and efficacy – has prompted the interventional community to design two new dedicated randomised trials comparing CABG and PCI: the NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) and EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trials. The aims of the present review are to describe the similarities and contrasts between these two trials as well to explore their future implications in ULMCA treatment.

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Introduction

The relevance of an unprotected left main coronary artery (ULMCA) stenosis was first described more than 100 years ago¹. James Herrick reported the story of a 55-year-old male who died in cardiogenic shock after a period of 52 hours. The autopsy found an extensive necrosis of the left ventricle associated with total occlusion of the left main coronary artery by a thrombus overlying an area of atherosclerotic narrowing¹. The explanation for this massive necrosis is the large area of myocardium at risk in patients with ULMCA. It has been shown that, in a usual right dominant coronary anatomy, the left coronary artery supplies approximately 84% of the flow to the left ventricle²⁻⁴.

Currently, the prevalence of significant ULMCA disease – diameter stenosis greater than 50 percent – may vary from 4-6% of all patients who undergo coronary arteriography to 24% of patients with acute coronary syndrome^{5,6}. Most of these patients are symptomatic and at high risk of cardiovascular events^{4,5,7}. In that sense, for over 30 years, coronary artery bypass grafting (CABG) has been regarded as the standard of care for ULMCA by improving long-term prognosis when compared with optimal medical therapy⁸.

Since its clinical introduction in 1977⁹, percutaneous coronary intervention (PCI) has gradually matured. The advent of drug-eluting stents (DES) has markedly improved the long-term outcomes in patients with complex coronary anatomy. Numerous studies have compared outcomes in subjects treated with either CABG or PCI¹⁰⁻¹². Meta-analytic combinations of these studies have basically shown that PCI has similar five-year mortality and myocardial infarction, with a lower incidence of stroke and increased risk of repeat revascularisation when compared to CABG^{11,12}.

The relatively high prevalence and substantial prognostic impact of ULMCA with an unclear optimal therapeutic option added to the introduction of the newer-generation DES – with proven improvements in both safety and efficacy¹³⁻¹⁹ – has prompted the design of two new dedicated randomised trials comparing CABG and PCI. The aim of the present manuscript is to describe the design and future perspectives proposed by the ongoing EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) trials.

EXCEL and NOBLE: similarities and contrasts

The EXCEL trial (ClinicalTrials.gov identifier: NCT01205776) is an international, prospective, unblinded, randomised multicentre trial which enrolled 1,905 subjects in 131 centres (Figure 1). EXCEL was designed to establish the safety and efficacy of the everolimus-eluting stent (XIENCE PRIME™ or XIENCE V® or XIENCE Xpedition™ or XIENCE PRO™; Abbott Vascular, Santa Clara, CA, USA) in patients with significant ULMCA disease.

The NOBLE trial (ClinicalTrials.gov identifier: NCT01496651) is an international, prospective, unblinded, randomised multicentre

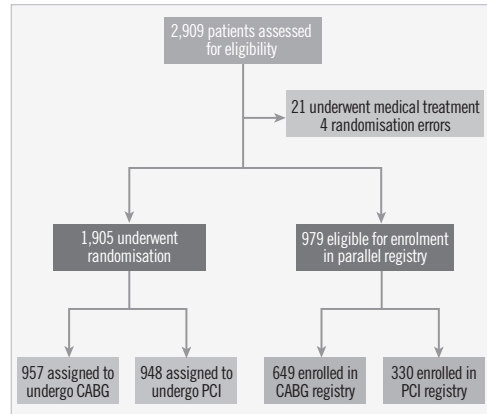


Figure 1. Enrolment and randomisation of patients with previously untreated left main coronary artery disease in the EXCEL trial.

trial which randomised 1,200 patients in 36 centres. The biolimus-eluting stent BioMatrix™ (Biosensors, Morges, Switzerland) is the recommended study stent but other CE-marked DES may be used at operators' discretion. As shown in Table 1, although both trials aim to compare PCI versus CABG for ULMCA treatment, they do not have exactly the same design.

Comparison of anatomic selection criteria in the EXCEL and NOBLE trials

The EXCEL and NOBLE trials have, as core for inclusion, an equipoised treatment for PCI and CABG as assessed by the local Heart Team. It is mandatory in both trials that the interventional cardiologist and surgeon determine appropriateness and eligibility in their respective area of expertise.

The first difference between EXCEL and NOBLE is how the Heart Team assesses the ULMCA as being significant. The NOBLE trial adopted as significant an ULMCA with a visually assessed diameter stenosis (DS) >50% or fractional flow reserve (FFR) <0.80. The EXCEL trial defines significant ULMCA as one of the following: DS ≥70% (visually estimated) or DS ≥50% but <70% (requiring non-invasive or invasive [FFR ≤0.80] evidence of ischaemia or intravascular ultrasound [IVUS] minimal lumen area [MLA] ≤6.0 mm²). Additionally, the EXCEL trial has enrolled patients with left main equivalent disease defined as Medina classification 0,1,1 bifurcation disease with both the ostial left anterior descending artery (LAD) and ostial left circumflex artery (LCX) stenoses having ≥70% DS. If one or both of the ostial LAD and ostial LCX stenoses are ≥50% and <70% stenotic by visual estimation, then this lesion(s) is demonstrated to be significant either by non-invasive or invasive (FFR ≤0.80) evidence of ischaemia in its myocardial distribution or IVUS MLA ≤4.0 mm². By protocol, in EXCEL, FFR was the preferred strategy to stratify lesion significance.

Table 1. Design of the EXCEL and NOBLE trials.

	EXCEL trial	NOBLE trial
Main inclusion criteria	<ul style="list-style-type: none"> – Significant unprotected left main coronary artery (ULMCA) disease or left main equivalent disease – Clinical and anatomic eligibility for both PCI and CABG as agreed to by the local Heart Team – Silent ischaemia, stable angina, unstable angina or recent MI (if recent MI, CK-MB must have returned to normal) – The subject must be ≥18 years of age 	<ul style="list-style-type: none"> – Stable, unstable angina pectoris or ACS – Significant unprotected left main coronary artery (ULMCA) with no more than three additional non-complex PCI lesions – Patient eligible to be treated by CABG and by PCI
Key clinical exclusion criteria	<ul style="list-style-type: none"> – Prior PCI of the left main at any time prior to randomisation or prior PCI of any other (non-left main) coronary artery lesions within one year prior to randomisation – Prior CABG – Need for any concomitant cardiac surgery – Subjects unable to receive dual antiplatelet therapy for at least one year – Subjects requiring or who may require additional surgery within one year – Pregnancy or intention to become pregnant – Non-cardiac comorbidities with life expectancy less than 3 years – Other investigational drug or device studies that have not reached their primary endpoint 	<ul style="list-style-type: none"> – ST-elevation infarction within 24 hours – Patient is too high risk for CABG – Expected survival <1 year – Allergy to aspirin, clopidogrel or ticlopidine – Allergy to biolimus
Key angiographic exclusion criteria	<ul style="list-style-type: none"> – SYNTAX score ≥33, as determined by the consensus of the local Heart Team – Visually estimated left main reference vessel diameter <2.25 mm or >4.25 mm (post-dilatation up to 4.5 mm is allowed) 	<ul style="list-style-type: none"> – CABG clearly better treatment option (LMCA stenosis and >3, or complex additional coronary lesions)
Primary endpoint	Death, MI and stroke (modified Rankin scale [mRS]) ≥1 and increase by ≥1 from baseline at 3 years)	Death, stroke, non-index treatment-related MI and new revascularisation (PCI or CABG)
Secondary endpoint	<ul style="list-style-type: none"> – Composite measure of all-cause mortality, myocardial infarction, stroke or unplanned revascularisation for ischaemia at 3 years post index procedure – Stroke at 30 days – Unplanned revascularisation for ischaemia at 3 years post index procedure – Health-related quality of life and treatment costs 	<ul style="list-style-type: none"> – Combined endpoint of death, stroke and non-index treatment-related MI – Individual endpoints of death, stroke and non-index treatment-related MI – New revascularisation by CABG or PCI – Definite stent thrombosis/symptomatic graft occlusion – Canadian Cardiovascular Society angina score – New York Heart Association functional class – Duration of admission for index treatment
Sample size	1,905 patients	1,200 patients
Participating centres	131 active sites worldwide	36
Current status	Enrolment complete (03/June/2014). Report of the primary endpoint is expected in 2016	Enrolment complete (22/January/2015). Report of the primary endpoint is expected in 2016

ULMCA disease should be regarded as a heterogeneous pathology when considering the choice of revascularisation modality. The anatomical complexity of the left main may vary from a single lesion in the shaft to distal trifurcation disease and its association with more complex downstream (three-vessel) disease, and may have been directly correlated to incomplete revascularisation and to late all-cause mortality following PCI^{20,22}. The prevailing international revascularisation guidelines recommend revascularisation of ULMCA with CABG or PCI in subjects with SYNTAX scores which are low (SYNTAX score <23: class I recommendation for CABG or PCI [level of evidence B for both]) and intermediate (SYNTAX score 23-32: class I for CABG and class IIa for PCI [level of evidence B for both]). The same guidelines recommend against revascularisation with PCI of ULMCA disease with high SYNTAX scores (SYNTAX score ≥33: class I for CABG and class III for PCI [level of evidence B for both])⁷.

The EXCEL trial adopted an enrolment criterion of subjects with ULMCA disease up to intermediate anatomical complexity defined by a SYNTAX score <33 (assessed by the local Heart Team)²³. On the other hand, the NOBLE trial has been enrolling patients with ostium, mid-shaft and/or bifurcation and with no more than three

additional non-complex PCI lesions. Non-complex lesions in the NOBLE trial were defined as length <25 mm, non-chronic total occlusion, non-two-stent bifurcation, non-calcified and non-tortuous coronary lesions.

Study device

The EXCEL and NOBLE trials were designed to study the impact of revascularisation on ULMCA disease, incorporating changes in medical therapies, PCI technology and techniques, and advances in CABG which had been introduced since the completion of the SYNTAX and FREEDOM studies²⁴⁻²⁶. In EXCEL, the workhorse stent was the everolimus-eluting stent (EES) (XIENCE). The randomised comparisons of everolimus- versus paclitaxel-eluting stents were designed and powered for a combination of angiographic, ischaemic and safety outcomes, and have consistently shown the EES to be associated with more favourable outcomes compared to paclitaxel-eluting stents¹³⁻¹⁶. In addition, the largest patient-level meta-analysis (n=4,989) of the SPIRIT clinical programme has shown that EES were superior to paclitaxel-eluting stents in reducing all-cause mortality (3.2% vs. 5.1%, HR: 0.65, 95% CI: 0.49 to 0.86; p=0.003)¹⁷.

In NOBLE, the workhorse drug-eluting stent is a biolimus-eluting stent (BES) (BioMatrix) with bioabsorbable polymer. The stent was selected due to its high radial strength and expansion capacity, especially cell opening²⁷. Furthermore, the biolimus-eluting stent with bioabsorbable polymer has shown excellent results in comparison with first^{28–30} as well as second-generation DES^{31,32}. The results of NOBLE and EXCEL may help to understand the clinical impact of EES and BES specifically for ULMCA.

Intravascular imaging to guide ULMCA PCI

IVUS guidance compared with angiography guidance has been associated with reduced one-year rates of definite/probable stent thrombosis, myocardial infarction and composite adjudicated major adverse cardiac events (i.e., cardiac death, myocardial infarction, or stent thrombosis)^{33,34}. Specifically for ULMCA PCI, a propensity score matching of the MAIN-COMPARE registry (n=201) has associated IVUS-guided PCI to lower three-year mortality³⁵. In both NOBLE and EXCEL, IVUS-guided PCI is strongly recommended pre-treatment and post-treatment to optimise lumen dimensions in the left main segment and for all non-left main lesions³⁶. An exception is made for distal lesions or tortuous vessels. All left main lesions in which IVUS is used will undergo rigorous core laboratory evaluation (Cardiovascular Research Foundation, New York, USA in the EXCEL trial and Belfast Health & Social Care Trust, Belfast, Northern Ireland in the NOBLE trial).

In this regard, these trials will help to understand the PCI results according to the baseline IVUS criteria and IVUS post-PCI predictors of clinical events. Although a two by two randomised trial for IVUS guidance would be ideal, the EXCEL and NOBLE protocols are already sufficiently complex that adding another level of randomisation is not practical. Moreover, although IVUS assessment is relatively simple, not all sites are expert in the use of IVUS guidance for complex left main stenosis.

Primary endpoints

EXCEL and NOBLE had different sample size calculation due to the difference in their respective primary endpoints. In NOBLE, the sample size calculation is based on the combined primary endpoint of death, stroke (defined as ischaemic or haemorrhagic cerebrovascular event verified by brain CT), non-index treatment-related MI and new revascularisation (MACCE) after two years (Table 1). In EXCEL, the primary endpoint is defined as death, MI and stroke (modified Rankin scale [mRS] ≥ 1 and increase by ≥ 1 from baseline at three years). EXCEL has completed its enrolment with a total number of 1,905 patients (Figure 1).

Recommendations on bifurcation treatment

Bifurcation lesions may be present in about 70% of ULMCA cases and have been associated with the occurrence of ischaemic events after PCI³⁷. In EXCEL and NOBLE protocols, a single-stent crossover provisional technique is recommended whenever possible for treatment of bifurcations. After implantation of the first stent, if there is uncertainty concerning the adequacy of side branch

patency, an FFR determination is recommended, with a value of ≤ 0.80 indicating that side branch dilatation should be performed.

The decision to use a primary two-stent technique is left to the operator's best judgement. However, a primary two-stent strategy rather than a single crossover stent technique should be considered when the side branch (usually the left circumflex) is large (>3 mm), with significant disease (by angiographic or IVUS assessment) and lesion length >5 mm, or when there are other special anatomic considerations (e.g., heavy calcification).

In both trials, the strategy of a two-stent technique (crossover or primary two stents) for bifurcation treatment may include any of the following: T-stent, TAP, mini-crush (reverse crush), or culotte bifurcation stent techniques. The final decision is made according to the lesion morphology and the experience of the operator. The use of kissing balloons after provisional second stents is strongly recommended in a two-stent strategy. However, based on the Nordic Bifurcation study³⁸, in NOBLE the culotte technique is preferred in case a two-stent strategy is needed.

Long-term forecasting and comparison of mortality in the EXCEL trial using the SYNTAX score II (SSII)

The SSII was developed in the landmark, all-comers, randomised SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) trial (n=1,800)^{24,25} where selection bias would have been minimal. The SSII is composed of the anatomical SYNTAX score, presence of ULMCA disease, and six clinical characteristics (age, creatinine clearance [CrCl], left ventricular ejection fraction [LVEF], sex, chronic obstructive pulmonary disease [COPD], and peripheral vascular disease [PVD]). SSII has been externally validated in the multinational DELTA (n=2,891) and CREDO-Kyoto (n=3,896) registries^{39,40}. Moreover, international guidelines have implemented the SSII as a risk stratification tool for complex coronary artery disease (class IIa, level of evidence B)⁷.

Recently, a prospective validation of the SYNTAX score II has been proposed to forecast and compare the four-year mortality in the EXCEL trial⁴¹. After completion of patient recruitment in EXCEL, using the actual baseline clinical and angiographic data from each enrolled patient, the SYNTAX score II was calculated. Scores were assigned for the presence and magnitude of each predictor directly based on the Cox proportional hazards model coefficients generating different scores and four-year mortality predictions for PCI and CABG⁴⁰. To determine the 95% prediction intervals (PI), the trial was simulated 10,000 times based on consecutive bootstrap samples⁴².

The SYNTAX score II indicated at least an equipoise for long-term mortality between CABG and PCI in subjects with ULMCA in the EXCEL trial. For the entire study cohort, the four-year predicted mortalities were 8.5% and 10.5% in the PCI and CABG arms, respectively (odds ratios [OR] 0.79; 95% PI: 0.43-1.50). Figure 2 demonstrates the first 1,000 trial simulations. It has been found that there is a 40.4% (n=4,040) chance that the mortality predictions will be significantly lower in favour of PCI, a 4.4% (n=440) chance that

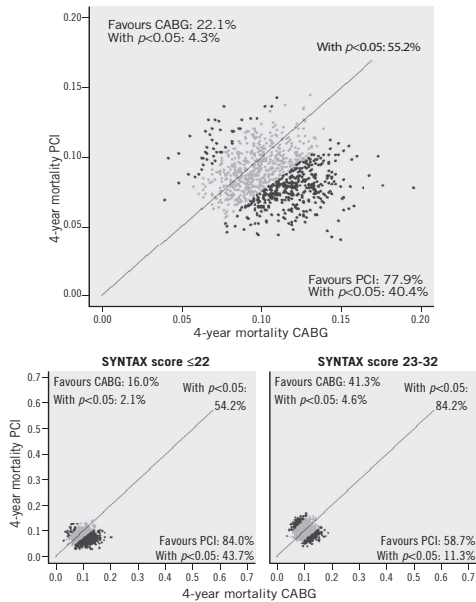


Figure 2. First 1,000 four-year mortality simulations of the EXCEL trial on the SYNTAX score II. Each dot represents one simulated trial mortality in both randomisation arms based on individual predictions. The diagonal line represents identical mortality for CABG and PCI. A dot plotted to the left of the diagonal line favours CABG (actual percentages shown in top left corner), and one to the right favours PCI (actual percentages shown in bottom right corner). Simulated trials with a significant ($p < 0.05$) mortality difference between CABG and PCI are coloured black (actual percentage shown in parentheses in respective corners). Simulated trials with a non-significant ($p \geq 0.05$) mortality difference between CABG and PCI are coloured grey. (Modified from Campos et al⁴¹)

the mortality will significantly favour CABG, and a 55.2% chance of having neutral results. In subjects with low (≤ 22) anatomical SYNTAX scores, the predicted OR was 0.69 (95% PI: 0.34-1.45); in intermediate anatomical SYNTAX scores²³⁻³², the predicted OR was 0.93 (95% PI: 0.53-1.62) (**Figure 2**).

Based on four-year mortality predictions in EXCEL, clinical characteristics shifted long-term mortality predictions either in favour of PCI (older age, male gender, COPD) or CABG (younger age, lower creatinine clearance, female gender, reduced LVEF) (**Table 2**). The explanation for these predictions is that, as mentioned previously, ULMCA revascularisation, when limited to intermediate anatomical complexity, may have adequate results with PCI⁷.

The major limitation of these predictions is also their greatest strength: the complete absence of the EXCEL trial outcomes. Therefore, at present, it not possible to assess whether these predictions are accurate. On the other hand, it enables unbiased validation of the SYNTAX score II, promoting understanding of the multiple risk factors involved in ULMCA disease and decision making on the most appropriate revascularisation modality.

Conclusion

The main results of both the EXCEL and the NOBLE trials are expected in 2016, which will therefore be a promising year for cardiology. The similarities and differences between these studies will, in the end, be complementary in the sense of throwing light on numerous aspects of revascularisation strategies and increasing our understanding of the role and mechanisms of their risk stratification and correlated therapeutic adjunctive tools.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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

Table 2. Four-year mortality prediction comparisons between CABG and PCI in the EXCEL trial⁴¹.

	Overall	SYNTAX score		Age*		CrCl, mL/min		LVEF, %		Gender		COPD		PVD	
		≤ 22	23-32	≤ 66	> 66	≤ 60	> 60	≤ 50	> 50	Female	Male	No	Yes	No	Yes
PCI, n (%)	948	563 (59%)	385 (40.6%)	483 (50.9%)	465 (49.1%)	168 (17.7%)	780 (82.3%)	118 (12.4%)	830 (87.6%)	226 (23.8%)	722 (76.2%)	881 (92.9%)	67 (7.1%)	851 (89.8%)	97 (10.2%)
CABG, n (%)	957	589 (61.5%)	368 (38.5%)	486 (50.8%)	471 (49.2%)	147 (15.4%)	810 (84.6%)	119 (12.4%)	838 (87.6%)	214 (22.4%)	743 (77.6%)	876 (91.5%)	81 (8.5%)	873 (91.2%)	84 (8.8%)
Predicted 4-year mortality PCI, % (95% PI)	8.5 (5.4-11.9)	7.3 (4.2-11.0)	10.1 (6.2-14.6)	5.4 (2.7-8.5)	11.8 (7.3-16.8)	19.7 (11.9-28.7)	6.1 (3.5-9.2)	18.3 (9.3-28.0)	7.1 (4.3-10.4)	13.1 (7.1-19.9)	7.1 (4.0-10.5)	7.9 (4.9-11.2)	16.7 (6.0-29.9)	6.9 (4.2-10.1)	22.5 (11.3-36.1)
Predicted 4-year mortality CABG, % (95% PI)	10.5 (6.6-15.1)	10.3 (5.9-15.6)	10.8 (6.5-15.5)	5.8 (2.7-9.5)	15.41 (9.3-22.5)	18.4 (9.5-28.6)	9.1 (5.2-13.6)	15.2 (6.1-25.8)	9.9 (5.9-14.4)	8.7 (3.3-15.9)	11.1 (6.7-15.9)	9.1 (5.3-13.5)	26.1 (12.4-40.7)	9.0 (5.3-13.3)	26.5 (13.1-41.7)
OR PCI:CABG (95% PI)	0.79 (0.43-1.50)	0.69 (0.34-1.45)	0.93 (0.53-1.62)	0.92 (0.38-2.25)	0.73 (0.37-1.48)	1.08 (0.48-2.64)	0.65 (0.31-1.35)	1.25 (0.49-3.27)	0.70 (0.36-1.39)	1.59 (0.61-5.00)	0.61 (0.30-1.23)	0.86 (0.44-1.72)	0.57 (0.16-1.75)	0.75 (0.38-1.54)	0.81 (0.27-2.32)

*Separated by the median. CABG: coronary artery bypass graft surgery; COPD: chronic obstructive pulmonary disease; CrCl: creatinine clearance; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PI: prediction intervals; PVD: peripheral vascular disease

Online data supplement

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Chapter 3.7

Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II

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Aims	To prospectively validate the SYNTAX Score II and forecast the outcomes of the randomized Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) Trial.
Methods and results	Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization is a prospective, randomized multicenter trial designed to establish the efficacy and safety of percutaneous coronary intervention (PCI) with the everolimus-eluting stent compared with coronary artery bypass graft (CABG) surgery in subjects with unprotected left-main coronary artery (ULMCA) disease and low-intermediate anatomical SYNTAX scores (<33). After completion of patient recruitment in EXCEL, the SYNTAX Score II was prospectively applied to predict 4-year mortality in the CABG and PCI arms. The 95% prediction intervals (PIs) for mortality were computed using simulation with bootstrap resampling (10 000 times). For the entire study cohort, the 4-year predicted mortalities were 8.5 and 10.5% in the PCI and CABG arms, respectively [odds ratios (OR) 0.79; 95% PI 0.43–1.50]. In subjects with low (≤ 22) anatomical SYNTAX scores, the predicted OR was 0.69 (95% PI 0.34–1.45); in intermediate anatomical SYNTAX scores (23–32), the predicted OR was 0.93 (95% PI 0.53–1.62). Based on 4-year mortality predictions in EXCEL, clinical characteristics shifted long-term mortality predictions either in favour of PCI (older age, male gender and COPD) or CABG (younger age, lower creatinine clearance, female gender, reduced left ventricular ejection fraction).
Conclusion	The SYNTAX Score II indicates at least an equipoise for long-term mortality between CABG and PCI in subjects with ULMCA disease up to an intermediate anatomical complexity. Both anatomical and clinical characteristics had a clear impact on long-term mortality predictions and decision making between CABG and PCI.
Keywords	Left main • Percutaneous coronary intervention • Coronary artery bypass surgery • SYNTAX score • SYNTAX Score II • Mortality • Drug-eluting stents

Introduction

Coronary artery bypass graft (CABG) surgery was introduced in 1967¹ with the aim of relieving angina pectoris, enhancing quality of life and improving survival. In patients with unprotected left-main coronary artery (ULMCA) disease, the superiority of CABG over optimal medical treatment has been demonstrated in multiple studies and meta-analyses^{2,3} and has been the standard of care for over 30 years.

Percutaneous coronary intervention (PCI) was introduced into clinical practice in 1977⁴ and was initially considered appropriate only for single-vessel disease. With the advent of drug-eluting stents (DES), long-term outcomes after PCI have markedly improved in patients with more complex coronary artery disease. Specifically for ULMCA disease, numerous registries and three randomized trials have compared outcomes in subjects treated with either CABG or PCI.^{5–7} Consequently, the prevailing international revascularization guidelines recommend revascularization of ULMCA with CABG or PCI in subjects with SYNTAX scores that are low [SYNTAX score <23: class I recommendation for CABG or PCI (level of evidence B for both)] and intermediate [SYNTAX score 23–32: class I for CABG and class IIa for PCI (level of evidence B for both)]. The same guidelines recommend against revascularization with PCI of ULMCA disease with high SYNTAX scores [SYNTAX score ≥33: class I for CABG and class III for PCI (level of evidence B for both)].⁸ These recommendations are based on similar 5-year mortality and myocardial infarction, with a lower incidence of stroke and increased risk of repeat revascularization with PCI compared with CABG in subjects with ULMCA disease and lower anatomical complexity.^{6,7}

The introduction of the newer-generation everolimus-eluting stent (EES)—with proven marked improvements in both safety and efficacy^{9–13}—has prompted the design of the randomized Evaluation of Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization (EXCEL) Trial.

Aiming to improve decision making between CABG and PCI in patients with complex coronary artery disease, the SYNTAX Score II combines anatomic and clinical factors.^{14,15} Importantly, the SYNTAX Score II was developed in the landmark, all-comers, randomized SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Trial where selection bias would have been minimal, and externally validated in two real world registries.^{14,16} In addition, the SYNTAX Score II has been included in international revascularization guidelines.⁸

Although numerous risk scores and prospective trials are available in the medical literature, their performances are reported when the outcomes are already known. The aim of the present study is to apply the SYNTAX Score II in the ongoing EXCEL trial, in order to prospectively validate the SYNTAX Score II before independent reporting of the outcomes of the trial, forecast the 4-year mortality outcomes in the PCI and CABG arms, and to describe how anatomical and clinical characteristics impact on the long-term mortality predictions and decision making between CABG and PCI.

Methods

Study population

The EXCEL trial (clinicaltrials.gov identifier: NCT01205776) is an international, prospective, unblinded, randomized multicenter trial that enrolled 1905 subjects in 131 centres. Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization was designed to establish the safety and efficacy of the EES (XIENCE PRIME™ or XIENCE V® or XIENCE Xpedition™ or XIENCE PRO™; Abbott Vascular, Santa Clara, CA, USA) in patients with ULMCA disease. Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization adopted an enrolment criteria of subjects with ULMCA disease up to intermediate anatomical complexity (SYNTAX Score <33), with minimal exclusion criteria to allow meaningful comparisons between revascularization modalities (Supplementary material online, Table S1). The information on the trial endpoints and sample size calculation is also available in the Supplementary material online.

Following diagnostic angiography demonstrating significant ULMCA disease and the consensus of the local Heart Team (qualified participating interventional cardiologist and cardiac surgeon), subjects were consented and randomized 1 : 1 to: (i) PCI with the EES or (ii) CABG. All randomized patients were scheduled to undergo follow-up telephone contact or office visit up to 5 years post-procedure.

The primary endpoint of the EXCEL trial is the composite measure of all-cause mortality, myocardial infarction or stroke [modified Rankin Scale (mRS) ≥1 and increase by ≥1 from baseline] at a median follow-up interval of 3 years post-index procedure.

SYNTAX Score II

The SYNTAX Score II has been described previously.¹⁴ In brief, the SYNTAX Score II augments the purely anatomical SYNTAX score with anatomical and clinical factors that were shown to alter the threshold value of the anatomical SYNTAX score in order for equipoise to be achieved between CABG and PCI for long-term mortality. The SYNTAX Score II is composed of the anatomical SYNTAX score, presence of ULMCA disease, and six clinical characteristics [age, creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), gender, chronic obstructive pulmonary disease (COPD) and peripheral vascular disease (PVD)]. The SYNTAX Score II allows for 4-year mortality predictions to be made following revascularization with CABG or PCI to aid decision making between CABG and PCI. Importantly, the SYNTAX Score II was developed in the randomized SYNTAX Trial ($n = 1800$), and externally validated in the multinational DELTA ($n = 2891$) and Credo-KYOTO ($n = 3896$) registries.^{14,16,17}

Using the actual baseline clinical and angiographic data from each enrolled patient in EXCEL, the SYNTAX Score II was calculated for each patient. Scores were assigned for the presence and magnitude of each predictor directly based on the Cox proportional hazards model coefficients generating different scores and 4-year mortality predictions for PCI and CABG.¹⁴ To mirror conventional clinical practice, investigator reported anatomical SYNTAX Scores were used in the analysis.¹⁸

Statistical analysis

Categorical variables are presented as numbers and percentages and are compared with the χ^2 test. Continuous variables are expressed as mean \pm SD or median with interquartile range (IQR), and are compared using the Student's *t*-test or Wilcoxon rank-sum test based on their

distributions. Within EXCEL, SYNTAX Score II predictor values were >99% complete with the exception of LVEF which was 95.1% complete. An advanced multiple imputation strategy which takes the correlation between all potential predictors (method of chained equations) was used to account for missing values as previously described.¹⁹

Comparison of predicted 4-year mortality between CABG and PCI arms

The individual predicted mortality and the odds ratio (OR) of the two randomized revascularization strategies were calculated using the SYNTAX Score II. To determine the 95% PIs, the trial was simulated 10 000 times and generated 4-year mortality from predictions based on consecutive bootstrap samples²⁰ of the original SYNTAX trial (Figure 1).^{17,21} A prediction interval is an estimate of an interval in which future observations will fall, with a certain probability, compared with what has already been observed (SYNTAX trial).²² All data analyses were performed using R version 2.15.3.²³

Results

Between 29 September 2010 and 6 March 2014, 2909 patients with ULMCA disease were screened and 1905 subjects randomized to CABG ($n = 957$) or PCI ($n = 948$) (Figure 2).

Subjects in the two randomization arms were well balanced with regards to baseline demographic and clinical characteristics included in the SYNTAX Score II (Table 1). Overall, the median age was 66.0 (IQR 59.0–73.0) years, 76.3% male, 24.7% female, 7.8% COPD and 8.6% PVD. The median LVEF was 60.0% (IQR 52.0–63.0%), median CrCl 85.0 mL/min (IQR 66.8–106.2 mL/min) and the median anatomical SYNTAX score 21.0 (IQR 15.0–26.0).

SYNTAX Score II 4-year mortality predictions in the cohorts

The predicted mortality was 8.5% (95% PI 5.4–11.9%) in the PCI arm and 10.5% (95% PI 6.6–15.1%) in the CABG arm (OR 0.79; 95% PI 0.43–1.50%) (Table 2).

Figure 3 demonstrates the first 1000 trial simulations. Based on numerical differences in 4-year mortality predictions, 77.9% of trial simulations ($n = 7790$) favoured PCI and 22.1% of trial simulations ($n = 2210$) favoured CABG. In 55.2% of trial simulations ($n = 5520$) 4-year mortality predictions between CABG and PCI could not be separated with statistical significance ($P > 0.05$). 40.4% ($n = 4040$) of trial simulations had mortality predictions separated with statistical significance ($P < 0.05$) in favour of PCI, and 4.4% ($n = 440$) had mortality predictions separated with statistical significance ($P < 0.05$) in favour of CABG.

Anatomical complexity

Anatomical complexity had a clear impact on mortality predictions. In subjects with low (≤ 22) and intermediate,^{23–32} anatomical SYNTAX scores the predicted OR were 0.69 (95% PI 0.34–1.45) and 0.93 (95% PI 0.53–1.62), respectively (Table 2).

In the low SYNTAX score group, 54.2% ($n = 5420$) of mortality predictions were similar ($P > 0.05$) between CABG and PCI; in the intermediate SYNTAX score group, 84.1% ($n = 8410$) of mortality predictions were similar ($P > 0.05$) between CABG and PCI (Figure 3).

Mortality predictions that were separated with statistical significance ($P < 0.05$) in favour of PCI were 43.7% ($n = 4370$) in the low SYNTAX score group, compared with 11.3% ($n = 1130$) in the intermediate SYNTAX score group. Conversely, mortality predictions that were separated with statistical significance ($P < 0.05$) in favour of CABG were 2.1% ($n = 210$) in the low SYNTAX score group, compared with 4.6% ($n = 460$) in the intermediate SYNTAX score group.

Impact of clinical characteristics

Clinical characteristics had a clear impact on 4-year mortality predictions (Table 2, Figure 4). In both arms the subgroup with the highest predicted mortalities was PVD [22.5% (95% PI 11.3–36.1%) in the PCI arm and 26.5% (95% PI 13.1–41.7% in the CABG arm)].

Based on 4-year mortality predictions, older age, male gender and COPD favoured PCI, whereas younger age, lower CrCl, impaired LVEF and female gender favoured CABG (Figure 4).

Diabetes

In subjects with diabetes, predicted mortality was 9.9% (95% PI 5.6–14.7%) in the PCI arm and 11.4% (95% PI 6.4–17.3%) in the CABG arm [OR 0.86 (PI 0.40–1.90; Table 2)]. Similar analyses in non-diabetics yielded predicted mortalities of 7.9% (95% PI 4.8–11.3%) in the PCI arm and 10.2% (95% PI 6.2–14.8%) in the CABG arm [0.75 (PI 0.39–1.48)]. The presence of diabetes had a clear impact on mortality predictions (Figure 5). Trial simulations were separated with statistical significance ($P < 0.05$) in favour of PCI in 14.2% ($n = 1420$) of diabetics, compared with 37.5% ($n = 3750$) in non-diabetics. Comparatively, trial mortality predictions were separated with statistical significance ($P < 0.05$) in favour of CABG in 3.3% ($n = 330$), compared with 2.5% ($n = 250$) in non-diabetics.

Discussion

The main findings of the study are: (i) The prospective use of a decision making and risk prediction tool (SYNTAX Score II) was feasible in a large-scale randomized trial on completion of enrolment of subjects, in which the follow-up results were unknown and blinded; (ii) based on the SYNTAX Score II, we predicted a 77.9% chance of a lower 4-year mortality in the PCI arm of the EXCEL trial, with a 40% chance that this will achieve statistical significance in favour of PCI; (iii) The interplay between angiographic and clinical characteristics has an important impact on decision-making and risk stratification of patients with ULMCA disease.

SYNTAX Score II and prospective mortality predictions

The unprecedented aspect of the present study was to prospectively validate the SYNTAX Score II in a randomized trial that is still ongoing, despite completion of enrolment of patients, with expected reporting of the primary outcome in another 2 years. It is important to emphasize that outcomes of EXCEL are being collected, analysed and reported by an independent clinical events committee (CEC), and that the current analyses were performed with all authors completely blinded to any outcome data. A second unique aspect of the present study was to report the

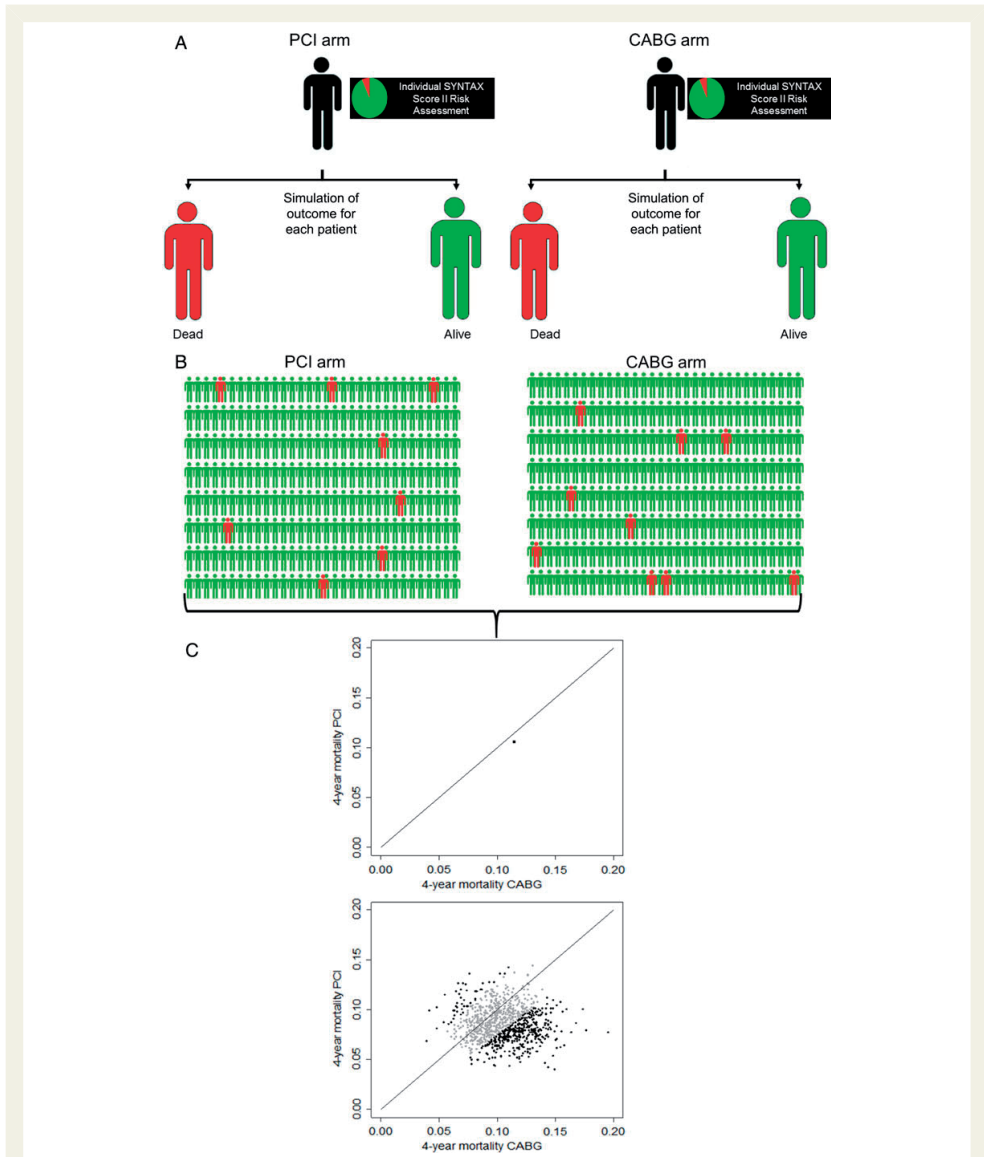


Figure 1 Schematic representation of the SYNTAX Score II predictions used in the Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization trial. (A) The mortality predictions of percutaneous coronary intervention and coronary artery bypass graft for each patient enrolled in the Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization trial were calculated using the SYNTAX Score II. The pie chart represents the individual risk of 4-year mortality (red slice). (B) Based on individual mortality predictions, patients' outcomes were simulated to obtain the 4-year mortality in both trial arms. (C) To determine the 95% prediction intervals steps A and B were repeated 10 000 times with 4-year mortality predictions based on consecutive bootstrap samples of the original SYNTAX trial.

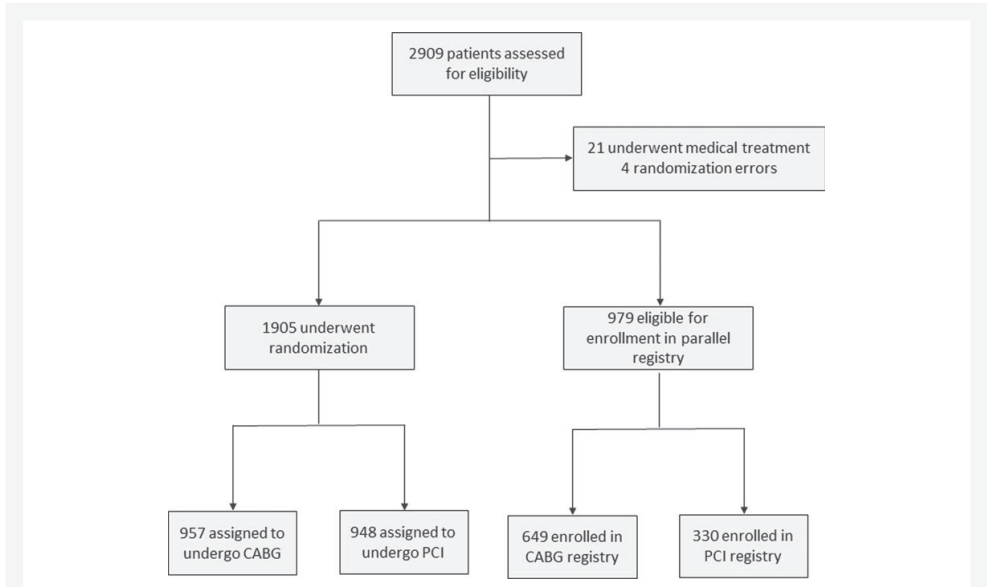


Figure 2 Enrolment and randomization of patients with previously untreated left-main coronary artery disease in the Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization trial.

Table 1 SYNTAX score II baseline variables

	PCI N = 948	CABG N = 957
Anatomical SYNTAX score (IQR)	21.0 (15–26)	20.0 (15.0–25)
Age (years) (IQR)	66.0 (59.0–73.0)	66.0 (60.0–73.0)
Creatinine clearance (mL/min) (IQR)	85.7 (66.2–107.5)	84.6 (67.1–105.0)
LVEF (IQR)	60.0 (52.0–62.0)	60.0 (52.0–63.0)
Left main coronary artery disease, n (%)	948 (100)	957 (100)
Female, n (%)	226 (23.8)	214 (22.4)
COPD, n (%)	67 (7.1)	81 (8.5)
PVD, n (%)	97 (10.3)	84 (8.8)

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; IQR, interquartile range; COPD, chronic pulmonary obstructive disease; PVD, peripheral vascular disease.

predicted long-term mortality of a randomized trial following completion of patient enrolment, blinded and *prior* to the actual reporting of the trial. This was only possible because the SYNTAX Score II was developed in the randomized SYNTAX trial—consisting of a population with complex coronary artery disease (ULMCA

disease or *de novo* three-vessel disease)—and importantly where selection bias was minimal secondary to the unique all-comers design of SYNTAX. In addition, the SYNTAX Score II has shown consistent and solid predictive performances in two multicenter registries for CABG and PCI-treated patients with left-main and/or complex coronary artery disease.^{14,16}

The SYNTAX Score II predicted a 55.2% likelihood that there will not be a statistically significant difference in mortality between the PCI and CABG arms of EXCEL at 4 years. This is likely to be secondary to the clinical profile of the patients recruited in EXCEL. On average subjects in EXCEL had preserved LVEF, reasonable renal function, were predominantly male, and importantly more complex coronary artery disease (SYNTAX score ≥ 33) was a key exclusion criteria. In the SYNTAX trial, female gender, reduced LVEF, lower CrCl, higher anatomical SYNTAX scores and younger age were all shown to favour CABG.^{14,16,22}

The combination of these angiographic and clinical profiles is therefore likely to explain the predicted favourable results for PCI, despite similar baseline clinical characteristics in the CABG and PCI arms of EXCEL. The present study therefore does not imply that PCI reduces mortality in all ULMCA revascularization, but predicts that subjects with ULMCA disease with a lower anatomical and risk profile may potentially derive a prognostic benefit from undergoing PCI, whilst more complex disease and a higher risk clinical profile would remain the domain of CABG on the grounds of prognosis.

Table 2 Four-year mortality predictions comparisons between coronary artery bypass graft and percutaneous coronary intervention

Overall	Syntaxscore			Age*		CrCl(mL/min)		LVEF (%)		Gender		COPD		PVD		Diabetes	
	≤22	23-32	>32	≤66	>66	≤60	>60	≤50	>50	Female	Male	No	Yes	No	Yes	No	Yes
PCI,n (%)	948 (5.9%)	385 (40.6%)	465 (49.1%)	168 (17.7%)	780 (82.3%)	118 (12.4%)	830 (87.6%)	226 (23.8%)	722 (76.2%)	881 (92.9%)	67 (7.1%)	851 (89.8%)	97 (10.2%)	286 (30.2%)	662 (69.8%)		
CABG,n (%)	957 (61.5%)	368 (38.5%)	486 (49.2%)	147 (15.4%)	810 (84.6%)	119 (12.4%)	838 (87.6%)	214 (22.4%)	743 (77.6%)	876 (91.5%)	81 (8.5%)	873 (91.2%)	84 (8.8%)	266 (27.8%)	691 (72.2%)		
Predicted 4-year mortality PCI, % (95% PI)	8.5 (5.4-11.9)	10.1 (6.2-14.6)	5.4 (2.7-8.5)	11.8 (7.3-16.8)	6.1 (3.5-9.2)	18.3 (9.3-28.0)	7.1 (4.3-10.4)	13.1 (7.1-19.9)	7.1 (4.0-10.5)	16.7 (9.1-24.2)	7.9 (4.9-11.2)	6.9 (4.2-10.1)	22.5 (11.3-36.1)	9.9 (5.6-14.7)	79 (48-113)		
Predicted 4-year mortality CABG, % (95% PI)	10.5 (6.6-15.1)	10.3 (6.5-15.5)	5.8 (2.7-9.5)	15.4 (9.5-22.5)	9.1 (5.2-13.6)	15.1 (7.6-23.5)	9.9 (5.9-14.4)	8.7 (3.3-15.9)	11.1 (6.7-15.9)	9.1 (5.3-13.5)	26.1 (12.4-40.7)	9.0 (5.3-13.3)	26.5 (13.1-41.7)	11.4 (6.4-17.3)	10.2 (6.2-14.8)		
OR PCI/CABG (95% PI)	0.79 (0.43-1.50)	0.69 (0.34-1.45)	0.92 (0.38-2.25)	0.73 (0.37-1.48)	0.65 (0.31-1.35)	1.25 (0.49-3.27)	0.70 (0.36-1.39)	1.59 (0.61-5.00)	0.61 (0.30-1.23)	0.86 (0.44-1.72)	0.57 (0.16-1.75)	0.75 (0.38-1.54)	0.81 (0.27-2.32)	0.86 (0.40-1.9)	0.76 (0.39-1.48)		

*Separated by the median. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; surgery; PI, prediction intervals; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

Impact of anatomic complexity in risk predictions

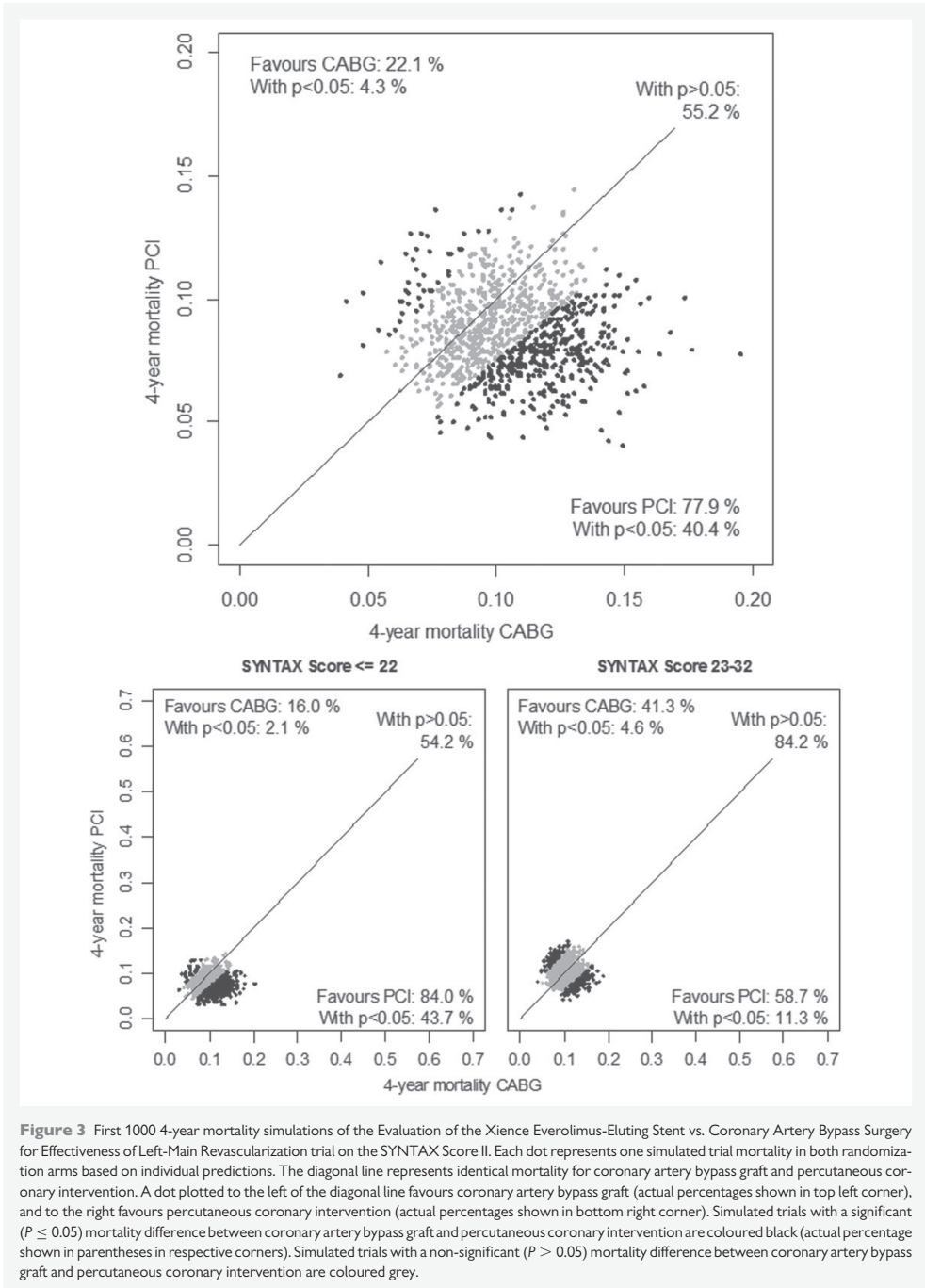
Unprotected left-main coronary artery disease should be regarded as a heterogeneous pathology when considering the choice of revascularization modality. The anatomical complexity of the left main may vary from a single lesion in the shaft to distal trifurcation disease and its association with more complex downstream (three-vessel) disease. These variances may influence the capacity of PCI to achieve complete revascularization, the number of stents implanted and complexity of interventional techniques employed. Moreover, incomplete revascularization and anatomical complexity have been directly correlated to late all-cause mortality following PCI.²⁴⁻²⁶ This was exemplified in the PCI arm of the left-main subgroup of SYNTAX, where the incidence of 5-year all-cause mortality was shown to markedly increase in subjects with a SYNTAX score ≥ 33 (5-year mortality 20.9%) compared with subjects with a SYNTAX score < 33 (5-year mortality 7.9%).

Conversely, in subjects undergoing CABG, anatomical complexity has been shown to not affect long-term prognosis, as exemplified in the CABG arm of the left-main subgroup of SYNTAX, where the incidence of 5-year all-cause mortality remained almost unchanged in subjects with a SYNTAX score ≥ 33 (5-year mortality 14.1%) compared with subjects with a SYNTAX Score < 33 (5-year mortality 15.1%).²⁴ In the present analysis, although the PIs were wide, the expected mortality favoured PCI in the low (≤22) anatomical SYNTAX score group (7.3 vs. 10.3%), and was practically equiposed between PCI and CABG in the moderate (>22) anatomical SYNTAX score group (10.1 vs. 10.8%; Table 2).

The aforementioned reasons explain why the risk predictions in EXCEL are not at variance with results of the recent randomized comparisons between CABG and PCI.⁶ Al Ali et al. pooled the results of three randomized trials of first-generation DES vs. CABG in left-main coronary artery disease and demonstrated that PCI did not reduce the overall mortality (HR 1.08; 95% CI 0.75-1.57), and was practically equiposed between PCI and CABG in the moderate (>22) anatomical SYNTAX score group (10.1 vs. 10.8%; Table 2).

Impact of clinical characteristics in risk predictions

The predictions provided by the SYNTAX Score II displayed in the Figure 4 deserve detailed examination since clinical characteristics markedly affect the simulation patterns. Although it was shown that certain subsets of patients were more likely to have a mortality reduction with PCI or CABG, it is important to emphasize that the associated mortality impact was not exclusively derived from these factors alone. The underlying principle of the SYNTAX Score II being that it balances the interaction of anatomical complexity and six clinical variables that were shown to directly effect decision making on the most appropriate revascularization modality, and not each individual anatomical/clinical characteristic (Supplementary material online, Figure S1). Within the SYNTAX Score II, younger age, female gender, impaired renal function and reduced LVEF were shown to favour CABG compared with PCI on long-term prognostic



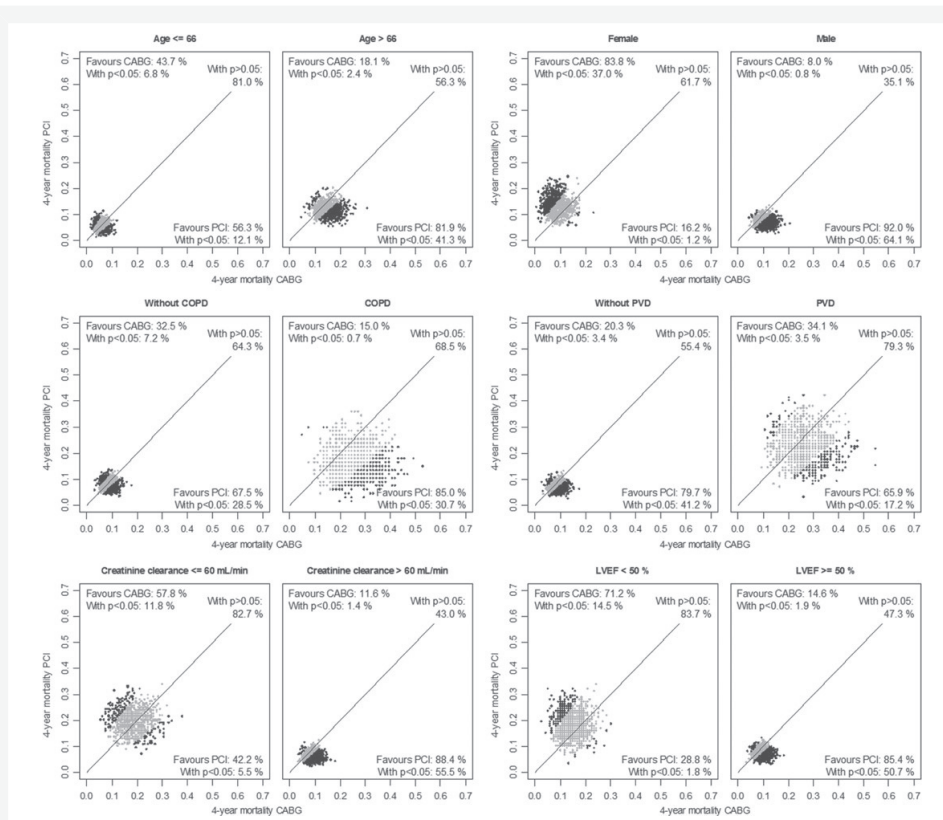


Figure 4 First 1000 4-year mortality simulations of the Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization trial on the SYNTAX Score II according to clinical characteristics. Each dot represents one simulated trial mortality in both randomization arms based on individual predictions. The diagonal line represents identical mortality for coronary artery bypass graft and percutaneous coronary intervention. A dot plotted to the left of the diagonal line favours coronary artery bypass graft and to the right favours percutaneous coronary intervention. Simulated trials with a significant ($P \leq 0.05$) mortality difference between coronary artery bypass graft and percutaneous coronary intervention are coloured black (actual percentage shown in parentheses in respective corners). Simulated trials with a non-significant ($P > 0.05$) mortality difference between coronary artery bypass graft and percutaneous coronary intervention are coloured grey. Some factors are more favourable for percutaneous coronary intervention and others for coronary artery bypass graft and had different impact in the simulation pattern. CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

grounds. As a result, patients with these specific characteristics were shown to derive a prognostic benefit from CABG, even when the anatomical complexity was lower. Conversely, older age, preserved renal and left ventricular function, and COPD were shown to favour PCI compared with CABG on long-term prognostic grounds. As a result, patients with these specific characteristics were shown to derive a prognostic benefit from PCI, even when the anatomical complexity was higher.

Diabetes

Diabetes has previously been shown not to be an independent predictor of mortality in the CABG or PCI arms of the SYNTAX trial, nor to have an interaction effect between CABG and PCI for long-term mortality when the end organ manifestations of diabetes were accounted for, as exemplified in the SYNTAX Score II.^{14,22} Conversely, the FREEDOM trial demonstrated a reduction in

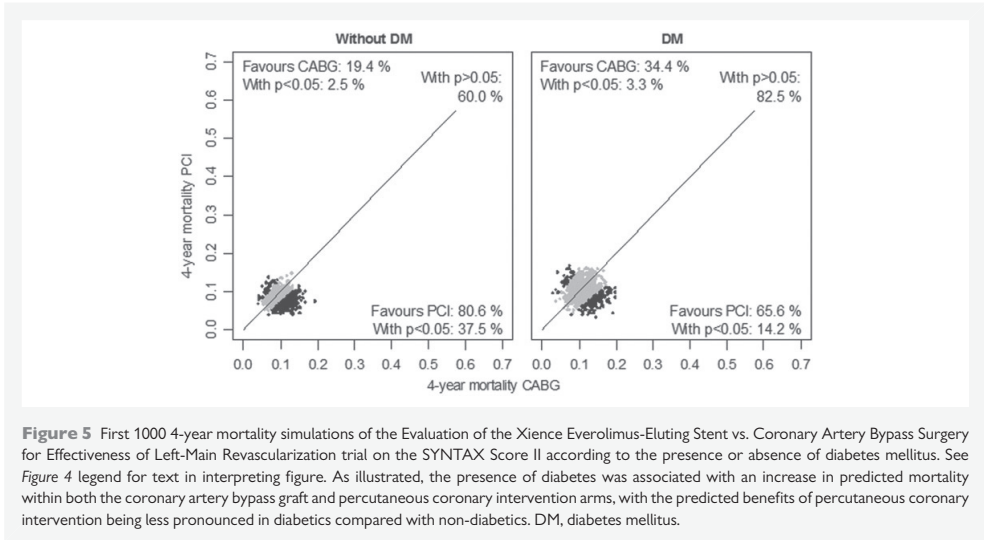


Figure 5 First 1000 4-year mortality simulations of the Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization trial on the SYNTAX Score II according to the presence or absence of diabetes mellitus. See Figure 4 legend for text in interpreting figure. As illustrated, the presence of diabetes was associated with an increase in predicted mortality within both the coronary artery bypass graft and percutaneous coronary intervention arms, with the predicted benefits of percutaneous coronary intervention being less pronounced in diabetics compared with non-diabetics. DM, diabetes mellitus.

mortality in diabetics with predominantly three-vessel disease treated by CABG compared with first-generation drug-eluting stents at a median follow-up of 3.8 years.²⁷ Importantly, ULMCA disease was an exclusion criteria in FREEDOM and is what prompted the presentation of mortality predictions in the diabetic subset of EXCEL. Notably in EXCEL, the presence of diabetes was associated with an increase in predicted mortality within both the CABG and PCI arms. Additionally, the predicted benefits of PCI were less pronounced in diabetics compared to non-diabetics, but remained similar to CABG (Figure 5; Table 2). In essence, despite the fact that diabetes was not contained within the SYNTAX Score II, the systemic metabolic effect of diabetes (such as age, CrCl, LVEF and other factors in the SYNTAX Score II) were associated with an increase in the patient risk profile and less favourable mortality predictions for PCI.^{14,28,29}

The SYNTAX Score II and medical advances

Evaluation of the Xience Everolimus-Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left-Main Revascularization was designed to study the impact of revascularization on ULMCA disease, incorporating changes in medical therapies, PCI technology and techniques, and advances in CABG that were introduced since the completion of the SYNTAX trial. For example, as the SYNTAX Score II was developed in the SYNTAX trial which—exclusively used the first-generation paclitaxel-eluting TAXUS stent, it is not inconceivable that the PCI arm of EXCEL may outperform the mortality predictions made in the present study. In EXCEL, the workhorse drug-eluting stent was the EES (XIENCE). The randomized comparisons of everolimus- vs. paclitaxel-eluting stents were designed and powered for a combination of angiographic,

ischemic and safety outcomes, and have consistently shown the EES to be associated with more favourable outcomes compared with paclitaxel-eluting stents.^{9–12} In addition, the largest patient level meta-analysis ($n = 4989$) of the SPIRIT clinical program has shown that EES was superior to paclitaxel-eluting stents in reducing all-cause mortality (3.2 vs. 5.1%, HR: 0.65, 95% CI: 0.49–0.86; $P = 0.003$).¹³ It is however important to emphasize that this difference was only driven by a lower non-cardiac mortality in the EES group and left-main revascularization was an exclusion criteria.¹³ More specifically in subjects undergoing ULMCA revascularization, a recent systematic review comparing EES with first-generation DES ($n = 2231$) and a propensity match study ($n = 344$) have shown no statistically significant differences in all-cause mortality.^{30,31} Furthermore, even within the SYNTAX Trial, when all stent thrombosis related deaths were removed, the impact on mortality reductions was shown to be modest (definite stent 0.5% reduction in mortality, definite to probable stent thrombosis 1.5% reduction in mortality).^{32,33}

Limitations

The major limitation of the present study is also its greatest strength, namely the complete absence of the EXCEL trial outcomes (expected in the fall of 2016). We therefore cannot verify that the SYNTAX Score II predictions are accurate. However, predicting today the results of a randomized trial which will not be known for 2 years, assuming these predictions are reasonably borne out, opens the door for how future randomized trials may be considered whilst the longer-term (5 year) results of EXCEL are awaited. In addition, the present study will also enable unbiased validation of the SYNTAX Score II, fostering understanding of the multiple risk factors involved in ULMCA disease and decision making on the

most appropriate revascularization modality. Although we are not using risk prediction for the primary endpoint of the trial, all-cause death is a hard, reproducible endpoint not subject to adjudication bias or definitional variation.

Conclusions

In the large-scale, prospective randomized EXCEL trial, the SYNTAX Score II indicated at least an equipoise for long-term mortality between CABG and PCI in subjects with ULMCA disease with low and intermediate anatomical complexity. Clinical characteristics had a clear impact on long-term mortality predictions and decision making between CABG and PCI. The accuracy of these mortality predictions will be compared with the actual individual outcome data from EXCEL in the coming years.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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PART 4

POST-REVASCLARIZATION RISK ASSESSMENT AND MANAGEMENT

Chapter 4.1

Residual SYNTAX score for left main intervention: Are we really ready to predict the future?

Carlos M. Campos, Pedro A Lemos

Catheter Cardiovasc Interv. 2013 Sep 1;82(3):341-2

Editorial Comment

Residual SYNTAX Score for Left Main Intervention: Are We Really Ready to Predict the Future?

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Over the last decades, during which coronary angioplasty was extensively scrutinized as a therapeutic option for patients with multivessel disease, the concept of completeness of revascularization naturally emerged as a central issue of concern [1]. At first, the revascularization completeness was simply estimated by the reduction of luminal stenosis to values lower than 50% in all “major epicardial vessels” with significant lesions by angiography, and procedures were categorized in a binary fashion into those resulting in complete or incomplete revascularization. That definition has several obvious caveats and was questioned since its inception. Nevertheless, even when applying such a strict classification, a clear evolution in the effectiveness of interventional cardiology over time could be clearly seen, moving from a 25% rate of complete revascularization with early balloon-only angioplasty to about 70% with current stent-based interventions, with impact on prognosis [1,2].

The recently developed residual SYNTAX Score is a quantitative measure of the degree and complexity of the residual disease left untreated after an invasive coronary procedure. It was validated in datasets derived from two randomized studies with over 3,500 patients, including an all-comers population (for which selection bias would have been minimal), and with a clinical follow-up of up to 5 years [3,4]. Most importantly, instead of only providing a dichotomous view of the completeness of revascularization, the residual SYNTAX Score appeared as a continuous metric that, eventually, would be able to assess the level of the atherosclerotic burden that could not be managed by an invasive approach.

In this issue of *CCI*, Capodanno et al. evaluated the prognostic impact of baseline and residual SYNTAX scores, as well as the change in the SYNTAX score

after the procedure, for patients treated with left main coronary stenting. The authors demonstrated that both the baseline and the residual SYNTAX scores had a statistical correlation with late mortality. In particular, the residual score yielded a predictive model of similar discrimination but better calibration than the baseline score. At first glance, these findings put into perspective the impact of incomplete revascularization on prognosis, suggesting that the more is left untreated, the worse is the prognosis. However, in the work of Capodanno et al., patients with that were grossly undertreated (i.e., high residual SYNTAX Score) were also older, had more diabetes, worse left ventricular function, higher EuroScore, and more extensive coronary disease. Indeed, patients with high residual SYNTAX score had worse prognosis because of the incomplete revascularization or simply because they were intrinsically a high risk population?

The analysis of residual SYNTAX score in the article of Capodanno et al. provided a (only) moderate predictive ability for late mortality. An issue of utmost importance in current days is the development of reliable tools to forecast the risk of adverse events. The SYNTAX score (both baseline and residual) is an indirect measure of the residual ischaemia burden. It is quite plausible that the prognostic value of residual SYNTAX score could be improved if enhanced by information from the functional significance of the respective coronary stenosis. Finally, it should not be forgot that the SYNTAX score is essentially an instrument created to assess the technical complexity of percutaneous coronary interventions. It is conceivable, therefore, that some of the features used to calculate the score have a marked impact on the success of the procedure (e.g., tortuosity of calcification) but may not add in prognostic information for future atherosclerosis-related events.

Conflict of interest: Nothing to report.

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Chapter 4.2

Reasonable incomplete revascularisation after percutaneous coronary intervention: the SYNTAX Revascularisation Index

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Patrick W Serruys, Gregg W Stone

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KEYWORDS

- incomplete revascularisation
- percutaneous coronary intervention
- SYNTAX Revascularisation Index
- SYNTAX score

Abstract

Aims: Incomplete revascularisation is common after percutaneous coronary intervention (PCI). While the absolute amount of residual coronary artery disease (CAD) after PCI has been shown to be associated with worse outcomes, whether the proportion of treated CAD is prognostically important remains to be determined. We sought to quantify the proportion of CAD burden treated by PCI and to evaluate its impact on outcomes using a new prognostic instrument - the SYNTAX Revascularisation Index (SRI).

Methods and results: The baseline SYNTAX score (bSS) and residual SYNTAX score (rSS) were determined from 2,618 angiograms of patients enrolled in the prospective ACUITY trial. The SRI was then calculated for each patient using the following formula: $SRI = (1 - [rSS/bSS]) \times 100$. Outcomes were examined according to three SRI groups (SRI=100% [complete revascularisation], 50-99%, and <50%). The median bSS was nine (IQR 5, 16), and after PCI the median rSS was one (IQR 0, 6). The median SRI was 85% (IQR 50, 100), and was 100% in 1,079 patients (41.2%), 50-99% in 907 patients (34.6%), and <50% in 632 patients (24.1%). One-year adverse outcomes, including death, were inversely proportional to the SRI. An SRI cut-off of <80% (present in 1,189 [45.4%] patients after PCI) had the best prognostic accuracy for prediction of death (area under the curve 0.60, 95% confidence interval [CI]: 0.53-0.67, $p < 0.0001$). By multivariable analysis, SRI was an independent predictor of one-year mortality (hazard ratio [HR] 2.17, 95% CI: 1.05-4.35, $p = 0.03$). However, when compared to other scores, the rSS showed superior accuracy and predictive capability for one-year mortality.

Conclusions: The SRI is a newly described method for quantifying the proportion of CAD burden treated by PCI. Given its correlation with mortality, and pending external validation, the SRI may be useful in assessing the degree of revascularisation after PCI, with SRI $\geq 80\%$ representing a reasonable goal. However, the rSS showed superior predictive capability for one-year mortality.

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Introduction

Achievement of complete revascularisation is intuitively desirable in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). However, despite major advances in PCI technology and technique, complete revascularisation is often not achieved (e.g., diffuse disease in small vessels, complex calcified lesions, chronic total occlusions), and whether it is always necessary is a matter of considerable debate¹⁻⁵. Indeed, whereas incomplete revascularisation may be unavoidable and detrimental in patients with complex coronary artery disease⁵⁻⁷, in other cases (e.g., low CAD burden) the long-term prognosis may be reasonable with optimal medical therapy⁸. Among patients treated by PCI in the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials, approximately 40-60% achieved complete revascularisation^{1,2,9}. Recently, we proposed a novel approach to characterise and quantify the completeness of revascularisation better – the residual SYNTAX score (rSS)¹. This score has subsequently been validated by other groups and been shown to have good prognostic accuracy for adverse ischaemic outcomes after PCI^{2,10-12}. Undetermined, however, is whether a threshold level exists for a reasonable degree of incomplete revascularisation. In the current report, we propose a novel index, the SYNTAX Revascularisation Index (SRI), which takes into account the severity and extent of baseline CAD (as assessed by the baseline SYNTAX score [bSS]) and the residual CAD after PCI (as assessed by the rSS) in determining the proportion of CAD that has been treated. We sought to determine the prognostic utility of the SRI among patients undergoing PCI from the large, prospective, randomised ACUITY trial.

Methods

STUDY PROTOCOL

The ACUITY trial design has previously been described in detail¹³. Briefly, ACUITY was a multicentre, prospective, randomised trial in which 13,819 patients were enrolled with moderate and high-risk non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) undergoing an early invasive strategy. Prior to coronary angiography, patients were randomly assigned to heparin (unfractionated or low-molecular-weight) plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin monotherapy. Angiography was performed within 72 hours of randomisation, after which patients were triaged to PCI, coronary artery bypass graft (CABG) surgery, or medical therapy. For patients who underwent PCI, stent type (bare metal or drug-eluting) was per operator discretion. Dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least one year. An independent clinical events committee, blinded to treatment assignment, adjudicated all major adverse events. The institutional review board/ethics committee at each participating centre approved the study, and all patients provided written informed consent.

OBJECTIVES, PATIENT POPULATION, AND ANGIOGRAPHIC ANALYSIS

Our primary objective was to quantify the disease burden treated by PCI using the SRI and to evaluate its impact on adverse ischaemic outcomes, including all-cause death, cardiac death, myocardial infarction (MI), and unplanned repeat revascularisation for ischaemia. The present study was limited to patients undergoing PCI in whom quantitative coronary angiography was performed as part of a formal substudy by experienced core laboratory technicians blinded to randomisation and clinical outcomes (Cardiovascular Research Foundation, New York, NY, USA)^{14,15}. Patients with prior CABG were excluded as the SYNTAX score (SS) had not been validated in this cohort at the time of analysis¹⁶.

SYNTAX REVASCUARISATION INDEX

For the present study, three experienced interventional cardiologists (PG, TP, and AC) blinded to randomisation and clinical outcomes assessed the bSS^{17,18} and rSS¹ for each angiogram (www.SYNTAXscore.org). The Fleiss κ statistic¹⁹ (tertile partitioning), determined from 50 independently read films, was 0.57 for bSS signifying a moderate level of interobserver agreement²⁰. The SRI, representing the proportion of CAD burden treated by PCI, was calculated using the following formula: $SRI = (1 - [rSS/bSS]) \times 100$. Patients were stratified into three groups and compared: SRI=100% (complete revascularisation), 50-99%, and <50%. Adverse ischaemic outcomes between groups were compared at one year.

ENDPOINT DEFINITIONS AND STATISTICAL ANALYSIS

Composite major adverse cardiovascular events (MACE) were defined as death from any cause, MI, or unplanned revascularisation for ischaemia. Definitions of the components of the MACE endpoint have been previously detailed¹⁵. All MACE endpoints were adjudicated by an independent committee blinded to randomisation.

Continuous data are presented as mean±SD or median (interquartile range; IQR) and were compared using the ANOVA or Kruskal-Wallis test as appropriate. Categorical variables were compared using the χ^2 test. Correlation (Spearman) between rSS and SRI was examined. Comparisons of one-year outcomes were performed (Kaplan-Meier curves) with the log-rank test between the three groups of SRI. Major subgroup analyses were examined for potential interaction. Receiver operating characteristic (ROC) curves for SRI were determined to assess the relative predictive accuracy for one-year all-cause mortality. Area under the curve for the SRI was computed to identify the Youden index (best cut-off) for one-year all-cause death. Differences in discrimination power between scores were evaluated using the χ^2 test. Stepwise Cox multivariable regression analysis was performed to ascertain variables independently associated with one-year mortality, with variable entry/stay criteria of 0.1/0.1. In addition to the SRI, variables historically known to be associated with these adverse events were included in the models, with the number carefully chosen to avoid overfitting¹. The following variables were included in the model: SRI, age, insulin-treated diabetes, renal insufficiency, baseline white blood

cell count, and baseline cardiac biomarker elevation or ST-segment deviation. A p-value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

PATIENT AND BASELINE CHARACTERISTICS

Of 6,921 patients included in the angiographic substudy of ACUTITY, 3,826 underwent PCI. After excluding patients with a history of CABG (n=862) and those in whom the bSS or rSS could not be calculated due to technical reasons (n=346), 2,618 patients remained, comprising the current study population. No significant differences in baseline characteristics or one-year adverse outcomes were observed between the 346 excluded patients and the study cohort (data not shown). The SYNTAX score ranged from one to 59, with a median of nine (IQR 5, 16). After PCI, the median of rSS was one (IQR 0, 6) ranging from zero to 47.5. The calculated SRI thus ranged from 0% to 100%, with a median of 85% (IQR 50, 100). The SRI was 100% in 1,079 patients (41.2%), 50-99% in 907 patients (34.6%), and <50% in 632 patients (24.1%).

Table 1 and Table 2 present clinical characteristics and angiographic findings, stratified by SRI. Patients with lower SRI were older and had a higher prevalence of diabetes, hyperlipidaemia, and hypertension. They were also more likely to have a history of prior MI and reduced baseline haemoglobin levels and creatinine clearance. Angiographically, patients with lower SRI were more likely to have multivessel disease, a greater number of lesions, and more extensive disease. They were also more likely to have baseline TIMI 0/1 flow, collaterals, and lesions with severe calcification or thrombus. Thienopyridines were less frequently used in the patients in the lowest SRI group at discharge and at 30-day follow-up, but not at one year.

The correlations between rSS and SRI are shown in Figure 1. There was a moderate significant negative correlation between rSS and SRI.

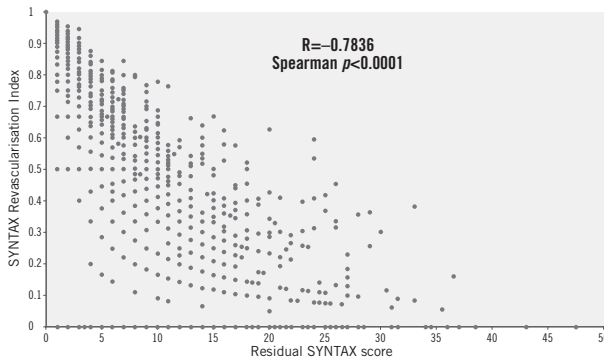


Figure 1. Correlation between the residual SYNTAX score and the SYNTAX Revascularisation Index. Scatter plot graph showing a significant moderate negative correlation between rSS and SRI (lower rSS is associated with higher SRI). One dot represents more than one patient. rSS: residual SYNTAX score; SRI: SYNTAX Revascularisation Index.

CLINICAL OUTCOMES

The one-year rates of MACE were inversely correlated with SRI, with the lowest MACE rates in the group with complete revascularisation and the highest MACE rate in the group with SRI <50%. Similar findings were seen for death, cardiac death, and MI, with non-significant trends for higher rates of unplanned revascularisation and definite/probable stent thrombosis in patients with the greatest degree of incomplete revascularisation (Table 3, Figure 2). By multivariable analysis, lower SRI was a strong independent predictor of one-year mortality (along with insulin-treated diabetes and advanced age) (Table 4).

ROC CURVE ANALYSIS

ROC curve analysis demonstrated a significant association between the SRI and one-year all-cause mortality. An SRI cut-off of 80% had the best prognostic accuracy for risk prediction of death (area

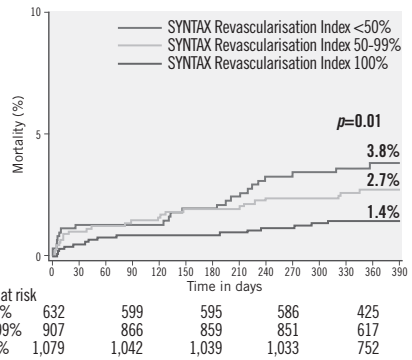


Figure 2. Kaplan-Meier curves showing cumulative mortality rates through one year. The rate of death significantly increased with less complete revascularisation as assessed by SRI.

Table 1. Baseline characteristics according to the SYNTAX Revascularisation Index.

	SRI, 100% n=1,079	SRI, 50-99% n=907	SRI <50% n=632	p-value for trend	
SRI, %	100 (100, 100)	75 (63, 85)	23 (0, 36)	<0.0001	
Age, years	59.0 (51.0, 68.0)	59.00 (52.00, 69.00)	62.0 (54.5, 71.0)	<0.0001	
Male	720/1,079 (66.7)	625/907 (68.9)	432/632 (66.9)	0.55	
Weight, kg	88.0 (75.0, 102.0)	86.00 (75.0, 99.0)	86.0 (76.9, 99.9)	0.43	
Diabetes	270/1,074 (25.1)	266/902 (29.5)	207/629 (32.9)	0.002	
Insulin-treated	69/1,074 (6.4)	78/903 (8.6)	58/632 (9.2)	0.07	
Hypertension	667/1,074 (62.1)	597/904 (66.6)	449/632 (71.0)	0.0008	
Hyperlipidaemia	574/1,062 (54.0)	493/891 (55.3)	382/626 (61.0)	0.02	
Current smoker	382/1,076 (35.5)	325/905 (35.9)	213/628 (33.9)	0.71	
Previous myocardial infarction	272/1,058 (25.7)	266/891 (29.9)	209/618 (33.8)	0.002	
Previous PCI	474/1,078 (44.0)	388/904 (42.9)	286/632 (45.3)	0.66	
Renal insufficiency	143/1,014 (14.1)	134/854 (15.7)	104/581 (17.9)	0.07	
Baseline biomarker elevation	580/1,009 (57.5)	518/841 (61.6)	368/583 (63.1)	0.13	
ST-segment deviation ≥ 1 mm	274/1,079 (25.4)	227/907 (25.0)	166/632 (26.3)	0.86	
TIMI risk score	Low (0-2)	156/862 (18.1)	124/740 (16.8)	64/521 (12.3)	0.02
	Intermediate (3-4)	526/862 (61.0)	440/740 (59.5)	290/521 (55.7)	0.14
	High (5-7)	180/862 (20.9)	176/740 (23.8)	167/521 (32.1)	<0.0001
Haemoglobin, g/dL	14.1 (13.0, 15.1)	14.0 (12.9, 15.2)	13.8 (12.7, 15.0)	0.04	
White blood cells, $\times 10^6$	8.0 (6.5, 9.7)	8.1 (6.5, 9.9)	8.3 (6.5, 10.2)	0.15	
Platelets ($\times 10^3$)	234.0 (195.0, 274.0)	232.0 (194.0, 277.0)	229.0 (192.0, 283.0)	0.86	
Creatinine clearance, mL/min	96.8 (71.7, 123.1)	94.1 (71.8, 119.0)	86.8 (66.6, 115.1)	0.001	
2-vessel disease	437/1,079 (40.5)	364/907 (40.1)	193/632 (30.5)	<0.0001	
3-vessel disease	272/1,079 (25.2)	398/907 (43.9)	377/632 (59.7)	<0.0001	
Extent of disease (mm)	28.9 (17.0, 42.4)	38.0 (23.0, 58.0)	41.6 (25.0, 62.4)	<0.0001	
Lesions per patient	3.0 \pm 1.8	3.9 \pm 2.0	4.6 \pm 2.4	<0.0001	
PCI vessel	Left anterior descending	534/1,079 (49.5)	494/906 (54.5)	80/534 (15.0)	<0.0001
	Right coronary artery	387/1,079 (35.9)	342/906 (37.7)	269/534 (50.4)	<0.0001
	Left circumflex	347/1,079 (32.2)	311/906 (34.3)	224/534 (41.9)	0.0005
TIMI 0/1 flow, any lesion	124/1,078 (11.5)	214/907 (23.6)	207/630 (32.9)	<0.0001	
Collateral vessels present	134/1,079 (12.4)	214/907 (23.6)	226/632 (35.8)	<0.0001	
Severe calcification, any lesion	49/1,078 (4.5)	60/906 (6.6)	56/631 (8.9)	0.002	
Thrombus, any lesion	0/1,079 (0.0)	15/907 (1.7)	60/632 (9.5)	<0.0001	
Ulceration, any lesion	54/1,078 (5.0)	67/907 (7.4)	52/631 (8.2)	0.02	
Drug-eluting stent(s) implanted	939/1,079 (87.0)	791/907 (87.2)	495/632 (78.3)	<0.0001	
Baseline SYNTAX score	6.0 (3.0, 10.0)	11.0 (7.0, 18.0)	14.0 (9.0, 21.0)	<0.0001	
Residual SYNTAX score	11.0 (7.0, 16.0)	2.0 (1.0, 5.0)	11.0 (7.0, 16.0)	<0.0001	
Delta SYNTAX score	6.0 (3.0, 10.0)	8.0 (5.0, 13.0)	3.0 (0.0, 5.0)	<0.0001	
Ejection fraction, %	66.7 (58.9, 73.5)	66.1 (57.8, 72.6)	65.7 (56.8, 72.9)	0.13	

Data presented as n/N (%), mean \pm standard deviation or median (interquartile range). MI: myocardial infarction; PCI: percutaneous coronary intervention; SRI: SYNTAX Revascularisation Index; TIMI: Thrombolysis In Myocardial Infarction

under the curve [AUC] 0.60, 95% CI: 0.53-0.67, $p < 0.0001$). When compared with the bSS and the rSS, the SRI demonstrated a slightly better sensitivity compared to the bSS and rSS (**Table 5**); however, the rSS, especially an rSS > 8 , demonstrated the best specificity and accuracy for one-year mortality when compared to other scores.

SUBGROUP ANALYSIS

The impact of SRI $< 80\%$ was consistent in all subgroups examined except for sex (p -value for interaction=0.03) (**Figure 3**). SRI had a significant impact on one-year mortality in men, but not in women.

Table 2. Medication use according to the SYNTAX Revascularisation Index.

		SRI, 100% n=1,079	SRI, 50-99% n=907	SRI <50% n=632	p-value for trend
Pre-PCI medications	Aspirin	807/1,079 (74.8)	697/907 (76.8)	488/632 (77.2)	0.42
	Thienopyridine	364/1,079 (33.7)	308/907 (34.0)	225/632 (35.6)	0.71
Procedural antithrombin agents	Bivalirudin	731/1,079 (67.7)	586/907 (64.5)	403/632 (63.8)	0.16
	Unfractionated heparin	212/1,079 (19.6)	164/907 (18.1)	140/632 (22.2)	0.14
	Enoxaparin	130/1,079 (12.0)	142/907 (15.7)	75/632 (11.9)	0.03
	Glycoprotein IIb/IIIa inhibitor	723/1,079 (67.0)	619/907 (68.2)	425/632 (67.2)	0.83
Discharge medications	Aspirin	950/1,066 (89.1)	793/900 (88.1)	546/625 (87.4)	0.54
	Thienopyridine	938/1,066 (88.0)	756/900 (84.0)	500/625 (80.0)	<0.0001
30-day medications	Aspirin	1,023/1,054 (97.1)	858/877 (97.8)	584/605 (96.5)	0.31
	Thienopyridine	991/1,054 (94.0)	833/877 (95.0)	554/605 (91.6)	0.03
	Statins	890/1,054 (84.4)	723/876 (82.5)	512/605 (84.6)	0.44
	Beta-blockers	814/1,054 (77.2)	686/876 (78.3)	477/605 (78.8)	0.72
	ACE inhibitors	552/1,054 (52.4)	498/875 (56.9)	358/605 (59.2)	0.02
1-year medications	Aspirin	941/1,029 (91.4)	771/848 (90.9)	536/585 (91.6)	0.88
	Thienopyridine	693/1,028 (67.4)	584/848 (68.9)	394/585 (67.4)	0.76
	Statins	817/1,029 (79.4)	650/848 (76.7)	480/585 (82.1)	0.044
	Beta-blockers	705/1,029 (68.5)	583/848 (68.8)	428/585 (73.2)	0.11
	ACE inhibitors	520/1,029 (50.5)	441/848 (52.0)	305/585 (52.1)	0.76

Data presented as n/N (%). ACE: angiotensin-converting enzyme; PCI: percutaneous coronary intervention; SRI: SYNTAX Revascularisation Index

Discussion

The present report describes a new prognostic tool, the SRI, which may be used to quantitate the effectiveness of a revascularisation procedure in “removing” the angiographic burden of CAD. As such, the SRI may be useful to examine the extent of incomplete revascularisation which may be considered reasonable. The SRI was developed and studied in a cohort of 2,618 patients with moderate and high-risk NSTEMI-ACS who underwent PCI. The principal findings of the present study are as follows. (1) The SRI was associated with one-year adverse ischaemic outcomes, with mortality, MI, and MACE being inversely correlated with SRI. (2) The SRI was a strong and independent predictor of one-year mortality. (3) In this regard, achievement of an SRI ≥80% may be considered a reasonable goal for PCI. (4) However, among our low-risk population, the rSS had better predictive capability for one-year mortality when compared to SRI.

Achieving complete revascularisation is not always possible, and whether it is necessary for favourable outcomes is still a matter of debate. Using a different definition of incomplete revascularisation, ~40% of PCI patients in the SYNTAX trial had incomplete

Table 4. Independent predictors of one-year mortality.

Variables	Hazard Ratio [95% confidence interval]	p-value
SYNTAX Revascularisation Index	2.17 [1.05, 4.35]	0.03
Insulin-treated diabetes	3.92 [2.17, 7.06]	<0.0001
Age (per 10-year increment)	1.48 [1.13, 1.94]	0.004

The following variables were included in the model: SYNTAX Revascularisation as a continuous variable, age, insulin-treated diabetes, renal insufficiency, baseline white blood cell count, and baseline cardiac biomarker elevation or ST-segment deviation.

Table 3. One-year outcomes according to the SYNTAX Revascularisation Index.

	SRI 100% (a) n=1,079	SRI 50-99% (b) n=907	SRI <50% (c) n=632	p-value (a) vs. (b)	p-value (a) vs. (c)	p-value (b) vs. (c)	p-value for trend
Major adverse cardiac events*	167 (16.4)	171 (19.2)	136 (22.1)	0.04	0.0009	0.19	0.004
Death	15 (1.4)	24 (2.7)	23 (3.8)	0.04	0.002	0.26	0.009
Cardiac death	4 (0.4)	18 (2.0)	12 (1.9)	0.0006	0.002	0.92	0.002
Myocardial infarction	75 (7.1)	97 (10.8)	67 (10.8)	0.003	0.007	0.96	0.005
Death or myocardial infarction	86 (8.2)	110 (12.3)	82 (13.2)	0.002	0.0007	0.64	0.0009
Unplanned revascularisation for ischaemia	109 (11.0)	99 (11.4)	86 (14.3)	0.51	0.02	0.09	0.052
Definite/probable stent thrombosis	12 (1.1)	17 (1.9)	12 (2.0)	0.16	0.18	0.96	0.29

Data presented as n (%). *Includes death, myocardial infarction, or unplanned revascularisation for ischaemia. SRI: SYNTAX Revascularisation Index

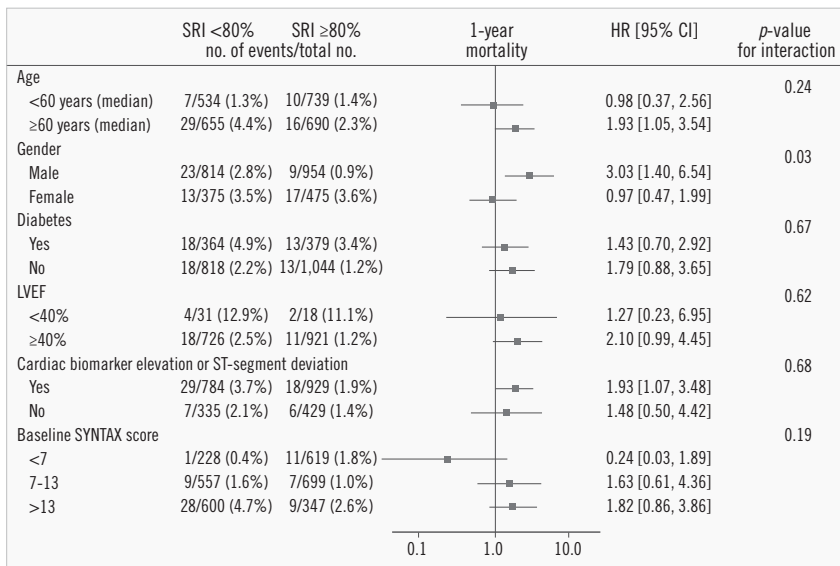


Figure 3. Major subgroup analysis and the impact of the SYNTAX Revascularisation Index on one-year mortality. The detrimental impact of incomplete revascularisation (SRI <80%) was consistent in all subgroups examined except for sex.

revascularisation, underlining the difficulty of achieving complete revascularisation with PCI in some patients with extensive CAD^{2,5,21}. As such, the construct of “reasonably incomplete revascularisation” has been proposed²²⁻²⁴. However, the extent of jeopardised myocardium which must be treated by PCI to improve prognosis has never been examined. It is well accepted that the amount of myocardium at risk at baseline and the complexity and extent of CAD are directly correlated with the occurrence of adverse events after revascularisation^{17,25,26}. Several studies have now shown that the amount of residual CAD after revascularisation is prognostically important, with an rSS >8 after PCI being associated with worse

outcomes^{12,9,10}. While achieving an rSS <8 after PCI might thus be seen as a reasonable goal, for patients with extensive CAD (e.g., bSS >32), characterisation of the proportion of CAD treated (SRI) may be more appropriate and informative when considering revascularisation options and for procedural planning.

The SRI represents a novel and complementary tool developed to characterise better the proportion of CAD treated by PCI and to describe the completeness of revascularisation better. Given its strong association with mortality, an SRI ≥80% could be seen as a reasonable goal when achieving incomplete revascularisation after PCI among patients presenting with NSTEMI-ACS and

Table 5. Comparison of predictive capability of the baseline SYNTAX score, residual SYNTAX score, and SYNTAX Revascularisation Index for one-year mortality.

	AUC [95% CI]	p-value	Optimal cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
bSS*	0.64 [0.56,0.71]	0.0004	13	59.7	64.4	3.9	98.5	64.3
rSS*	0.63 [0.56,0.71]	0.0003	5	51.6	69.6	4.0	98.3	69.1
SRI*	0.60 [0.53,0.67]	0.004	80%	62.9	53.6	3.2	98.4	53.9
rSS >8†	0.59 [0.53,0.65]	0.005	8†	37.1	80.2	4.4	98.1	79.2
SRI <80%‡	0.56 [0.50,0.63]	0.04	80%‡	58.6	54.9	3.0	98.2	55.0

* Predictive metrics derived using score as a continuous variable and using the best cut-off as determined by the Youden index from the current studied cohort. † Predictive metrics derived using score as a binary variable (rSS >8 and SRI <80%) and using historical proven cut-off¹². Overall comparison of AUC for bSS, rSS, and SRI: p=0.003. Pairwise comparison of AUC SRI vs. rSS: p=0.0014. Pairwise comparison of AUC SRI vs. bSS: p=0.30. AUC: area under the curve; bSS: baseline SYNTAX score; NPV: negative predictive value; PPV: positive predictive value; rSS: residual SYNTAX score; SRI: SYNTAX Revascularisation Index

relatively low-risk CAD. However, the rSS, characterising the absolute amount of residual CAD after PCI, remains the most specific and accurate score for prediction of one-year mortality. That being said, the bSS, rSS and SRI have different meanings and roles during the patient assessment and clinical decision-making process, and therefore each may have utility in practice and during clinical trials (Table 6). The bSS is an important prognostic tool to assess patient outcomes prior to revascularisation and helps discriminate between the choice of PCI and CABG for individual patients. Alternatively, the rSS and the SRI not only have post-procedural prognostic utility, but can also serve as a guide for clinical decision making, depending on the expected degree of revascularisation. Unless at least a reasonable and appropriate²⁷ level of revascularisation can be achieved, CABG may be a better alternative to PCI.

Table 6. SYNTAX score concepts at different times relative to revascularisation.

Scores	Definition
Baseline SYNTAX score (bSS)	Quantification of CAD pre-revascularisation
Residual SYNTAX score (rSS)	Quantification of CAD post-revascularisation
Delta SYNTAX score (Δ SS)	Quantification of the absolute CAD burden treated
SYNTAX Revascularisation Index (SRI)*	Quantification of the proportion of CAD burden treated
*SRI: $(1 - [rSS/bSS]) \times 100$. CAD: coronary artery disease	

It is important to emphasise that, while an SRI of $\geq 80\%$ might be used as a benchmark for “reasonably incomplete” revascularisation, the ACUITY trial represents a population with angiographically low-risk CAD (median bSS of nine). External validation of the SRI concept in a population of patients involving more complex CAD would be interesting, especially to determine the stability of its predictability among different levels of CAD complexity (as previously demonstrated by an rSS < 8)². The extent of incomplete revascularisation (SRI) in SYNTAX is not known, and would be useful both to validate the concepts presented in the present report, and to examine the extent to which more complete revascularisation after PCI might have narrowed the differences observed between PCI and CABG in that trial. That being said, the impact of incomplete revascularisation on mortality has been shown to be significantly lower with CABG when compared to PCI^{21,27,28}, and using a different method to quantify the incompleteness of revascularisation will probably not result in different findings.

Limitations

Despite being conducted in a large cohort of patients from a randomised controlled trial with detailed angiographic core laboratory analysis, several limitations should be acknowledged. First, the ACUITY trial enrolled patients with NSTEMI-ACS. Whether achieving an SRI $\geq 80\%$ in an external population of patients with

NSTEMI-ACS or stable CAD has similar prognostic implications remains to be proven. Second, the baseline anatomic complexity in the ACUITY trial was low (median bSS of nine); whether the SRI cut-off of 80% is optimal in a more complex CAD population (e.g., SYNTAX trial cohort) is unknown. Third, the SYNTAX score (bSS, rSS and SRI) is based on identifying lesions with diameter stenosis $\geq 50\%$ in vessels ≥ 1.5 mm in diameter. Using a different threshold for vessel diameter (e.g., 2 mm) and lesion severity (e.g., diameter stenosis $\geq 70\%$) would lead to different results⁹, although whether the prognostic accuracy would be greater is unknown. Fourth, assessment of the SYNTAX score is well known to have high variability, an issue that could be overcome by appropriate training²⁰ or by consensus of several readers²⁹. While the three readers involved in the current study were appropriately trained and achieved an excellent level of agreement before initiating the SYNTAX score evaluation²⁰, each SYNTAX score was not performed by consensus of the three readers, but rather by a single reader. Given that the rSS, the delta SS, and the SRI are all derived from the bSS, different results might have been obtained if carried out by consensus²⁹. Fifth, CABG patients were not included in our analysis, and the results of the present analysis do not apply to this group. Sixth, the relatively short follow-up (one year), the modest number of deaths ($n=62$), and the retrospective nature of this study preclude definitive conclusions. The findings from this study are hypothesis-generating, and await external validation from other databases. In this regard, the subgroup interaction implying that SRI may be of greater utility in men as compared to women deserves further study. Finally, the SYNTAX score concept (bSS, rSS and SRI) is based on coronary anatomy complexity only, and recent studies have demonstrated the value of an ischaemic-oriented revascularisation³⁰ or a combination of both (angiographic and ischaemic)³¹. Future studies are necessary to determine whether greater prognostic accuracy can be achieved by assessing the degree of functional or ischaemic revascularisation. The ongoing ISCHEMIA (NCT01471522), EXCEL (NCT01205776) and COMPLETE (NCT01740479) trials are prospectively examining this issue in different patient populations.

Conclusion

In conclusion, derived from a population of NSTEMI-ACS with low complexity of CAD at baseline, the SRI is a newly described method for quantifying the proportion of CAD burden successfully treated by PCI. Pending external validation, the SRI may be useful in anticipating or assessing the degree of revascularisation in patients with CAD, with SRI $\geq 80\%$ a reasonable goal. Nonetheless, the rSS remains the best metric for completeness of revascularisation, showing the best predictive capability and accuracy for one-year mortality.

Guest Editor

This paper was guest edited by Antonio Colombo, MD, San Raffaele Scientific Institute, Milan, Italy.

Impact on daily practice

Complete revascularisation after percutaneous coronary intervention is often not achieved, especially in patients with complex multivessel coronary artery disease. Derived from the baseline and residual SYNTAX scores, the current report proposes a new index, the SYNTAX Revascularisation Index (SRI), which provides insight into what might constitute a reasonable level of complete revascularisation. The SRI, paired with the two previously developed scores, offers the full quantitative language necessary to characterise the baseline, residual, and treated burden of coronary disease appropriately at any stage of revascularisation. Anticipating the SRI after PCI may be useful for clinical decision making, when choosing between revascularisation modalities.

Conflict of interest statement

P. Généreux has received speaker fees from Abbott Vascular and Cardiovascular Systems Inc., and is a consultant for Cardiovascular Systems Inc. T. Palmerini and A. Caixeta have received speaker fees from Abbott Vascular. M. Leon is on the scientific advisory board for Medtronic, Boston Scientific Corporation and Abbott Vascular. G. Dangas and R. Mehran have received institutional research grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi, Eli Lilly and Company/Daiichi-Sankyo, Regado Biosciences, and STENTYS, consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen Pharmaceuticals, Maya Medical, and Merck & Co, and are on the advisory board for Covidien, Janssen Pharmaceuticals, Merck, and Sanofi. The other authors have no conflicts of interest to report. The Guest Editor has no conflicts of interest to declare.

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Chapter 4.3

Validation of the SYNTAX revascularization index to quantify reasonable level of incomplete revascularization after percutaneous coronary intervention.

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Incomplete revascularization is common after percutaneous coronary intervention (PCI). Whether a “reasonable” degree of incomplete revascularization is associated with a similar favorable long-term prognosis compared with complete revascularization remains unknown. We sought to quantify the proportion of coronary artery disease burden treated by PCI and evaluate its impact on outcomes using a new prognostic instrument—the Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) Revascularization Index (SRI). The baseline SYNTAX score (bSS), the residual SYNTAX score, and the delta SYNTAX score (Δ SS) were determined from 888 angiograms of patients enrolled in the prospective SYNTAX trial. The SRI was then calculated for each patient using the following formula: $SRI = (\Delta SS/bSS) \times 100$. Outcomes were examined according to the proportion of revascularized myocardium (SRI = 100% [complete revascularization], 50% to <100%, and <50%). The Youden index for the SRI was computed to identify the best cutoff for 5-year all-cause mortality. The mean bSS was 28.4 ± 11.5 , and after PCI, the mean Δ SS was 23.8 ± 10.9 and the mean residual SYNTAX score was 4.5 ± 6.9 . The mean SRI was $85.3 \pm 21.2\%$ and was 100% in 385 patients (43.5%), <100% to 50% in 454 patients (51.1%), and <50% in 48 patients (5.4%). Five-year adverse outcomes, including death, were inversely proportional to the SRI. An SRI cutoff of <70% (present in 142 patients [16.0%] after PCI) had the best prognostic accuracy for prediction of death and, by multivariable analysis, was an independent predictor of 5-year mortality (hazard ratio [HR] 4.13, 95% confidence interval [CI] 2.79 to 6.11, $p < 0.0001$). In conclusion, the SRI is a newly described method for quantifying the proportion of coronary artery disease burden treated by PCI. The SRI is a useful tool in assessing the degree of revascularization after PCI, with SRI $\geq 70\%$ representing a “reasonable” goal for patients with complex coronary artery disease. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;116:174–186)

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See page 185 for disclosure information.

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The Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) score (SS) has become a well-established instrument to quantify the extent and complexity of baseline coronary artery disease (CAD).¹ It has been validated in many populations and patient subsets.^{2–5} The residual SYNTAX score (rSS) was designed⁶ and validated to quantify the absolute amount of untreated CAD after percutaneous coronary intervention (PCI) revascularization.^{7,8} An rSS ≥ 8 was identified as a level of incomplete revascularization strongly associated with increased mortality and adverse ischemic events.^{6,7} Recently, the SYNTAX Revascularization Index (SRI), representing the proportion of treated baseline CAD (baseline SYNTAX score [bSS]; delta SYNTAX score [Δ SS]), was developed as a tool to better quantify and describe the proportion of the disease treated ($SRI = \Delta SS / bSS \times 100$) by PCI revascularization.⁹ The SRI has been shown to be an independent predictor of 1-year mortality in patients with non-ST-elevation acute coronary syndrome

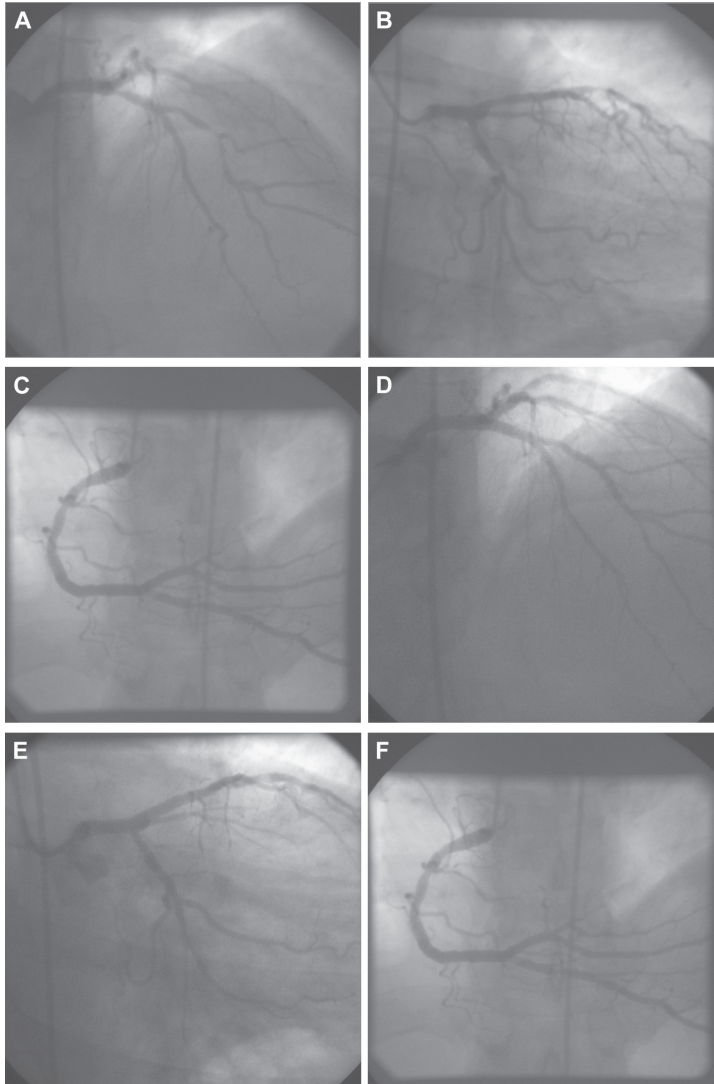


Figure 1. Case examples with bSS, rSS, Δ SS, and SRI. Baseline angiogram showing angiographic 3-vessel disease with a lesion of the proximal left anterior descending artery (LAD) and first diagonal (A), a lesion of the left proximal circumflex (LCx) and second marginal (B), and a lesion of the posterior descending artery (C). The baseline SYNTAX score was 21. After percutaneous revascularization of the LAD and diagonal (D) and LCx and marginal (E) (Δ SS of 19), the residual SYNTAX score was 2 (F), with an SRI of \sim 90% (19 of 21).

and can be used as a “goal” to be achieved by PCI. However, external validation of this concept in a different population and who underwent longer follow-up is lacking.

We, therefore, aimed to externally validate the SRI as a new prognostic tool in patients who underwent PCI from the randomized SYNTAX trial.

Table 1
Baseline and procedural characteristics according to the SYNTAX Revascularization Index

Variables	SRI = 100% (N=386)	SRI 50% to <100% (N=454)	SRI <50% (N=48)	p Value
Age (years)	64.6±9.8	65.7±9.5	65.9±8.5	0.11
Men	280 (72.5%)	362 (79.7%)	35 (72.9%)	0.04
Diabetes mellitus	85 (22.0%)	148 (32.6%)	19 (39.6%)	0.001
Insulin-requiring diabetes	27 (7.0%)	53 (11.7%)	9 (18.8%)	0.009
Body mass index (kg/m ²)	28.0±4.7	28.1±4.9	29.3±4.9	0.27
Hypertension	273 (71.5%)	341 (75.6%)	39 (81.3%)	0.20
Hyperlipidemia	300 (77.9%)	353 (78.6%)	41 (87.2%)	0.34
Current smoker	79 (20.5%)	76 (16.7%)	9 (18.8%)	0.38
Chronic obstructive pulmonary disease	34 (8.8%)	34 (7.5%)	3 (6.3%)	0.70
Peripheral vascular disease	32 (8.3%)	45 (9.9%)	5 (10.4%)	0.69
History of gastrointestinal bleeding/peptic Ulcer disease	17 (4.4%)	16 (3.5%)	3 (6.5%)	0.57
History of stroke/Transient ischemic attack	27 (7.0%)	37 (8.2%)	5 (10.4%)	0.65
Creatinine >200 µmol/L	4 (1.0%)	6 (1.3%)	0 (0.0%)	0.69
Dialysis	1 (0.3%)	2 (0.4%)	0 (0.0%)	0.83
Previous myocardial infarction	114 (29.8%)	144 (32.1%)	19 (39.6%)	0.36
Unstable angina	100 (25.9%)	146 (32.2%)	10 (20.8%)	0.06
Baseline anatomical and clinical scores				
Baseline SYNTAX score	23.6±10.0	32.2±10.9	29.35±13.10	<0.001
Residual SYNTAX score	0.0±0.0	6.2±3.9	23.9±12.9	<0.001
SYNTAX Revascularization Index (%)	100.0±100.0	79.9±11.1	17.3±22.3	<0.001
Total Parsonnet Score	8.2±7.1	8.7±6.8	10.2±7.3	0.07
Logistic EuroSCORE	3.8±5.5	3.8±3.6	3.5±3.1	0.78
Left ventricular ejection fraction (%)	60.3±12.2	59.8±12.9	57.4±13.9	0.002
Procedural Characteristics				
Intra-aortic Balloon Pump	11 (2.8%)	8 (1.8%)	3 (6.3%)	0.14
Bifurcation	221 (57.3%)	305 (67.2%)	28 (58.3%)	0.10
Trifurcation	28 (7.3%)	33 (7.3%)	4 (8.3%)	0.96
Ostial lesion	66 (17.3%)	61 (13.4%)	9 (18.8%)	0.25
Total occlusion	47 (12.3%)	145 (31.9%)	20 (41.7%)	<0.001
Severe tortuosity	213 (55.8%)	338 (74.4%)	32 (66.7%)	<0.001
Lesion length >20 mm	176 (46.1%)	292 (64.3%)	24 (50.0%)	<0.001
Heavy calcification	163 (42.7%)	245 (54.0%)	28 (58.3%)	0.002
Left main lesion	164 (42.5%)	173 (38.1%)	18 (37.5%)	0.41
Left main + 3-vessel disease	37 (9.6%)	87 (19.2%)	10 (20.8%)	<0.001
3-vessel disease only	211 (54.7%)	276 (60.8%)	30 (62.5%)	0.17
Right coronary lesion	289 (74.9%)	384 (86.8%)	44 (91.7%)	<0.001
Left anterior descending lesion	328 (85.0%)	421 (92.7%)	43 (89.6%)	0.001
Left circumflex lesion	300 (77.7%)	413 (91.0%)	44 (91.7%)	<0.01
Procedure time (hours)	1.6±0.9	1.8±0.9	2.2±1.0	<0.001
Total number of stents	4.5±2.4	4.8±2.1	4.1±2.2	0.47
Total stent length (mm)	85.8±51.6	87.1±45.0	73.1±37.5	0.75

Data present as n (%) or mean ± SD.

SRI = SYNTAX Revascularization Index.

Table 2
Five-year outcomes according to the SYNTAX Revascularization Index

Variables	SRI = 100% (N=386)	SRI 50% to <100% (N=454)	SRI <50% (N=48)	p Value*
Death	33 (8.6%)	73 (16.1%)	16 (33.3%)	<0.0001
Cardiac death	17 (4.3%)	51 (11.2%)	13 (26.2%)	<0.0001
Myocardial infarction	27 (7.1%)	48 (10.6%)	13 (26.5%)	<0.0001
Unplanned revascularization	73 (18.9%)	131 (28.9%)	30 (62.5%)	<0.0001
Stent thrombosis (definite/probable)	26 (6.7%)	43 (9.4%)	11 (22.2%)	<0.0001
MACCE	107 (27.7%)	192 (42.3%)	34 (69.9%)	<0.0001

Values are KM rate estimate.

Data presented as n (%).

MACCE = major adverse cardiac and cerebrovascular events.

* Log-rank test.

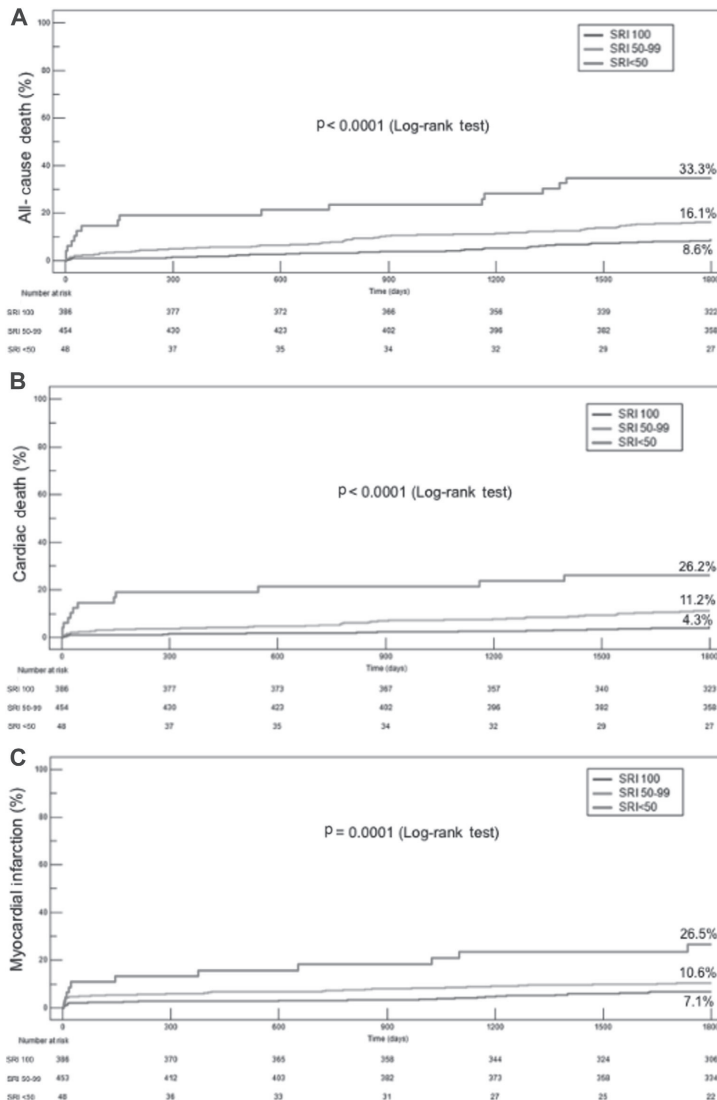


Figure 2. Kaplan-Meier curves showing cumulative mortality and adverse event rates through 5 years according to SRI. The rate of death (A), cardiac death (B), MI (C), revascularization (D), and MACCE (E) significantly increased with the degree of incomplete revascularization as assessed by the SRI.

Methods

The SYNTAX trial was a randomized, prospective, multicenter trial investigating patients with de novo 3-vessel CAD and/or unprotected left main CAD (isolated or associated with 1-, 2-, or 3-vessel disease).^{2,10} In brief, a total of 1,800 patients were recruited and randomized to PCI

($n = 903$) or coronary artery bypass grafting (CABG; $n = 897$) from 85 centers in Europe and the United States. Exclusion criteria were limited to subjects with previous coronary revascularization, the requirement of concomitant cardiac surgery, or ongoing acute myocardial infarction (MI). During the local Heart Team meeting, the interventional

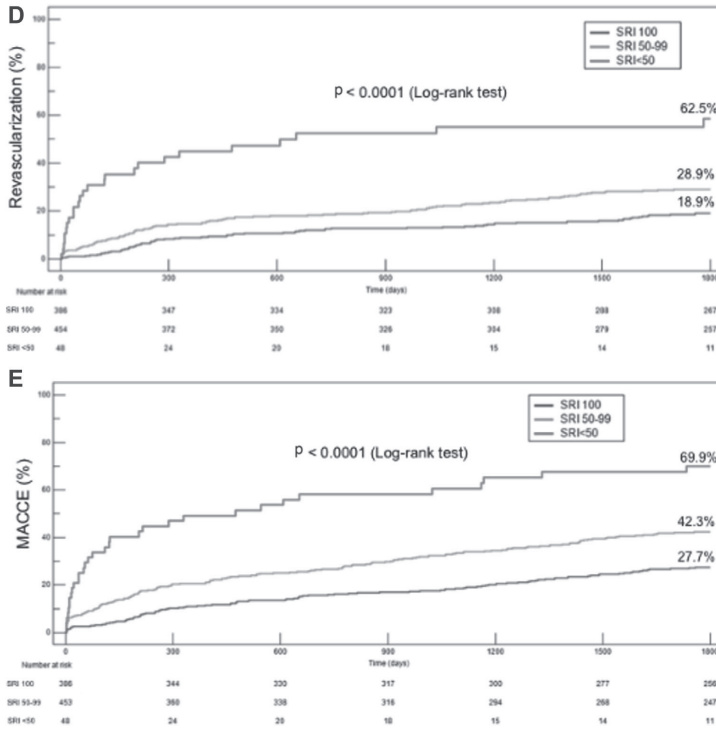


Figure 2. (continued).

cardiologist and cardiac surgeon specified the number of coronary lesions requiring treatment, their angiographic location, and characteristics using the bSS (<http://www.syntaxscore.com>). In case equivalent anatomical revascularization could be achieved with both treatment strategies, were randomized on a 1:1 basis (n = 1,800) to either PCI with TAXUS Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Massachusetts) or CABG. Stratification was performed by 3 ways: by clinical site, the absence or presence of unprotected left main disease, and by the presence or absence of medically treated diabetes mellitus (requiring oral medications or insulin). Baseline and peri- and post-procedural data were prospectively collected by the individual participating centers. The calculation of the bSS¹ was carried out by the Heart Team before randomization and corroborated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) blinded to the treatment assignment. Baseline and procedural coronary angiograms were centrally stored. The baseline and procedural coronary angiograms were analyzed side by side by a panel of 3 interventional cardiologists blinded to the clinical outcomes.

The bSS and its components, including anatomic location of all lesions, recorded by the core laboratory in calculation

of the original SS, were used to identify all coronary lesions in the baseline and procedural coronary angiogram. The rSS was calculated based on the remaining obstructive CAD after treatment with PCI. The intraobserver variability for calculation of the rSS (quartile partitioning), based on reanalyzing 50 cases at a 3-month interval, indicated a high level of agreement (κ statistic 0.89, 95% confidence interval [CI] 0.79 to 0.99, $p < 0.001$).^{11,12} The Δ SS, representative of the burden of disease treated by PCI, was calculated by subtracting the rSS from the bSS.⁶ The SRI was calculated with the following formula: $(\Delta\text{SS}/\text{bSS} \times 100)$.⁹ Figure 1 illustrates the bSS and all its derived scores. Patients were stratified into 3 groups (as previously described)⁹ and compared: SRI = 100% (complete revascularization), SRI <100% to 50%, and SRI <50%. Adverse ischemic outcomes between groups were compared at 5 years.

Clinical outcomes included all-cause death major adverse cardiac and cerebrovascular events (MACCE; a composite of all-cause death, MI, cerebrovascular accident, and all-cause revascularization), and stent thrombosis using the Academic Research Consortium definition.¹³ An independent clinical events committee, including cardiologists, cardiac surgeons, and a neurologist, reviewed all the primary clinical end points.¹⁴ A separate independent clinical events committee

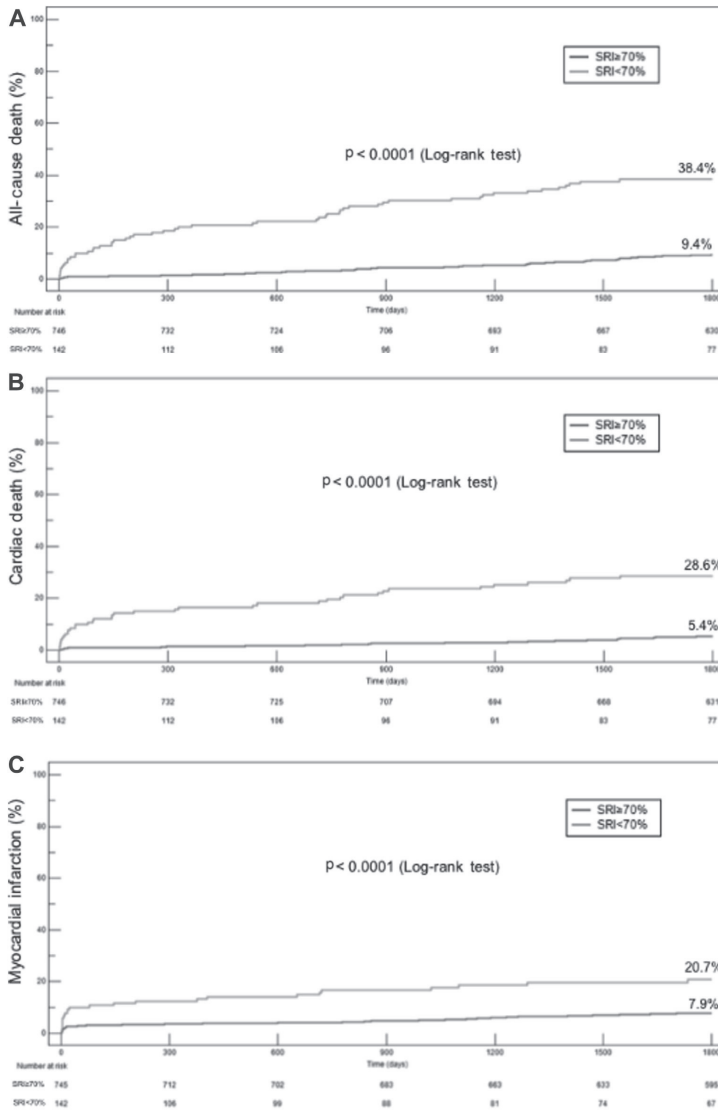


Figure 3. Kaplan-Meier curves showing cumulative mortality and adverse event rates through 5 years according to SRI cutoff of 70%. The rate of death (A), cardiac death (B), MI (C), revascularization (D), and MACCE (E) are significantly higher with an SRI <70% compared with an SRI ≥70%.

adjudicated the Academic Research Consortium stent thrombosis events.

Categorical variables are presented as numbers and percentages and are compared with the chi-square test. Continuous variables are expressed as mean ± SD and are compared using the Student's *t* test or Wilcoxon rank-sum

test based on their distributions. Time-to-event variables are presented as Kaplan-Meier estimates and compared using the log-rank test. Multivariable analyses were performed to identify independent predictors of incomplete revascularization (SRI <100%). Multivariable analyses were conducted to identify independent predictors of 5-year

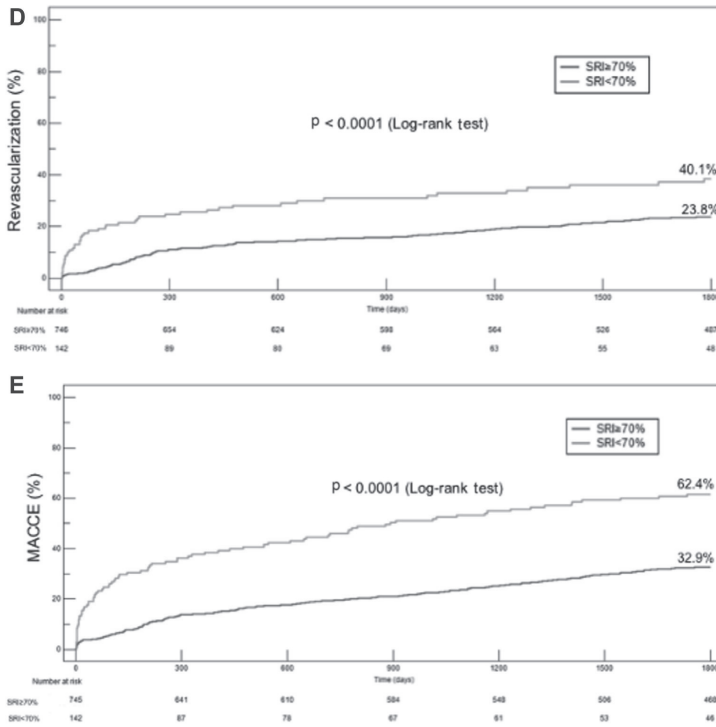


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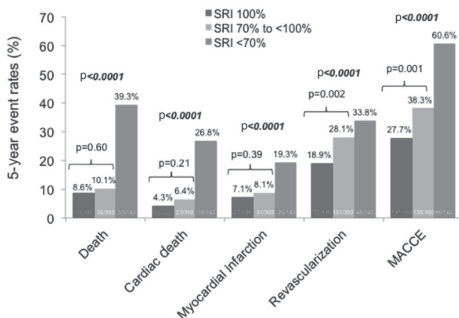


Figure 4. Five-year adverse event rates between different degrees of completeness of revascularization. Reasonable incomplete revascularization (SRI < 100% to 70%) and complete revascularization (SRI 100%) had significantly and similarly lower mortality, cardiac mortality, and MI rates at 5 years compared with incomplete revascularization (SRI < 70%). Unplanned revascularization proportionally increased with the degree of incompleteness of revascularization.

Table 3

Independent predictors of 5-year mortality

Variables	Hazard Ratio [95% CI]	p Value
SYNTAX Revascularization Index < 70%	4.13 [2.79, 6.11]	< 0.0001
No post-procedural antiplatelet therapy*	64.18 [24.29, 169.54]	< 0.0001
Left ventricular ejection fraction < 30%	5.60 [2.43, 12.93]	< 0.0001
Age (per increase in 10 years)	1.45 [1.22, 1.69]	< 0.0001
Peripheral vascular disease	1.90 [1.18, 3.06]	0.008
SYNTAX score (per increase in 10 points)	1.23 [1.08, 1.37]	0.002
Amiodarone therapy on discharge	3.09 [1.10, 8.65]	0.03
History of GI bleeding or peptic ulcer disease	2.10 [1.05, 4.20]	0.04

GI = gastrointestinal.

* Neither aspirin nor thienopyridine.

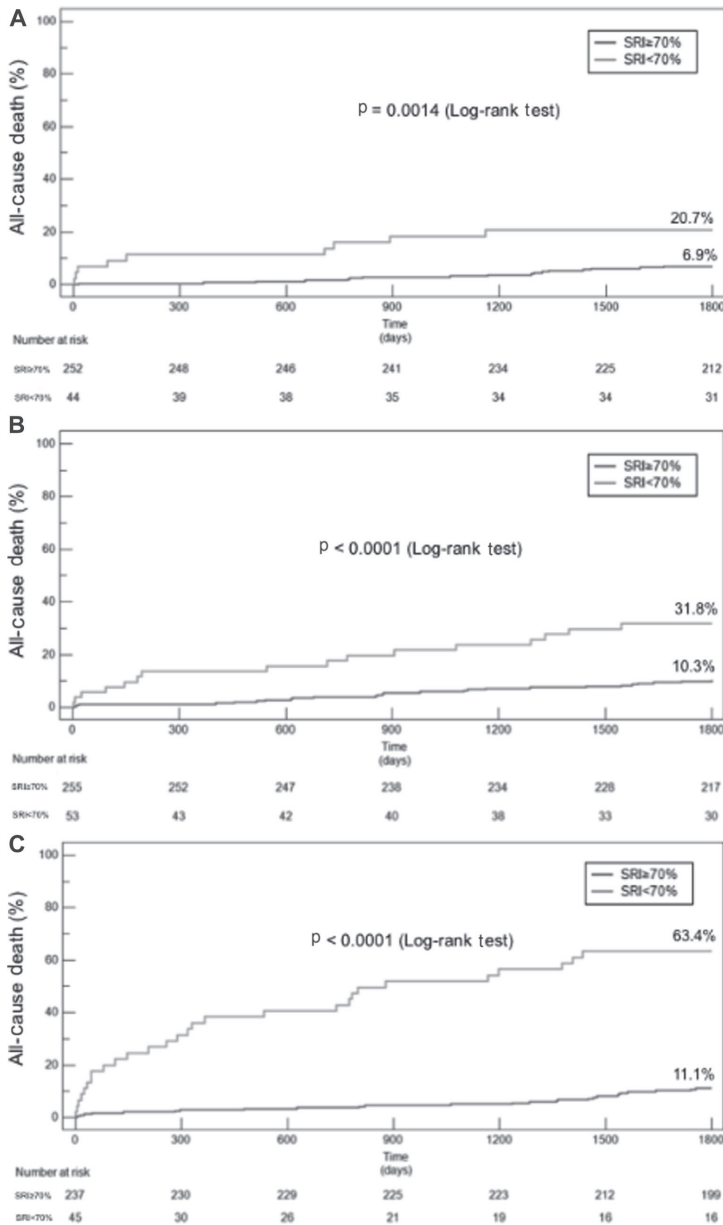


Figure 5. Kaplan-Meier curves showing cumulative mortality and MACCE through 5 years according to baseline SYNTAX score tertiles. The impact of achieving an SRI $<70\%$ versus $\geq 70\%$ on the 5-year rate of death stratified by bSS tertiles (A: bSS <22 , B: bSS 22 to 32, and C: bSS >32) and the impact of achieving an SRI $<70\%$ versus $\geq 70\%$ on the 5-year rate of MACCE stratified by bSS tertiles (D: bSS <22 , E: bSS 22 to 32, and F: bSS >32).

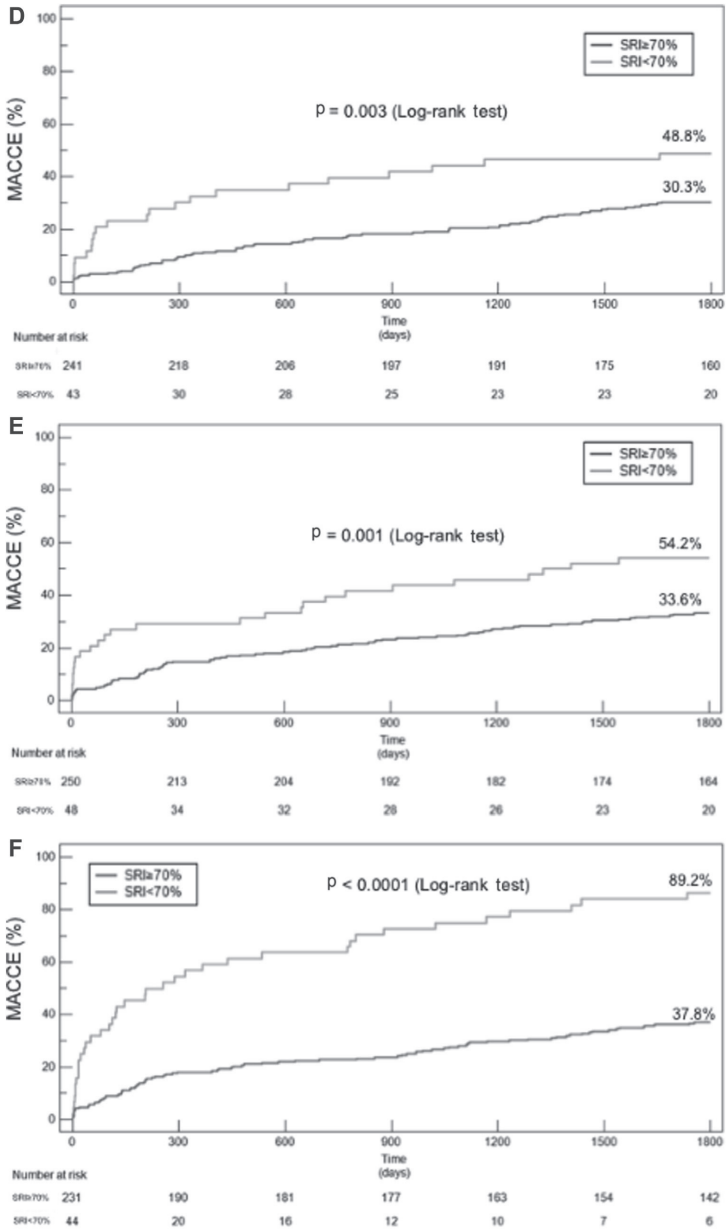


Figure 5. (continued).

	RIS≥70%	RIS<70%	Hazard Ratio (95%CI)	P Value	P interaction
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.18 (3.62-7.43)	<0.001	0.92
Male	48/560 (8.6%)	34/95 (35.8%)	5.19 (3.34-8.06)	<0.001	
Female	21/165 (12.7%)	19/40 (47.5%)	5.13 (2.75-9.56)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.22 (3.65-7.48)	<0.001	0.74
Age<65	17/327 (5.2%)	11/52 (21.2%)	4.74 (2.22-10.12)	<0.001	
Age>65	52/398 (21.2%)	42/83 (50.6%)	5.28 (3.51-7.94)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.08 (3.51-7.24)	<0.001	0.85
DM	22/186 (11.8%)	27/56 (48.2%)	5.65 (3.21-9.94)	<0.001	
Non-DM	47/539 (8.7%)	26/79 (11.8%)	4.54 (2.81-7.34)	<0.001	
All cause death*	22/186 (11.8%)	27/56 (48.2%)	5.80 (3.29-10.23)	<0.01	0.04
DM non insulin	17/126 (13.5%)	11/30 (36.7%)	3.31 (1.55-7.07)	0.002	
DM insulin	5/60 (8.3%)	16/26 (61.5%)	12.07 (4.38-33.28)	<0.001	
All cause death	63/686 (9.2%)	50/117 (42.7%)	6.02 (4.14-8.74)	<0.001	0.61
CrCl<90	17/255 (6.7%)	14/35 (40.0%)	5.44 (3.51-8.42)	<0.001	
CrCl≥90	46/431 (10.7%)	36/82 (43.9%)	7.73 (3.80-15.70)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.58 (3.88-8.02)	<0.001	0.34
LVEF<50	22/154 (14.3%)	25/40 (62.5%)	6.62 (3.71-11.80)	<0.001	
LVEF≥50	44/549 (8%)	28/88 (31.8%)	4.85 (3.02-7.80)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.28 (3.69-7.56)	<0.001	0.68
COPD	8/54 (14.8%)	8/14 (57.1%)	6.42 (2.39-17.25)	<0.001	
non-COPD	61/671 (9.1%)	45/121 (37.2%)	5.09 (3.46-7.48)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.00 (2.46-9.06)	<0.001	0.43
PVD	57/674 (8.5%)	39/110 (35.5%)	3.42 (1.58-7.42)	0.002	
non-PVD	12/51 (23.5%)	14/25 (56%)	5.20 (3.46-7.82)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.71 (3.97-8.21)	<0.001	0.64
Unstable Angina	28/217 (12.9%)	16/30 (53.3%)	6.25 (3.37-11.59)	<0.001	
Stable CAD	41/508 (8.1%)	37/105 (35.2%)	5.36 (3.43-8.36)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.31 (3.70-7.60)	<0.001	0.22
LM†	28/294 (9.5%)	16/51 (44%)	6.24 (4.01-9.78)	<0.001	
3VD	41/431 (9.5%)	37/84 (44%)	3.90 (2.11-7.22)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.79 (4.00-8.38)	<0.001	0.01
Amy TO	16/152 (10.5%)	13/53 (24.5%)	2.57 (1.24-5.34)	0.012	
No TO	53/569 (9.3%)	40/82 (48.8%)	7.43 (4.92-11.22)	<0.001	
All cause death	69/725 (9.6%)	53/125 (39.3%)	5.55 (3.87-7.96)	<0.001	0.04
SYNTAX Score≤22	17/241 (7.1%)	9/43 (20.9%)	3.39 (1.51-7.61)	<0.001	
SYNTAX Score 23-32	26/250 (10.4%)	16/48 (33.3%)	3.80 (2.03-7.08)	<0.001	
SYNTAX Score>32	26/232 (11.2%)	28/44 (63.6%)	9.37 (5.46-16.07)	<0.001	

*Within diabetic cohort; †Prestratified at randomization

Figure 6. Important subgroup analysis for 5-year all-cause mortality according to SRI <70% versus ≥70%. The impact of SRI <70% was consistent in all subgroups except for the subgroups of CTO, diabetes requiring insulin, and bSS, in which significant interaction was detected. 3VD = 3-vessel disease; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; DM = diabetes mellitus; LM = left main; LVEF = left ventricular ejection fraction; PVD = peripheral vascular disease; TO = total occlusion.

mortality, with a Cox regression model using the forced enter method. Previously demonstrated anatomic and clinical variables, shown to be independent predictors of long-term mortality in the SYNTAX trial ($p < 0.1$),¹⁵ were entered into the model, with no exit criteria. Area under the curve for the SRI was computed to identify the Youden index (best cutoff) for 5-year all-cause death.¹⁶ The Youden index is defined for all points of a receiver operating characteristic curve, and the maximum value of the index was used as a criterion for selecting the optimum cut-off point for the SRI. The index is represented graphically as the height above the chance line. It is equivalent to the area under the curve represented by a single operating point. All variables were stratified according to an SRI >70% (best cutoff). A 2-sided probability value <0.05 was considered significant for all tests. All analyses were conducted using SPSS, version 21.0 (IBM, Armonk, New York).

Results

In the randomized PCI cohort ($n = 903$), the bSS was available in 899 of 903 subjects (99.6%). The mean bSS was 28.4 ± 11.5 . The SRI was available in 888 of 903 subjects

(98.3%). The SRI ranged from 47.1% to 100%, with a mean of 85.3 ± 21.2 . The SRI was 100% in 386 patients (43.5%), from 50% to <100% in 454 patients (51.1%), and <50% in 48 patients (5.4%). Table 1 presents the clinical characteristics and angiographic findings, stratified by SRI. Patients with lower SRI had a higher prevalence of diabetes, diabetes requiring insulin, and lower left ventricular ejection fraction. Angiographically, patients with a lower SRI were more likely to have more complex and extensive disease, with a more frequent presence of chronic total occlusion (CTO), heavily calcification, long (>20 mm) and tortuous lesions, involvement of the left main with 3-vessel disease, resulting in higher bSS and rSS, and longer procedural time. Independent predictors of incomplete revascularization (SRI <100%) included bSS (HR 1.08, 95% CI 1.07 to 1.10, $p < 0.0001$) and diabetes mellitus (HR 1.82, 95% CI 1.31 to 2.54, $p = 0.0003$).

The 5-year rates of all adverse ischemic events were strongly associated with SRI, with the lowest rates of adverse events in the group with complete revascularization and the highest rates in the group with SRI <50% (Table 2, Figure 2).

Receiver operating characteristic curve analysis demonstrated a significant association between the SRI and 5-year all-cause mortality. An SRI cutoff of 70% had the best

prognostic accuracy for risk prediction of death (area under the curve 0.68, 95% CI 0.65 to 0.71, $p < 0.0001$). Baseline and procedural variables associated with an SRI $< 70\%$ (occurring in 142 patients [16%]) versus an SRI $\geq 70\%$ (occurring in 746 patients [84.0%]) are presented in Supplementary Table 1. Figure 3 shows the occurrence of adverse events over time according to an SRI cutoff of 70%. Figure 4 shows and compares 5-year adverse event rates among SRI 100%, 70% to $< 100\%$, and $< 70\%$. By multivariable analysis, SRI $< 70\%$ remains one of the strongest independent predictors of 5-year mortality (Table 3).

Figure 5 shows the impact of achieving an SRI $< 70\%$ versus $\geq 70\%$ on the 5-year rate of death and MACCE (Figure 5) according to the bSS tertiles (< 22 , 22 to 32, > 32) of the study cohort. Mortality and MACCE were significantly reduced in patients with an SRI $\geq 70\%$ compared with $< 70\%$ at all levels of bSS (p for interaction = 0.037 for mortality and 0.01 for MACCE) with the group with the highest bSS having the greatest absolute reduction in 5-year mortality and MACCE with achievement of SRI $\geq 70\%$ compared with SRI $< 70\%$.

The higher mortality of an SRI $< 70\%$ was consistent in all subgroups examined. For patients with diabetes requiring insulin and high bSS, the impact of an SRI $< 70\%$ was markedly higher. In patients with at least 1 CTO, the negative impact of an SRI $< 70\%$ was still relevant but less evident (Figure 6).

Discussion

The present study validates the concept of SRI, a new practical angiographic tool aiming to quantify the level of “reasonable” incomplete revascularization after PCI. Drawn from a cohort of 888 patients with multivessel disease who underwent PCI, the main findings of the current report are as follows: (1) the SRI was associated with all 5-year adverse ischemic outcomes, with mortality, MI, revascularization, stent thrombosis, and MACCE being inversely correlated with SRI; (2) the SRI was a strong and independent predictor of 5-year all-cause mortality; (3) achievement of an SRI $\geq 70\%$ was associated with similar mortality and adverse event rates as an SRI of 100% and may be considered a “reasonable” or acceptable result for PCI; and (4) achieving a reasonable revascularization (SRI $\geq 70\%$) was beneficial in all tertiles of bSS but especially in patients with more complex and extensive CAD (bSS > 32).

Complete revascularization has been shown to be associated with favorable outcomes compared with incomplete revascularization.^{6,7,17–21} However, complete revascularization is not always possible. The SYNTAX and Acute Catheterization and Urgent Intervention Triage Strategy trials demonstrated a rate of $\sim 40\%$ of incomplete revascularization.^{6,7,20,22} Complete revascularization is not always necessary,²³ but no precise instrument has demonstrated what should represent a “reasonable” level of complete (or incomplete) revascularization.

Based on the bSS¹ and the rSS,^{6,7} we recently developed the SRI, an index representing the proportion of CAD treated, and demonstrated its strong association with 1-year mortality.⁹ The present report confirms and extends our previous findings and externally validates this concept. In

the present study, SRI was associated with all adverse ischemic events and was identified as one of the independent predictors of 5-year all-cause mortality. This finding underlines the central importance not only of the baseline anatomy, while risk-stratifying patients, but also of the potential residual “untreated” CAD after PCI.

Importantly, we identified a threshold of reasonable incomplete revascularization (SRI $\geq 70\%$) at which long-term mortality is not affected by the incompleteness of revascularization. Even more important, the achievement of an SRI $\geq 70\%$ substantially improved the prognosis among each bSS tertile, especially the highest bSS tertile (bSS > 32), with a 50% absolute reduction in 5-year mortality (69.9% vs 11.1%) and a similarly low 5-year mortality rate as SRI = 100% (8.6%). These findings are extremely important, and the concept of reasonable incomplete revascularization should be integrated into the Heart Team discussion.

There are several explanations for how achieving a reasonable level of incomplete anatomic revascularization, compared with absolute complete revascularization, does not affect 5-year mortality. First, it is well accepted that medical therapy for low-risk CAD is associated with a similar prognosis to more invasive strategy.²⁴ Second, it has been well demonstrated from several fractional flow reserve studies that nonfunctional or ischemic lesions could be medically treated without affecting prognosis.²⁵ SYNTAX investigators classified patients anatomically/angiographically as having 3-vessel disease, whereas $\sim 35\%$ were not when assessed by fractional flow reserve.²⁶ Not treating “severe” angiographic lesions that are nonischemic will probably not affect long-term prognosis. Recent evidence challenges the importance of an angiographic versus ischemic-driven treatment (or a combination of both).²⁷ Third, bifurcation studies demonstrated that a provisional stenting approach (leaving behind frequently untreated side branches) has not affected long-term prognosis. Similarly, revascularization of CTOs (not involving a large ischemic area)²⁸ never demonstrated improved survival and still remains a matter of debate.²⁹ The positive interaction in our study between the presence of CTO and incomplete revascularization and 5-year mortality rate suggests that incomplete revascularization involving a CTO negatively affects long-term mortality less than patients with no CTO lesions. This requires confirmation in larger study. These concepts are of central importance, especially knowing that CTO are the subset of lesions the most frequently associated with incomplete revascularization,^{6,20} and that bifurcation accounts for $> 15\%$ to 20% of PCI lesions. The findings of our report, identifying a threshold of reasonable incomplete revascularization, offers a practical revascularization strategy in the management of multivessel disease without compromising long-term mortality, a strategy that has already been partially proved and embedded in current practices and guidelines recommendation.

Left main disease characterizes a subset of patients where the concept of reasonable revascularization may be useful. In case the left main stenosis has been treated, accounting for a large proportion of the baseline risk or myocardium at risk, the amount of residual disease (and its subsequent treatment) may affect long-term prognosis proportionally to the extent of the non-left main CAD. For example, when

facing a complex distal left main involving a bifurcation lesion with the ostial left anterior descending artery and ostial left proximal circumflex, resulting in a baseline SS of at least 25, the treatment or not of a mid-right coronary artery lesion and first obtuse marginal (rSS of 4, SRI of 86%) may not jeopardize the long-term prognosis. In contrast, the same patient with additional 3-vessel disease may benefit from a more substantial revascularization if the long-term prognosis is to be preserved. Aiming for a reasonably complete revascularization, with treatment of ~70% of the CAD burden, may be a more achievable goal in such patients and not negatively affect the prognosis. The EXCEL (Evaluation of XIENCE Everolimus Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (NCT01205776) may bring some meaningful answers to this question.

The present study has some limitations that should be acknowledged. First, this study is a retrospective post hoc analysis, and despite being derived from a large, well-conducted randomized trial, results and conclusions should be seen as hypothesis generating. Second, the completeness of revascularization definition used in the present report was purely anatomic (angiographic), and the derivation of a “functional SRI” would be interesting, with a “reasonable” level of ischemia-guided revascularization being the ultimate goal.²⁶ The current ongoing ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) (NCT01471522) and EXCEL trials (NCT01205776) could bring meaningful insight to this important question. Third, the SRI had the inherent limitations of the SS itself, including all lesions $\geq 50\%$ diameter stenosis and vessels ≥ 1.5 mm in diameter.¹ Using a different threshold for vessel diameter (e.g., 2 mm), lesion severity (e.g., diameter stenosis $\geq 70\%$) would lead to different results, although whether the prognostic accuracy would be greater is unknown. Finally, the prognostic value of reasonable revascularization using the SRI should be also validated (and compared) in the CABG arm, so its application could be broadened.

Disclosures

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Supplementary Data

Supplementary data related with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.amjcard.2015.03.056>.

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Chapter 4.4

Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: Insights from the SYNTAX trial at 5-year follow-up

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ABSTRACT

BACKGROUND Cigarette smoking is a well-known risk factor for development of coronary artery disease (CAD). However, some studies have suggested a “smoker’s paradox,” meaning neutral or favorable outcomes in smokers who have developed CAD, especially myocardial infarction (MI).

OBJECTIVES The study aimed to examine the association of smoking status with clinical outcomes in the randomized controlled SYNTAX (SYnergy Between PCI With TAXUS and Cardiac Surgery) trial at 5-year follow-up.

METHODS Detailed smoking history was collected at baseline, 6-month, 1-year, 3-year, and 5-year follow-up. The composite endpoints included death/MI/stroke (primary endpoint) plus major adverse cardiac and cerebrovascular events (MACCE) (combination of death/MI/stroke and target lesion revascularization) according to patient smoking status. The comparison of 5-year clinical outcomes between the groups according to smoking status was performed with Cox regression using smoking status at baseline or smoking as a time-dependent covariate.

RESULTS A sizeable proportion (n = 322, 17.9%) of patients had changing smoking status during 5-year follow-up. One in 5 patients with complex CAD was smoking at baseline. However, 60% stopped after revascularization while others continued to smoke. Smokers had worse clinical outcomes due to a higher incidence of recurrent MI in both revascularization arms. Smoking was an independent predictor of the composite endpoint of death/MI/stroke (hazard ratio [HR]: 1.8; 95% confidence interval [CI]: 1.3 to 2.5; p = 0.001) and MACCE (HR: 1.4; 95% CI: 1.1 to 1.7; p = 0.02).

CONCLUSIONS Smoking is associated with poor clinical outcomes after revascularization in patients with complex CAD. This places further emphasis on efforts at smoking cessation to improve revascularization benefits. (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries; NCT00114972) (J Am Coll Cardiol 2015;65:1107-15) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS**

CABG = coronary artery
bypass grafting

CI = confidence interval

HR = hazard ratio

MACCE = major adverse
cardiac and cerebrovascular
event(s)

MI = myocardial infarction

PCI = percutaneous
coronary intervention

Cigarette smoking is a globally well-recognized risk factor for coronary artery disease (CAD) (1-5). Smokers with ischemic heart disease also have higher incidence of death and other adverse events (5,6). However, some studies have suggested existence of a “smoker’s paradox,” meaning the outcomes in smokers who have developed CAD, especially myocardial infarction (MI), may be neutral or better than nonsmokers (7-9). It is likely that the observed paradox is largely due to differences

in the baseline characteristics of smokers and nonsmokers in these studies (7,8), or there may be an interaction between smoking and efficacy of antiplatelet drugs (10,11). However, such reports can have a negative public health impact. Indeed, more than one-third of smokers believe that the dangers of smoking are greatly exaggerated (12). It is, therefore, important to study the effect of smoking on outcomes in patients with established CAD to better understand the effects of smoking on outcomes.

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The deleterious effects of smoking after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have been shown previously (13-17), although other studies suggested a smoker’s paradox in this context as well (18,19). However, the smoking status in most of these studies is usually taken at baseline and not collected again at regular intervals. Conversely, smokers who learn they have established CAD may stop smoking permanently or intermittently. Therefore, assessing the impact of smoking status at baseline for long-term outcomes may be unreliable. Additionally, most studies were performed in the era of PCI without stents or with bare-metal stents, providing little insight into the impact of smoking in patients undergoing revascularization with drug-eluting stents. Furthermore, the effect of smoking on clinical events in patients with complex CAD undergoing PCI or CABG remains undefined.

This study aimed to examine the smoking status in patients with complex coronary artery disease undergoing PCI or CABG and its prognostic significance in the SYNTAX (SYnergy Between PCI With TAXUS and Cardiac Surgery) trial at the final 5-year follow-up.

METHODS

The SYNTAX trial (NCT00114972) was a prospective, multicenter, randomized trial that compared PCI with CABG for patients with complex CAD (left main

stem and/or 3-vessel disease) (20). Eligible patients ($n = 1,800$) were randomized on a 1:1 ratio to CABG ($n = 897$) or PCI ($n = 903$) with TAXUS Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, Massachusetts) and followed for 5 years. The study complied with the Declaration of Helsinki and was approved by the ethical review board of the institution involved.

Smoking status was checked for all patients at baseline, 6 months, and 1, 3, and 5 years. The study endpoint was the impact of smoking on a composite endpoint (death/MI/stroke) at 5-year follow-up. We also evaluated impact of smoking on other clinical endpoints including major cardiac and cerebrovascular events (MACCE) (combination of death/MI/stroke/target vessel revascularization). Definitions of various clinical endpoints (e.g., MI, stroke) in the SYNTAX trial have been previously reported (20). All events were adjudicated by an independent clinical event committee comprising interventional cardiologists, cardiac surgeons, and a neurologist (21).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean \pm SD and categorical variables are shown as counts and percentages of the total. Comparison of 5-year clinical outcomes between the groups according to the smoking status was performed with Cox regression using smoking status at baseline or smoking as a time-dependent covariate. Hazard ratios (HR) with 95% confidence intervals (CI) are shown. Chi-square test was used to assess interaction p values for treatment arms. A probability value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, New York) and STATA version 12.0 (Stata Corp. LP, College Station, Texas).

RESULTS

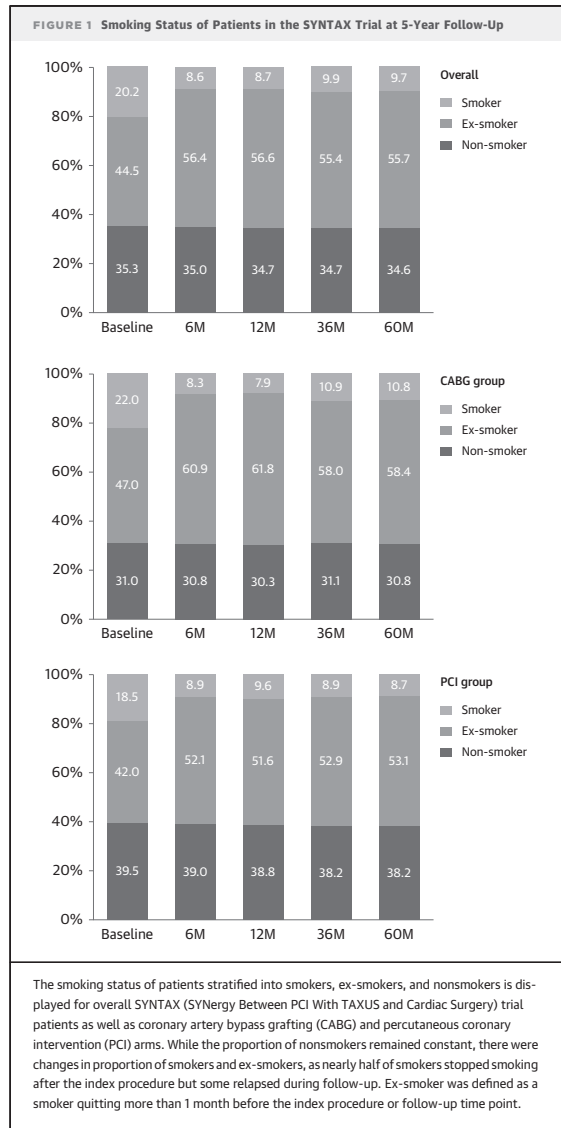
In the randomized SYNTAX trial ($n = 1,800$), information on smoking status was available for 1,793 (99.6%) patients. The proportion of patients smoking at different time points is shown in **Figure 1**. While 20.2% patients with extensive CAD were still smoking at baseline, a significant number stopped smoking after revascularization (8.6% were smokers at 6 months and 8.7% at 1 year). However, after 1 year, there was a modest increase in number of smokers, especially in the CABG arm (10.8% were smokers in the CABG arm vs. 8.7% in the PCI group at 5-year follow-up). Overall, 321 (17.9%) patients had a change in smoking status during follow-up. While nonsmokers remained nonsmokers, current and ex-smokers had considerable change in their smoking status across the 5 years (**Table 1**).

Comparison of baseline characteristics according to smoking status—stratified as smokers, ex-smokers, and nonsmokers (Online Table 1A) and smoking or nonsmoking at baseline (Online Table 1B)—revealed that smokers were younger and predominantly male and had extensive CAD despite lower prevalence of other cardiovascular risk factors including diabetes mellitus, hypertension, or dyslipidemia. Conversely, smokers had more prevalent chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), and poor left ventricular ejection fraction.

EFFECT OF SMOKING ON CLINICAL OUTCOMES. Baseline smoking status appeared to have no impact on death/MI/stroke and MACCE at 5-year follow-up (Figure 2A). Analyzing the data for those smoking or not smoking at baseline also yielded similar results (Figure 2B). However, considering that the smoking status changed during 5-year follow-up, the analysis with smoking as a time-dependent variable revealed that smoking was associated with increased risk of death/MI/stroke (HR: 1.38; 95% CI: 1.02 to 1.86; $p = 0.035$) and MACCE (HR: 1.28; 95% CI: 1.01 to 1.61; $p = 0.041$) at 5-year follow-up (Figure 2C). In total, 1,374 patients never smoked and 98 patients always smoked during 5-year follow-up. The patients who always smoked had significantly higher risk of MI and stent thrombosis/graft occlusion, but not all-cause revascularization, compared with those who never smoked (Online Figure 1).

The baseline smoking status (current smoker vs. ex-smoker vs. nonsmoker) was associated with higher risk of MI during 5-year follow-up (Online Figure 2A). Analyzing the data for those smoking or not smoking at baseline yielded similar results (Online Figure 2B). The predominant effect of smoking as a time-dependent covariate was on subsequent MI (unadjusted HR: 1.86; 95% CI: 1.21 to 2.86; $p = 0.005$; adjusted HR: 2.08; 95% CI: 1.30 to 3.32; $p = 0.002$) (Figure 3, Table 2), whereas no statistically significant effect was observed on mortality or repeat revascularization at 5-year follow-up (Figure 3). The interaction p values for these outcomes between CABG and PCI arms were not significant, suggesting smoking was associated with poor outcomes independent of revascularization strategy (Figure 3).

On multivariable Cox regression analysis using smoking status as a time-dependent covariate, smoking was an independent predictor of death/MI/stroke as well as MACCE (Table 3). Subgroup analysis showed that smoking was an independent predictor of poor outcomes in CABG patients (HR: 1.52; 95% CI: 1.02 to 2.25; $p = 0.038$) as well as the PCI arm



(HR: 1.26; 95% CI: 0.90 to 1.75; $p = 0.177$). After adjusting for other independent predictors, baseline smoking status also was associated with poor outcomes (Central Illustration).

TABLE 1 Smoking Pattern in SYNTAX Patients During 5-Year Follow-Up*

Baseline	6 Months	12 Months	36 Months	60 Months	n (%)
Smoking status unchanged during follow-up					
+	+	+	+	+	1,472 (82.1)
+	+	+	+	+	98 (5.5)
-	-	-	-	-	1,374 (76.6)
Smoking status changing during follow-up					
Smoking at baseline but changing status during follow-up					
+	+	+	+	-	265 (14.8)
+	+	+	+	-	14 (0.78)
+	+	+	-	+	4 (0.22)
+	+	+	-	-	17 (0.95)
+	+	-	+	+	2 (0.11)
+	+	-	-	+	2 (0.11)
+	+	-	-	-	13 (0.73)
+	-	+	+	+	12 (0.67)
+	-	+	-	+	2 (0.11)
+	-	+	-	-	3 (0.17)
+	-	-	+	+	16 (0.89)
+	-	-	+	-	4 (0.22)
+	-	-	-	+	11 (0.61)
+	-	-	-	-	122 (6.80)
+	-	x	x	x	6 (0.33)
+	+	-	x	x	8 (0.45)
+	-	-	x	x	8 (0.45)
+	+	+	-	x	1 (0.06)
+	+	-	+	x	1 (0.06)
+	+	-	-	x	3 (0.17)
+	-	+	+	x	2 (0.11)
+	-	+	-	x	1 (0.06)
+	-	-	+	x	5 (0.28)
+	-	-	-	x	8 (0.45)
Nonsmoking at baseline but changing status during follow-up					
-	+	+	+	+	56 (3.1)
-	+	+	+	-	6 (0.33)
-	+	+	+	-	2 (0.11)
-	+	+	-	+	1 (0.06)
-	+	-	-	-	1 (0.06)
-	-	+	+	+	3 (0.17)
-	-	+	-	+	1 (0.06)
-	-	+	-	-	5 (0.28)
-	-	-	+	+	16 (0.89)
-	-	-	+	-	4 (0.22)
-	-	-	-	+	10 (0.56)
-	+	+	+	x	1 (0.06)
-	-	+	+	x	1 (0.06)
-	-	-	+	x	4 (0.22)
-	+	x	x	x	1 (0.06)

Values are n (%). *+ = smoking; - = nonsmoking; x = the subjects who died or were lost during follow-up.
SYNTAX = SYnergy Between PCI With TAXUS and Cardiac Surgery.

DISCUSSION

The most important finding in this paper is that among patients with complex CAD undergoing revascularization with either PCI or CABG, those who are smokers have a higher incidence of adverse outcomes including MI than those who never smoked or

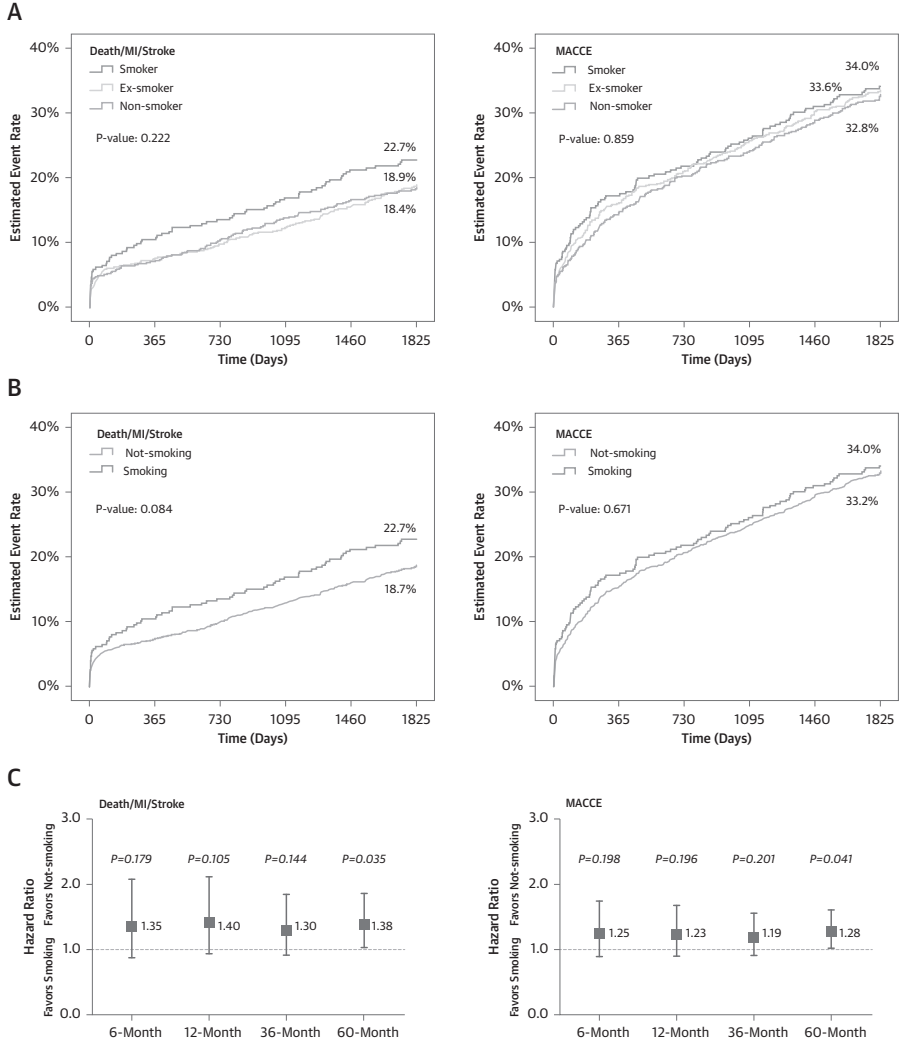
stopped smoking. This finding is seen irrespective of the specific revascularization strategy.

The SYNTAX trial enrolled patients with complex CAD requiring coronary revascularization. It is noteworthy that 1 in 5 patients with extensive coronary disease were still smoking at the time of trial enrollment. These data are consistent with other studies showing that a sizeable proportion (10% to 30%) of patients with established CAD continue to smoke (18,22-24). The number of smokers was halved after coronary revascularization, suggesting that most of the patients took the smoking cessation advice at the time of revascularization seriously (24). The time of revascularization, therefore, presents a good opportunity to reinforce smoking cessation advice and to offer practical help.

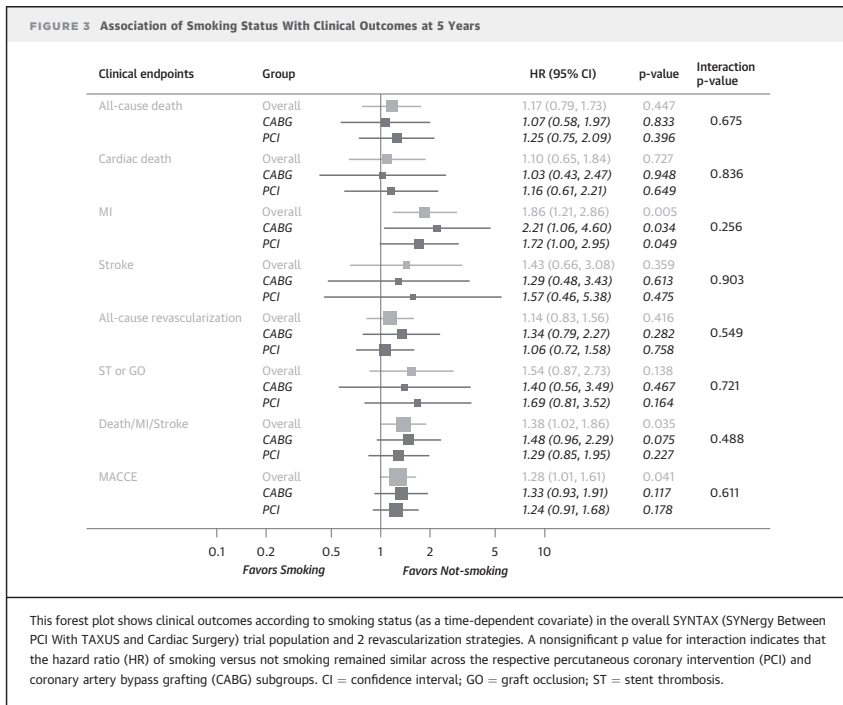
Smoking is a modifiable risk factor, and not all current smokers remain smokers after a coronary event or procedure. Conversely, patients may start smoking again at any time during follow-up. Thus, using baseline smoking status to predict long-term outcomes is a potentially flawed approach. We have, therefore, used smoking status as a time-dependent variable. Indeed, our results confirm that this approach, not unadjusted baseline smoking status, is able to identify the link between smoking and poor outcomes after revascularization. Another study looking at the effect of smoking in patients undergoing CABG has suggested that smoking status at baseline (pre-surgery) was not associated with adverse outcomes but smoking status at follow-up (post-surgery) predicted poor outcomes (13).

IMPACT OF SMOKING ON OUTCOMES: NO PARADOX EXISTS. Smoking was associated with adverse outcomes, especially recurrent MI in our study. This was seen after adjusting for confounding variables or using smoking as a time-dependent covariate. Smoking is a well-established risk factor for acute MI; quitting reduces the risk of subsequent myocardial infarctions (25). It has also been shown in multiple studies that a ban on smoking substantially reduces the incidence of MI, even at the population level (26-28). Adherence to behavioral advice, including smoking cessation, after an acute coronary syndrome is associated with a substantially lower risk of recurrent cardiovascular events (29). There was no significant effect of smoking on repeat revascularization, consistent with previous reports (18,30), although some studies have reported opposing results (31). It is possible that drug-eluting stents are associated with a lower incidence of target lesion revascularization even in those who continue to smoke (30). Our study did not show any statistically significant influence of smoking on

FIGURE 2 Kaplan-Meier Cumulative Events for Primary Endpoint and MACCE



(A) The baseline smoking status (current smoker vs. ex-smoker vs. nonsmoker) appeared to have no impact on death/myocardial infarction (MI)/stroke (primary endpoint) and major adverse cardiac and cerebrovascular events (MACCE) (defined as a combination of death/MI/stroke and target lesion revascularization) at 5-year follow-up. (B) Analyzing the data for those smoking or not smoking at baseline also yielded similar results. (C) However, using smoking status as a time-dependent covariate at follow-up, smoking was associated with an increased risk of death/MI/stroke and MACCE at final 5-year follow-up. The hazard ratio with 95% confidence interval was calculated for outcomes at different follow-up time points. The beneficial effect of nonsmoking, although less pronounced within the short term, was maintained throughout 5-year follow-up.



mortality despite a 17% higher relative risk of mortality in smokers, possibly reflecting lack of adequate power to demonstrate an effect on mortality. Other studies with larger sample sizes have shown higher mortality in smokers undergoing CABG or PCI (15,23). It has also been shown that smokers demonstrate less improvement in quality of life after coronary revascularization (32). Therefore, it is prudent to highlight that smoker's paradox does not exist for patients undergoing coronary revascularization and that smoking cessation before such revascularization is strongly advised to improve outcomes.

TABLE 2 Adjusted Cumulative Effect of Smoking Status on MI

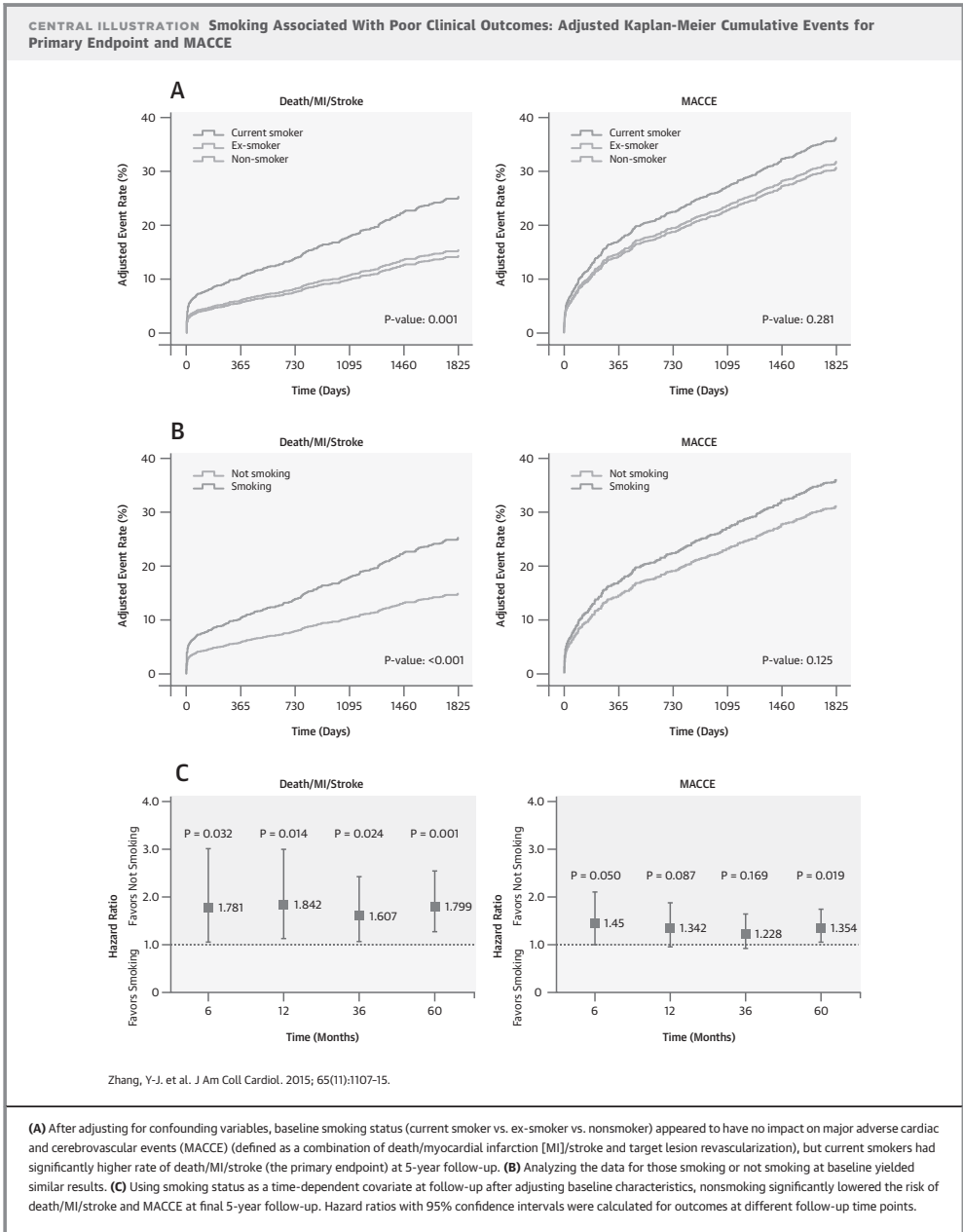
Follow-Up (Months)	HR (Smoking vs. Nonsmoking)	95% CI	p Value
6	2.156	1.201-3.871	0.010
12	2.326	1.325-4.084	0.003
36	1.915	1.132-3.242	0.015
60	2.081	1.304-3.319	0.002

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

TABLE 3 Independent Predictors of Outcomes Using Smoking as Time-Dependent Covariate

Variables	HR	95% CI	p Value
Death/MI/stroke			
Smoking	1.799	1.273-2.543	0.001
PCI vs. CABG	1.292	1.015-1.645	0.038
Age per increase in 10 years	1.548	1.345-1.781	<0.001
COPD	1.523	1.071-2.168	0.019
PVD	1.849	1.344-2.543	<0.001
LVEF <30%	2.029	1.022-4.031	0.043
Amiodarone therapy on discharge	2.970	1.451-6.079	0.003
MACCE			
Smoking	1.354	1.052-1.743	0.019
PCI vs. CABG	1.451	1.220-1.726	<0.001
Age per increase in 10 years	1.162	1.060-1.273	0.001
COPD	1.311	0.997-1.724	0.052
PVD	1.673	1.306-2.142	<0.001
Diabetes	1.324	1.102-1.589	0.003
LVEF <30%	1.853	1.084-3.167	0.024
SYNTAX score per point	1.009	1.001-1.017	0.027

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiac and cerebrovascular event(s); PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; SYNTAX = SYnergy Between PCI With TAXUS and Cardiac Surgery; other abbreviations as in Table 2.



CLINICAL IMPLICATIONS. Smoking is associated with poor outcomes after coronary revascularization with PCI or CABG. This message needs to be disseminated to patients, primary and secondary care physicians, and the general population. It is important to inquire about smoking status at each clinical encounter, and appropriate advice should be offered to help patients stop smoking. Dedicated smoking cessation programs may help patients achieve smoking cessation (33). However, these patients remain at risk of relapse. Patients who had bypass surgery are more prone to return to smoking than those who had an MI (34). Primary care and community-based physicians and nurses may play an important role improving smoking cessation rates.

STUDY STRENGTHS AND LIMITATIONS. The main strength of our study is that smoking status was checked at serial time points in this all-comers clinical trial in patients with complex CAD. However, this is a post-hoc analysis and has limitations inherent to any such analysis. The smoking status presented here is self-reported; there was no biochemical testing (e.g., cotinine measurement) or cross validation of smoking status. Number of cigarettes smoked by current or ex-smokers was not recorded. However, it could be argued that for cardiovascular outcomes, including MI and stroke, smoking status is more important than actual number of cigarettes smoked; in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial, 1-year mortality rates were similar among those smoking less than a half pack per day, half to 1 pack per day, or more than 1 pack per day (19). Smoking may have an acute effect on platelets and endothelial function, leading to arterial thrombosis and MI (35,36).

Another limitation is that the smoking status was collected at pre-defined intervals, and exact date of change was not available. For example, if a patient was smoking at 1 year and not smoking at 3 years, we considered the patient a smoker at 1 year and ex-smoker at 3 years, although the patient could have stopped smoking at any time between 1 and 3 years. However, we also performed a sensitivity analysis in a completely opposite manner with the assumption that patient stopped smoking just after the last visit (data not shown), and the results remained unchanged.

Finally, the association does not confer a cause-effect relationship. It is plausible that those who continue to smoke may have additional lifestyle risk factors (e.g., lack of exercise, unhealthy diet) that could be contributing to the adverse outcomes observed.

CONCLUSIONS

Baseline smoking status may not provide adequate information to predict the longer-term effects of smoking on clinical outcomes due to changes in smoking pattern during follow-up. Smoking is associated with adverse clinical outcomes, especially MI, after revascularization for complex CAD. Abstinence from smoking may improve the outcomes achieved with coronary revascularization, and all patients undergoing PCI or CABG should be encouraged to stop smoking indefinitely before revascularization. Smoking cessation programs may help improve the benefits achieved with revascularization.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Cigarette smoking is an established risk factor for development of coronary artery disease, and studies suggesting that smokers with coronary disease might enjoy paradoxically better outcomes than nonsmokers have not sufficiently considered baseline differences in clinical risk factors or changes in smoking status over time. After PCI or CABG, smokers with complex coronary disease face a higher incidence of myocardial infarction, and abstinence from smoking improves outcomes.

COMPETENCY IN PATIENT CARE: All patients undergoing PCI or CABG should be encouraged to completely and permanently stop smoking.

TRANSLATIONAL OUTLOOK: Additional work is needed to develop more effective and well-tolerated methods to facilitate cessation and sustained abstinence from cigarette smoking.

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KEY WORDS cessation, major adverse cardiac and cerebrovascular event(s), smoker's paradox

APPENDIX For supplemental tables and figures, please see the online version of this article.

Chapter 4.5

Challenges in achieving guidelines recommended cholesterol levels and risk factors associated with not achieving the target: Insights from the ABSORB-II randomised clinical trial

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ABSTRACT

Background: Optimal control of dyslipidaemia improves clinical outcomes in patients with coronary artery disease but remains challenging to achieve. This study analyses the management of dyslipidaemia in patients enrolled in the ABSORB II clinical trial and investigates the risk factors associated with not achieving the ESC recommended cholesterol levels.

Methods: The ABSORB II trial (n=501) aimed to adhere with the 2007 ESC guidelines on cardiovascular disease prevention, which recommended achieving low density lipoprotein cholesterol (LDL-C) level of less than 2 mmol/L. A number of measures including serial lipid monitoring, central laboratory analysis, regular communication and optimization of lipid-lowering therapy were employed to achieve lipid control. Medication status was checked for all patients at baseline, 1-, 6- and 12-month follow-up.

Results: 98% patients received a lipid-lowering drug throughout the 1-year follow-up. At baseline, 33% patients were on simvastatin, 41% on atorvastatin and 12% on rosuvastatin. During 1-year follow-up, use of atorvastatin and rosuvastatin increased to 48% and 17% respectively. The addition of ezetimibe also increased from 4% to 6%. Only 33% patients had LDL-C level within the target range at baseline. There was a significant drop in LDL-C levels during 1-year; nevertheless a significant proportion of patients (55% at 6-months and 58% at 1-year) remained above the target LDL-C level. The lipid profile at 1-year was: mean total cholesterol 4.24 ± 0.91 mmol/L, LDL 2.21 ± 0.73 mmol/L, high density lipoprotein 1.36 ± 0.37 mmol/L and triglycerides 1.48 ± 1.09 mmol/L. Factors associated with not achieving target LDL levels included higher baseline LDL, prior history of myocardial infarction and lack of statin therapy.

Conclusions: Achieving guideline recommended cholesterol targets remains challenging. Identifying high risk patients for closer monitoring, specialist treatment and measures that improve patient compliance are warranted.

INTRODUCTION

Low density lipoprotein cholesterol (LDL-C) is a risk factor for the development and progression of coronary artery disease¹. As dyslipidaemia is a modifiable risk factor, evidence-based use of lipid-lowering therapy is recommended for primary prevention in high risk patients and secondary prevention in all patients with established coronary artery disease²⁻⁵. A recent meta-analysis from Cholesterol Treatment Trialists' Collaboration (CTT) with >170,000 patients from several trials confirmed the dose-dependent reduction in cardiovascular disease with LDL-C⁶. Every 1.0 mmol/L (~40 mg/dL) reduction in LDL-C has been associated with 22% reduction in cardiovascular morbidity and mortality⁶.

Patients undergoing coronary revascularization remain at a high risk for adverse cardiovascular events as the progression of atherosclerosis continues after the revascularization procedure⁷. Therefore, all patients after coronary revascularisation, especially those with percutaneous coronary intervention (PCI), should continue optimal medical therapy including appropriate lipid lowering medication⁸. Guidelines on the management of dyslipidaemias from the European Society of Cardiology (ESC) and European Atherosclerosis Society consider established cardiovascular disease as a very high risk group^{9,10}. ESC guidelines 2011 recommend that in patients with a very high cardiovascular risk, the target of treatment is to achieve LDL-C levels <1.8 mmol/L (less than <70 mg/dL) and/or more than 50% relative reduction in LDL-C when the target level cannot be reached⁹. However, it remains challenging to achieve these target levels in clinical practice, which are more stringent than the ESC guidelines of

2007 (Target LDL-C levels <2.0 mmol /L or 80 mg/dL). The use of optimal medical therapy for secondary prevention remains low after revascularisation¹¹⁻¹⁵. Moreover, the best lipid lowering strategy to reduce cardiovascular risk remains debatable^{9,16-18}.

ABSORB-II is a multicentre randomised, controlled, clinical trial comparing the second-generation Absorb bioresorbable vascular scaffold (BVS) with XIENCE-V everolimus-eluting metallic stent. The clinical protocol of ABSORB-II clearly documents the importance of- and strategies to- improve lipid profile. The data on lipid profile as well as details of lipid-lowering therapy were recorded at baseline, 1-month, 6-month and 12-month follow-up. We aimed to analyse the management of dyslipidaemia in the ABSORB-II trial, with a view to identifying the risk factors associated with not achieving the ESC recommended LDL-C levels.

METHODS

ABSORB II trial: The design of the ABSORB II trial (ClinicalTrials.gov ID: NCT01425281) has been described previously^{19,20}. In brief, it is a randomised, active-controlled, single-blinded, multicentre clinical trial comparing the second-generation Absorb BVS with the XIENCE everolimus-eluting metallic stent, (both Abbott Vascular, Santa Clara, CA)²⁰.

Management of dyslipidaemia in ABSORB II: The ABSORB II trial aimed to adhere with the 2007 ESC guidelines on cardiovascular disease prevention in clinical practice¹⁰. These guidelines recommended achieving a LDL-C level of less than 2 mmol/L (approximately 80 mg/dL). A number of measures, as summarised in *Table 1*, were employed to achieve guideline recommended lipid targets.

Table 1: Measures to achieve target LDL-Cholesterol levels in the ABSORB-II trial

Global communication	Regular newsletter and investigator meetings to emphasize the importance of well controlled LDL-C and the level of compliance to ESC guidelines in the ABSORB-II trial
Regular lipids monitoring	The lipid profile was regularly monitored during enrolment and follow-up.
Independent analysis	Central laboratory (ICON Plc, Dublin Ireland)
Central review	Available results from laboratory were checked and reviewed within a week to check if a patient was on target for LDL-C according to the 2007 ESC guidelines (2.0 mmol/L, 80 mg/dL).
Communication with sites	For patient not on-target LDL-C levels, a letter was sent to the site investigator to review the lipid profile of the patient and check/adjust the treatment strategy for dyslipidaemia.
6-month review	For every patient with LDL-cholesterol > 2.0 mmol/L (80 mg/dL) at 6 month a ranking of this value compared to all the patients in ABSORB II was sent to the site with recommendations to address dyslipidaemia.
Treatment recommendations	Practical approach to reach LDL-cholesterol goal as described in the ESC 2007 Guidelines* was emphasised regularly via the newsletters and meetings with trial investigators.

LDL-C low density lipoprotein cholesterol, ESC European Society of Cardiology. * European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur J Cardiovasc Prev Rehabil. 2007;14 Suppl 2:E1-40

Demographic and clinical characteristics of all patients were recorded at baseline. Blood samples were taken for all patients at baseline, 1-month, 6-month and 12-month. All samples were analysed at an independent core laboratory (ICON Plc, Dublin Ireland). Lipid profile (including total cholesterol, LDL-C calculated, high density lipoprotein cholesterol [HDL-C], and Triglycerides [TG]) were checked. The Friedewald formula ($LDL-C = Total\ Cholesterol - [HDL-C + TG/2.20]$ in mmol/L) was used for calculation of LDL-C concentration²¹. If plasma TG levels were above 4.52 mmol/L (400 mg/dL), the measured LDL-C concentration was then reported. Medication status for statin or other lipid-lowering drug was checked for all patients at baseline, 1-month, 6-month and 12-month follow-up.

Statistical Analysis: Continuous variables are expressed as mean \pm standard deviation and compared using t-test. Categorical variables are shown as counts and percentages of the total and were compared using Chi-square

test. A multivariate logistic regression model was used to identify factors independently associated with not achieving target LDL levels. All statistical analyses were performed with SAS 9.3 (SAS Institute Inc. Cary, NC, USA).

RESULTS

Study participants: Between November, 2011, and June, 2013, 501 patients from 46 sites in Europe and New Zealand, were enrolled in the ABSORB II trial. Out of these 501 patients at baseline, 500 patients, 496 patients and 493 patients have completed the 1-month, 6-month and 12-month follow-up respectively¹⁹. Overall demographics and clinical characteristics of the patients are shown in *Table 2*. Information on lipid profile at baseline, 1-month, 6-month and 1-year follow-up was available for 448 (89%), 435 (87%), 451 (91%) and 448 (91%) patients respectively.

Table 2. Overall Baseline Patients' Characteristics

Age (mean \pm SD)	61.3 \pm 10.0
Male (%)	76.8
Body Mass Index (kg/m ²) (mean \pm SD)	28.0 \pm 4.0
Current tobacco use (%)	23.0
Hypertension (history or needing medication, %)	69.9
Dyslipidaemia (history or needing medication, %)	76.8
Diabetes (%)	24.0
Diabetes mellitus treated with insulin (% of Diabetes patients)	30.0
Family history of premature coronary artery disease (%)	38.2
Previous myocardial infarction (%)	28.3
Recent myocardial infarction with normalised enzyme (%)	2.8
Stable angina (%)	64.1
Unstable angina (%)	21.0
Silent ischaemia (%)	12.2

Table 3. Patients taking various lipid lowering drugs through 1-year

Drug ¹	Baseline ² N=501	1-month ³ N=500	6-month ³ N=496	12-month ³ N=493
Atorvastatin, n (%)	203 (40.5%)	218 (43.6%)	230 (46.4%)	236 (47.9%)
Dose (mg) \pm SD	43.4 \pm 22.2	44.7 \pm 23.0	44.4 \pm 22.7	43.4 \pm 22.1
Simvastatin, n (%)	163 (32.5%)	159 (31.8%)	138 (27.8%)	126 (25.6%)
Dose \pm SD	33.4 \pm 9.6	33.4 \pm 9.6	33.7 \pm 9.6	33.1 \pm 9.9
Pravastatin, n (%)	15 (3%)	17 (3.4%)	15 (3.0%)	16 (3.2%)
Dose (mg) \pm SD	26.0 \pm 18.0	26.5 \pm 17.3	26.4 \pm 18.6	27.3 \pm 18.3
Rosuvastatin, n (%)	60 (12.0%)	75 (15.0%)	79 (15.9%)	84 (17.0%)
Dose (mg) \pm SD	14.7 \pm 12.3	14.7 \pm 11.2	14.5 \pm 11.2	15.6 \pm 11.9
Ezetimibe, n (%)	21 (4.2%)	24 (4.8%)	32 (6.5%)	35 (7.1%)
Ezetimibe in combination	18 (3.6%)	20 (4.0)	25 (5.0%)	28 (5.7%)
Dose ⁴ (mg) \pm SD	10.8 \pm 2.9	10.8 \pm 2.8	10.6 \pm 2.4	10.2 \pm 2.5
Polyunsaturated fatty acids, n (%)	11 (2.2%)	14 (2.8%)	14 (2.8%)	10 (2.0%)
Other statin, n (%)	4 (0.8%)	4 (0.8%)	3 (0.6%)	2 (0.4%)
Other Lipid Lowering Drug, n (%)	11 (2.2%)	12 (2.4%)	12 (2.4%)	12 (2.4%)
None	53 (10.6%)	22 (4.4%)	19 (3.8%)	19 (3.9%)

¹Some of the medications may be combined

²Medication started before index procedure or at index procedure date

³Medication present at least up until the visit (do not include medication started at the follow-up)

⁴Mean dose of Ezetimibe used in combination

Lipid lowering therapy: A large majority of the patients received a lipid-lowering medication through the 1-year follow-up. *Table 3* shows the lipid lowering drug usage at various follow-up time points. At baseline

32.5% (n=163) of the patients were receiving simvastatin whilst 40.5% (n=203) and 12.0% (n=60) were receiving atorvastatin or rosuvastatin respectively. Through the 1-year follow-up, use of simvastatin reduced

to 25.6%, whilst usage of more potent drugs, atorvastatin and rosuvastatin, increased to 47.9% and 17.0% respectively. The use of ezetimibe, as a monotherapy or in combination with a statin, increased from 4.2% at baseline to 7.1% at 1-year follow-up.

Lipid profile at baseline and follow-up: The mean levels for various cholesterol fractions at baseline were: total cholesterol 4.18±1.12 mmol/L, LDL-C 2.49±0.97 mmol/L, HDL-C 1.17±0.33 mmol/L and TG 1.18±0.94 mmol/L. The temporal trend in different fraction of lipid profile is shown in *Figure 1*. Using baseline as reference, LDL-C was significantly lower at all follow-up time points. However, the mean

difference decreased progressively after 1-month follow-up (from -0.34 [95% CI -0.44 to -0.24] at 1-month to -0.28 mmol/L [-0.39 to -0.16] at 1-year follow-up). Conversely, TG significantly increased after the procedure at all the time points and was, on average, 0.30 (95% Confidence Interval [CI] 0.19 to 0.41) mmol/L higher at 1-year follow-up (P<0.01). HDL-C increased progressively from baseline, being 0.19 (95% CI 0.16 to 0.22) mmol/L at 1-year follow-up (P<0.01). The total cholesterol, therefore, remained unchanged during the 1-year follow-up. The lipid profile at 1-year was: total cholesterol 4.24±0.91 mmol/L, LDL 2.21±0.73 mmol/L, high density lipoprotein

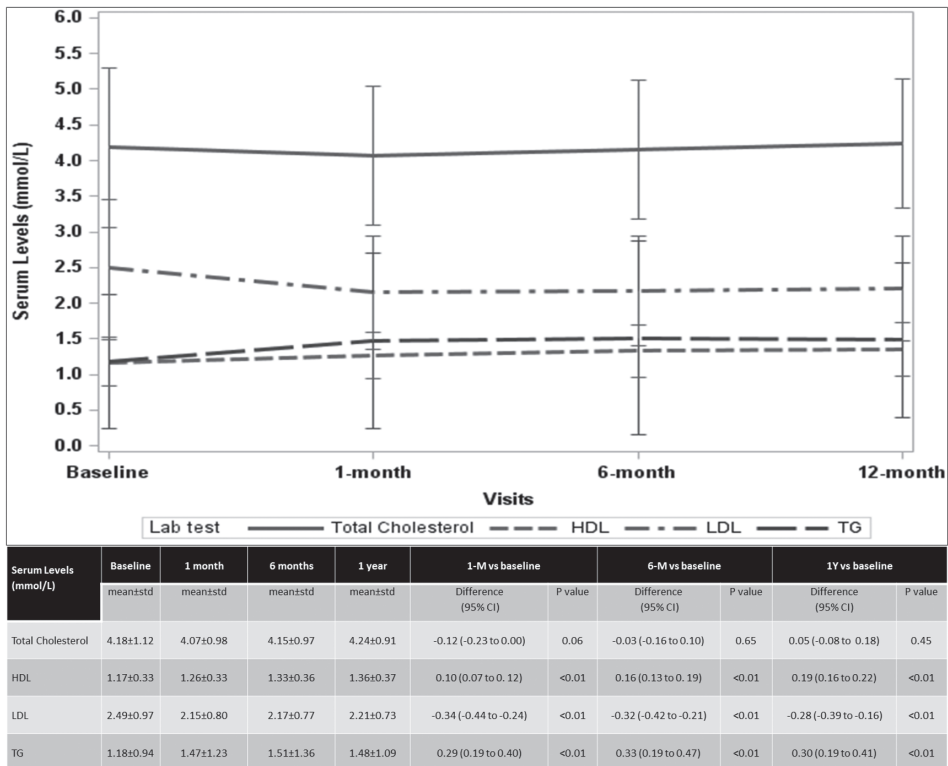


Figure 1: Average lipid profile at baseline and during the follow-up in the ABSORB-II trial HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol, TG triglycerides, SD standard deviation

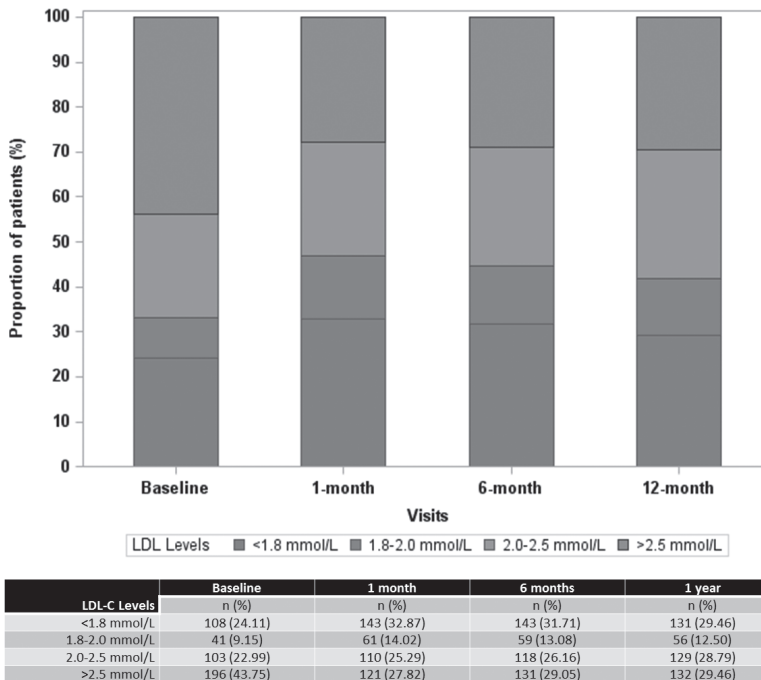


Figure 2: Proportion of patients achieving LDL-cholesterol targets in the ABSORB-II trial

1.36±0.37 mmol/L and triglycerides 1.48±1.09 mmol/L.

At baseline, only 33% patients had a LDL-C level within the target range of <2 mmol/L (Figure 2). As per the ABSORB-II protocol, this triggered a direct communication to the investigators to modify the therapeutic strategy for dyslipidaemia management or communicate with patients' general practitioner. Following this recommendation, 47% patients were within target range at 1-month follow-up. However, a significant proportion of patients (53.1% at 1-month, 55.2% at 6-month and 58.3% at 1-year) remained above the target for LDL-C level. If the more stringent target level of 1.8 mmol/L was used, as specified in the ESC 2011 guidelines, then only 24-32% patients were within the optimal LDL-C range

(Figure 2). However, there was a trend toward improvement over-time with an increase in the number of patients on moderate-high intensity statin therapy (as defined by 2013 the American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults)¹⁶ and proportion of those achieving target LDL-C levels (Figure 3).

Risk factors associated with not-achieving target LDL levels: Clinical characteristics of patients on-target vs off-target for LDL-C levels of <2 mmol/L are shown in Table 4. It appears that patients with low body mass index (BMI), higher cholesterol levels at baseline, untreated hypertension and family history of premature coronary artery disease

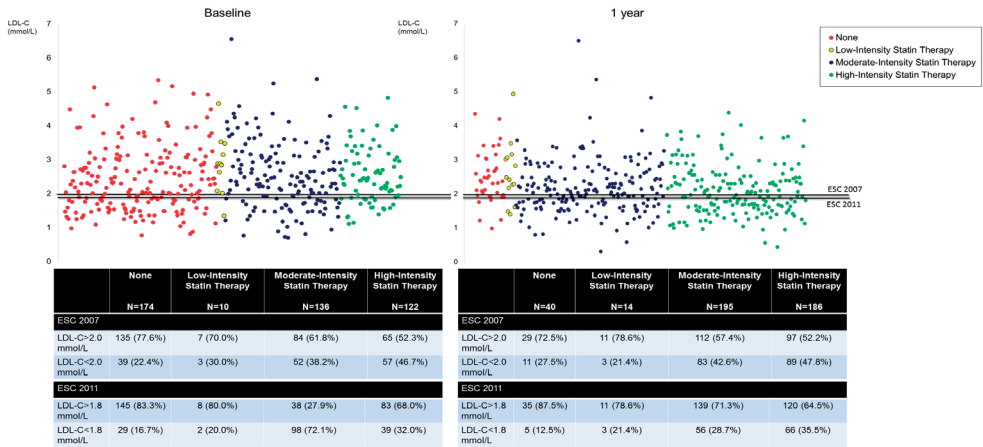


Figure 3. Effects of statin regimen on LDL-C levels. Patients on statin therapy with fasting LDL-C at baseline and 1-year is shown according to the 2007 and 2011 ESC guidelines. Subjects were classified in High- Moderate- and Low-Intensity Statin Therapy according to the 2013 American College of Cardiology/American Heart Association Guideline.

Table 4: Comparison of patients achieving versus not achieving LDL-Cholesterol targets at 1-year

Target	On Target N=187	Off-Target N=261	Difference(95% CI)	P
Age	61.8 ± 9.8	61.2 ± 9.9	0.6 [-1.3, 2.4]	0.540
Male	78% (146/187)	77% (200/261)	1.4% [-6.6%, 9.1%]	0.719
BMI	28.39 ± 4.24	27.70 ± 3.68	0.68 [-0.07, 1.44]	0.076
Baseline Total Cholesterol	3.87 ± 1.11	4.40 ± 1.04	-0.54 [-0.75, -0.32]	<0.001
Baseline LDL-C	2.18 ± 0.96	2.68 ± 0.90	-0.50 [-0.69, -0.31]	<0.001
Baseline HDL-C	1.13 ± 0.33	1.20 ± 0.34	-0.07 [-0.14, -0.01]	0.031
Baseline TG	1.29 ± 1.30	1.15 ± 0.68	0.13 [-0.09, 0.35]	0.232
On lipid lowering agents	69% (129/187)	73% (191/261)	-4.2% [-12.8%, 4.2%]	0.332
Smoking				
Non-smokers	37% (69/187)	38% (98/261)	-0.6% [-9.6%, 8.4%]	0.889
Ex-smokers	43% (80/187)	41% (106/261)	2.2% [-7.0%, 11.4%]	0.646
Smokers	20% (38/187)	22% (57/261)	-1.5% [-9.0%, 6.3%]	0.698
Hypertension				
No	32% (60/187)	30% (79/261)	1.8% [-6.7%, 10.6%]	0.682
Treated	66% (123/187)	64% (168/261)	1.4% [-7.6%, 10.2%]	0.758
Untreated	2% (4/187)	5% (14/261)	-3.2% [-6.9%, 0.7%]	0.087
Diabetes mellitus	28% (53/187)	20% (51/261)	8.8% [0.9%, 16.9%]	0.030
Family history of premature CAD	32% (54/171)	43% (102/239)	-11.1% [-20.2%, 1.6%]	0.023
Prior MI	25% (47/186)	31% (79/259)	-5.2% [-13.4%, 3.3%]	0.227
Prior PCI	33% (61/187)	35% (92/261)	-2.6% [-11.3%, 6.3%]	0.563
Prior CABG	2% (4/187)	2% (6/261)	-0.2% [-3.1%, 3.3%]	1.000

BMI body mass index, LDL-C low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, TG triglycerides, CAD coronary artery disease, MI myocardial infraction, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting

were more likely to be off-target. On multiple regression analysis, higher baseline LDL-C, prior myocardial infarction and lack of statin therapy were independent predictors of not achieving the target levels.

DISCUSSION

The main findings of the present study can be summarized as follows: (1) the vigorous effort to achieve guidelines recommended lipid targets in the ABSORB II trial resulted in an extremely high lipid-lowering therapy prescription; (2) nevertheless a sizable proportion of the patients (58.3%) failed to achieve ESC guidelines recommended target levels of LDL-C.

Atherosclerosis progression remains a potential enemy at the longer-term follow-up of coronary revascularization^{22,23}. Lipid lowering agents have been shown to improve clinical outcomes and are recommended as secondary prevention therapy in patients with clinically evident coronary artery disease, including patients who have undergone CABG or PCI^{5,24-27}. Intensive lipid-lowering therapy can cause regression of atherosclerotic plaques²⁸ and reduction in future cardiovascular events²⁹. However, adherence to lipid lowering therapy remains low in clinical practice. A large international observational registry (REACH) of 37,154 patients with established atherosclerotic disease showed that only 68% of patients were taking statins³⁰. Only two-thirds of patients in the SYNTAX trial were taking a lipid-lowering drug, despite the fact that they had complex and extensive coronary disease³¹. Similar results were seen in patients undergoing CABG in the PREVENT-IV trial³². Conversely, in the present study almost all

patients were on a lipid lowering therapy highlighting the success of the educational and motivational tools employed in the ABSORB-II trial to manage dyslipidaemia, despite it being a head-to-head trial of two different types of coronary devices.

In spite of taking lipid lowering therapy and achieving a significant reduction in LDL-C levels, only 41.7% achieved the LDL-C goals at 1-year follow-up. If we use the stringent recommendations set by the 2011 ESC Guidelines (LDL-C <1.8 mmol/L)⁹, the proportion of patients achieving the target would be even less (43.08% at 1-month, 40.18% at 6-month and 37.50% at 1-year). These data are consistent with other studies suggesting that it remains challenging to achieve guideline based levels in clinical practice³³⁻³⁵. In another recent study of 366 patients with acute myocardial infarction, one-third of patients had LDL-C levels above 2.5 mmol/L at 6-month follow-up³⁶. It is important to try to understand why patients could not achieve guideline recommended levels. A sizable proportion of patients in our study were receiving moderate and high intensity statins and yet did not achieve target LDL-C; therefore, inadequate prescription and doses are unlikely to be responsible for these sub-optimal results. It is plausible that patients were not adherent to their medical therapy³⁷. The importance of lipid lowering should be emphasised to patients at each clinical encounter to improve compliance³⁸. Combining the statin with other cardiovascular drugs in a single tablet (polypill) may also improve adherence³⁹. It is also possible that the currently used drugs are not potent enough to achieve the desired results without the danger of actual/perceived side effects. In this regard, the new inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9) were well tol-

erated in short-term trials and have produced an additional 50–60% decrease in the LDL-C. However information about the long-term safety of these drugs, and their efficacy in preventing cardiovascular events is not known⁴⁰. Finally, it is also worth mentioning that these targets are rather arbitrary and not directly tested in any randomised clinical trials. Indeed some authorities have suggested to abolish these target LDL-C levels altogether¹⁶⁻¹⁸.

It is also important to identify patient populations at high risk of not achieving the target to allow closer monitoring and intensive therapy. Patients with diabetes mellitus are generally considered to have a poor metabolic profile; however, these patients were more likely to achieve target levels in this study. This may be due to the fact that these patients are more likely to be closely followed and have their medication optimised. Patients with a family history of premature coronary disease were unlikely to achieve target levels possibly due to an element of familial dyslipidaemia requiring specialist intervention or simply a marker of unhealthy life style. There was an unexpected finding of rising TG levels over the 1-year follow-up period. Statins are expected to reduce TG levels. We did find a few outliers (data not shown) which may have skewed the results. However, it is also well-known that reliable and reproducible TG measurements can be challenging due to variability in levels and effect of comorbidities including diabetic control. Finally, TG distribution is markedly skewed, which often necessitates categorical definitions or log transformations⁴¹.

Interventions to improve the use of optimal medical therapy including lipid lowering agents in high-risk subgroups may be beneficial⁴²⁻⁴⁴. Educating patients and health care providers in the community is of paramount importance.

In the state funded health systems, adopting reimbursement based on results may help to achieve targets (for example blood pressure, HbA1c and LDL-C levels. This approach has been successfully implemented in the United Kingdom. In the private/insurance funding systems, prescription of potent generic agents (for example, atorvastatin) may be more helpful to balance treatment costs and benefits⁴⁵. Local preventive cardiology programmes adapted to individual countries can be very helpful⁴⁶. In the United States, programmes, such as the Get With The Guidelines and the Guidelines Applied in Practice initiatives, may help to improve statin prescription and patients' compliance⁴²⁻⁴⁴.

Study limitations

The main strength of our study is the quality of serial data on lipid profile and medication, despite this being a trial of coronary stents/scaffolds. However, this is a *post-hoc* analysis and has limitations inherent to any such analysis. Adherence to medical therapy was assessed by patients self-reporting, without any external validation. Nevertheless, patient self-report has been shown to be a good method to assess adherence in clinical practice⁴⁷.

CONCLUSIONS

A physician-oriented motivational and educational approach to control LDL-C levels resulted in a very high percentage of patients receiving lipid-lowering agents but with the majority not reaching the guidelines recommended LDL-C levels. Identifying high risk patients for closer monitoring, specialist treatment and measures that improve patient compliance are warranted.

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Conflicts of interest

SV is an employee of Abbott Vascular. LW and TV are contractors working for Abbott Vascular. All other authors have reported no conflict of interest relevant to this paper.

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PART 5

**IMPACT OF BIORESORBABLE SCAFFOLDS IN THE NATURAL HISTORY
OF CORONARY ATHEROSCLEROSIS**

Chapter 5.1

Assessing Bioresorbable Coronary Devices: Methods and Parameters

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ABSTRACT

Bioresorbable vascular scaffolds (BRS) represent a novel approach to provide transient vessel support to drug-delivery capability without the long-term limitations of metallic drug-eluting stents (DES). The technology has the potential to overcome many of the safety concerns associated with metallic DES and possibly even convey further clinical benefit. In particular, the BRS are designed to provide short-term lumen support, and after being completely bioresorbed, eliminate the permanent caging typical of metallic DES. However, this technology has required new imaging modalities and methodologies for its assessment because the design, degradation rate, loss of mechanical property, and drug deliverability may affect its safety and efficacy. We provide an overview of all existing methods for assessing bioresorbable devices, from noninvasive to invasive, from light to sound based, and from morphological to functional parameters. (*J Am Coll Cardiol Img* 2014;7:1130-48) © 2014 by the American College of Cardiology Foundation.

The clinical introduction of bioresorbable scaffolds (BRS) resulted in a revolutionary change in the application of local coronary therapies. These devices have the unique ability to provide a temporary scaffold that is necessary to maintain the patency of the vessel after intervention, releasing antiproliferative drugs. The BRS then gradually degrade, liberating the vessel from its cage and permitting the restoration of vascular physiology and integrity (1,2).

Percutaneous coronary intervention with BRS has potential advantages over the current use of metallic stents because after resorption, there should be no trigger for thrombosis, thereby reducing stent/scaffold thrombosis. The lack of foreign material may also reduce the requirements for long-term dual antiplatelet therapy and its correlated bleeding

complications. The absence of a rigid metallic cage can facilitate restoration of the vessel vasomotor tone, adaptive shear stress, late luminal enlargement, and late expansive remodeling. In the long term, BRS may allow a percutaneous/surgical revascularization of the treated segment or pharmacologically induced plaque regression, whereas traditional stents often preclude this option. For clinical follow-up, BRS enable noninvasive evaluation by multislice coronary tomography (MSCT), enabling visualization of the vascular lumen in the treated segment without the blooming effect observed with metallic stents.

Over the last 10 years, considerable effort has been put forth to develop new fully bioresorbable devices. BRS technology has gradually matured, and there are numerous devices available for preclinical or clinical evaluation (**Table 1**). However, this

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technology has required new imaging modalities and methodology for the assessment of BRS because their design, degradation rate, loss of mechanical properties, coating, and drug deliverability may affect safety and efficacy (Table 2). This review describes the imaging methods for BRS, compares BRS with metallic stents, and describes the clinical relevance of BRS.

INVASIVE QUANTITATIVE CORONARY ANGIOGRAPHY

Invasive quantitative coronary angiography (QCA) remains one of the most commonly used methods for the assessment of lumen parameters for BRS. Coronary restenosis is influenced by both acute gain provided by the intervention and the subsequent late lumen loss (Figure 1). Considering the variety of BRS under development, clear understanding of the coronary restenotic mechanics is needed.

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In each patient, the treated segment (in-scaffold) and the peri-scaffold segments (defined by a length of 5 mm proximal and distal to the scaffold edge—in-segment) should be analyzed by QCA in paired matched angiographic views after the procedure and at follow-up. Because these devices are radiolucent, the only visible structures for QCA analysis are the

metallic markers at the proximal and distal ends of the device (Figure 2).

The following QCA parameters are computed: minimal luminal diameter (MLD), reference vessel diameter obtained by an interpolated method, late loss, and binary restenosis.

LATE LOSS AND/OR LATE LUMINAL GAIN.

Late loss and/or late luminal gain are defined as the difference between MLD at post-procedure minus MLD at follow-up. For lumen diameter reduction, this will be a positive number; for late increase in lumen size, this will be a negative number. Figure 1 summarizes the lumen size changes of current BRS tested in clinical scenarios. Please note the unique effect of all BRS, which is the late increase in lumen size (late gain). This luminal gain starts when BRS start to lose their mechanical integrity (Table 3).

ACUTE RECOIL. For acute recoil assessment, 2 specific views are analyzed. One is an image of complete expansion of the last balloon (either the device delivery balloon or the post-dilation balloon) at the highest pressure. The other is a cine frame immediately after the last balloon deflation and the subsequent nitrate injection. These 2 images should be analyzed in the same angiographic projection selected to minimize foreshortening.

ABBREVIATIONS AND ACRONYMS

BRS = bioresorbable scaffolds
FF = fibrofatty
FFR = fractional flow reserve
ISA = incomplete scaffold apposition
IVUS = intravascular ultrasound
MLD = minimal lumen diameter
MPS = metallic platform stents
MSCT = multislice coronary tomography
OCT = optical coherence tomography
QCA = quantitative coronary angiography
VH = virtual histology

TABLE 1 Bioresorbable Scaffolds: Materials and Current Development

Company	Product	Material	Development	Pre-Clinical	Clinical	Post-Clinical
Abbott Laboratories	Absorb	PLLA/PDLLA	✓	✓	✓	✓
Elixir	DESolve	PLLA/PDLLA	✓	✓	✓	✓
Meril	MeRes	PLLA	✓	✓	✓	
Amaranth Medical	FORTITUDE	PLLA	✓	✓	✓	
ART/Terumo	ART18Z	PDLLA	✓	✓	✓	
Biotronik	DREAMS	Magnesium + PLLA	✓	✓	✓	
Huaan	XINSORB	PLA/PCL/PGA	✓	✓	✓	
Kyoto Medical	IGAKI-TAMAI	PLLA	✓	✓	✓	
Xenogenics	Ideal BioStent	Polyanhydride (ASA/adipic acid anhydride)	✓	✓	✓	
Arterius	ReBioStent	Bioresorbable polymer	✓	✓		
Cardionovum	ReNATURAL	Metal	✓	✓		
Medtronic	Mg Spiral	Magnesium	✓	✓		
OrbusNeich	On-AVS	PLLA/PDLA/TMC/eCAP	✓	✓		
Reva	Fantom	Tyrosine polycarbonate	✓	✓		
S3V	Avatar	Not available	✓	✓		
Zorion Medical	ZMED	Magnesium + polymer	✓	✓		
LifeTech	Lifetech Iron Stent	Iron	✓	✓		
Boston Scientific	BSC BRS	Magnesium	✓	✓		
Sahajanand	Sahajanand BRS	PLLA?	✓			

ASA = salicylic acid; BRS = bioresorbable scaffolds; PCL = polycaprolactone; PDLA = poly-D-lactide; PDLLA = poly(L-lactide-co-D,L-lactide); PGA = polyglycolic acid; PLA = poly(lactic acid); PLLA = poly-L-lactide; TMC = trimethylene carbonate.

TABLE 2 Mechanical Properties and Degradation Rate of Different Material Candidates for Bioresorbable Coronary Scaffolds

Material	Tensile Strength, MPa	Elongation, %	Degradation Time
Poly(L-lactide)	60-70	2-6	24 months*
Poly(DL-lactide)	45-55	2-6	12-16 months*
Poly(glycolide)	90-110	1-2	6-12 months*
50/50 DL-lactide/glycolide	40-50	1-4	1-2 months*
82/18 L-lactide/glycolide	60-70	2-6	12-18 months*
70/30L-lactide/ ϵ -aprolactone	18-22	>100	12-24 months*
Pure Fe	200	40	0.19 mm/year
Fe-35Mn alloy	430	30	0.44 mm/year
WE43 alloy	280	2	1.35 mm/year

*Degradation time depends on geometry (44,45).
MPa = megapascals.

Acute stent/scaffold recoil is calculated as follows.

- When a stent/scaffold delivery balloon was used for stent/scaffold expansion, acute absolute stent/scaffold recoil is defined as the difference between the mean diameter of the stent/scaffold delivery balloon at the highest pressure at implantation of stent/scaffold (X) and mean luminal diameter of stented/scaffolded segment after implantation (Y). Absolute acute stent/scaffold recoil is calculated as $X - Y$, whereas relative acute stent/scaffold recoil is defined as $(X - Y)/X$ and is expressed as a percentage.
- When a post-dilation balloon was used in the procedure, acute absolute recoil is defined as the difference between the mean diameter of the post-dilation balloon at the highest pressure in the post-dilated segment (X_0) and mean luminal diameter after post-dilation (Y_0). Relative acute recoil is defined as $(X_0 - Y_0)/X_0$ and is expressed as a percentage.

The same methodology was used throughout the ABSORB Cohort A and Cohort B trials. The absolute acute recoil in Absorb BVS 1.1 (Abbott Laboratories, Abbott Park, Illinois) was 0.19 ± 0.18 mm ($6.7 \pm 6.4\%$), which was not statistically different than that in BVS 1.0 (0.20 ± 0.21 mm; $6.9 \pm 7.0\%$) or the metallic everolimus-eluting stent (0.13 ± 0.21 mm; $4.3 \pm 7.1\%$). In multivariable models of the 3 pooled populations, the balloon/artery ratio was an independent predictor of acute recoil, whereas the type of device (scaffold or stent) was not (3). The DESolve Nx BRS (Elixir Medical, Sunnyvale, California) and the ART stent (ART,

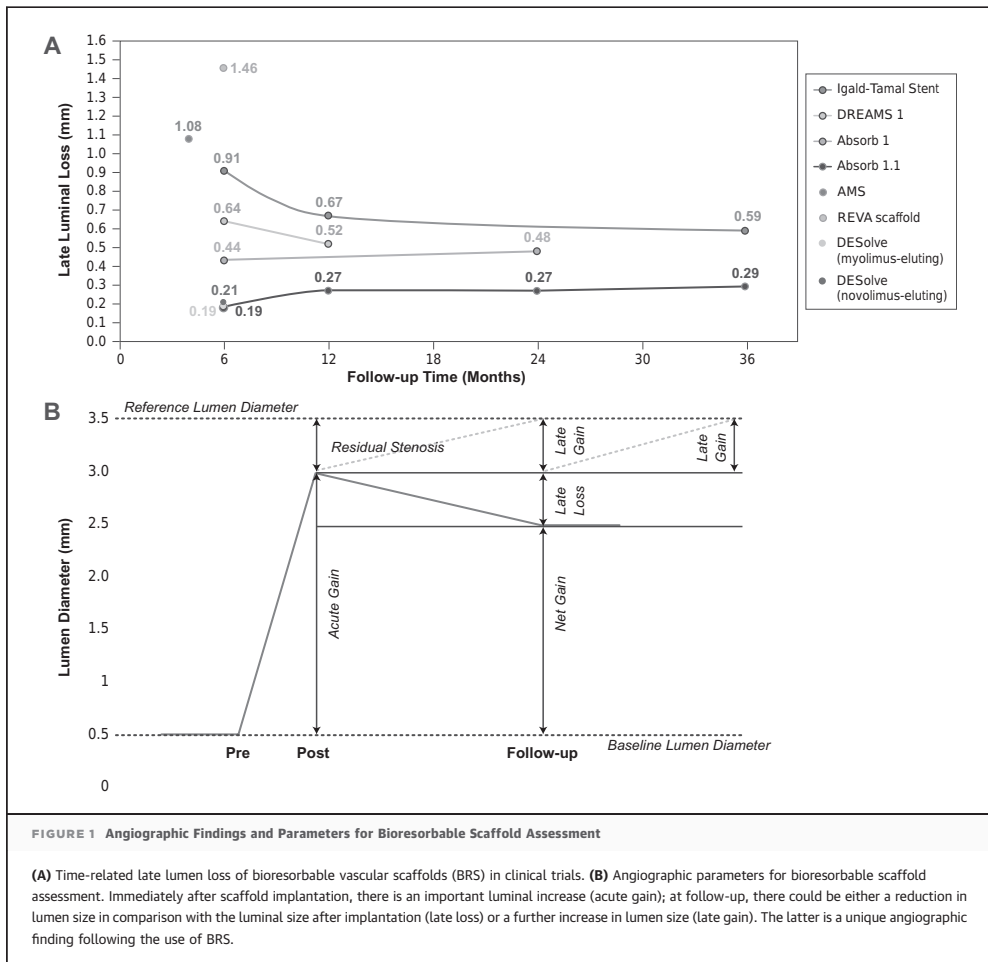
Noisy le Roi, France) have acute recoils of $6.4 \pm 4.6\%$ (4) and 4.0% (data on file, ART), respectively.

CONFORMABILITY. Coronary geometry changes after stenting might result in wall shear stress changes and adverse events. These changes in 3-dimensional (3D) vessel geometry are associated with decreased and increased shear stress zones close to the stent edges. These changes were found to be related to the asymmetrical patterns of in-stent restenosis (5). Angiographically, the geometric changes can be assessed by measuring the curvature and angulation. “Curvature” is defined as the infinitesimal rate of change in the tangent vector at each point of the center line. This measurement has a reciprocal relationship with the radius of the perfect circle defined by the curve at each point. The curvature value is calculated as $1/\text{radius}$ of the circle in cm^{-1} (6). “Angulation” is defined as the angle in degrees that the tip of an intracoronary guidewire would need to reach the distal part of a coronary bend (Figure 3) (6).

For the Absorb scaffold, from post-implantation to follow-up, curvature increased by 8.4% ($p < 0.01$) with BRS and decreased 1.9% ($p = 0.54$) with the metallic platform stents (MPS) ($p = 0.01$). Angulation increased 11.3% with BRS ($p < 0.01$) and 3.8% with MPS ($p = 0.01$); $p < 0.01$. From pre-implantation to follow-up, the artery curvature decreased 3.4% with BRS ($p = 0.05$) and the artery angulation decreased 3.9% ($p = 0.16$), whereas MPS presented with 26.1% decrease in curvature ($p < 0.01$) and 26.9% decrease in angulation ($p < 0.01$) (both $p < 0.01$ for the comparison between BRS and MPS) (7). For drug-eluting absorbable magnesium scaffolds (DREAMS), the vessel curvature decreased 40.5% post-implantation ($p < 0.01$), but the difference between baseline and 12-month follow-up was reduced to 7.4% ($p = 0.03$) (8). This means that the BRS tended to restore the coronary configuration and systolodiastolic movements to those seen before implantation, whereas the coronary geometry remained similar to that seen after implantation with MPS.

VASOMOTION. Vasomotor testing, using nitroglycerin, methylethylergometrine (endothelium-independent vasoconstrictor), and acetylcholine (Ach) (endothelium-dependent vasoactive agent), can be performed at various time points.

Vasomotion of the scaffolded segment following intraluminal administration of Ach suggests that: 1) the scaffolding function of the struts has completely disappeared and the so-called scaffolded segment can now exhibit vasomotion; 2) the endothelial lining (coverage) is coalescent; 3) the ciliary function of the endothelial cell is functional; and



4) the biochemical process through which nitric oxide is released properly works. A positive Ach test with vasodilation of the scaffold is indirect proof that the endothelium is functional (9).

Mean lumen diameters in the scaffolded proximal and distal segments are measured by QCA after a baseline infusion of saline and subselective intracoronary administration of Ach, infused through a microcatheter at increasing doses up to a maximum of 10^{-6} M. In particular, a 2-min selective infusion of Ach (10^{-8} , 10^{-7} , and 10^{-6} mol/l) is administered with a washout period of at least 5 min between each dose (10). Nitrate (200 μ g) is administered following Ach. Vasoconstriction to Ach is defined as

a 3% change in the mean lumen diameter, beyond the variability of the method of analysis, after infusion of the maximal dose of Ach (10^{-6} M), as previously shown.

In the Absorb scaffold, patients at 24 months ($n = 8$) exhibited, on average, a significant increase in the mean lumen diameter after Ach administration compared with patients at 12 months [$+6.16$ (-1.07 , $+13.14$) vs. -6.41% (-11.74 , -1.17); $p = 0.006$] (11).

The timing of restored vasomotion after BRS is also a surrogate for loss of structural integrity of the device and an indication when the vessel may respond to normal and exercise-induced changes in coronary blood flow and pressure. For the Absorb scaffold, the

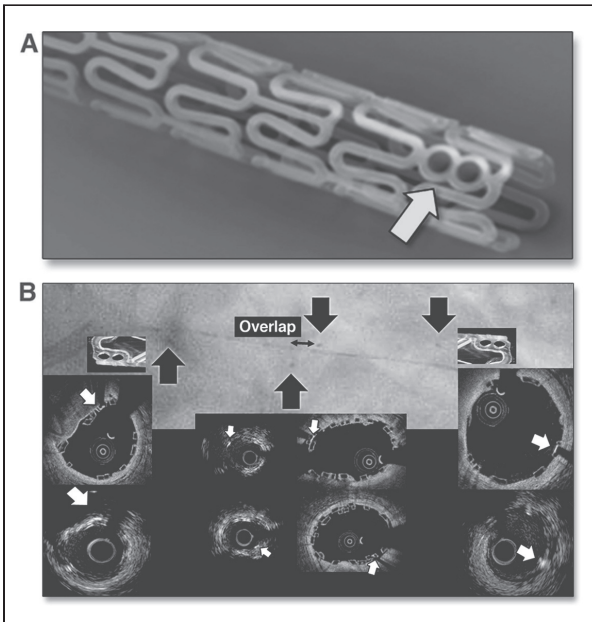


FIGURE 2 Absorb BRS

The metallic markers are mounted at the proximal and distal ends of the Absorb BRS (Cohort B device, revision 1.1) (A, yellow arrow). These markers can be seen in cine angiography, which represents the overlapping of 2 BRS (B, black arrow and double arrow). In the cross-sectional images of intravascular ultrasound and optical coherence tomography, the metallic markers can be identified as high echogenic and high light-intensity structures accompanied by backward shadows, respectively (B, white arrows). Abbreviation as in Figure 1.

time seems to be 12 months; for the DREAMS scaffold, the time seems to be 6 months (8).

NONINVASIVE QCA BY MSCT

Unlike any other metallic prosthesis, polymeric BRS allow in-scaffold assessment of the coronary lumen because the struts are radiolucent; the exception is BRS made of tyrosine polycarbonate and iron, which are radiopaque. Similarly to coronary angiography, the only recognizable structures are the metallic markers at both ends of the devices (Figure 4). BRS technologies use radiopaque markers that are made of platinum, gold, or tantalum. These materials should not interfere with angiographic assessments.

LATE LOSS/LATE LUMINAL GAIN. As mentioned previously, MSCT provides QCA-like parameters, and the same definitions are used.

CONFORMABILITY. In MSCT, the center line of the vessels can be precisely determined and both curvature and angulation can be easily computed (Figure 5). We compute the radius of the circumscribed circle through 3 sequential center-line coordinates. The curvature at P_i is defined as the inverse of the radius of the circumscribed circle around the 3 coordinates (P_a , P_i , and P_b), where P_a and P_b are equally distant from P_i over a 4-mm moving window at 0.1-mm intervals along the coronary center line (12). Different than the curvature measured in a fixed 2D projection in angiography, this curvature assessment in MSCT can be performed in a 3D reconstructed image.

NONINVASIVE FRACTIONAL FLOW RESERVE. Computational fluid dynamics, as applied to MSCT images, is a novel method that enables prediction of blood flow and pressure fields in coronary arteries and calculation of lesion-specific fractional flow reserve (FFR) (13-15). The FFR is computed from commonly acquired MSCT scans (FFR_{CT}) without any modification of MSCT protocols, additional image acquisition, or administration of medications.

The FFR_{CT} technology is based on 3 key principles. The first is that coronary supply meets myocardial demand at rest (total resting coronary flow is relative to ventricular mass). The second is that resistance of the microcirculation at rest is inversely but not linearly proportional to the size of the feeding vessel. The third principle is that microcirculation reacts predictably to maximal hyperemic conditions in patients with normal coronary flow. On the basis of these principles, a lumped parameter model representing the resistance to flow during simulated hyperemia is applied to each coronary branch of the segmented MSCT model. The FFR_{CT} is modeled for conditions of adenosine-induced hyperemia; an $FFR_{CT} \leq 0.80$ is considered diagnostic of lesion-specific ischemia (Figures 6A and 6B) (16).

GRAY-SCALE INTRAVASCULAR ULTRASOUND

Treated coronary vessels are examined after the procedure and at follow-up with intravascular ultrasound (IVUS) catheters. The scaffolded segment and its 5-mm distal and proximal segments are also examined. The vessel area, scaffold area, lumen area, intrascaffold neointimal area, and luminal area stenosis are measured with a computer-based contour detection program.

PERCENTAGE OF LUMEN AREA STENOSIS. The percentage of lumen area stenosis is calculated as

TABLE 3 Definitions and Formulas of Parameters for Assessment of BRS

Parameter	Imaging Modality	Formula	Definition and Notes
Late loss/late luminal gain	Angiography (QCA)/MSCT	MLD (post-procedure) - MLD (follow-up)	For a lumen diameter reduction, this will be a positive number; for a late increase in lumen size, this will be a negative number
Acute recoil	Angiography (QCA)/MSCT	1. Without post-dilation: mean diameter (delivery balloon at the highest pressure) - mean luminal diameter (after implantation) 2. With post-dilation: mean diameter (post-dilation balloon at the highest pressure) - mean luminal diameter (after post-dilation)	Two specific views need to be analyzed: one is an image of complete expansion of the last balloon (either the device delivery balloon or the post-dilation balloon) at the highest pressure and the other is a cine frame immediately after the last balloon deflation and subsequent nitrate injection; these 2 images are analyzed in the same angiographic projection selected to minimize foreshortening
Curvature	Angiography (QCA)/MSCT	$1/\rho$ (cm^{-1})	Defined as the infinitesimal rate of change in the tangent vector at each point of the center line; this measurement has a reciprocal relationship with the radius of the perfect circle defined by the curve at each point
Angulation	Angiography (QCA)/MSCT		Defined as the angle in degrees that the tip of an intracoronary guidewire would need to reach the distal part of a coronary bend
Vasomotion	Angiography (QCA)	1. Vasoconstriction: Δ mean lumen diameter (post-pre) $\leq -3\%$ 2. Vasodilation: Δ mean lumen diameter (post-pre) $\geq 3\%$	Vasoconstriction/vasodilation are defined as at least 3% change in the mean lumen diameter after infusion of the maximal dose of Ach/nitrates, respectively
Noninvasive fractional flow reserve (FFR _{CT})	MSCT		Computed by a dedicated program; FFR _{CT} was modeled after conditions of adenosine-induced hyperemia; FFR _{CT} ≤ 0.80 is considered diagnostic of lesion-specific ischemia
Lumen area stenosis	Gray-scale IVUS/OCT	$(\text{Mean lumen area} - \text{minimum lumen area}) / \text{mean lumen area} \times 100$	
Eccentricity index	Gray-scale IVUS/OCT	Minimum scaffold diameter/maximum scaffold diameter in a frame	The average of all eccentricity indexes of each frame within a scaffolded segment is calculated
Symmetry index	Gray-scale IVUS/OCT	$(\text{Minimum scaffold diameter} - \text{maximum scaffold diameter}) / \text{maximum scaffold diameter}$ within a scaffolded segment	The maximum and the minimum stent/scaffold diameters in this calculation are possibly located in 2 different frames over the length of the device implanted
Neointima hyperplasia area	Gray-scale IVUS	Scaffold area - lumen area	Applicable in frames where all struts are apposed
Percentage area obstruction	Gray-scale IVUS	Neointima hyperplasia area/scaffold area $\times 100$	
Late recoil	Gray-scale IVUS/OCT	Scaffold area at post-procedure - scaffold area at follow-up	
Incomplete apposition/late incomplete apposition	Gray-scale IVUS/OCT		Defined as 1 or more scaffold struts separated from the vessel wall; acquired late incomplete apposition is defined as incomplete apposition at follow-up that is not present after the procedure
Compositional area	Virtual histology		Necrotic core, dense calcium, fibrofatty, and fibrous areas are analyzed; polymeric struts are usually recognized as dense calcium
Compositional area	iMap		Fibrotic, lipidic, necrotic, and calcified tissues are analyzed
Compositional area	IB-IVUS		Lipid, fibrous, dense fibrous, and calcified tissues are analyzed
Strain value	Palpography		Radiofrequency data obtained at different pressure levels are compared to determine local tissue deformation; strain value is normalized to a pressure difference of 2.5 mm Hg per frame, which allows the construction of a "strain" image in which hard (low strain/compliance) and soft (high strain/compliance) values range between 0% and 2%
Scaffold area	OCT		At baseline, the scaffold area is measured by joining the middle point of the black core abluminal side of the apposed struts or the abluminal edge of the frame borders of malapposed struts; at follow-up, the back (abluminal) side of the central black core has been used to delimit the scaffold area
Blood flow area	OCT	$(\text{Scaffold area} + \text{ISA area}) - (\text{intraluminal strut areas} + \text{prolapse area} + \text{intraluminal defect})$	
Neointimal hyperplasia area	OCT	1. When all struts are apposed: scaffold area - (lumen area + black box area) 2. When malapposed struts: (scaffold area + ISA area + malapposed strut with surrounding tissues) - (lumen area + strut area)	Note the difference in methodology versus that of gray-scale IVUS
Thickness of tissue coverage	OCT	Distance between the abluminal site of the strut and the lumen - strut thickness	

Ach = acetylcholine; ISA = incomplete stent apposition; IB = integrated backscattered; IVUS = intravascular ultrasound; MLD = minimal lumen diameter; MSCT = multislice coronary tomography; OCT = optical coherence tomography; QCA = quantitative coronary angiography; other abbreviation as in Table 1.

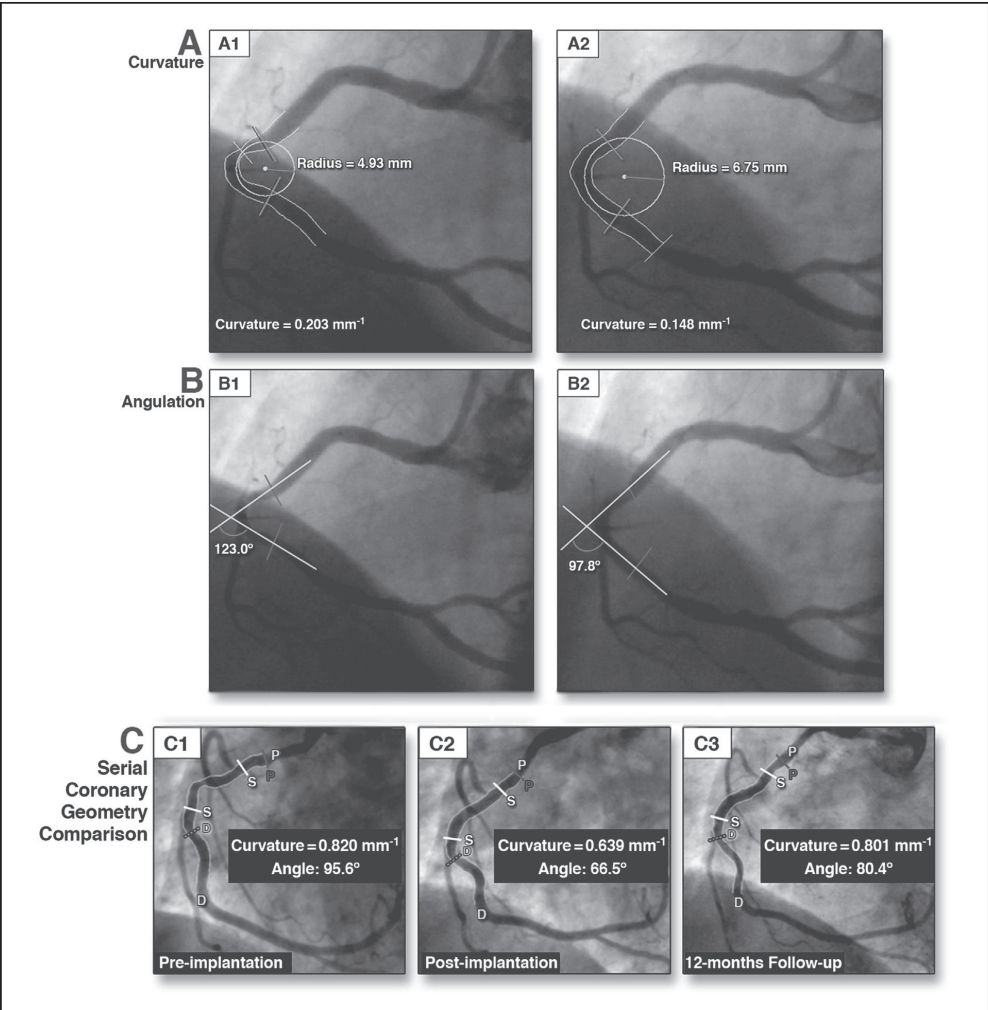


FIGURE 3 Curvature and Angulation Analyses

Curvature (**A**) and angulation (**B**) analyses are shown before deployment (**A1 and B1**) and after deployment (**A2 and B2**). Curvature is estimated as $1/\text{radius}$ (0.203 mm^{-1} in A1 and 0.148 mm^{-1} in A2). Angulation is defined by the tangents of the center lines (6). BVS tends to allow restoration of the coronary geometry and systo-diastolic movements of the coronary arteries similar to that seen before implantation (**C1 to C3**). Modified with permission from Gomez-Lara et al. (7).

100 times the mean lumen cross-sectional area minus the minimal lumen area divided by the mean lumen cross-sectional area within the scaffolded segment.

ECCENTRICITY AND SYMMETRY. The eccentricity and symmetry, easily detectable by IVUS, have

previously been demonstrated to be related to either favorable or adverse clinical outcomes (17,18). With the transition from a metallic stent to a polymeric bioresorbable platform, re-evaluation of these geometric parameters is required at short- and long-term follow-ups.

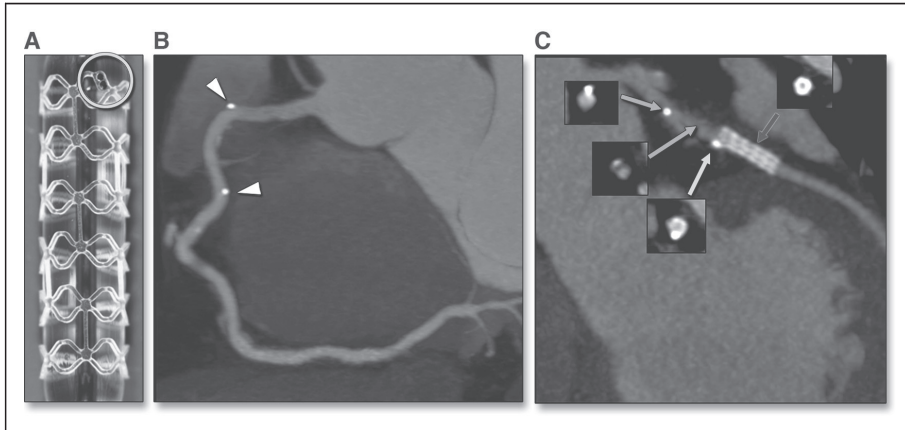


FIGURE 4 Multislice Coronary Tomography

Multislice coronary tomography (MSCT) shows the radio-opaque markers visible in the scaffolded vessel (A). The radio-opaque markers appear much larger (arrows) than the actual size because of an artefact (i.e., blooming effect) due to partial volume averaging which is typical of highly radio-opaque objects that are imaged by MSCT (B). (C) shows a comparison of lumen assessment by MSCT for a bioresorbable scaffold (green arrows), an overlap scaffold-metallic stent (yellow arrow), and a metallic stent (red arrow).

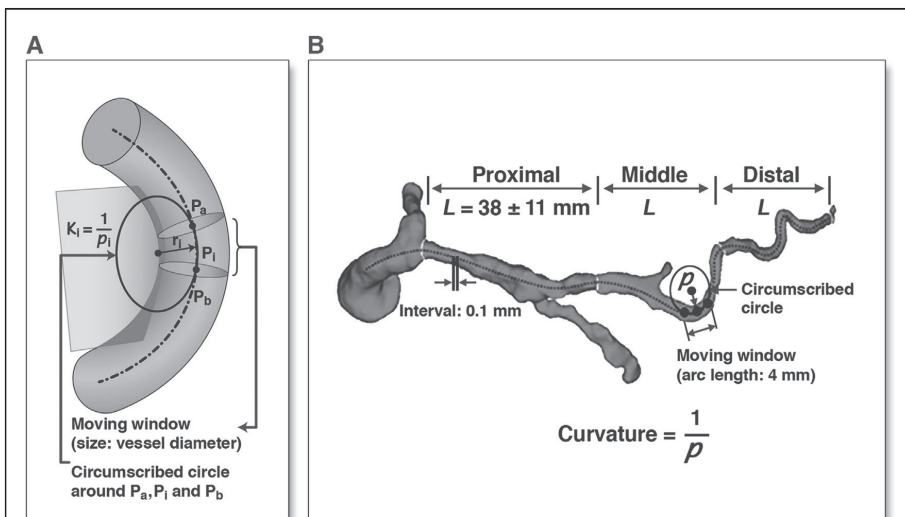


FIGURE 5 Curvature

(A) Method to calculate vessel curvature. A window size of the vessel diameter was moved down along the center-line path incrementally to identify 3 adjacent points on the center-line path for the curvature calculation. In MSCT, curvature is computed as the inverse of the radius of a circumscribed circle over a 4-mm moving window at 0.1-mm intervals along the left anterior descending artery center line (B). Modified with permission from Choi et al. (12).

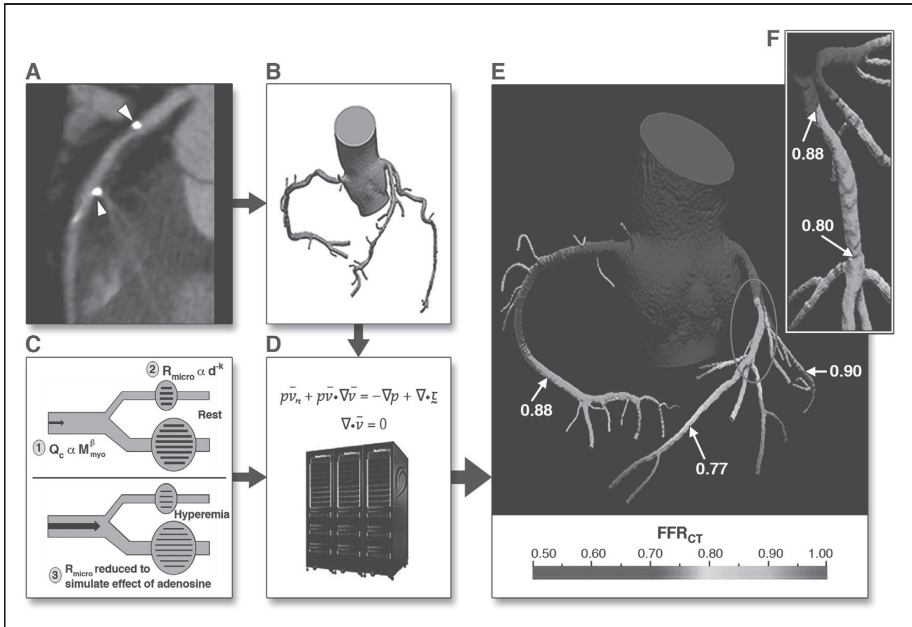


FIGURE 6 Principles of Fractional Flow Reserve

Standard coronary computed tomography angiography data are obtained. (A) Five-year results following an Absorb implantation are shown. Arrowheads indicate the 2 metallic markers in the left anterior descending artery. Noncalcified plaque results in 62% area stenosis. (B) A quantitative 3-dimensional anatomic model is generated. (C) A physiological model of the coronary microcirculation is derived from patient-specific data with 3 main principles: 1) resting coronary flow proportional to myocardial mass; 2) microvascular resistance inversely proportional to vessel size; and 3) microvascular resistance reduced to simulate maximal hyperemia. (D) Physical laws of fluid dynamics are applied to compute coronary blood flow. (E) Fractional flow reserve (FFR_{CT}) is calculated throughout the coronary arteries. (F) From the proximal to the distal edge of the scaffold, the FFR_{CT} decreases from 0.88 to 0.80. Modified with permission from Onuma et al. (46), Norgaard et al. (47), and Nieman et al. (48).

Eccentricity index is defined as the ratio of the minimum and maximum diameters in each frame; thereafter, the average of all eccentricity indexes is calculated. Symmetry index is calculated as (maximum stent/scaffold diameter in a single frame – minimum stent/scaffold diameter in a single frame) divided by the maximum stent/scaffold diameter. Note that the maximum and minimum stent/scaffold diameters in this calculation are possibly located in 2 different frames over the length of the device implanted (Figure 7).

NEOINTIMA HYPERPLASIA. Assessment of the neointima hyperplasia by IVUS is in principle similar to the methodology used for metallic devices. Neointimal hyperplasia area is defined as scaffold area minus lumen area if all struts are apposed. Percentage

volume obstruction is defined as neointima hyperplasia volume divided by scaffold volume.

LATE RECOIL. Although “late recoil” has been used frequently in interventional cardiology to describe the constrictive remodeling of the external elastic membrane area, here it relates more specifically to the area reduction of the scaffolded segment, a phenomenon not previously observed in metallic stents. Attributed to the early alteration of the mechanical integrity of the scaffold, this phenomenon can be controlled by polymer processing.

Late absolute stent recoil is defined as stent area at post-procedure (X) – stent area at follow-up (Y). Late percent stent recoil was defined as $(X - Y)/X \times 100$.

The assessment of late recoil helped to clarify the reasons for the suboptimal performance of the

first-generation magnesium scaffold. For the AMS-1 (Biotronik, Bülach, Switzerland), this parameter was responsible for 42% of luminal obstruction due to its rapid scaffold degradation and led to its design modification (19,20).

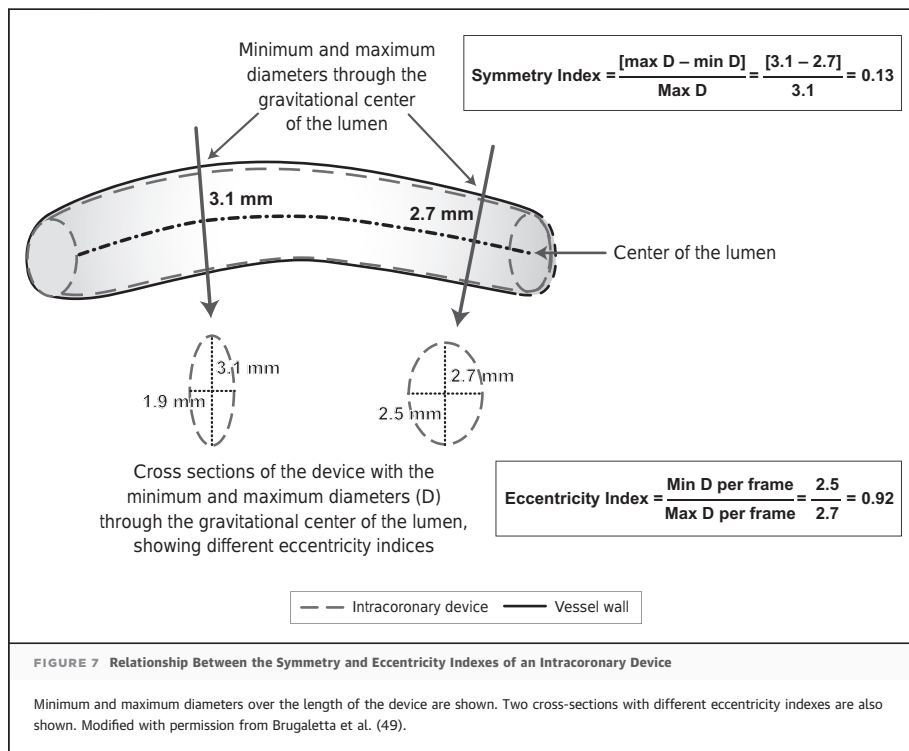
Late absolute and percent recoil of the Absorb BVS 1.0 was $0.65 \pm 1.71 \text{ mm}^2$ (95% confidence interval: 0.49 to 0.80 mm^2) and $7.60 \pm 23.3\%$ (95% confidence interval: 5.52% to 9.68%) (21). With the newer iteration of the device, BVS 1.1, the mean scaffold area increased from baseline to 3 years by IVUS (6.3 to 7.1 mm^2) and by optical coherence tomography (OCT) (7.8 to 8.6 mm^2) (22). Similarly, the DESolve Nx BRS showed an increase in mean scaffold area by IVUS (5.4 to 5.6 mm^2) and OCT (6.6 to 6.8 mm^2) (4).

INCOMPLETE APPPOSITION. Incomplete apposition is defined as 1 or more scaffold struts separated from the vessel wall; acquired late incomplete apposition is defined as incomplete apposition at follow-up that is not present after the procedure.

With BVS 1.1 at baseline, 4 patients showed incomplete stent apposition (ISA). One ISA persisted

at follow-up, and 3 ISAs resolved. At 6 months' follow-up, 3 patients developed a late acquired ISA (23). In the other group followed up to 1 year, at baseline, there were 5 patients with ISA and at follow-up there were only 4 (24). At 2 years, incomplete apposition by IVUS was only observed in 2 patients. At 3 years, 3 patients presented late acquired malapposition (22). The DESolve Nx BRS resulted in only 1 patient with malapposition at 6 months by OCT (4).

EDGE EFFECTS. The edge effect was first introduced in the era of endovascular brachytherapy using radioactive stents of various activity levels to describe tissue proliferation at the nonirradiated proximal and distal edges and resulted in the failure of this invasive treatment. The advent of first- and second-generation drug-eluting stents (DES) reduced in-stent restenosis to approximately 5% to 10% depending on the lesion subset and type of DES. When in-segment restenosis (stent and 5-mm proximal and distal margins) occurred, it was most commonly focal and located at the proximal edge.



The ABSORB Cohort B trial enrolled 101 patients and was divided into B1 (n = 45) and B2 (n = 56) subgroups. The adjacent (5-mm) proximal and distal vessel segments to the implanted Absorb BVS were investigated at either 6 months (B1) or 1 year (B2) with intravascular ultrasound-virtual histology (IVUS-VH) imaging.

At the 5-mm proximal edge, the only significant change was modest constrictive remodeling at 6 months (change in vessel cross-sectional area: -1.80% [-3.18%; 1.30%]; p < 0.05), with a tendency to regress at 1 year (change in vessel cross-sectional area: -1.53% [-7.74%; 2.48%]; p = 0.06). The relative changes in the fibrotic and fibrofatty (FF) tissue areas at this segment were not statistically significant at either time point. At the 5-mm distal edge, a significant increase in the FF tissue areas of 43.32% (-19.90%; 244.28%; p < 0.05) 1 year post-implantation was evident. Changes were also observed in dense calcium areas, which need to be interpreted with caution. The polymeric struts are detected as “pseudo” dense calcium structures with the IVUS-VH imaging modality, and the edges of the polymeric scaffold are not sharply demarcated because the vessel surrounding the imaging device are affected by the “to and fro” motion of the cardiac

contraction, causing a longitudinal displacement of the IVUS catheter relative to the arterial wall (25).

VIRTUAL HISTOLOGY

Ultrasound backscattered signals are acquired using either a 20-MHz (electronic) or 45-MHz (mechanical) IVUS catheter. Backscattering of radiofrequency signals provides information on vessel wall tissue composition. Four tissue components (necrotic core [red], dense calcium [white], fibrous, [green], and FF [light green]) are identified with autoregressive classification systems and expressed as percentages per cross-section (necrotic core, dense calcium, FF, and fibrous) (26). In each cross-section, polymeric scaffold struts are detected as areas of apparent dense calcium and necrotic core resulting from the strong backscattering properties of the polymer. We use the change in quantitative analyses of these areas between implantation and follow-up as a surrogate assessment of the chemical and structural alterations of the polymeric struts (Figure 8). The recent analysis of the ABSORB Cohort B study showed that the mean dense calcium areas were 29.84 mm² (post-implantation), 28.16 mm² (6 months), 24.25 mm² (1 year), 27.74 mm² (2 years), and 21.52 mm² (3-year

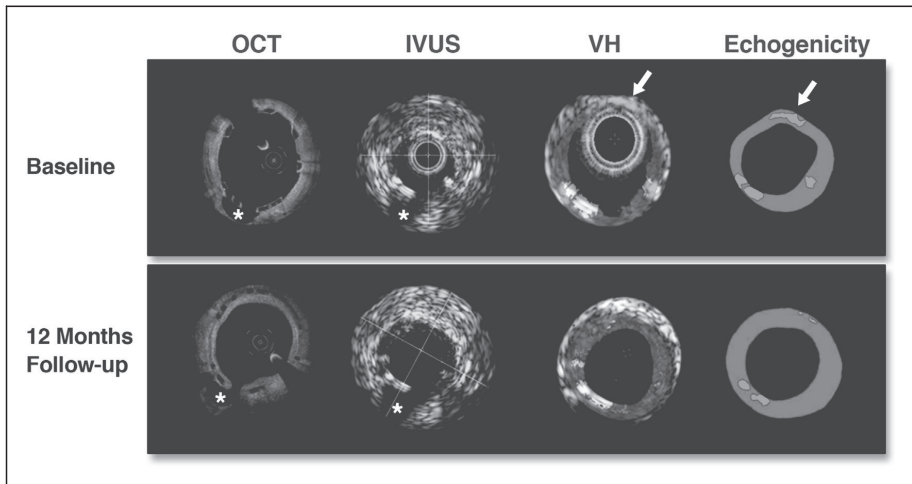


FIGURE 8 Comparison Between Imaging Techniques in Detecting the Degradation Parameters in Matched Frames

After implantation, the polymeric struts are seen as open boxes in optical coherence tomography (OCT), whereas they are white structures in gray-scale intravascular ultrasound (IVUS) (at 4 and 7 to 8 o'clock). The color-coded virtual histology (VH) image depicts them in white (dense calcium), whereas echogenicity shows them in green (hyperechogenic). Note that at follow-up, OCT shows all struts integrated (covered with tissue) into the vessel wall. Gray-scale IVUS shows that the strut at 4 o'clock is less apparent, whereas the corresponding ones in VH and echogenicity are also not detected. These latter observations reflect some biodegradation.

follow-up). The average necrotic core areas, at the same aforementioned time points, were 31.31 mm², 30.11 mm², 30 mm², 31.67 mm², and 26.49 mm², respectively. The sharp decrease in dense calcium and necrotic core areas between 24 and 36 months may also reflect the end of the inflammatory process, with regression of the plaque behind the struts (22).

In addition, the other critical observation with IVUS between the 6-month and 2-year follow-ups was a late luminal enlargement (10.9%) with significant plaque media reduction (12.7%) and without significant change in the vessel wall area (27). It is still unknown whether this “plaque media regression” on IVUS is a true atherosclerotic regression, with change in vessel wall composition and plaque morphology (from thin-cap atheroma to thick-cap atheroma) or a pseudo-regression due to bioresorption of the polymeric struts. True atherosclerotic regression could only be hypothesized based on animal and in vitro experiments showing that mammalian target of rapamycin can trigger a complex chain of biological reactions that lead finally to activation of genes related to autophagy of macrophages. Systemic application of everolimus decreased atherosclerotic plaque formation in low-density lipoprotein receptor knockout mice (28).

IMAP

Ultrasound backscattered signals are acquired using a 40-MHz mechanically rotating IVUS catheter. iMap is another radiofrequency-based processing method for coronary plaque tissue characterization (29). iMap uses a pattern recognition algorithm on the spectra that were obtained from a fast Fourier transformation and a histology-derived database (29). The color code for tissue types is different than that for IVUS-VH. iMap depicts fibrotic (light green), lipidic (yellow), necrotic (pink), and calcified (blue) tissues, whereas IVUS-VH depicts fibrous (green), FF (yellow-green), necrotic core (red), and dense calcium (white) tissues (30). Although iMap has been validated for characterization of stents/scaffolds, we have observed that it detects polymeric struts as calcified tissue (**Figure 9**); however, it misses some of the polymeric struts, which makes this technology not suitable to serially follow the absorption process of these polymeric scaffolds.

INTEGRATED BACKSCATTERED IVUS

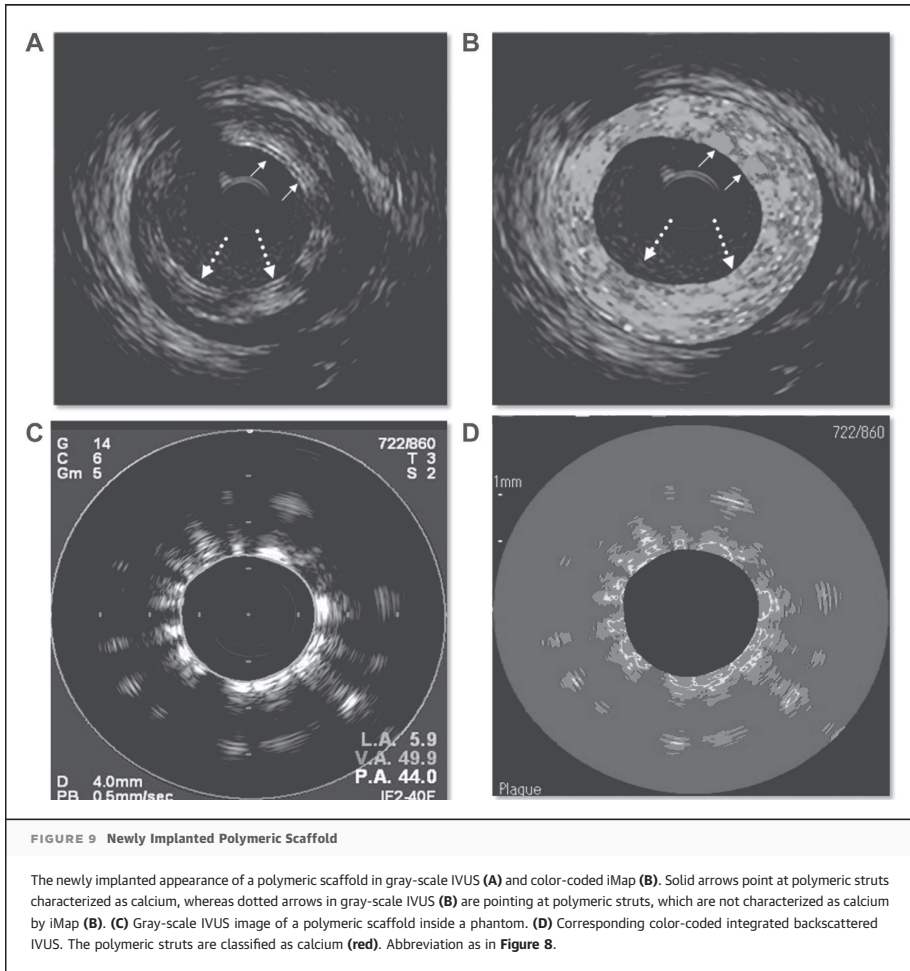
Ultrasound backscattered signals are acquired using a 40-MHz mechanically rotating IVUS catheter. Integrated backscattered values for each tissue

component were calculated as an average power using a fast Fourier transformation, measured in decibels, of the frequency component of the back-scattered signal from a small volume of tissue. With predefined ranges of integrated backscattered values, each plaque component is characterized as lipid (blue), fibrous (green), dense fibrous (yellow), or calcified (red) tissue (**Figure 9**) (31,32).

PALPOGRAPHY

Percutaneous implantation of metallic prostheses has been used to alleviate flow-limiting lesions by overstretching the plaque and the underlying vessel wall. From a mechanical perspective, this treatment may locally stiffen the artery, reducing its compliance and creating a mismatch in compliance with respect to the segments contiguous to the implanted device (5). This mismatch may eventually provoke flow disturbances and wall shear stress alterations, with subsequent blood stasis. The wall shear stress distribution in a stented artery has been reported as a determinant factor for cellular growth and thrombus formation. The Absorb everolimus-eluting BVS theoretically has many advantages compared with rigid metallic stents. In particular, because the scaffold is made completely of polylactide, it does not have the same stiffness as metal, thereby having the potential to overcome in part the problems related to local stiffening of the artery and compliance mismatch associated with MPS. In addition, the mismatch in compliance after scaffold implantation may potentially disappear in the long term once the scaffold is completely bioresorbed.

IVUS palpography is a technique that allows for the assessment of local mechanical tissue properties. The underlying principle is that at defined pressure, differences in soft-tissue (e.g., lipid-rich) components deform more than hard-tissue components (e.g., fibrous calcified) (33). In coronary arteries, the tissue of interest is the vessel wall, whereas the blood pressure, with its physiological changes during the heart cycle, is used as the excitation force. Radiofrequency data obtained at different pressure levels are compared to determine local tissue deformation. The strain value is normalized to a pressure difference of 2.5 mm Hg per frame; this allows the construction of a “strain” image in which hard (low strain/compliance) and soft (high strain/compliance) values range between 0% and 2%. In post-mortem coronary arteries, the sensitivity and specificity of palpography to detect high strain values have previously been reported as 88% and 89%, respectively (34).



Local strain is calculated from the gated radio-frequency traces using cross-correlation analyses, displayed and color-coded from blue (for 0% strain) to yellow (for 2% strain) via red, as previously described.

Strain values were assigned a Rotterdam classification (ROC) score ranging from I to IV (ROC I 0 to 0.5%; ROC II 0.6% to <0.9%; ROC III 0.9% to 1.2%; and ROC IV >1.2%). A region was defined as a high-strain spot when it had high strain (ROC III to IV) that spanned an arc of at least 12° at the surface of a plaque (identified on the IVUS recording) adjacent to low-strain regions (<0.5%), as previously reported (33). The highest value of strain in the cross-section

was taken as the strain level of the spot. The compliance of each segment is calculated per segment (proximal edge, scaffold segment, and distal edge) and defined as the mean of the maximum strain values per cross-section in ROC I/II/III/IV spots, expressed as ROC/mm.

ECHOGENICITY

Echogenicity uses the gray-scale IVUS data to further evaluate the distribution of the gray values within a specific coronary segment. The mean gray value of the adventitia is used to classify tissue components as either hypoechoic or

hyperechogenic (**Figure 8**). The adventitia surrounding the coronary artery is defined as a layer extending from 0.2 to 0.5 mm outside the external elastic membrane. To avoid artifacts, tissue within acoustic shadowed areas is excluded and very high gray-level pixels are identified as upper tissue. After the tissue identification process, the relative fraction of hypoechogenic versus hyperechogenic tissue volumes is calculated for the entire scaffolded segment. The software calculates the echogenicity as a volume and percentage for each scaffolded segment (setting hypoechogenicity and hyperechogenicity to 100%). The percent differential echogenicity was calculated for each scaffolded coronary segment, as follows (35,36).

$$\% \text{Differential Echogenicity} = \frac{(\% \text{Hyper6M} - \% \text{HyperPre}) - (\% \text{HyperPost} - \% \text{HyperPre})}{(\% \text{HyperPost} - \% \text{HyperPre})} \cdot 100\%$$

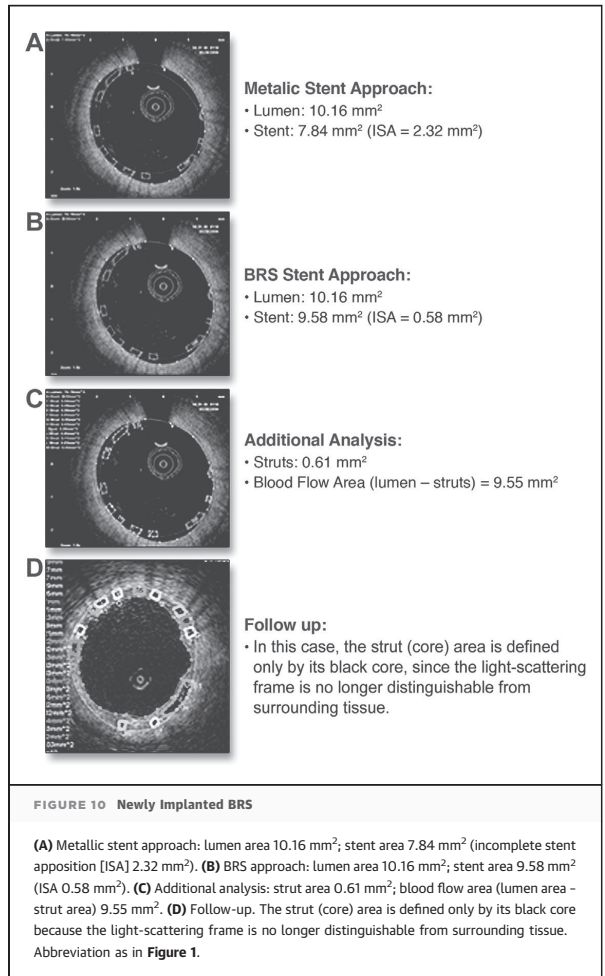
Echogenicity parameters have been shown to be able to detect temporal changes in the gray-level intensities for Absorb and DREAMS, being putatively correlated to scaffold degradation over time (8,35).

OPTICAL COHERENCE TOMOGRAPHY

The BVS presents important differences with respect to metallic stents when imaged by OCT. The optically translucent polymeric struts appear as black central cores framed by light-scattering borders that do not shadow the vessel wall and allow complete imaging of the strut thickness. The main quantitative measurements (strut core area, strut area, lumen area, scaffold area, ISA area, and neointimal area) require different analysis rules than the metallic stents (**Figure 10**).

Qualitatively, the diagnosis of acute strut fracture resulting from balloon overdistension or late structural strut discontinuity can be established if 2 struts overhang each other in the same angular sector of the lumen perimeter, with or without malapposition, or if isolated struts are located more or less at the center of the vessel without obvious connection to other surrounding struts in 2D OCT. For confirmation of the diagnosis, it is helpful to perform 3D OCT reconstruction of the disrupted strut. A case description of strut fracture is shown in **Figure 11**.

At baseline, the strut area is imaged as a central black core and a light-scattering frame border. However, at follow-up, embedding, coverage, and thickening of the frame borders, with apparent reduction of the central core, render the analysis of the struts



more complex. At this time point, the strut (core) area is defined only by its black core because the light-scattering frame is no longer distinguishable from surrounding tissue. At follow-up, the strut area starts to gain some tissue filling that can be seen as “white core” (**Figure 12**).

The lumen and scaffold contours are obtained with a semiautomated detection algorithm available in many offline software packages, and additional manual corrections are performed if necessary. At baseline, because the polymeric struts are translucent, the vessel wall lumen area can be imaged and delineated at the back (abluminal) side of the struts. At follow-up, the luminal area is drawn by

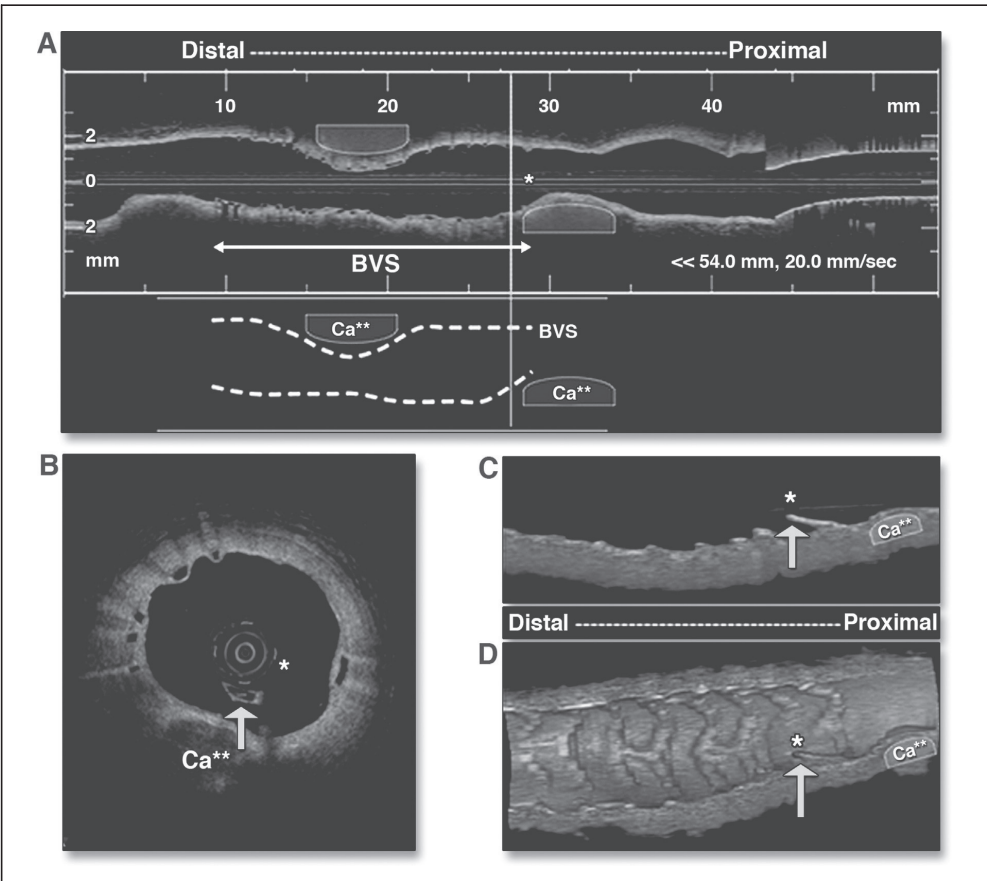


FIGURE 11 Bioreabsorbable Scaffold Discontinuity

A 59-year-old man with treated hypercholesterolemia as his only cardiovascular risk factor was admitted to the hospital with stable angina. The coronary angiogram revealed a stenotic lesion in the mid left anterior descending coronary artery. As protocol mandated, pre-dilation was performed with a single inflation of a 2.5 × 12 mm Voyager balloon (Abbott Laboratories, Abbott Park, Illinois) at 10 atm, followed by implantation of a 3.0 × 18.0 mm bioreabsorbable everolimus-eluting scaffold at 10 atm. A post-dilation was performed with a 3.25 × 15.0 mm Voyager balloon at 20 atm (expected balloon diameter 3.41 mm). The patient continued to be asymptomatic up to 6 months when he visited the hospital for a re-catheterization because he was enrolled in a clinical study. By a 2-dimensional (cross-sectional) OCT image, an extreme malapposition of 1 strut was observed (B, yellow arrow). In a 3-dimensional OCT reconstruction, the overhanging strut was clearly identified in its whole trajectory (C and D, yellow arrow). This patient was left untreated due to lack of ischemic symptoms. Abbreviation as in Figure 8.

semiautomatic detection, following the endoluminal contour of the neointima between and on top of the apposed struts. For malapposed struts, the endoluminal contour of the vessel wall behind the malapposed struts is used.

At baseline, the scaffold area is measured by joining the middle point of the black core abluminal side of the apposed struts or the abluminal edge of

the frame borders of malapposed struts. The scaffold area is identical to the lumen area in the absence of ISA and prolapse. At follow-up, the back (abluminal) side of the central black core is used to delimit the scaffold area. Three different situations deserve special consideration. First, incomplete strut apposition is defined as a clear separation between the back (abluminal) side of the strut and the vessel wall. For

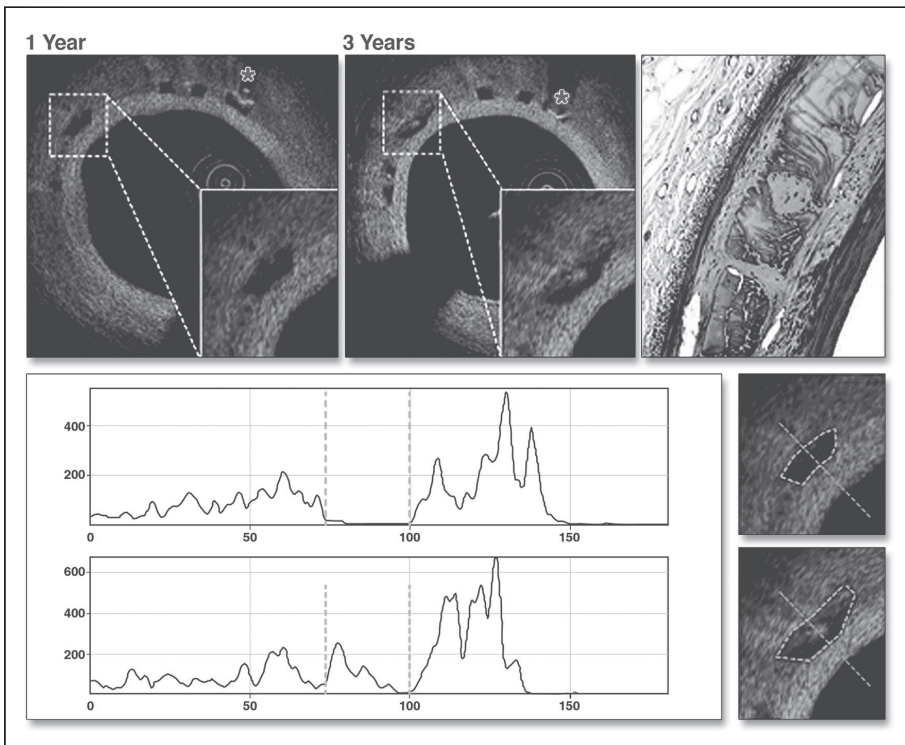


FIGURE 12 Optical Coherence Tomography Light Intensity Analysis

Corresponding OCT cross-sections (red asterisks indicate distal metallic markers) at 1 and 3 years. The strut next to the marker (asterisk) was analyzed by light reflectivity. At 3 years, the strut core was partially filled by a white nucleus exhibiting high light reflectivity. Tracings at the bottom showed graphically the light reflectivity along the scan line of incident light (red). The vertical green dotted lines correspond to the adluminal and abluminal boundaries of the black core either empty or partially occupied by white nucleus. Histological image (Movat staining, 20 \times) of porcine coronary artery 36 months after implantation of Absorb scaffold shows provisional matrix (glycoconjugates) in purple, filling the void previously occupied by the polymeric strut. A cellularized (black dot) area with connective tissue (green) is located at the center of the strut void and is connected by a peduncle to the subintima. Multiple layers of smooth muscle cells are overlying the strut voids. OCT images of the histological structures in a porcine model are very similar to those observed in humans. The light intensity was analyzed using open-source software (ImageJ, National Institutes of Health, Bethesda, Maryland). Modified with permission from Serruys et al. (22).

malapposed struts, incomplete strut apposition area is delineated by the abluminal side of the frame border of the malapposed strut (covered or uncovered) and the endoluminal contour of the vessel wall. Second, in prolapse protruding between struts into the lumen at baseline, the prolapse area can be estimated between the prolapsed contour (lumen contour) and the scaffold area. Third, an intraluminal defect free from the vessel wall (e.g., thrombus) is also quantified as an area. According to these findings, the flow area is defined as (scaffold area + ISA area) – (intraluminal strut areas + prolapse area + intraluminal defect).

Neointimal hyperplasia area is defined as (scaffold area – [lumen area + black box area]) if all struts are apposed (Figure 10D), whereas it is calculated as ([scaffold area + ISA area + malapposed strut with surrounding tissues] – [Lumen area + strut area]) for malapposed struts.

The thickness of the coverage is measured in every strut between the abluminal site of the strut core and the lumen. Because the strut thickness is 150 μm , the strut is considered covered whenever the thickness of the coverage is above this threshold value. This method may slightly underestimate the thickness of the coverage because it does not take into account

changes in the size of the strut core over time. Consequently, the percentage of uncovered struts may be slightly overestimated.

This OCT Healing Score is a weighted index that combines the following parameters (37):

1. Presence of intrastent structure (ISS) is assigned a weight of “4.”
2. Presence of both malapposed and uncovered struts (%MU) is assigned a weight of “3.”
3. Presence of uncovered struts alone (%U) is assigned a weight of “2.”
4. Presence of malapposition alone (%M) is assigned a weight of “1.”

$$\text{Neointimal Healing Score} = (\text{ISS} \times 4) + (\%MU \times 3) + (\%U \times 2) + (\%M \times 1)$$

LESSONS FROM OCT FOR BRS RESORPTION. OCT may not be sensitive enough to assess the resorption process of the polymer, but it provides critical information on the integration of the polymer into the vessel wall. At the beginning, the absence of strut footprints on OCT was interpreted as a sign of complete bioresorption, but now we know that the preserved box appearance with optical translucency is compatible with complete polymer dissolution (38). The DESolve Nx BRS showed significant reduction in the number of struts with the black box appearance at 6 months (4).

TWO-DIMENSIONAL VERSUS 3-DIMENSIONAL OCT. Three-dimensional OCT provides much more useful information at bifurcations and overlapping segments than 2D OCT. Indeed, 3D OCT enables a detailed assessment of both the longitudinal and cross-sectional relationship between the jailed side branches orifice and the overhanging struts (39). Serial 3D OCT also provides information about anatomic modifications such as the presence of neointimal bridges, which usually appear as an extension of the pre-existing carina. From the quantitative point of view, using 3D OCT reconstructed models, one can assess the changes over time in the number of compartments and their geometric areas.

Three-dimensional OCT offers a unique opportunity to observe the modifications of the shape of the struts after side branch dilation.

In the overlapping regions, 2D OCT helps to identify single or stacked struts (inner vs. outer) and stacked strut clusters (**Figure 2**). Lumen area is drawn in nonoverlapping segments, and the following considerations should be made for the scaffold area: it is drawn from the abluminal side of the black core area

of the outermost strut or stacked strut cluster (where all of the struts appose the vessel endothelium) apposing the vessel wall. Where there does not appear to be any apposition of a single strut or stacked strut cluster to the vessel endothelium, the contour of the scaffold area continues to follow the outermost (most abluminal) scaffold strut or stacked strut cluster. Three-dimensional OCT of overlapping regions also helps us to assess the type of overlapping: interdigitating struts versus complete overlap (40,41).

AGREEMENT OF QCA, IVUS, AND OCT FOR ASSESSMENT OF BRS

For scaffold length measurement, QCA has shown a typical systematic bias: variable underestimation of length but consistent underestimation of the same magnitude at the index procedure and at follow-up, eventually due to the effect of foreshortening. OCT is the most accurate technique for measuring scaffold length, whereas solid-state IVUS presents a random error, mostly due to lack of smooth and continuous pullback; therefore, volumetric analysis is not reliable. There is poor agreement for minimal lumen area estimation between all of the imaging modalities studied, including IVUS-OCT; hence, their values are not interchangeable (42).

IVUS, due to its limited resolution, is unable to detect incomplete malapposition and struts at side branches compared with OCT. IVUS also has poor reproducibility for the assessment of these 2 variables, whereas OCT has excellent assessment (43).

CONCLUSIONS

The upcoming bioresorbable era requires new imaging modalities, parameters, and methodologies for the longitudinal assessment of BRS. One of the manifested characteristics of BRS is bioresorption of the polymeric struts into the arterial wall. Although proper validation with VH, echogenicity, and palpography to evaluate this phenomenon has been lacking, other observations with OCT and histology have demonstrated convincing results. We introduced a detailed description of the parameters and methodologies for the assessment of BRS that should be needed in the future longitudinal studies.

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KEY WORDS bioresorbable scaffolds, coronary, imaging, intravascular ultrasound, multislice computed tomography, optical coherence tomography

Chapter 5.2

Echogenicity as a Surrogate for Bioresorbable Everolimus-Eluting Scaffold Degradation: Analysis at 1-, 3-, 6-, 12-, 18-, 24-, 30-, 36- and 42-month Follow-up in a Porcine Model

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Abstract The objective of the study is to validate intravascular quantitative echogenicity as a surrogate for molecular weight assessment of poly-l-lactide-acid (PLLA) bioresorbable scaffold (Absorb BVS, Abbott Vascular, Santa Clara, California). We analyzed at 9 time points (from 1- to 42-month follow-up) a population of 40 pigs that received 97 Absorb scaffolds. The treated regions were analyzed by echogenicity using adventitia as reference, and were categorized as more (hyperechogenic or upperechogenic) or less bright (hypoechogenic) than the reference. The volumes of echogenicity

were correlated with the measurements of molecular weight (Mw) by gel permeation chromatography. Scaffold struts appeared as high echogenic structures. The quantification of grey level intensity in the scaffold-vessel compartment had strong correlation with the scaffold Mw: hyperechogenicity (correlation coefficient = 0.75; $P < 0.01$), upperechogenicity (correlation coefficient = 0.63; $P < 0.01$) and hyper + upperechogenicity (correlation coefficient = 0.78; $P < 0.01$). In the linear regression, the R^2 for high echogenicity and Mw was 0.57 for the combination of hyper and upper echogenicity. IVUS high intensity grey level quantification is correlated to Absorb BVS residual molecular weight and can be used as a surrogate for the monitoring of the degradation of semi-crystalline polymers scaffolds.

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Keywords Absorb · Bioresorbable vascular scaffold ·
Degradation · Echogenicity · IVUS · Porcine

Abbreviations

IVUS	Intravascular ultrasound
BRS	Bioresorbable scaffolds
PLLA	Poly-l-lactide-acid
PDLLA	Poly-D, L-lactide
Mw	Molecular weight
Absorb	Poly-l-lactide-acid everolimus eluting
BVS	bioresorbable scaffold
CAD	Coronary artery disease

Impact on daily practice

Changes in bioresorbable vascular scaffolds (BRS), design and compositions may affect their degradation and loss of

biomechanical characteristics (with the risk of late recoil) and may be associated with a second wave of arterial wall inflammation. Therefore, studying the BRS degradation is crucial to fully understand this technology. The present work validates echogenicity as a surrogate for polylactide scaffold degradation.

Introduction

Bioresorbable vascular scaffolds (BRS) are a novel approach to the interventional treatment of coronary artery disease (CAD), providing short-term vascular scaffolding combined with drug-delivery capability. They may offer potential advantages compared to metallic drug-eluting stents (e.g. adaptive remodeling, restoration of vasomotion and late luminal enlargement). The so called 4th revolution in coronary artery disease revascularization steered extensive scientific research in BRS developments [1–3].

It has been shown that the designs and materials of BRS platforms—either metallic or polymeric—influence the resorption process [3–5]. Considering the variety of possible platforms, it is necessary to establish tools capable of monitoring the degradation process and its correlated mechanical characteristics.

Intravascular ultrasound-derived parameters have shown to be useful to assess the BRS resorption of metallic and polymeric scaffolds in humans [6–8]. One of the most studied intravascular ultrasound (IVUS) techniques to evaluate the resorption process is called differential echogenicity [8, 9]. This method consists in an automated and quantitative three-dimensional analysis of coronary tissue components scored for echogenicity using as reference the mean level of the adventitia brightness [9] where scaffold struts appear as bright hyperechogenic structures. In clinical studies, a continuous decrease of echogenicity over time has been shown in regions treated with BRS, being putatively correlated to BRS degradation [7, 8]. However, in serial human assessments, changes in the adventitia and plaque-media compartment of the treated regions during the follow-up period could possibly affect these interpretations [10–14].

The objectives of the current study were: (1) to describe a novel method of echogenicity for tissue analysis; (2) to evaluate its reproducibility; and (3) to assess its aptitude to assess the BRS degradation process through a direct correlation with the molecular weight (Mw) in a preclinical model using a drug-eluting poly-L-lactide-acid (PLLA) bioresorbable scaffold (Absorb BVS, Abbott Vascular, Santa Clara, California).

Methods

Study devices

The device used in the present preclinical study is the same used in Cohort B of the ABSORB clinical trial [15, 16]. Absorb is a balloon-expandable BRS that consists of a polymer backbone of Poly (L-lactide) (PLLA) coated with a thin layer of a 1:1 mixture of Poly-D, L-lactide (PDLLA) polymer with the antiproliferative drug everolimus to form an amorphous drug-eluting coating matrix containing 100 µg of everolimus/cm² of scaffold [17].

Experimental model

For validation purposes, we analyzed non-atherosclerotic Yorkshire-Landrace swine which had been implanted with Absorb BVS via femoral access according to published procedures [18]. Absorb sizes were matched to the vessel size at a target balloon-to-artery ratio of 1.0–1.1 (10 % overstretch). Each animal received a single Absorb (3.0 × 18 mm for 1-, 3-, and 6-month and 3.0 × 12 mm for 12- to 42-month) in 2 or 3 main coronary arteries. Forty pigs (98 arteries) underwent IVUS acquisition and were then euthanized at 1-month (n = 12 scaffolds), 3-(n = 12), 6-(n = 14), 12-(n = 12), 18-(n = 12), 24-(n = 12), 30-(n = 8), 36-(n = 8) or 42-months (n = 8). Each scaffold had quantification of polymer degradation by gel permeation chromatography (GPC). Experimental studies received protocol approval from the institutional animal care and use committee and were conducted in accordance with American Heart Association guidelines for pre-clinical research and the Guide for the Care and Use of Laboratory Animals (National Institutes of Health 2010).

Gel permeation chromatography (GPC)

A previously reported GPC method, with a slightly modified sample extraction/purification process, was employed to investigate the degradation of polymer over time by evaluating the number-average molecular weight (Mn) of polymer in the Absorb [19]. In the present method, the extraction and purification of the polymer was repeated up to five times until the polymer was fully extracted from the tissue (i.e., the polymer signal in the last extract below the quantitation limit of 0.3 mg/mL). The samples were analyzed prior at 1-, 3-, 6-, 12-, 18-, 24-, 30-, 36- and 42-months after implantation.

IVUS acquisition and analysis

All IVUS runs were acquired with 40 MHz mechanical systems, using Galaxy V2.02 (Boston Scientific, MA,

USA) at 1-, 3-, 6- and 12-month follow-ups and iLab at 18-, 24-, 30-, 36- and 42-month (Boston Scientific, MA, USA). We used motorized pullback of 0.5 mm/s with a frame rate of 30 frames/second. The regions of interest were restricted to the scaffolded areas, identified by the first and the last cross-sectional IVUS frame in which scaffold struts could be identified and/or where the proximal or distal metallic markers could be identified. Vessel, scaffold and lumen contours were delimited every 0.5 mm blind to molecular weight results. We analysed four compartments by IVUS: the luminal, scaffold, vessel and the neointimal volume (vessel volume-lumen volume). The scaffold was delineated semiautomatically at the luminal leading edge of the struts and the lumen was delineated at the inner detectable tissue (Fig. 1).

To evaluate inter-observer reproducibility, 2 readers (C.C. and Y.I.) independently analyzed 30 segments randomly selected from the total number of the investigated segments. To determine intra-observer reproducibility, one reader (C.C.) analyzed these segments twice, with the second reading occurring 3 months later. The inter- and intra-observer reproducibility were good according to the conventional norms [20] (hyperechogenicity inter-observer interclass correlation coefficient [ICC] = 0.80, intra-observer ICC = 0.95; hypoechogenicity: inter-observer ICC = 0.78, intra-observer ICC = 0.97; uperechogenicity: inter-observer ICC = 0.92, intra-observer ICC = 0.97) (Supplementary material).

Automatic quantitative echogenicity analysis

The principle of echogenicity has been previously described elsewhere [9, 21, 22]. Echogenicity aims to classify the vessel wall components located between the luminal boundary and the external elastic membrane (EEM) into categories based on their grey-level intensity in B-mode IVUS images rather than based on radiofrequency ultrasound signal analysis [23–26] (Fig. 1). Here we quantified 5 tissue types: hypoechogenic, hyperechogenic, calcified, uperechogenic and unknown.

Comparison with the adventitia allows for normalization with respect to transducer variability, gain settings and across populations [21]. However, in the analysis of atherosclerotic tissue, the adventitia can be partially obscured or darkened as a result of the guide-wire shadowing or the presence of dense tissue (e.g. calcium) which reduces the average grey-level values of the adventitia. Therefore, these parts need to be excluded from the reference adventitial area. To determine the reference adventitia area in each frame, the full adventitial area located just outside the EEM is first determined based on a minimum (0.01 mm) and maximum (0.21 mm) distance from the EEM contour (Fig. 1). To

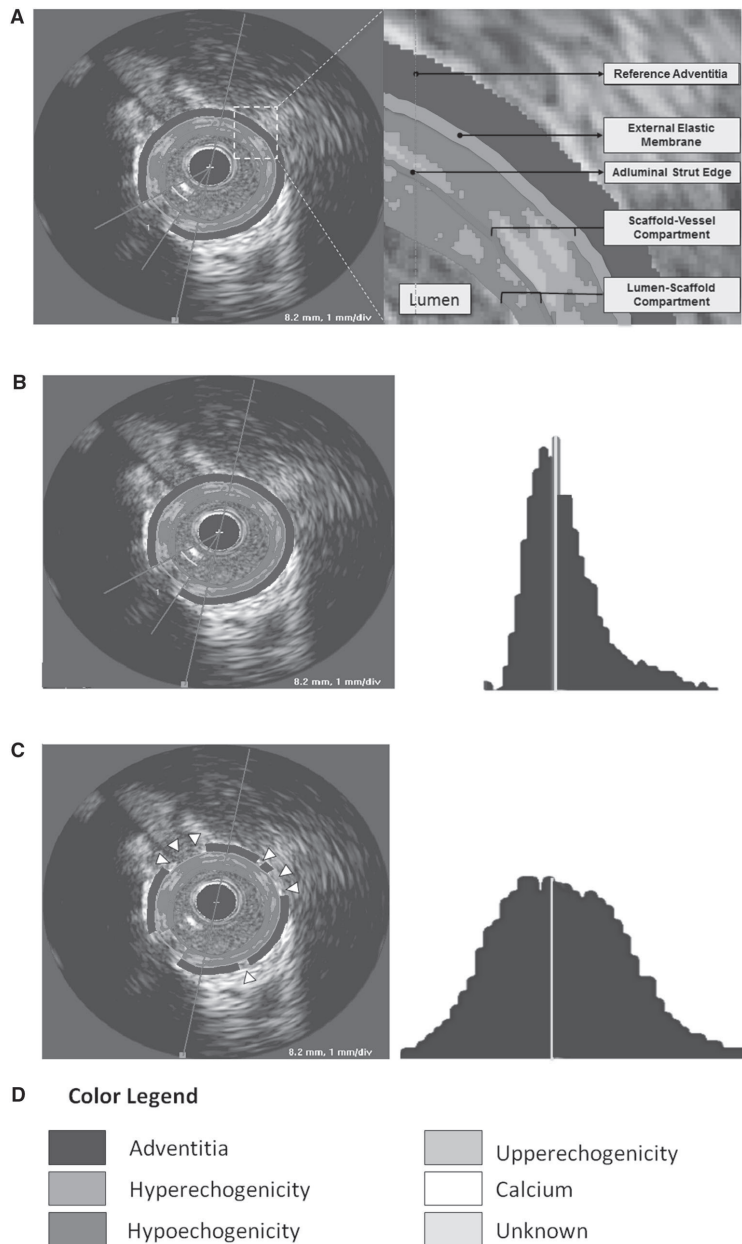
remove the low echogenic parts of the adventitia an adaptive threshold value for the entire adventitia area is determined based on Otsu's method [27]. Otsu's method is a classic automatic non-parametric threshold selection method which maximizes the between-class variance. Next, the adventitial area is divided into 2-degree wide sectors. If more than half of the pixels inside of a sector is below the adaptive threshold, the sector is excluded from the reference adventitia area. Finally, the histograms of the reference adventitial areas of the individual frames are combined into a global adventitia grey-level intensity histogram and the median value is computed as a threshold. Cross-section pixels with an intensity lower than the median value are classified as hypoechogenic, pixels with an intensity higher than the median value threshold are classified as hyperechogenic.

Calcified plaque is typically identified in B-mode IVUS images as a highly echogenic area creating an acoustic shadow [21]. To determine the high-intensity grey-level threshold for highly echogenic components we use the adaptive threshold selection method described in [28]. First Otsu's method is applied to the entire grey-level histogram of an image resulting in an optimal threshold value. In the next 2 iterations, Otsu's method is applied to the histogram of all intensities above the threshold found in the previous step. Next, we apply an in-house developed acoustic shadow detection algorithm. Highly echogenic areas with a grey-level intensity higher than the high-intensity threshold but without acoustic shadow behind them are classified as uperechogenic, while highly echogenic areas with acoustic shadow are classified as calcified and the shadow itself is classified as unknown. The entire method has been implemented and tested in QCU-CMS-Research v4.69 (research version of QIvus, developed by the Leiden University Medical Center) [29].

Data analysis

Continuous variables are presented as mean \pm SD or medians (interquartile range). The ANOVA test was used to compare continuous variables. As we had different scaffold lengths we normalized all measurements by the mean length for all pigs as described previously [30]. This adjusts for differing segment lengths across animals, thereby providing equal weighting of each individual in the calculation of echogenicity volumes. The residual scaffold molecular weight by GPC was compared to the echogenicity findings and the correlation coefficient was used as a measure of the degree of relationship (Pearson's correlation coefficient). A linear regression was used to evaluate if hyper and/or uperechogenicity were able to predict the residual molecular weight. A

Fig. 1 Differential echogenicity methodology. **a** The first step was to determine the lumen-scaffold and scaffold-vessel compartments by defining the vessel, lumen and luminal scaffold contours in every 0.5 mm. After guidewire masking, the software identifies the adventitia as a ring between 0.01 and 0.21 mm outside vessel contours. **b** However, if the software uses as reference the whole layer around the vessel contour, it will include low intensity structures (e.g., pericardium, side branches, low attenuated tissues, etc.) resulting in a histogram with a non-normal distribution (*right panel*). **c** The present software detects automatically high signal adventitia as reference, excluding low intensity structures (*arrow heads*). The *right panel* shows that the combination of high signal adventitia in all frames obtains a bell shaped normally distributed histogram. The yellow line represents the referential adventitial median value. **d** The color legend of each echogenicity classification is provided. As we used a non-atherosclerotic porcine model there was no calcification and unknown tissue. Nevertheless, the present software is able to detect these tissues



hierarchical cluster analysis using Ward’s method (Squared Euclidean distance) was applied for hyper + uperechogenicity and hypoechoogenicity volumes. The differences were regarded significant when $P < 0.05$ (two-tailed). SPSS version 21.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

Results

The main grey scale IVUS volumetric findings are shown in Fig. 2 and the comparisons between each group are given in the supplementary material (Tables 2-5). The mean scaffold length was 16.5 mm. Compared with 1-month follow-up, the vessel, scaffold and lumen volumes had a trend to be larger after 18-month follow-up. These three aforementioned volumes were significantly larger at 36- and 42-month. Additionally, the neointima had the biggest volume at 1-month follow-up, being similar among groups thereafter (Fig. 3).

Differential echogenicity and molecular weight

Table 1 summarizes the main findings on differential echogenicity and mean Mw at each time point. The highest total hypoechoogenicity volume was found at 1-month follow-up, the time point with also the highest neointimal hyperplasia as aforementioned. The lumen-scaffold compartment had an increase in hyper + uperechogenic volumes up to 12-month and subsequently a decrease until 42-month. Using the as reference the 1-month group, the hyper + uperechogenic decreased significantly in the scaffold compartment after 12 months (supplementary material).

The GPC results indicated a continuous decrease in molecular weight over time. The rate of reduction was slower during the first 6-months of scaffold implantation followed by a more rapid decline thereafter, being fully resorbed 36-months after implantation (Fig. 2).

To validate the scaffold degradation by echogenicity we took into consideration the hyper- and uperechogenicity in

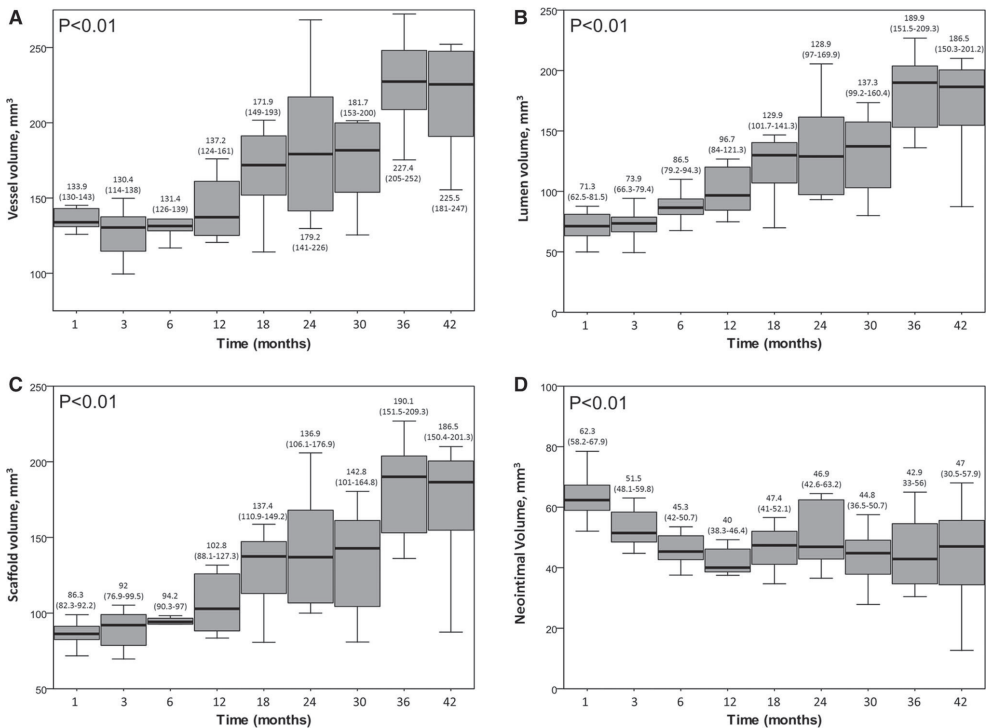
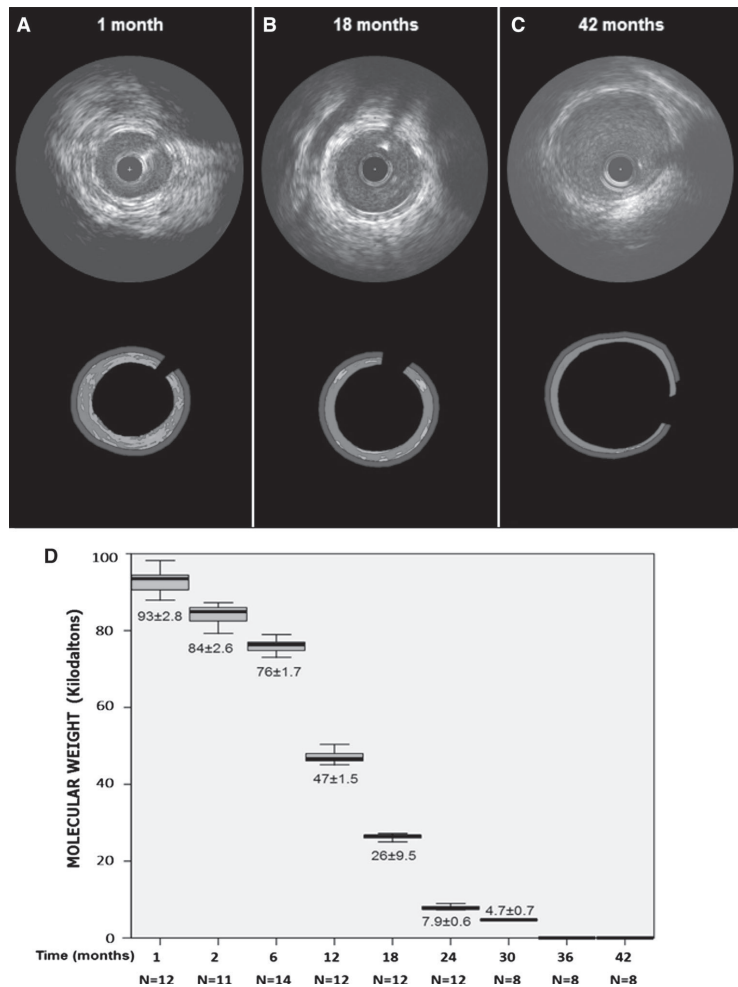


Fig. 2 Grey Scale intravascular ultrasound volumetric findings at different time points. **a** Vessel volume; **b** Lumen Volume; **c** Scaffold Volume and **d** Neointimal Volume. Values are median and interquartile range

Fig. 3 IVUS echogenicity analysis at 1- (a), 18- (b) and 42-month (c). The high echogenic (including hyper = light green and upper = light blue) parameters decrease over time. **d** Gel permeation chromatography (GPC) for the assessment of degradation of Absorb showing the in vivo degradation of polymer of Absorb over time



the scaffold-vessel compartment (Fig. 1). As shown in Table 1, the earlier IVUS were more likely to present higher grey-level intensity (hyper + uperechogenicity). The scaffold-vessel hyperechogenicity (Pearson correlation coefficient = 0.75; $P < 0.01$), uperechogenicity (Pearson correlation coefficient = 0.63; $P < 0.01$) and hyper + uperechogenicity (Pearson correlation coefficient = 0.78; $P < 0.01$) had strong correlation with the scaffold molecular weight. As shown in Fig. 4, in linear regression, the best correlation found in linear regression model for molecular weight was scaffold-vessel hyper + uperechogenicity (R squared = 0.57; $P < 0.01$); i.e., all grey-level intensity

higher than median adventitia in the scaffold-vessel compartment should be considered for monitoring the degradation process of this semi-crystalline polymers scaffold. Post-Hoc comparisons between each group are given in the supplementary material (Tables 6-8).

Additionally, a cluster analysis was run for scaffold-vessel hyper + uperechogenicity and hypoechogenicity. It produced five clusters, among which the variables were significantly different in the main (Fig. 5). The comparison among clusters of hyper + uperechogenicity showed a clear positive association scaffold-vessel hyper + uperechogenicity and molecular weight (Fig. 5).

Table 1 Differential echogenicity findings and polymer molecular weight by gel permeation chromatography

	1 Month (n = 12)	3 Months (n = 12)	6 Months (n = 14)	12 Months (n = 12)	18 Months (n = 12)	24 Months (n = 12)	30 Months (n = 8)	36 Months (n = 8)	42 Months (n = 8)	P value for overall comparison
Total hypoechoogenicity Volume (mm ³)	49.3 ± 6.9	34.7 ± 6.8	31.4 ± 5.5	28.7 ± 4.5	33.3 ± 6.2	42.2 ± 8	28.4 ± 7	38.6 ± 12.2	37.6 ± 14.3	<0.01
% Total hypoechoogenicity	79.4 ± 4.9	68.3 ± 7.8	70.3 ± 6.5	71.6 ± 6.7	80.5 ± 5.0	86.8 ± 5.4	78.1 ± 6.1	89.7 ± 4.3	92.0 ± 3.4	<0.01
Total hyperechoogenicity volume (mm ³)	8.5 ± 2.7	8.7 ± 4	6.6 ± 1	6.5 ± 2.8	4.8 ± 1	3.9 ± 1.5	4.3 ± 1.3	2.8 ± 1.2	2.2 ± 1.1	<0.01
% Total Hyperechoogenicity	13.6 ± 3.6	17.2 ± 7.0	15.5 ± 2.7	16.1 ± 6.1	11.8 ± 2.4	8.0 ± 2.6	12.0 ± 2.9	6.7 ± 2.5	5.3 ± 1.9	<0.01
Total upperechoogenicity volume (mm ³)	6.3 ± 3.5	13.7 ± 5	12.9 ± 3.6	14.1 ± 7.1	9.5 ± 5.5	6.1 ± 3.6	11.3 ± 4.3	3.9 ± 2.1	2.9 ± 1.9	<0.01
% Total upperechoogenicity	7.0 ± 3.9	14.5 ± 5.5	14.1 ± 5.3	12.3 ± 5.3	7.7 ± 4.0	5.2 ± 2.9	9.9 ± 3.4	3.7 ± 1.9	2.8 ± 1.6	<0.01
Total hyper and upperechoogenicity volumes (mm ³)	14.9 ± 4.5	22.4 ± 5.2	19.6 ± 4.4	20.6 ± 6.8	14.4 ± 6.1	10 ± 4.9	15.6 ± 5.3	6.7 ± 3.16	5.1 ± 3	<0.01
% Total hyper and upperechoogenicity	20.6 ± 4.9	31.7 ± 7.8	29.7 ± 6.5	28.4 ± 6.7	19.5 ± 5.1	13.2 ± 5.4	21.9 ± 6.1	10.3 ± 4.3	8.1 ± 3.4	<0.01
Lumen-scaffold hypoechoogenicity Volume (mm ³)	13.6 ± 5.5	13.4 ± 4.3	7.7 ± 7.5	3.9 ± 1.9	6.7 ± 2.5	7.8 ± 4.1	2.9 ± 2	0 ± 0.1	0 ± 0.1	<0.01
% Lumen-scaffold hypoechoogenicity	91.9 ± 4.3	88.8 ± 4.5	88.4 ± 4.1	80.5 ± 11.6	89.3 ± 3.7	92.3 ± 2.9	86.1 ± 4.5	22.0 ± 41.3	44.5 ± 48.3	<0.01
Lumen-scaffold hyperechoogenicity volume (mm ³)	1.25 ± 0.9	1.5 ± 0.8	1.2 ± 1.8	0.8 ± 0.5	0.4 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0	0	<0.01
% Lumen-scaffold hyperechoogenicity	8.1 ± 4.4	10.7 ± 4.7	11.0 ± 3.8	19.0 ± 11.6	6.5 ± 3.0	4.0 ± 2.0	9.9 ± 3.5	1.8 ± 5.0	3.7 ± 8.7	<0.01
Lumen-scaffold upperechoogenicity volume (mm ³)	1.9 ± 1.3	6.6 ± 2.8	6.6 ± 2.8	9.3 ± 5.1	6.6 ± 3.9	3.8 ± 2.2	7.7 ± 3.22	2.4 ± 1.4	1.8 ± 1.3	<0.01
% Lumen-scaffold upperechoogenicity	0.1 ± 0.1	0.5 ± 0.7	0.5 ± 0.7	0.4 ± 0.5	4.2 ± 0.9	3.1 ± 1.2	4.0 ± 1.7	1.2 ± 3.4	1.8 ± 5.1	<0.01
Lumen-scaffold hyper and upperechoogenicity Volumes (mm ³)	3.2 ± 1.5	8.1 ± 3.1	7.9 ± 2.6	10.1 ± 5.4	7.1 ± 4	4.1 ± 2.4	8 ± 3.3	2.4 ± 1.4	1.8 ± 1.3	<0.01
% Lumen-scaffold hyper and upperechoogenicity	8.1 ± 4.3	11.2 ± 4.5	11.6 ± 4.1	19.5 ± 11.6	10.7 ± 3.7	7.1 ± 2.9	13.9 ± 4.5	3.0 ± 8.4	5.5 ± 10.3	<0.01
Scaffold-vessel hypoechoogenicity volume (mm ³)	35.7 ± 4	21.3 ± 5.1	23.8 ± 9.3	24.9 ± 4.6	26.6 ± 4.9	34.4 ± 7.9	25.5 ± 7.9	38.5 ± 12.2	37.7 ± 14.3	<0.01
% Scaffold-vessel hypoechoogenicity	75.5 ± 6.0	59.6 ± 8.6	66.9 ± 8.3	70.1 ± 6.9	78.4 ± 6.2	85.3 ± 6.3	77.0 ± 6.3	89.7 ± 4.3	91.9 ± 3.4	<0.01
Scaffold-vessel hyperechoogenicity volume (mm ³)	7.3 ± 2	7.2 ± 4.2	5.4 ± 2.3	5.7 ± 2.5	4.4 ± 0.9	3.5 ± 1.3	4 ± 1.4	2.8 ± 1.1	2.2 ± 1.2	<0.01
% Scaffold-vessel hyperechoogenicity	15.4 ± 4.1	19.5 ± 7.3	16.3 ± 2.9	15.9 ± 5.7	13.1 ± 2.8	8.9 ± 3.0	12.3 ± 3.0	6.7 ± 2.5	5.3 ± 1.9	<0.01
Scaffold-vessel upperechoogenicity volume (mm ³)	4.4 ± 2.6	7.1 ± 2.5	6.3 ± 1.8	4.8 ± 2.1	2.9 ± 1.7	2.3 ± 1.4	3.5 ± 1.5	1.5 ± 0.8	1.1 ± 0.8	<0.01
% Scaffold-vessel upperechoogenicity	9.2 ± 5.3	20.8 ± 8.3	16.7 ± 6.7	14.4 ± 6.4	8.5 ± 4.9	5.8 ± 3.5	10.7 ± 3.7	3.7 ± 1.9	2.8 ± 1.6	<0.01

Table 1 continued

	1 Month (n = 12)	3 Months (n = 12)	6 Months (n = 14)	12 Months (n = 12)	18 Months (n = 12)	24 Months (n = 12)	30 Months (n = 8)	36 Months (n = 8)	42 Months (n = 8)	P value for overall comparison
Scaffold-vessel hyper and upperchogenicity volumes (mm ³)	11.7 ± 3.4	14.3 ± 3.8	11.7 ± 3.8	10.5 ± 2.4	7.3 ± 2.3	5.8 ± 2.7	7.5 ± 2.7	4.3 ± 1.9	3.2 ± 1.9	<0.01
% Scaffold(vessel hyper and Upperchogenicity	24.6 ± 6.0	40.4 ± 8.6	33.1 ± 8.3	29.9 ± 6.9	21.7 ± 6.2	14.7 ± 6.3	23.0 ± 6.3	10.4 ± 4.3	8.1 ± 3.4	<0.01
Molecular weight (kDa)	92.9 ± 2.8	84.2 ± 2.5	76 ± 1.7	47.1 ± 1.5	26.2 ± 0.9	7.9 ± 0.6	4.7 ± 73.9	0	0	<0.01

Discussion

In the present study, using IVUS grey scale derived parameters we attempted to assess the degradation process of the Absorb poly-L-lactide bioresorbable everolimus-eluting scaffold at multiple time points in a porcine model. The major findings of this study can be summarized as follows: (1) hyperechogenic and upperchogenic thresholds had strong and positive correlations with the scaffold molecular weight assessment; (2) the combination of hyper and upperchogenicity could be used as a surrogate for the chromatographic assessment of scaffold molecular weight and (3) echogenicity demonstrated good inter- and intra-observer reproducibility (Supplementary Material).

The present manuscript describes a new software designed to assess the differential echogenicity and, for the first time, ascertained the correlation between IVUS grey scale intensities and quantitative assessment of Mw by GPC. The first novelty is that it was not necessary to use ECG gating and therefore, it is not needed a dedicated IVUS console or post-processing correction. The robustness of this method and the aforementioned good reproducibility demonstrate, for the first time, good correlation of echogenicity with the degradation of the scaffold without being mandatory correction for motion artifacts [30].

Image resolution can be defined as the capability of making distinguishable the individual parts of an object. Therefore, the use of 40 MHz IVUS catheter in the present study has potential to be more precise to detect scaffold degradation than the previous methodology with the 20 MHz ultrasound [7, 31]. Ultrasound at a center frequency of 10 MHz has demonstrated to detect decline in the acoustic impedance of PLA when molecular weight varied from 60 to 24 kDa, but further decrease in molecular weight to 15 kDa did not result in discernible change [32]. In the present study, working with the higher resolution of the 40 MHz IVUS catheter, we were able to detect acoustic differences in 150 m thick samples degrading from ~100 to <4 kDa.

The use of ultrasound to monitor the degradation process of polymers has been initially proposed with a wave pulse-echo method in an in vitro essay [31]. We succeeded to monitor by ultrasound the degradation process of three biodegradable polymers: poly(glycolic acid) (PGA), poly(L-lactic acid) (PLLA) and 50:50 poly(D, L-lactide-co-glycolide) (PDLLG) [33]. Another IVUS based approach to detect the resorption process in human is virtual histology [6]. The spectral analysis of the raw backscattered ultrasound misrepresents polymeric struts as dense calcium (DC) and necrotic core (NC). As these parameters are shown to decrease over time after implantation, they have been correlated putatively with resorption [6, 16, 34, 35].

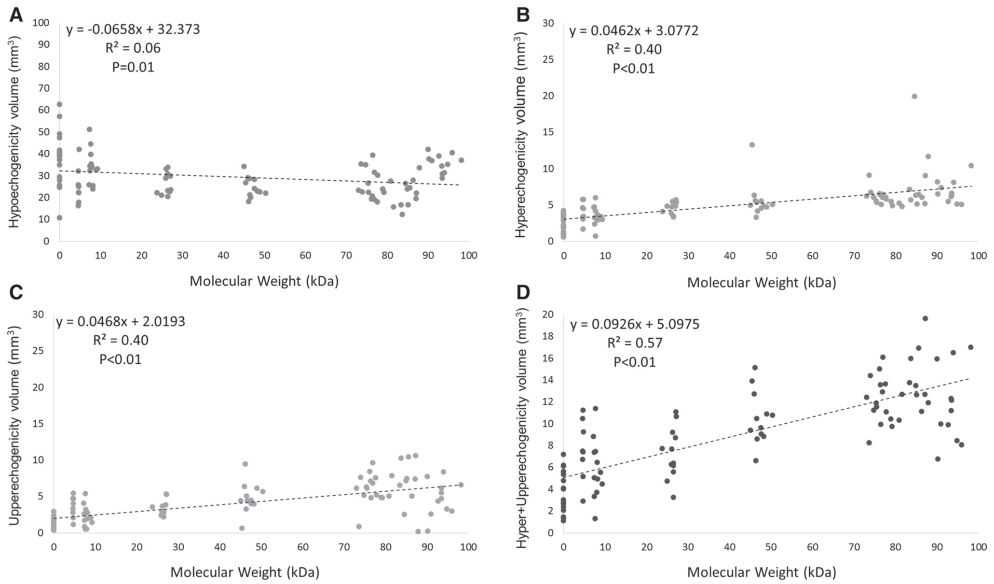


Fig. 4 Linear regressions between molecular weight and echogenicity derived parameters in the scaffold-vessel compartment

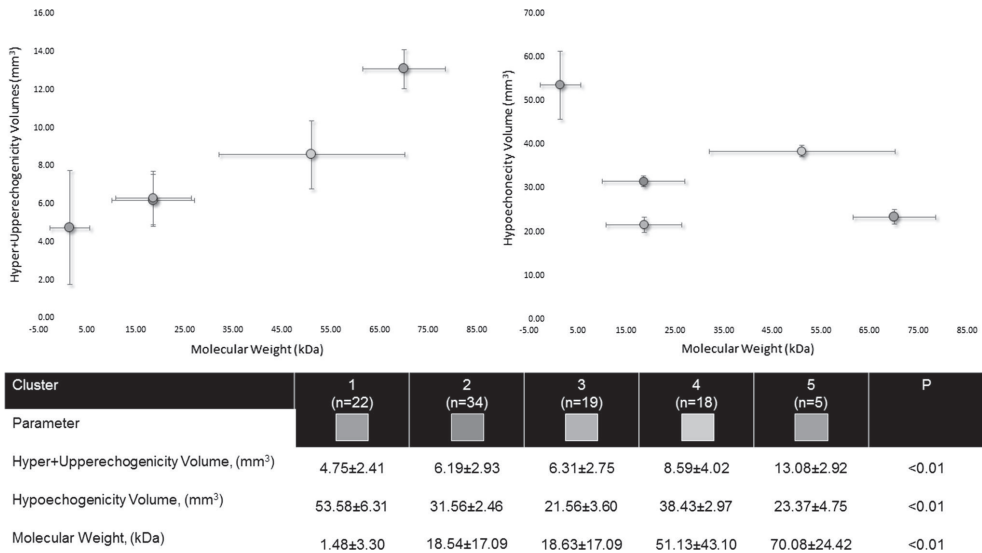


Fig. 5 A hierarchical cluster analysis labeled by animal was run for scaffold-vessel hyper + upperechogenicity and hypochoecity. Cluster 2 and 3 had similar hyper + upperechogenicity but statistically significant greater hypochoecity volumes in the cluster 2. Cluster 3 and 5 had similar hypochoecity but markedly higher

hyper + upperechogenicity volumes in cluster 5. There was a clear positive association between scaffold-vessel hyper + upperechogenicity and molecular weight. The sample sizes are number of scaffolds included in each pig cluster. The values are mean ± standard deviation and the errors bars are 95 % confidence interval

Previously, echogenicity has been used to assess paired serial acoustic properties of coronary plaques in BRS-treated segments in the clinical setting [7, 8, 35]. It has been shown that these segments had an increase in hyperechogenic tissue after implantation which decreased over time [7, 8, 35]. The aforementioned methodology succeeds to document the progressive decrease of high intensity grey level tissues in both metallic and polymeric BRS [8, 35].

However, until now, the link between echogenicity and the degradation process has been hypothetically assumed. The pending question was whether temporal plaque changes could interfere with the multistage degradation of the polymer and confound the echogenicity analysis. It has been shown that coronary atherosclerosis is a dynamic phenomenon and numerous factors can influence the atherosclerotic changes as detected by IVUS-derived parameters. For instance, statin treatment may reduce the percentage lipid volume index over time [13] and may increase the calcified plaque component [11]. Additionally, there is a significant decrease in NC (16 %) and DC (30 %) content in coronary plaque located behind the struts of the everolimus-eluting bioresorbable vascular scaffold [36]. All the above-mentioned confounding factors might influence the acoustic properties in the lumen-vessel compartment and hinder the clinical relevance of echogenicity for BRS degradation assessment.

As we have used a porcine non-atherosclerotic model, we did not have the confounding presence of coronary artery disease, thus enabling the evaluation of Poly-L-Lactide's echogenic characteristics over time. Hyperechogenic, uperechogenic and hyper + uperechogenic tissues had strong and positive correlations between echogenicity and the degradation process. Echogenicity is determined by the difference in acoustic impedance between two mediums, which is proportional to density and acoustic velocity. The acoustic velocity is proportional to the square root of the stiffness (bulk and shear moduli). Many factors impact the stiffness of PLA, including molecular weight, polydispersity, crystallinity, orientation of crystalline microstructure, and other environmental conditions [37]. As a result, one would expect to change the impedance of PLA as it degrades and molecular weight to have a generalized relationship to this decline.

Qualitatively, the correlation was however not perfectly linear. For instance, at 1-month the combination hyper + upper tended (without statistical significance; Table 6, supplementary material), in average, to be lower than at 3-months whereas the molecular weight had a continuous decrease in the same period. From the ultrasonic point of view, the significantly higher neointimal hyperplasia (Fig. 2) at 1-month might have affected the ultrasound penetration and therefore the echogenicity interpretation. Additionally,

the scaffold-vessel hyper + uperechogenicity at 30-months was numerically comparable to that at 18-month. However, the degradation process may be influenced by individual biological factors and it has to be emphasized that these assessments were not serial. However, we showed a consistent individual positive correlation between the molecular weight and echogenicity (Figs. 4 and 5).

Limitations

Arteries used for molecular weight assessment could not be evaluated histologically. Therefore, changes in the observed echogenicity (both lumen-scaffold and scaffold-vessel) could not be related to the histologic changes over time [19, 38]. As this study has been performed in a non-atherosclerotic model, it should be acknowledged that the rate of degradation has not been confirmed in atherosclerotic coronary arteries. However, as the degradation of PLLA is a hydrolytically driven and not enzymatically driven process, it is expected that the rates would be largely equivalent.

We could not test the reproducibility of the echogenicity IVUS findings in the two different consoles. However as we worked at the same ultrasound frequency (40 MHz) and the tissue classifications were normalized by the individual adventitia grey scale intensity we could show a robust correlation between scaffold degradation and high echogenic parameters. It has been shown that the comparison with the adventitia allows for normalization with respect to transducer variability, gain settings and across populations [21].

The changes in vessel, lumen, scaffold and neointima volumes over time are in line with the serial IVUS findings in the pre-clinical model and clinical setting showing progressive increase in vessel, lumen area and scaffold area [16, 18, 39, 40]. However, in the porcine model the somatic growth can influence our findings [39]. As we do not have the IVUS at baseline we could not normalize these geometrical changes for the increase in the reference vessel size. Nevertheless, this information has been described in the literature and are beyond the main scope of the current manuscript.

Conclusion

IVUS high intensity grey level quantification is correlated to Absorb scaffold residual molecular weight assessment. Echogenicity is a reproducible technique which could be considered as a surrogate assessment of polylactide molecular weight decrease as assessed by chromatography and allows for monitoring of the degradation of semi-crystalline polymeric scaffolds.

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Conflict of interest Alexander Sheehy, Marika Kamberi, Richard Rapoza and Laura Perkins are full-time employee of Abbott Vascular, Santa Clara, California, and at the time of this work, Jennifer Lane also was a full-time employee of Abbott Vascular. The others authors have no conflict of interest and did not receive grants or financial support from industry or from any other source to prepare this manuscript.

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Chapter 5.3

Acute and long-term evaluation of bioresorbable scaffolds by optical coherence tomography

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KEYWORDS

• Bioresorbable scaffolds • Optical coherence tomography • Drug-eluting stents

KEY POINTS

- The analysis of bioresorbable scaffolds (BRSs) by optical coherence tomography (OCT) requires a dedicated methodology, as the polymeric scaffold has a distinct appearance and undergoes dynamic structural changes with time, unlike metallic stents.
- The high resolution of OCT allows for the detailed assessment of scaffold implantation, rupture, discontinuity, and strut integration.
- OCT does not provide reliable information on the extent of scaffold degradation, as it cannot differentiate between polylactide polymer and the provisional matrix of proteoglycan formed by connective tissue.
- Three-dimensional OCT reconstruction can aid in the evaluation of BRS in special scenarios such as overlapping scaffold segments and bifurcations.

INTRODUCTION

BRSs represent a novel approach in the treatment of coronary artery disease. They support the vessel transiently to maintain patency after intervention, deliver antiproliferative drug to the vessel wall, and then gradually degrade.^{1,2} BRS technology has matured, and there are numerous devices that are commercially available outside the United States or are undergoing preclinical or clinical evaluation (Fig. 1). BRS has required new imaging modalities, methodologies, and strategies, because

scaffold design, degradation rate, loss of mechanical properties (Table 1), coating, and drug deliverability may affect BRS safety and efficacy.^{3,4} OCT has played a central role in understanding the short and long term BRS performance, OCT provides more detailed and precise morphologic information about BRS than does intravascular ultrasonography (IVUS) because of its higher resolution.^{5,6} This review summarizes the methodology and clinical application of OCT in the assessment of BRS, in particular for the commercially available Absorb Bioresorbable

The authors have nothing to disclose.

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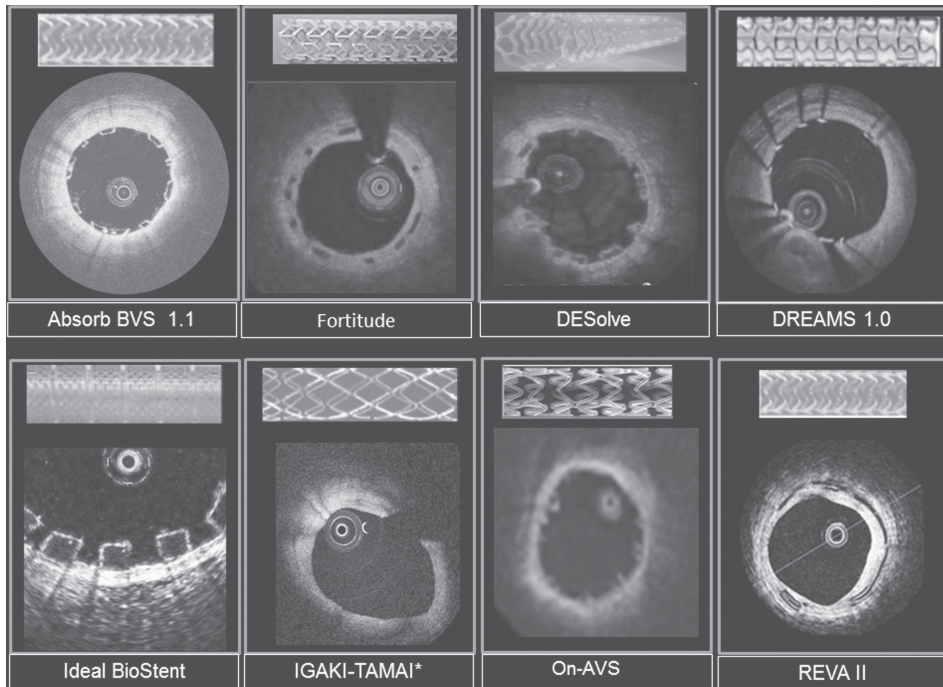


Fig. 1. Optical coherence tomography images of different bioresorbable vascular scaffolds. Absorb BVS 1.1 (Abbott Vascular, Santa Clara, CA, USA); Fortitude (Amaranth Medical, Mountain View, CA, USA); DESolve BRS (Elixir, Sunnyvale, CA, USA); DREAMS 1.0 absorbable metallic scaffold (Biotronik, Berlin, Germany); Ideal II BioStent (Xenogenics, Philadelphia, PA, USA); Igaki-Tamai scaffold (Kyoto Medical Planning Co, Kyoto, Japan); On-AVS (Orbus Neich, Wanchai, Hong Kong); REVA (REVA Medical Inc, San Diego, CA, USA). An OCT image for Igaki-Tamai was not available at baseline.

Table 1
Mechanical properties and degradation rate of different material candidates for bioresorbable coronary scaffolds

Material	Tensile Strength (MPa)	Elongation (%)	Degradation Time
Poly(L-lactide)	60–70	2–6	24 mo ^a
Poly(DL-lactide)	45–55	2–6	12–16 mo ^a
Poly(glycolide)	90–110	1–2	6–12 mo ^a
50/50 DL-lactide/glycolide	40–50	1–4	1–2 mo ^a
82/18 L-lactide/glycolide	60–70	2–6	12–18 mo ^a
70/30 L-lactide/ε-aprolactone	18–22	>100	12–24 mo ^a
Pure Fe	200	40	0.19 mm/y
Fe-35 Mn alloy	430	30	0.44 mm/y
WE43 alloy	280	2	1.35 mm/y

^a Degradation time depends on geometry.

Data from Moravej M, Mantovani D. Biodegradable metals for cardiovascular stent application: interests and new opportunities. *Int J Mol Sci* 2011;12:4250–70; and van Alst M, Eenink MJ, Krufft MA, et al. ABC's of bioabsorption: application of lactide based polymers in fully resorbable cardiovascular stents. *EuroIntervention* 2009;5(Suppl F):F23–7.

Vascular Scaffold (BVS) (Abbot Vascular, Santa Clara, CA, USA), as this device had the most extensive short- and long-term follow-up data.

RATIONALE FOR THE NEED FOR A DEDICATED ANALYSIS METHODOLOGY FOR THE OPTICAL COHERENCE TOMOGRAPHIC ASSESSMENT OF BIORESORBABLE SCAFFOLDS

The OCT appearance of polymeric scaffolds differs significantly from that of metallic scaffolds and stents (Fig. 2A). The appearance of magnesium scaffolds immediately after implantation is similar to that of a permanent metallic stent, that is, a bright strut with well-delimited borders with a shadow behind (see Fig. 2A). In contradistinction, polymeric struts are optically translucent and appear as a black central core framed by light-scattering borders that do not shadow the vessel wall, and therefore the complete thickness of the scaffold strut can be visualized (see Fig. 2B). The main quantitative measurements for scaffold evaluation by OCT include strut core area, strut area, lumen area, scaffold area, incomplete strut apposition (ISA) area, and neointimal area. Because polymeric scaffolds scatter light differently and have different OCT characteristics than metallic stents/scaffolds (see Fig. 2B, C), these measurements must be acquired using different image analysis rules.

OPTICAL COHERENCE TOMOGRAPHIC EVALUATION OF BIORESORBABLE SCAFFOLDS AT TIME OF IMPLANTATION

Several OCT parameters can be collected at the time of short-term implantation of the BRS; these are summarized in Table 2. Key quantifications include the lumen and scaffold areas, the magnitude of ISA, lumen prolapse, and flow area. The high resolution provided by OCT also allows the operator to visualize the quality of scaffold implantation and the potential complications related to it. Important analyses include assessments of short-term strut fracture, edge dissection, eccentricity, and symmetry.

Contours

At baseline, the lumen and scaffold contours are obtained with a semiautomated detection algorithm available in numerous off-line software packages. These contours can be corrected manually if necessary.

Lumen and Scaffold Areas

Because the polymeric struts are translucent, the vessel lumen border can be visualized and the

vessel lumen area delineated along the external (abluminal) side of the struts. The scaffold area is measured by joining the internal middle points of the abluminal side of the black cores of the apposed struts or the abluminal edge of the frame borders of malapposed struts. In the absence of ISA and plaque prolapse, the scaffold area is identical to the lumen area (see Fig. 2C).

Incomplete Strut Apposition

ISA is defined by a clear separation between the abluminal side of the strut and the vessel wall. ISA area is delineated by the abluminal side of the frame border of the malapposed struts and the endoluminal contour of the lumen.

Lumen Prolapse

Several different parameters can be collected in the case of lumen or plaque prolapse protruding between the struts into the lumen. The prolapse area can be estimated by the planimetric difference between the prolapsed contour (ie, lumen contour) and the scaffold area. An intraluminal defect that is separated from the vessel wall (eg, thrombus) can also be quantified as an area.

Flow Area

Flow area takes into account ISA, plaque prolapse, and intraluminal defects. It is defined as the difference between the sum of the scaffold and ISA areas and the sum of the areas of intraluminal struts, prolapse, and intraluminal defect (ie, flow area = [scaffold area + ISA area] – [intraluminal strut areas + prolapse area + intraluminal defect area]).

Short-term Strut Fracture

The diagnosis of short-term strut fracture due to balloon overdilation can be established if 2 struts overhang each other within the same angular sector of the lumen perimeter (Fig. 3). This complication may be observed with or without concomitant strut malapposition. However, if isolated struts are located more or less at the center of the vessel without an obvious connection with other surrounding struts, strut fracture may also be present. It is helpful to perform 3-dimensional reconstruction of the OCT dataset to confirm the diagnosis.

Edge Dissection

Edge dissection is defined by OCT as the disruption of the endoluminal vessel surface at the proximal and distal edges of the BRS (Fig. 4).⁷ In the ABSORB Cohort B trial, 24% of patients had proximal and 42% had distal edge dissection flaps postprocedure.⁸ On follow-up, proximal and distal edge dissection flaps seem to

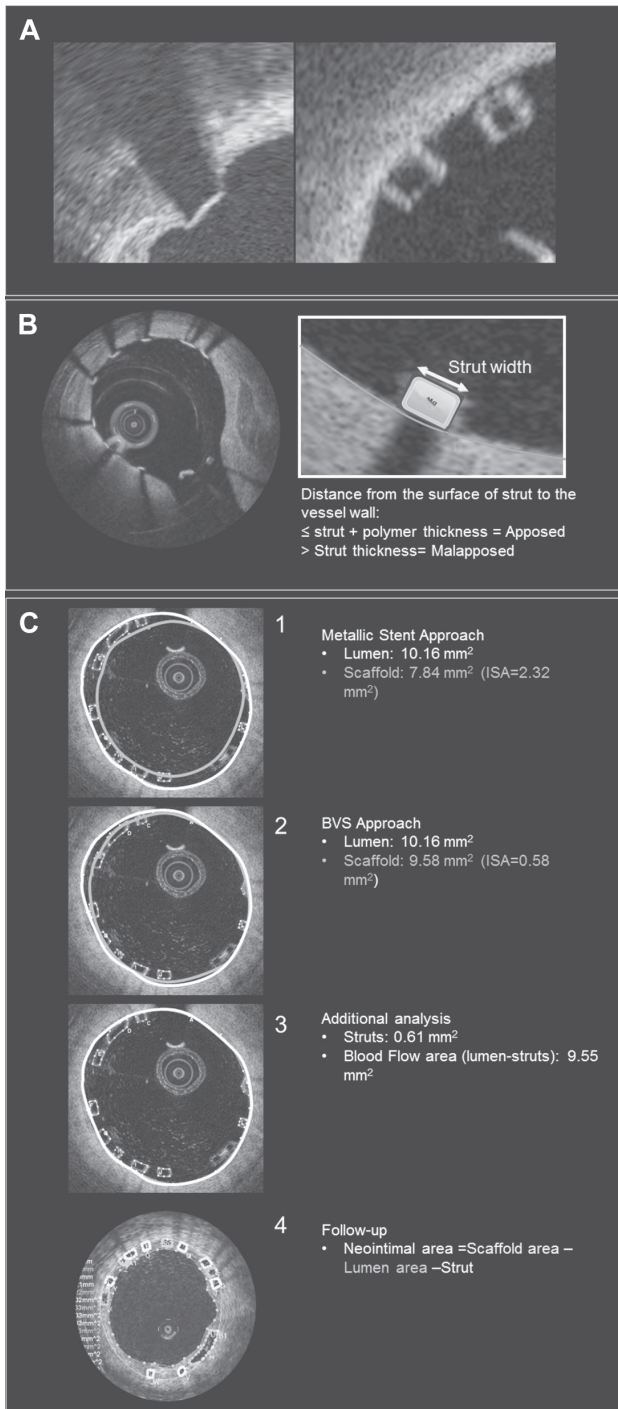


Fig. 2. (A) Representative optical coherence tomographic image of the drug-eluting absorbable metal scaffold DREAMS (Biotronik, Bülach, Switzerland) immediately after implantation looks like a permanent metallic stent (*left*). Absorb BVS has optically translucent struts and appears as a black central core framed by light-scattering borders that do not shadow the vessel wall and allow complete imaging of the strut thickness (*right*). (B) Methodology for the assessment of incomplete scaffold apposition (ISA) with the drug-eluting absorbable metal scaffold DREAMS. (C) Newly implanted bioresorbable scaffold. Differences in the methodology of OCT assessment between metallic stents and BVS are illustrated. Panel 1. Metallic stent approach. Note that with metallic scaffold/stent analysis, device area is calculated by planimetry of the endoluminal border of the struts. Lumen area, 10.16 mm²; stent area, 7.84 mm², ISA, 2.32 mm². Panel 2. BVS approach. Lumen area, 10.16 mm²; stent area, 9.58 mm²; ISA, 0.58 mm². Panel 3. Additional BVS analyses. Strut area, 0.61 mm²; blood flow area (lumen area – strut area), 9.55 mm². Panel 4. Follow-up OCT imaging of BVS. Strut area is defined only by its black core, because the light-scattering frame is no longer distinguishable from the surrounding tissue. Neointimal area is defined by (scaffold area – lumen area – strut area). ([C] Adapted from Garcia-Garcia HM, Serruys PW, Campos CM, et al. Assessing bioresorbable coronary devices: methods and parameters. *JACC Cardiovasc Imaging* 2014;7:1130–48.)

Parameter	Formula	Definition and Notes
Eccentricity index	Minimum scaffold diameter/maximum scaffold diameter in a frame	The average of all eccentricity indices of each frame within scaffolded segment is calculated
Symmetry index	(Minimum scaffold diameter – maximum scaffold diameter)/ maximum scaffold diameter within a scaffolded segment	The maximum and the minimum stent/scaffold diameters in this calculation were possibly located in 2 different frames along the length of the device implanted
Scaffold area		At baseline, the scaffold area is measured by joining the middle points of the abluminal sides of the black cores of the apposed struts or the abluminal edge of the frame borders of malapposed struts. At follow-up, the abluminal side of the central black core is used to delimit the scaffold area
Blood flow area	(Scaffold area + ISA area) – (intraluminal strut areas + prolapse area + intraluminal defect area)	
Neointimal hyperplasia area	i. In case of all struts apposed Scaffold area – [lumen area + black box area] ii. In case of malapposed struts [Scaffold area + ISA area + malapposed strut with surrounding tissues] – [lumen area + strut area]	Note the difference of methodology with that of gray-scale IVUS
Thickness of tissue coverage	Distance between the abluminal site of the strut and the lumen – strut thickness	Since the strut thickness is 150 μm (ABSORB), the strut was considered as covered whenever the thickness of the coverage was more than this threshold value. This method may slightly underestimate the thickness of the coverage because it does not take into account changes in the size of the strut core over time

Adapted from Garcia-Garcia HM, Serruys PW, Campos CM, et al. Assessing bioresorbable coronary devices: methods and parameters. *JACC Cardiovasc Imaging* 2014;7:1130–48.

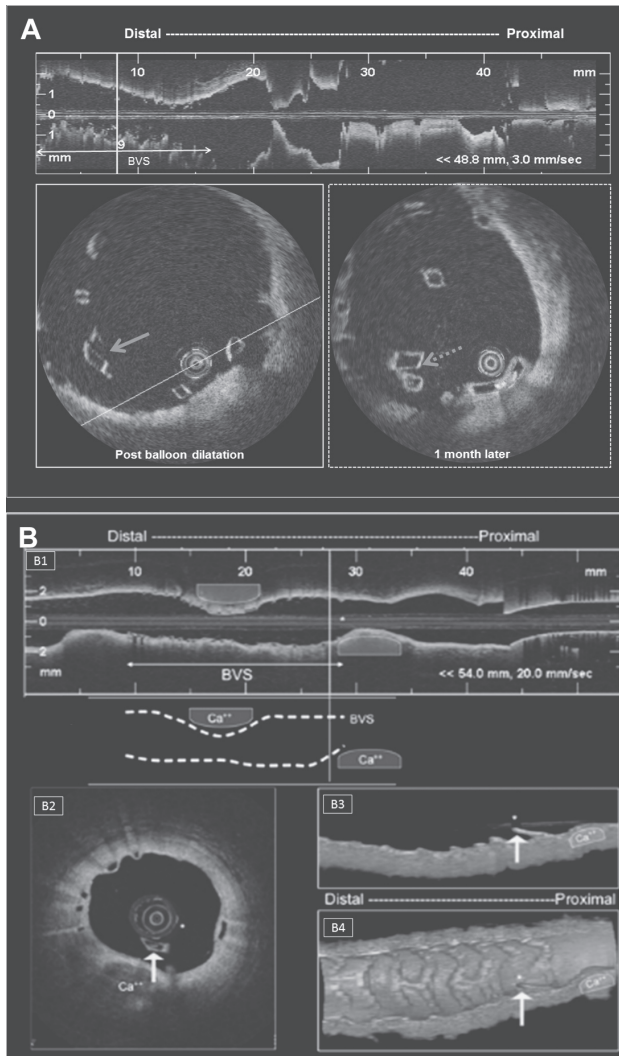


Fig. 3. Representative OCT image of scaffold fracture and discontinuity. (A) Scaffold fracture. During the index procedure after postdilatation of an Absorb BVS, OCT cross-sectional image shows scaffold fracture (*blue arrow, left*). The strut luminal and abluminal surfaces are no longer orientated perpendicular to the light source. OCT cross-sectional image 1 month later shows extensive strut disarray (*dotted blue arrow, right*). (B) Scaffold discontinuity. OCT acquisition 6 months after Absorb BVS implantation. In the 2-dimensional (cross-sectional) OCT image, extreme malapposition of 1 strut is seen (panel *B2, yellow arrow*). In the 3-dimensional reconstruction, the overhanging strut is clearly identified in its whole trajectory (panel *B3, B4; yellow arrow*). Further intervention was deferred because of lack of ischemic symptoms. ([A] Adapted from Ormiston JA, De Vroey F, Serruys PW, et al. Bioresorbable polymeric vascular scaffolds: a cautionary tale. *Circ Cardiovasc Interv* 2011;4:535–8; and [B] From Garcia-Garcia HM, Serruys PW, Campos CM, et al. Assessing bioresorbable coronary devices: methods and parameters. *JACC Cardiovasc Imaging* 2014;7:1130–48.)

have resolved. In serial OCT analysis of BRSs, postprocedural proximal edge dissection was noted in 21% of cases and distal edge dissection in 38% of cases, compared with 2% and 5% at 6 months, respectively. At 1 year, an edge dissection was present in only 2% (proximal) and none were observed at 2- and 3-year follow-up. No scaffold thrombosis was reported in this trial.⁸ Therefore, although edge dissection by OCT is often detected, most of these dissections healed within 6 months without any clinical

sequelae. However, the small sample size of this study limits any definitive conclusion with respect to the effect of residual edge dissection on clinical outcomes.

Eccentricity and Symmetry

The eccentricity and symmetry of implanted BRSs are easily assessed by OCT (see Table 2). These parameters have been shown to be associated with clinical outcomes after metallic stents.^{9,10} With the clinical adoption of various

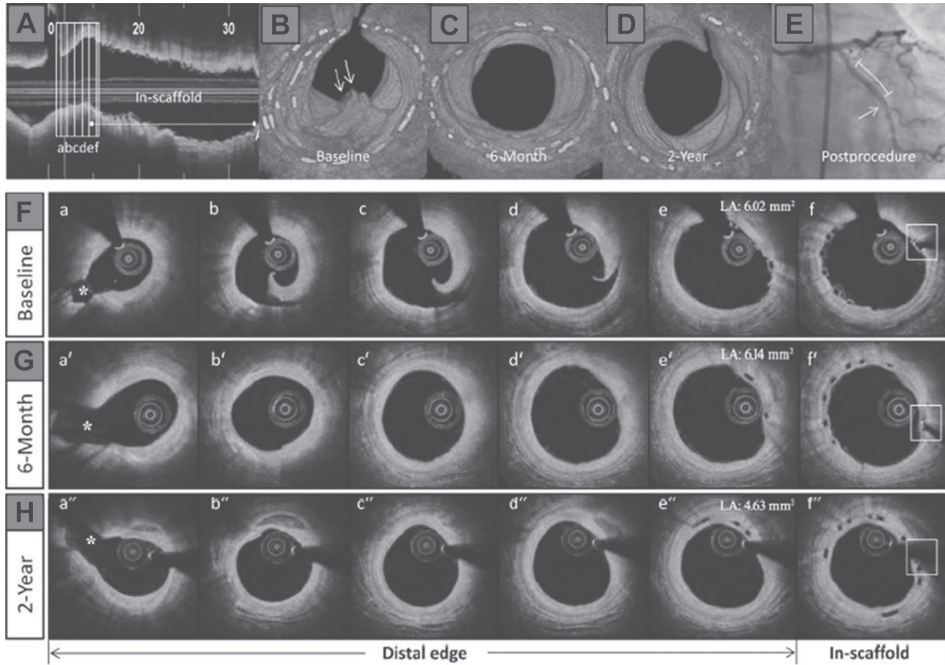


Fig. 4. Representative imaging of a dissection at the distal edge of Absorb BVS. (A) Longitudinal view of a distal dissection. (B) Three-dimensional reconstruction of OCT pullback showing luminal disruption at distal edge of the scaffold (double white arrow). (C, D) Three-dimensional reconstruction at 6-month and 2-year follow-up, respectively, demonstrating that the dissection has healed. (E) No distal edge dissection is visible from the angiograms postprocedure (yellow arrow). (F) OCT cross-sectional images immediately after implantation show that a dissection extends into the media. (G) OCT image at 6-month follow-up demonstrates an increase in lumen area at that region without visible dissection. (H) At 2-year follow-up, the lumen area has decreased with detected calcific tissue. Asterisk, side branch. (From Zhang YJ, Iqbal J, Nakatani S, et al. ABSORB Cohort B Study Investigators. Scaffold and edge vascular response following implantation of everolimus-eluting bioresorbable vascular scaffold: a 3 year serial optical coherence tomography study. *JACC Cardiovasc Interv* 2014;7(12):1361-9.)

bioresorbable devices, the reevaluation of the clinical effect of these geometric parameters is required at short- and long-term follow-up. The eccentricity ratio is defined as the ratio of the minimum and maximum diameters of the scaffold in each frame. The eccentricity index is obtained by calculating the average of all eccentricity ratios along the length of the scaffold.³ The symmetry index is derived from the maximum scaffold diameter and minimum scaffold diameter along the length of the BRS, which may be located within different frames. It is calculated as the difference between the maximum scaffold diameter and the minimum scaffold diameter, divided by the maximum scaffold diameter.³ It must be emphasized that the maximum and the minimum scaffold diameters

in this calculation may be located in 2 different frames along the length of the implanted device (Fig. 5).

Bioresorbable Scaffold Versus Drug-Eluting Stent at Time of Implantation

BRSs have distinct mechanical properties compared with metallic stents that could influence the aforementioned OCT parameters. Mattesini and colleagues¹¹ compared the final, postimplantation results of the Absorb BVS and second-generation drug-eluting stents (DESs) using OCT. A total of 50 complex coronary lesions (class B2/C by the American College of Cardiology/American Heart Association definition) treated with a BVS undergoing a final OCT examination were compared with an equal

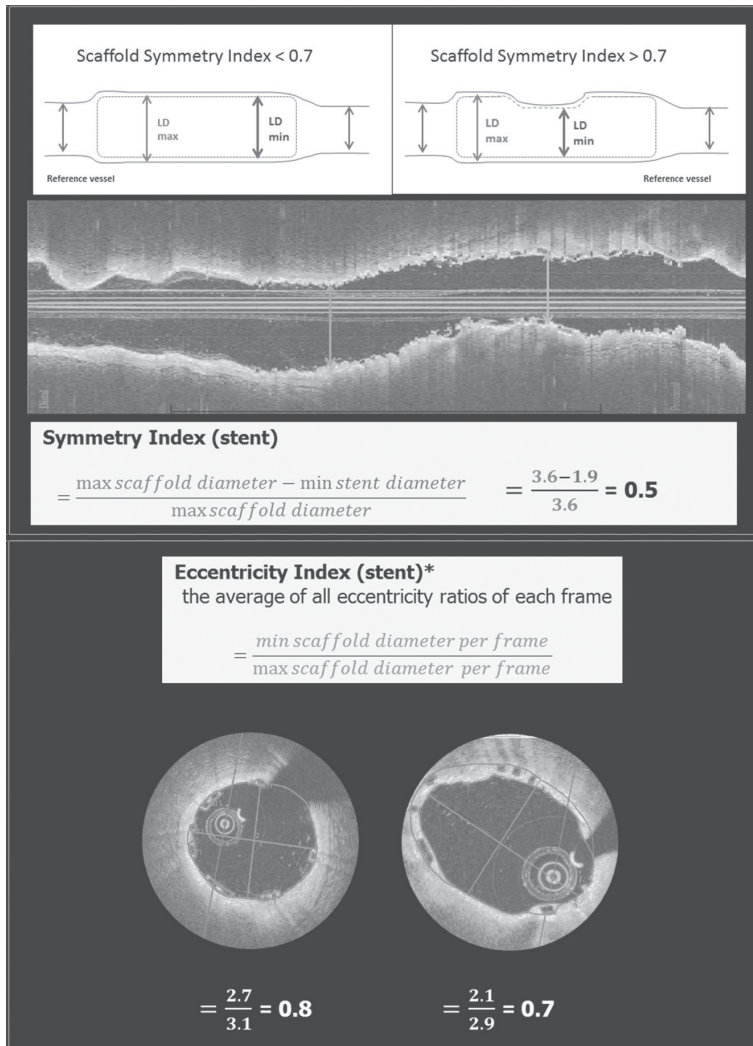


Fig. 5. Definition of the symmetry and eccentricity indices according to OCT. Minimum and maximum diameters along the length of the device are shown. Two cross-sections with different eccentricity indices are also shown.

number of matched lesions treated with second-generation DESs. In the BRS group, there was more extensive lesion preparation (eg, significantly greater balloon diameter:reference vessel diameter ratio and higher inflation predilatation pressure) and significantly higher postdilatation pressure used. Final OCT examination demonstrated a trend toward greater tissue prolapse area ($P = .08$) and a significantly higher rate of proximal edge ISA ($P = .04$) in the BVS group. There was no significant difference in the overall ISA, mean lumen area, and eccentricity index between the 2 groups. There

were 2 cases of strut fractures in the lesions treated with BVS, whereas none was observed with DES.¹¹

OPTICAL COHERENCE TOMOGRAPHIC EVALUATION OF BIORESORBABLE SCAFFOLD OVER LONG-TERM FOLLOW-UP

Because BRSs are designed to degrade with time after implantation, the structural characteristics of the scaffold are dynamic and can be well visualized by OCT imaging. Key parameters that may

be assessed during ongoing follow-up include the presence of any scaffold discontinuity, scaffold eccentricity, strut coverage, and neointimal hyperplasia.

Scaffold Discontinuity

OCT may detect scaffold discontinuity during the process of resorption. The assessment of scaffold discontinuity is the same as that of scaffold fracture after short-term BRS implantation, that is, discontinuity is present if 2 struts overhang each other in the same angular sector of the lumen perimeter, with or without malapposition, or if isolated struts are located near the center of the vessel lumen without obvious connection with other surrounding struts in the 2-dimensional image. Three-dimensional OCT reconstruction is helpful to better understand scaffold discontinuity (see Fig. 3B).

Eccentricity

As the scaffold degrades, its biomechanical properties are altered, and therefore, eccentricity may change with time and should be assessed for new BRSs. In a small series of 8 patients with 5-year follow-up after Absorb BVS implantation, eccentricity decreased with time (see Fig. 5, Table 2).¹²

Strut Coverage and Neointimal Hyperplasia

The analysis of strut coverage is complex, as it must take into account the embedding and thickening of the frame borders, along with a reduction of the strut central core. The strut area is defined only by its black core, because the light-scattering frame is no longer distinguishable from the surrounding tissue and the tissue begins to fill the strut area, a phenomenon that can be identified by irregular, high-intensity areas. At follow-up, the luminal area follows the endoluminal contour of the neointima between and on top of the apposed struts; this can be traced by semiautomatic detection. In the case of malapposed struts, the endoluminal contour of the vessel wall behind the malapposed struts should be used to define the luminal border. The abluminal side of the central black core is used to delimit the scaffold area. If all struts are apposed, neointimal hyperplasia area is calculated as the difference between the scaffold area and the sum of the lumen and black box areas (ie, scaffold area - [lumen area + black box area]). In the setting of malapposed struts, neointimal hyperplasia area is calculated by subtracting the sum of the lumen and strut areas from the sum of the scaffold area, ISA area, and the area of malapposed struts and

surrounding tissues (ie, [scaffold area + ISA area + malapposed strut with surrounding tissues] - [lumen area + strut area]) (see Fig. 2C, Table 2).

SERIAL OPTICAL COHERENCE TOMOGRAPHIC OBSERVATIONS IN SCAFFOLDED SEGMENTS

The OCT results of Absorb BVS Cohorts B1 and B2 have been reported up to 3-year follow-up. The findings of these OCT analyses are illustrated in Fig. 6. There was an initial decrease

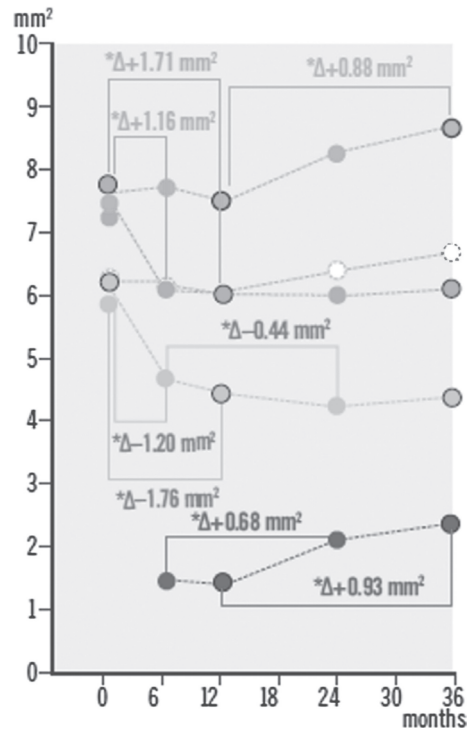
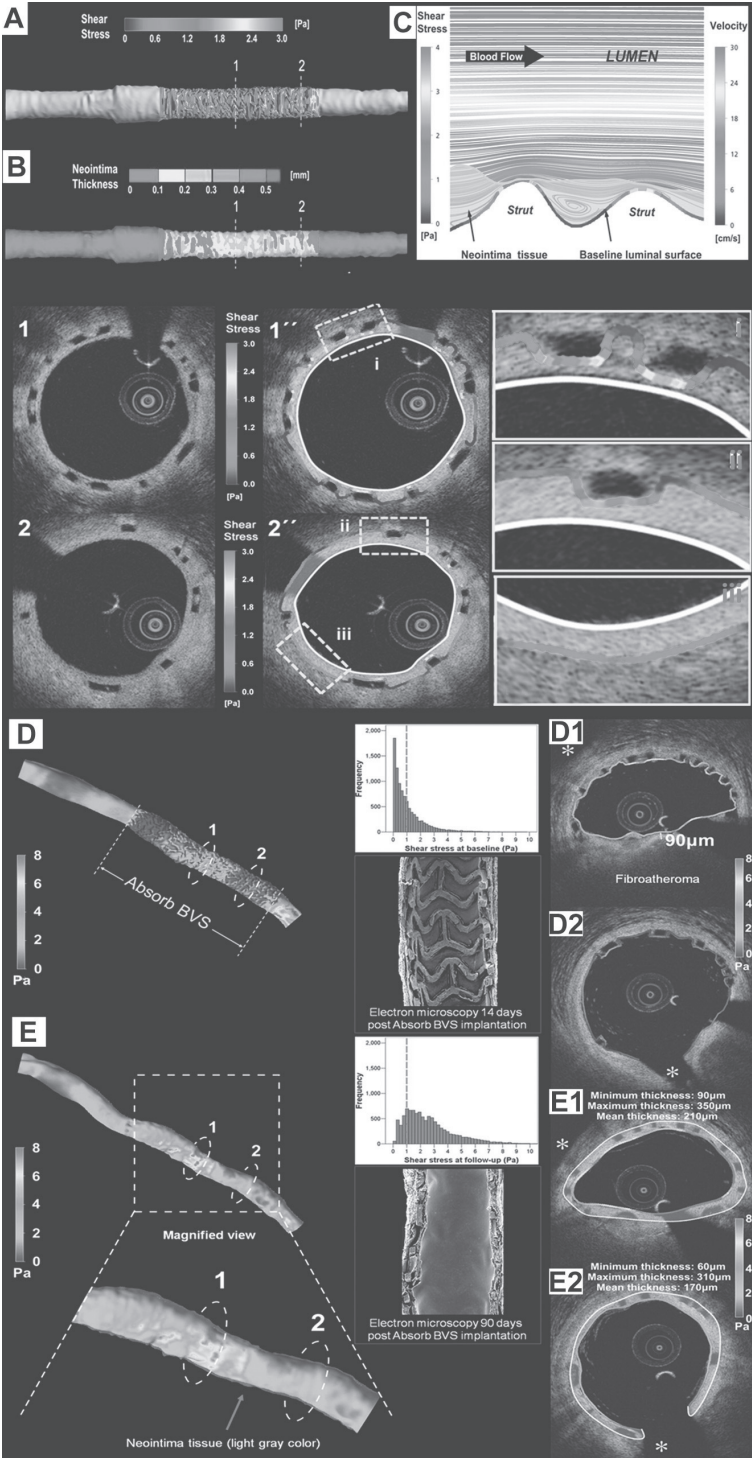


Fig. 6. Optical coherence tomography (OCT) findings in ABSORB Cohort B trial. OCT was performed post-procedure, at 6, 12, 24, and 36 months. The different parameters are color coded. ●, Scaffold area in cohort B1; ○, scaffold area in cohort B2; ●, mean lumen area in cohort B1; ○, mean lumen area in cohort B2; ○, minimum scaffold area in cohort B1; ○, minimum scaffold area in cohort B2; ●, minimum lumen area in cohort B1; ○, minimum lumen area in cohort B2; ●, neointimal area in cohort B1; ○, neointimal area in cohort B2. (Adapted from Serruys PW, Onuma Y, Garcia-Garcia HM, et al. Dynamics of vessel wall changes following the implantation of the absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. *EuroIntervention* 2014;9(11):1271-84.)



in the minimal and mean lumen area that stabilized over the longer term. Although there was an increase in neointima between 1 and 3 years, it was compensated by the parallel increase in the mean and minimum scaffold area, thereby maintaining the lumen area unchanged. A total of 98% percent of struts were covered, and 3 of the 13 scaffolds had malapposed struts with an average malapposition area of 0.60 mm².¹³ Serial OCT evaluation of edge and scaffold vascular responses of the Absorb BVS showed less lumen loss at the edges than lumen loss within the scaffold.⁸ Neointimal coverage of the Absorb BVS seems to be driven by shear stress patterns of the blood flow (Fig. 7).

Serial OCT examinations have demonstrated that Absorb BVS may potentially passivate vulnerable plaques (Fig. 8).¹⁴ In one such study, 46 patients treated with Absorb BVS and 20 patients treated with bare metal stents (Svelte coronary Integrated Delivery System, a balloon-expandable, cobalt-chromium, thin-strut fixed wire stent) had thin-capped fibroatheromas (TCFAs) identified within the device implantation regions and in the adjacent native coronary segments. At 6- to 12-month follow-up, only 8% of

the TCFAs detected at baseline were still present within the Absorb BVS compared with 27% within the bare metal stent implantation segments ($P = .231$). A total of 60% of the TCFAs in native segments did not change their phenotype at follow-up. The more aggressive neointimal response to the bare metal stent resulted in a greater reduction in luminal dimensions compared with the Absorb BVS. The loss of the scaffold's structural integrity allowed the device to expand and accommodate the tissue that developed and recapped the underlying high-risk plaques.¹⁴

The serial changes in atherosclerotic plaques after BRS implantation can be quantified by OCT. In *ex vivo* validation studies, highly attenuating regions (attenuation coefficient $\mu \geq 8 \text{ mm}^{-1}$) seen on OCT have been associated with the presence of necrotic core or macrophages. Conversely, attenuation coefficient less than 6 mm^{-1} was associated with healthy vessels, calcified plaque, or intimal thickening.^{15,16} In a small series of 8 patients with 5-year follow-up after Absorb BVS implantation, OCT demonstrated a low-attenuating layer covering the treated atherosclerotic plaques (Fig. 9). In 1 patient, a TCFA was observed at



Fig. 7. (A–C) Distribution of the endothelial shear stress (ESS) and neointimal thickness (NT) in a scaffolded segment. The dashed lines in the reconstructed segment in (A) and (B) indicate the location of the optical coherence tomographic images in 1 and 2. 1' and 2' show the ESS distribution across the circumference of the vessel wall; the neointimal thickness is portrayed in a semitransparent manner. As shown in i, ii, and iii, the ESS is low in the between-strut areas and high on top of the struts. The neointimal tissue appears to be increased in segments with low ESS and reduced in segments with high ESS values. The blood flow streamlines are shown with velocity color coding (right), whereas the ESS distribution along the baseline luminal surface is portrayed according to the color-coded map (left). The neointimal thickness at 1-year follow-up is shown in a semitransparent fashion. Low ESS and recirculation zones are noted in the interstrut areas, whereas ESS values are high on top of the struts. The ESS distribution seems to affect neointimal formation, because there is increased neointimal tissue in the regions between the struts and minimal neointimal tissue over the struts. (D) Three-dimensional reconstruction of coronary anatomy from the baseline coronary angiographic and OCT data and blood flow simulation, with the local ESS being portrayed in a color-coded map (blue indicates low ESS and red, high ESS). The distribution of the ESS in the scaffolded segment is illustrated at the top right side of the panel, whereas below there is an electron microscopic image acquired 14 days after Absorb BVS implantation in an animal model showing the rugged luminal surface. (D1, D2) Baseline ESS distribution around the circumference of the vessel wall in 2 OCT cross-sectional images. Normal to high ESS noted over a fibroatheroma with a cap thickness of 90 mm in D1, whereas in D2, the ESS is low over the vessel wall and normal over the struts. The asterisk in both images indicates a side branch. At follow-up, the ESS values are normalized in the scaffolded segment and seem to be increased when compared with baseline (E). The magnified view demonstrates the thin layer of neointima that has developed and is portrayed with light gray. High ESS was noted over the fibroatheroma detected at baseline, but the neointimal tissue has sealed the plaque (E1). The low ESS estimated at baseline across the circumference of the vessel wall in D2 is normalized at follow-up (E2). ([A–C] Adapted from Bourantas CV, Papafaklis MI, Kotsia A, et al. Effect of the endothelial shear stress patterns on neointimal proliferation following drug-eluting bioresorbable vascular scaffold implantation: an optical coherence tomography study. *JACC Cardiovasc Interv* 2014;7:315–24; and [D, E] From Bourantas CV, Papafaklis MI, Garcia-Garcia HM, et al. Short- and long-term implications of a bioresorbable vascular scaffold implantation on the local endothelial shear stress patterns. *JACC Cardiovasc Interv* 2014;7:100–1.)

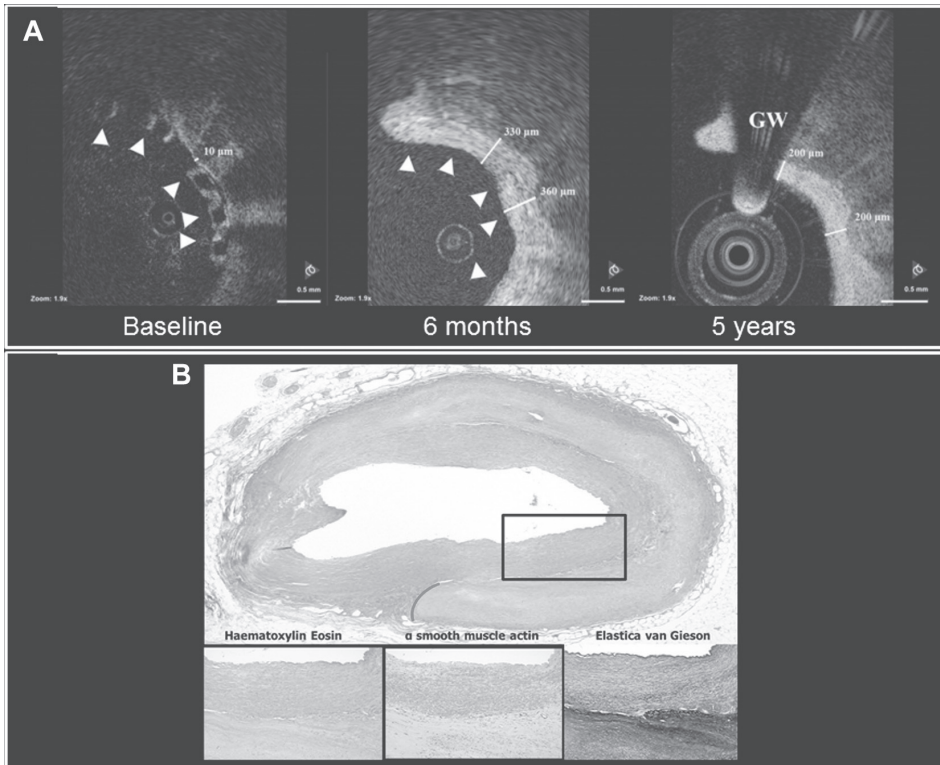


Fig. 8. (A) OCT images acquired from a matched site at baseline, 6 months, and 5 years after Absorb BVS implantation. The amount of tissue overlying the calcific deposition increased from baseline to 6 months because of neointimal response to scaffold implantation. At 5 years, the scaffold struts and neointima have merged into a thick layer of tissue covering the underlying plaque. Arrowheads indicate scaffold struts. GW indicates guidewire artifact. (B) Histologic findings 10 years after Igaki-Tamai bioresorbable scaffold implantation at the left anterior descending coronary artery. The spaces previously occupied by PLLA scaffold struts disappeared. Elastica van Gieson staining shows thick intima. This thick intima consisted of smooth muscle cells and fibrotic tissues without almost no inflammatory cells. ([A] Adapted from Karanasos A, Simsek C, Gnanadesigan M, et al. OCT assessment of the long-term vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffold. *J Am Coll Cardiol* 2014;64(22):2343–56.)

the distal scaffold segment with cap disruption and small thrombus.¹⁶ Qualitatively, comparison with prior follow-up OCT examinations did not demonstrate any evidence for the accumulation of de novo adluminal necrotic core within the scaffolded segments.¹⁶ Conversely, patients treated with metallic DESs seemed to develop neoatherosclerosis within the neointima (see Fig. 9).¹⁶ Given the small sample size, and the observation of a different tissue response in 1 patient, these findings require confirmation in larger studies.

OPTICAL COHERENCE TOMOGRAPHY AND SCAFFOLD DEGRADATION

OCT may not be sensitive enough to assess the extent of polymer degradation. The absence of strut footprints on OCT was at first interpreted as a sign of complete bioresorption; however, it was subsequently shown that OCT cannot differentiate the polylactide of the polymer from the provisional matrix of proteoglycan formed by connective tissue.^{13,17} Thus, polymer may no longer be present in the black core areas

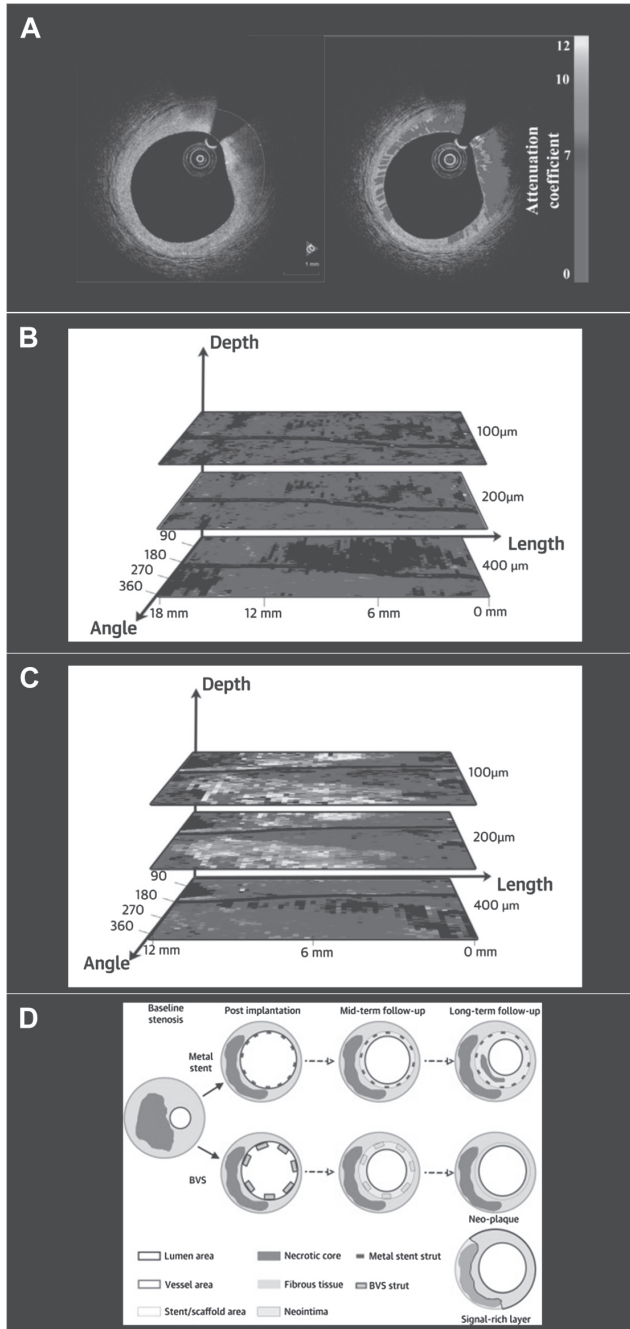


Fig. 9. (A) Example of attenuation analysis. Tissue attenuation properties within adluminal and abluminal contour are measured in all frames and displayed on a color scale (blue represents low-attenuation regions, whereas red and yellow represent high-attenuation regions). For intimal thickness less than 200 μm , as in the 6-o'clock to 7-o'clock position, analysis is not performed because of lack of a sufficient imaging window. (B, C) Spread-out maps demonstrating attenuation coefficient in predefined depths from the vessel surface (100, 200, and 400 μm). In (B) there is a low-attenuating layer of 200 μm separating the underlying plaque (starting at $\sim 400 \mu\text{m}$) from the lumen. In (C), this layer was absent, and attenuating areas were close to the lumen. (D) Potential paradigm shift in the treatment of atherosclerosis with Absorb BVS. After metal stent implantation, struts are preserved and the neointimal area clearly delineated between stent and lumen contour even at long-term follow-up. There is a possible development of neoatherosclerosis within the neointima. Conversely, bioresorbable scaffolds in long-term follow-up of the neointimal boundaries are unclear after degradation (dotted line), and the intima resembles native plaque, defined as neoplague. The signal-rich layer is the layer that separates the underlying plaque components from the lumen. (Adapted from Karanasos A, Simsek C, Gnanadesigan M, et al. OCT assessment of the long-term vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffold. *J Am Coll Cardiol* 2014;64(22):2343–56.)

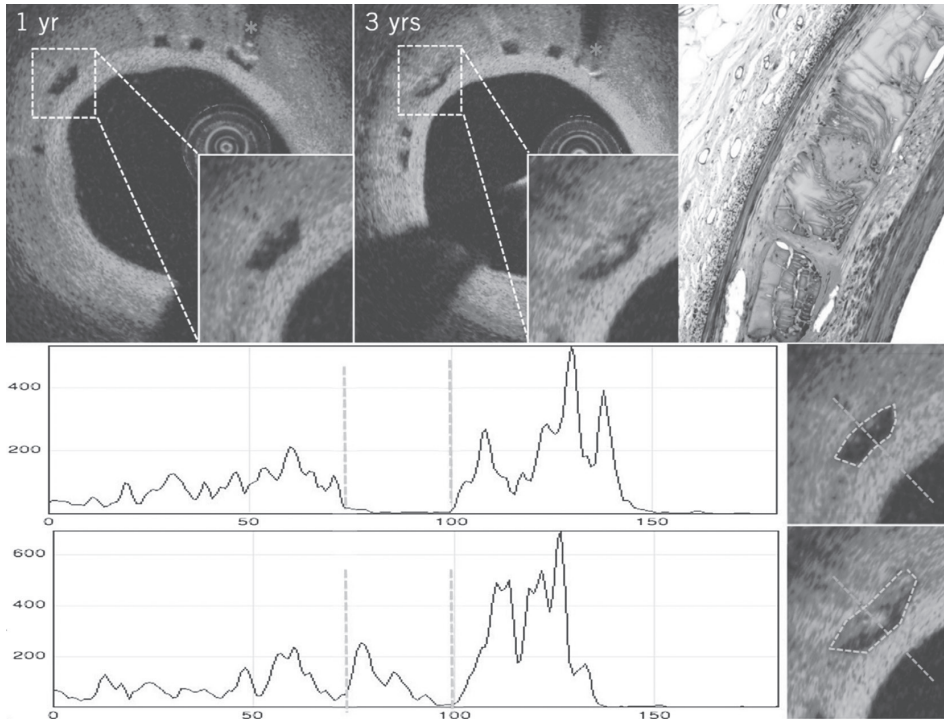


Fig. 10. Comparison of serial OCT and histologic findings in a porcine model. OCT cross sections were matched according to the presence of distal metallic markers (red asterisks) at 1 and 3 years. One of the matched struts next to the marker (asterisk) was analyzed by light reflectivity.²¹ At 3 years, the strut core that was initially black became partially filled by a nucleus exhibiting high light reflectivity. Tracings at the bottom showed graphically the light reflectivity along the scan line of incident light (red). The vertical green dotted lines correspond to the adluminal and abluminal boundaries of the black core either empty or partially occupied by white nucleus. Histologic picture (Movat staining) of porcine coronary artery 36 months after implantation of Absorb scaffold showed provisional matrix (glycoconjugates) in purple, filling the void previously occupied by the polymeric strut. A cellularized (black dots) area with connective tissue (green staining) is located at the center of the strut void and is connected to the subintima. Multilayers of smooth muscle cells are overlying the strut voids. OCT images of the histologic structures in a porcine model are similar to those observed in human. (Adapted from Serruys PW, Onuma Y, Garcia-Garcia HM, et al. Dynamics of vessel wall changes following the implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. *EuroIntervention* 2014;9(11):1271–84.)

seen on OCT. OCT does provide information regarding scaffold integration, that is, when the scaffold struts start to have cellular areas with connective tissue (Fig. 10).^{13,17}

OVERLAPPING SEGMENTS, BIFURCATIONS, AND 2-DIMENSIONAL VERSUS 3-DIMENSIONAL OPTICAL COHERENCE TOMOGRAPHY

Three-dimensional OCT provides much more useful information at bifurcations and

overlapping segments than does 2-dimensional OCT. In overlapping regions, 2-dimensional OCT helps to identify single or stacked struts (inner vs outer) and stacked strut clusters (Fig. 11). Lumen area should be calculated similarly to nonoverlapping segments. Scaffold area at overlapping segments should be calculated by planimetry from the backside (ie, abluminal side) of the black core area of the outermost strut or stacked strut cluster (at the point of all the struts apposing the vessel endothelium) apposing the vessel wall. Where there does not

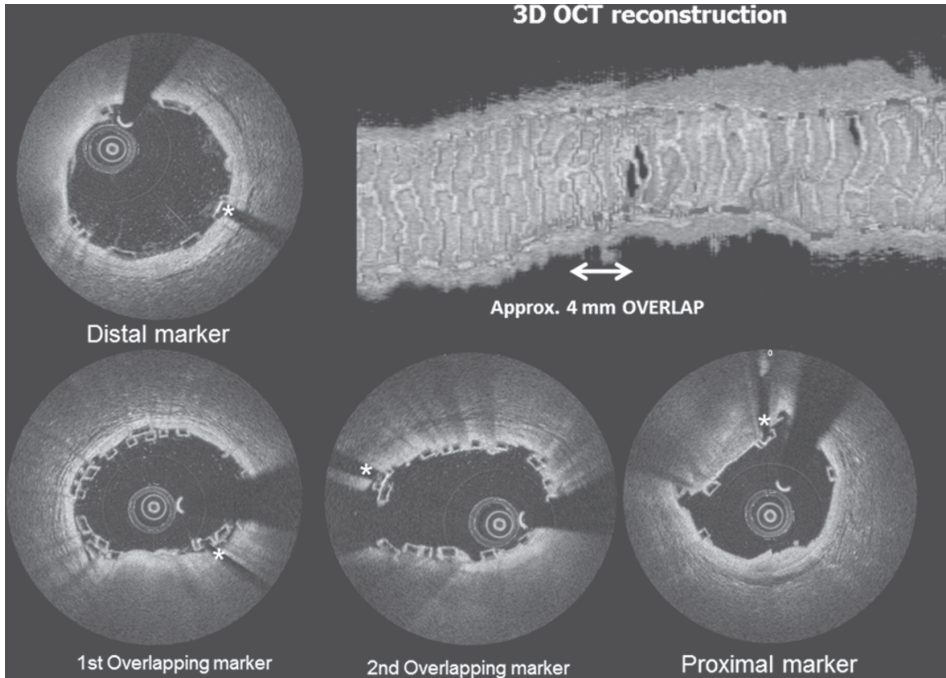


Fig. 11. In the cross-sectional images of optical coherence tomography, the metallic markers can be identified as high-echogenic and high-light intensity structures accompanied with backward shadows (*asterisks*). The 3-dimensional OCT reconstruction helps to understand the overlapping region. (From Garcia-Garcia HM, Serruys PW, Campos CM, et al. Assessing bioresorbable coronary devices: methods and parameters. *JACC Cardiovasc Imaging* 2014;7:1130–48.)

appear to be any apposition of a single strut or stacked strut cluster to the vessel endothelium, the contour of the scaffold area continues to follow the outermost (most abluminal) scaffold strut or stacked strut cluster. Three-dimensional OCT of overlapping regions helps define the type of overlapping, interdigitating struts versus complete overlap.¹⁸

Within bifurcations, 3-dimensional OCT enables a detailed assessment of both the longitudinal and cross-sectional relationship between the jailed side branch orifice and the overhanging struts.¹⁹ Modifications of the shape of the struts after side branch dilatation can be observed with 3-dimensional OCT. Serial 3-dimensional OCT provides information regarding the evolution of the bifurcation anatomy after scaffold implantation, such as the presence of neointimal bridges, which usually appear as an extension of the preexisting

carina. From a quantitative point of view, 3-dimensional OCT reconstruction can be used to assess the changes over time in the number of compartments and their geometric areas (Fig. 12).

AGREEMENT AND REPRODUCIBILITY OF OPTICAL COHERENCE TOMOGRAPHY FOR THE ASSESSMENT OF BIORESORBABLE SCAFFOLDS

OCT has excellent reproducibility for the assessment of incomplete malapposition and struts at side branches.²⁰ OCT is the most accurate technique for measuring scaffold length. There is a moderate agreement with IVUS in the measurement of in-scaffold minimum lumen area assessment at the same coronary segment, and therefore their values should not be used interchangeably.⁵

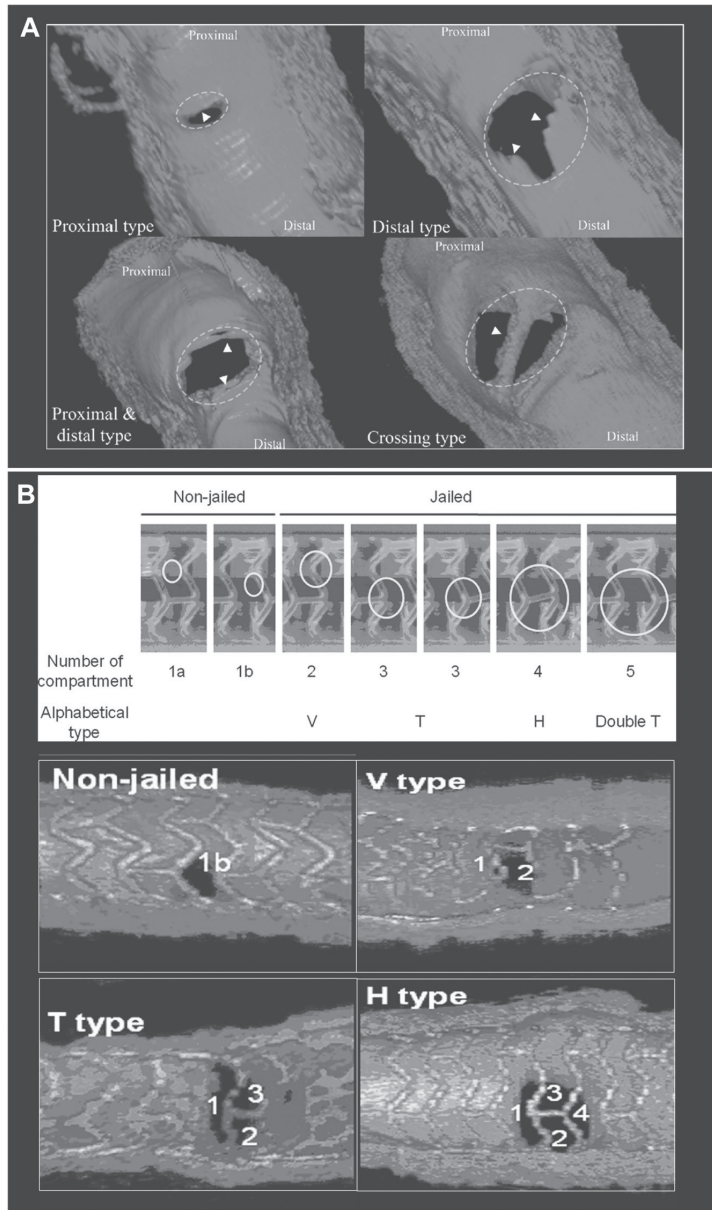


Fig. 12. Three-dimensional OCT side branch classification. (A) Classification based on the relative location with the side-branch ostium. Four different types could be identified: proximal, distal, proximal and distal, or crossing. Dotted lines indicate side-branch ostia; arrowheads indicate tissue bridge. (B) Upper panel shows the bioresorbable vascular scaffold (BVS) with polymeric struts. Yellow circles represent the orifice of the side branch (SB). A nonjailed SB is defined as the complete absence of struts across the orifice (1a) or BVS struts located over the orifice without compartmentalization (1b). Lower panel shows jailed SB orifices are separated into various compartments. Types of SB jailing are expressed in alphabetical letters given according to resemblance of the strut structure across the orifice. ([A] From Karanasos A, Simsek C, Gnanadesigan M, et al. OCT assessment of the long-term vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffold. *J Am Coll Cardiol* 2014;64(22):2343–56; and [B] Adapted from Okamura T, Onuma Y, Garcia-Garcia HM, et al. 3-Dimensional optical coherence tomography assessment of jailed side branches by bioresorbable vascular scaffolds: a proposal for classification. *JACC Cardiovasc Interv* 2010;3:836–44.)

SUMMARY

OCT is a valuable tool for BRS assessment because of its high resolution. It provides detailed and reproducible information regarding the interaction between the device and lumen surface. A dedicated methodology for OCT analysis, different from that for metallic stents, is required for the short- and long-term assessment of BRS.

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Chapter 5.4

Differential impact of five coronary devices on plaque size: Insights from the ABSORB and SPIRIT trials.

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ABSTRACT

Background: Coronary plaque size modification, by either local (device) or systemic treatments, has been the target for many years.

Methods: From ABSORB Cohort A (Absorb BVS 1.0), ABSORB Cohort B (Absorb BVS 1.1), SPIRIT FIRST (Multi-Link Vision vs. Xience V) & SPIRIT II (Xience V vs. Taxus), we calculated the total plaque area (vessel minus lumen area – thus it comprises both compartments – the plaque behind struts and the neointima.) changes by IVUS.

Results: A total of 313 patients were included. Comparison-at-6-month follow-up: All devices induced an increase in the total plaque area. The largest increase occurred with Vision and Taxus stents as compared to other devices [Absorb BVS (1.0 and 1.1) and Xience V], ($p = 0.0002$). Comparison-at-2-year follow-up: Absorb BVS 1.1 had a larger increase from post procedure in total plaque compared to Absorb BVS 1.0, Xience V and Taxus ($p = 0.0499$). However, in Absorb BVS 1.1 total plaque showed a reduction of 2.2% from 1 to 3 years. Specifically, the total plaque in the sequential cohorts of Absorb BVS 1.1 increased 16.2% from baseline to 2 years (Cohort B1) while at 3 years this increase is only 5% compared to baseline (Cohort B2).

Conclusions: Local devices affect coronary plaque size differently and it depends on the platform (metallic vs. polymeric) and on whether it is a bare – or drug eluting stent. Coronary scaffolds appear to be a promising alternative to metallic stents since they allow plaque regression at long-term follow-up.

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1. Introduction

Coronary atherosclerosis is a worldwide pandemic disease. Treatment options vary according to the clinical presentation. [1] Broadly speaking, most of patients are medically treated, and in addition some also require percutaneous coronary intervention (PCI) or surgical treatment. PCI offers different options: bare metal or drug eluting stents and more recently everolimus eluting bioresorbable scaffolds. Medical and stenting treatments affect uniquely coronary plaque size and its composition (IBIS 2 and APPROACH restenosis) [2,3]. Commonly, patients receive concomitantly medical treatment and PCI and therefore the coronary vessel wall response will vary in relation to the interaction of both treatments. At follow-up, implants will be surrounded by plaque, behind (peri-stent) the struts and endoluminally (neointima). These two compartments are biologically active and will be influenced differently by the presence of a complex interaction formed by the platform (metallic/polymeric) + polymer + drug. For example, stents/scaffolds eluting everolimus will similarly affect plaque size (i.e. by clearing

macrophages and inhibiting formation of neointima), but the net effect will be dissimilar since the platforms are different (metallic vs. polymeric). Thus, the effects on plaque size of this complex interplay (eluted drug/platform) can only be explored by measuring serially the size of the coronary plaque-media and neointima compartment.

The objective of this study is therefore to assess serially the changes in plaque size using IVUS by evaluating five different stent types (Absorb bioresorbable everolimus eluting scaffold – Absorb BVS 1.0 and 1.1; everolimus eluting metallic stent – Xience V –; bare metal stent – Vision and paclitaxel-eluting metallic stent – Taxus)

2. Methods

2.1. Study population

For the present analysis, we screened all the patients from ABSORB Cohort A and Cohort B trials and from the SPIRIT First [4] and SPIRIT II trials [5] and we selected only the patients with available IVUS data post-stent/scaffold implantation and truly serial imaging at different time points at follow-up. In total, there are 5 groups according to the implanted device (Absorb BVS 1.0, Absorb BVS 1.1, Xience V, Taxus and Vision). The design of the ABSORB studies has been already described. [6,7] Briefly, in the ABSORB Cohort A ($n = 30$) and ABSORB Cohort B trials ($n = 101$), patients with a diagnosis of stable or unstable angina or silent ischemia, were enrolled. In Cohort A, all treated lesions were single and de novo in a native coronary artery of 3.0 mm diameter, shorter than 8 mm for the 12 mm scaffold and shorter than 14 mm for the 18 mm scaffold, with a diameter stenosis greater

^{*} All authors declare no conflicts of interest relevant to the content of this paper.

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than 50% and less than 100%, and with a thrombolysis in myocardial infarction (TIMI) flow grade more than 1. In Cohort B, similar lesion types were treated by implantation of Absorb BVS revision 1.1 (3.0 × 18 mm).

The SPIRIT FIRST and SPIRIT II trials were planned to assess the safety and efficacy of the everolimus eluting stent (Xience V) in patients with coronary artery disease. Both trials were prospective, multicenter, single-blinded, randomized-controlled clinical investigations and compared Xience V with bare metal stent (Vision – SPIRIT FIRST trial) or paclitaxel-eluting stent (Taxus – SPIRIT II trial). These trials were approved by ethics committee at each participating institution and each patient gave written informed consent before inclusion.

2.2. Study devices

The Absorb BVS (Abbott Vascular, Santa Clara, California, USA) has an amorphous poly-DL-lactide (PDLLA) coating that contains and controls the release of an anti-proliferative drug everolimus. The scaffold body is made of semi-crystalline poly-L-lactide (PLLA). PLLA is completely degraded via hydrolysis and bioresorbed via the Krebs cycle [6,7]. The scaffold has struts with an approximate thickness of 150 µm.

Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, California, USA) is a cobalt chromium alloy device. The platform consists of serpentine rings connected by links fabricated from a single piece, with a strut thickness of 81 µm; the polymer and drug coating add a combined thickness of 7 µm.

Taxus paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts, USA) is a stainless stent, with a strut thickness of 132 µm; the polymer and drug coating add a combined thickness of 16 µm.

Lesions were treated with routine interventional techniques that included mandatory pre-dilatation using a balloon shorter than the study device and 0.5 mm less in diameter. The Absorb BVS was implanted at a pressure not exceeding the rated burst pressure (16 atm). Post-dilatation with a balloon shorter than the implanted device was allowed at the operator's discretion, as was bailout treatment.

2.3. Intravascular ultrasound analysis

Post-procedure treated vessel segment was examined with phased array or mechanical intravascular ultrasound (Eagle-eye Volcano, Rancho Cordova, California; Atlantis, Boston Scientific, Natick, Massachusetts), using automated pullback at 0.5 mm per second after administration of 0.2 mg intracoronary nitroglycerin. IVUS analyses were performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands). A computer-based contour detection software was used for automated 2D reconstruction of the treated segment (CURAD Vessel Analysis, Curad B.V. Wijk bij Duurstede, The Netherlands). The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm [8].

In all treated vessel segments, we assess in each analysed frame (every 1 mm), lumen, stent/scaffold, vessel and plaque areas. Total plaque area is defined as the difference of vessel minus lumen area. This includes then the stent/scaffold components (metal or polymer). Plaque behind the stent is defined as the difference of the vessel minus stent area and neointima area as the difference of stent area and lumen area. These variables were available at all time points and for all different study devices except for Absorb BVS 1.0 at 2 years where only total plaque area was available since plaque behind stent was not determined due to the absence of struts (scaffold was resorbed).

2.4. Statistical analysis

There are 2 main comparisons, one at 6 months (*comparison-at-6-month*) where the five different devices were imaged and the other one at 2 years (*comparison-at-2-year*) where all devices (except Vision) were imaged at baseline and 2 years.

Categorical variables are presented as counts and percentages and compared by means of the Fisher's exact test. Continuous variables are presented as means ± standard deviation (SD). The distribution of the variables used has been tested as normal or not normal distribution by Kolmogorov-Smirnov test. Comparison between two groups has been made by Wilcoxon signed ranked test or Kruskal Wallis test when there are more than 2 groups. A p-value < 0.05 was considered as significant.

3. Results

3.1. Baseline clinical and angiographic characteristics (Table 1)

We studied 313 patients (313 lesions) enrolled in ABSORB Cohort A and B and in SPIRIT FIRST and II trials. Particularly, patients with available post-stent implantation IVUS analysis and at different follow-up time points were included. In Table 1, the baseline characteristics are reported. The range of mean age is from 62 to 64.2 years and most of patients were male. There were many more patients with previous MI in the Xience V group ($p = 0.0003$) and more patients with unstable angina in the Taxus group ($p = 0.012$) of the SPIRIT II trial compared to the other groups. The rest of the baseline and demographic characteristics of the groups were comparable.

In Table 1 on the supplement online, the quantitative IVUS and coronary angiography findings are described. Since the vessel and lumen areas were significantly different post-PCI, although no the plaque

Table 1
Clinical baseline characteristics.

	Absorb A		Absorb B		Spirit first		Spirit II		p-Value
	BVS 1.0 (n = 30)	BVS 1.1 (n = 45)	BVS 1.1 (n = 55)	XIENCE-V (n = 27)	Multilink vision (n = 29)	XIENCE-V (n = 94)	TAXUS (n = 33)		
Age, mean ± SD	62.46 ± 8.98	64.60 ± 9.47	60.50 ± 8.10	64.21 ± 9.56	61.37 ± 9.31	62.01 ± 10.85	62.22 ± 8.86	0.427	
Men, % (n)	60.0 (18)	73.3 (33)	70.9 (39)	70.4 (19)	75.9 (22)	72.3 (68)	78.8 (26)	0.782	
Hypertension requiring medication, % (n)	60.0 (18)	60.0 (27)	63.0 (34)	70.4 (19)	41.4 (12)	63.8 (60)	51.5 (17)	0.307	
Hyperlipidaemia requiring medication, % (n)	65.5 (19)	93.3 (42)	67.3 (37)	70.4 (19)	75.9 (22)	74.4 (67)	75.8 (25)	0.073	
Smokers, % (n)	20.0 (6)	11.4 (5)	21.8 (12)	29.6 (8)	31.0 (9)	33.0 (31)	31.3 (10)	0.155	
Diabetes, % (n)	3.3 (1)	13.3 (6)	20.0 (11)	11.1 (3)	10.3 (3)	25.5 (24)	25.0 (8)	0.064	
Previous cardiac intervention, % (n)	20.0 (6)	28.9 (13)	16.4 (9)	18.5 (5)	6.9 (2)	19.1 (18)	9.1 (3)	0.230	
Previous MI, % (n)	10.0 (3)	35.6 (16)	16.7 (9)	22.2 (6)	13.8 (4)	41.9 (39)	15.2 (5)	0.0003	
Stable angina, % (n)	70.0 (21)	73.3 (33)	63.6 (35)	77.8 (21)	79.3 (23)	59.6 (56)	51.5 (17)	0.118	
Unstable angina, % (n)	26.7 (8)	13.3 (6)	16.4 (9)	18.5 (5)	13.8 (4)	28.7 (27)	45.5 (15)	0.012	
Silent ischaemia, % (n)	3.3 (1)	0 (0)	7.3 (4)	3.7 (1)	6.9 (2)	3.2 (3)	0 (0)	0.407	
Target vessel, % (n)									
Left anterior descending	46.7 (14)	37.8 (17)	47.3 (26)	48.1 (13)	44.8 (13)	48.9 (46)	63.6 (21)	0.506	
Left circumflex	30.0 (9)	26.7 (12)	21.8 (12)	22.2 (6)	20.7 (6)	25.5 (24)	9.1 (3)	0.511	
Right coronary artery	23.3 (7)	36.6 (16)	30.9 (17)	29.6 (8)	34.5 (10)	25.5 (24)	27.3 (9)	0.866	

PCI = percutaneous coronary interventions; AMI = acute myocardial infarction.

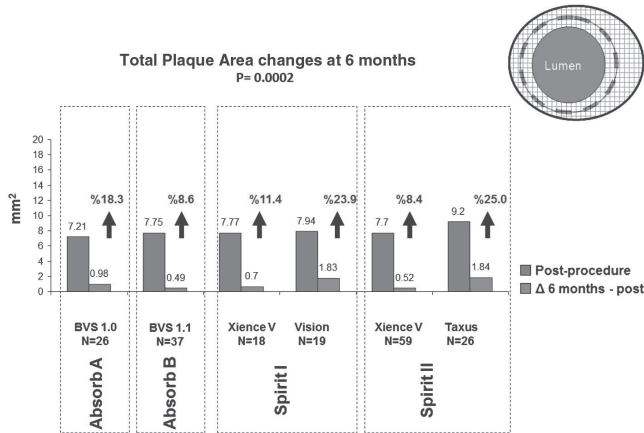


Fig. 1. Change from baseline to 6 months in total plaque (B) areas. In green bars the post-procedure areas in mm². In red bars, the absolute difference (also in mm²) between baseline and 6 months. The black arrows indicate the direction of the change and also the relative difference (%) is given.

areas, we decided to make most of the comparisons based on the relative changes.

3.2. Intravascular Total Plaque area changes – Figs. 1 and 2 (supplement online: Table 1)

The total plaque comprises both compartments, the plaque behind struts and the neointima.

3.2.1. Comparison-at-6-month

All devices induced an increase in the total plaque area. The largest increase occurred with Vision and Taxus stents as compared to other

[Absorb BVS (1.0 and 1.1) and Xience V], (p = 0.0002). Comparison-at-2-year: Absorb BVS 1.1 had a larger increase from post procedure in total plaque compared to Absorb BVS 1.0, Xience V and Taxus (p = 0.0499). This was due to a shrinkage in total plaque between 6 months and 2 years in the Absorb BVS 1.0, Xience V and Taxus vs. a further increase in total plaque in Absorb BVS 1.1 (p < 0.001 for the change between 6 months and 2 years). Importantly, Absorb BVS 1.1 total plaque showed a reduction of 2.2% from 1 to 3 years. Also interesting to note is that the total plaque in the sequential cohorts of Absorb BVS 1.1 increased by 16.2% from baseline to 2 years (cohort B1) and at 3 years this increase is of only 5% compared to baseline (cohort B2; supplement online: Fig. 3).

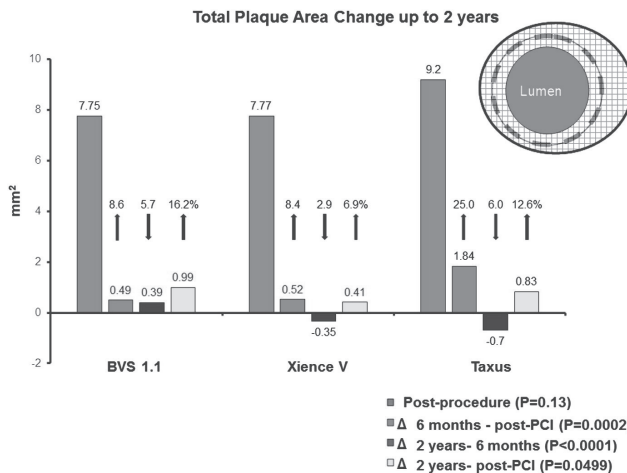


Fig. 2. Serial changes in total plaque (C) areas up to 2 years. In green bars, the post-procedure areas in mm². In red bars, the absolute difference (also in mm²) between 6 months and post-procedure; in blue bars, the absolute difference (mm²) between 2 years and 6 months and; in yellow bars, the absolute difference (mm²) between 2 years and post-procedure. The black arrows indicate the direction of the change and also the relative difference (%) is given.

3.3. Intravascular Ultrasound Vessel area changes (remodelling) – (supplement online: Fig. 1 and Table 1)

Comparison-at-6-month: All devices but one (Vision) induced a relative increase in the vessel area (i.e. expansive remodelling). Thus Vision was associated with restrictive remodelling ($p = 0.0018$). **Comparison-at-2-year:** Absorb BVS 1.1, Xience V and Taxus showed an expansive remodelling while Absorb BVS 1.0 showed the opposite ($p = 0.0006$). Interestingly, when looking at the changes between 6 months and 2 years, all devices except the Absorb BVS 1.1 were associated with restrictive remodelling. Thus, DES (with the exception of BVS 1.1) present at 6 months important expansive remodelling followed by mild restrictive remodelling from 6 months to 2 years. The Vision showed at all time points restrictive remodelling. In contrast, Absorb BVS 1.1 showed at all time points expansive remodelling.

3.4. Intravascular Ultrasound Plaque behind struts area changes (supplement online: Table 1, Fig. 2A)

All the changes observed in the vessel area were related to changes in the plaque behind the struts in the same direction. **Comparison-at-6-month:** All devices but one (Vision) induced increase in the plaque area behind the struts. Thus Vision was associated with a decrease in plaque size ($p = 0.0009$). **Comparison-at-2-year:** Absorb BVS 1.1 had a larger increase in plaque behind the struts compared to Xience V and Taxus ($p = 0.0007$). This was due to a shrinkage in total plaque between 6 months and 2 years in the Xience V and Taxus vs. a further increase in total plaque in Absorb BVS 1.1 ($p < 0.001$ for the change between 6 months and 2 years).

3.5. Intravascular Ultrasound Neointimal Area (supplement online: Table 1, Fig. 2B)

Comparison-at-6-month: the neointimal area was significantly suppressed in the drug eluting devices irrespective of the platform (i.e. metallic vs. polymeric), as detected by IVUS and compared to bare metal stent (i.e. Vision), ($p < 0.0001$).

When relative changes within the Absorb BVS 1.1, Xience and Taxus groups were compared, the Taxus group showed compaction of the neointima between 6 months and 2 years (**Comparison-at-2-year**), as demonstrated by a mild decrease in neointimal area of 4.5% but without reaching statistical significance.

4. Discussion

The main findings of this report are: i. at six months, the vessel wall experienced a change in its size that goes from a 2.4% shrinkage (i.e. restrictive remodelling in Vision) to a maximal 9.0% increase in size (i.e. expansive remodelling in DES). After the first six months, all devices (except Absorb BVS 1.1) had a decrease in their vessel wall size (i.e. restrictive remodelling). Thus, bare metal stents had a distinctive pattern of remodelling which is restrictive at all time points. Within the metallic DES, after the first increase, all present a regression in their vessel wall size. While in the polymeric (bioresorbable scaffolds) DES, these changes are associated with the rate of absorption (e.g. Absorb BVS 1.0 has a faster bioresorption rate and therefore it behaves like the other metallic DES; in contrast the Absorb BVS 1.1 has a slower bioresorption rate and the vessel wall continues to expand for a longer period). ii. Changes in the vessel area are associated in magnitude and direction to the changes in the plaque behind the struts area. iii. All devices showed first an increase in total plaque size and thereafter a reduction; all devices, except for Absorb BVS 1.0, had at follow-up a larger total plaque compared to post-procedure.

4.1. Remodelling changes in the vessel wall after stenting or scaffolding

In pathological studies, the differential effect of the metallic intracoronary devices (either bare or drug eluting stents) on the vessel area has been characterised [9]. The Taxus had a significantly larger vessel area than bare metal stents (Express) and a limus eluting stent (Cypher). This increase in vessel area after stenting has been also described in previous IVUS studies [10]. In the report by Aoki J et al., Taxus had a larger increase in vessel area compared to the BMS (NIR conformer stent) up to 6 months. Thereafter, there was a decrease in both stents between 6 months and 2 years. These results are in line with our findings: at six months, Taxus showed a 9% increase in vessel area which was much larger to that of Absorb BVS, Xience V or Vision.

In contrast, the paclitaxel drug-eluting absorbable metal scaffold (DREAMS) showed a vessel area reduction at 6 months and even more between 6 months and 12 months [11]. These observations highlight the fact that the vessel wall response varies according to the stent design and that it is almost impossible to discern at this point whether it is the drug, the polymer or the constituents of the back bone (metal vs. polymer) which play the most determinant role in triggering these changes.

4.2. Plaque size changes in the vessel wall

All the changes observed in the vessel area are mostly related to changes in the same direction of the plaque area changes. Ultimately, the main goal of any intervention is to modify the natural history of coronary atherosclerosis disease, coronary metal devices achieved that at a short term (redistributing the plaque and scaffolding the vessel wall) but failed to achieve that in a long term since they remain in the vessel wall preventing the restoration of the architecture (i.e. angulation and curvature of the vessel) and physiology (i.e. cyclic strain and shear stress) of the coronaries.

In addition, permanent devices hinder any further reduction of the size of the plaque by lastingly staying in the vessel wall. On the contrary, bioresorbable scaffolds are designed to fulfil the short-term needs (scaffolding the coronary vessel wall while inhibiting effectively neointima formation by eluting everolimus) and also to prevent late complications such as stent thrombosis by their disappearance. Everolimus is a mTOR inhibitor and its systemic application decreases atherosclerotic plaque formation in both apolipoprotein E (ApoE^{-/-}) and low-density lipoprotein-receptor (LDL-R^{-/-}) knockout mice [12]. Moreover, everolimus has been associated with clearance of the macrophages via autophagia and thereby making those plaques less inflamed [13]. These additional effects may further modify the native plaque where the device was placed.

The full absorption of the Absorb BVS brings back the response to cyclic strain and shear stress with all the positive effects related to them. Also important, the coronary plaque may respond again to pharmacological treatments. Though, the pharmacological treatment, even using the best of the options, in the study using intravenous recombinant ApoA-I Milano/phospholipid complexes (ETC.-216), there was, albeit significant, a reduction in percent atheroma volume of 1.06% [14] and in the SATURN study patients treated with rosuvastatin showed also only a minor reduction in the percent atheroma volume by 1.22% after 2 years of treatment [15], the combination of a temporary coronary scaffold (i.e. BVS) plus mTOR inhibitors (i.e. everolimus) as a first strategy, followed by an intensive statin treatment appears the best approach so far.

4.3. Limitations

"This is a post hoc analysis and therefore there are some differences at baseline (post-PCI) in patient characteristics. In the BVS 1.0 group, patients had lower risk for conventional pro-atherogenic factors (e.g., DM, prior MI). This is due to the fact that the BVS 1.0 was used in the first-in-man ABSORB Cohort A trial. Likewise, a lower risk profile was also to be observed in Xience V and Vision groups included in the SPIRIT First trial

(Table 1). IVUS had also distinct baseline characteristics among groups. This is the reason why the comparisons were made based on relative differences. IVUS is often not performed pre-TLR so that changes described here are based on the patients who did not have events.”

5. Conclusions

Coronary plaque size is affected differently by local devices and this modification depends on the platform (metallic vs. polymeric) and on whether it is a bare — or drug eluting stent. Coronary scaffolds appear to be a promising alternative to metallic stents since they allow plaque regression.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2014.06.026>.

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Chapter 5.5

Implications of a bioresorbable vascular scaffold implantation on vessel wall strain of the treated and the adjacent segments

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Abstract *Background* Metallic stents change permanently the mechanical properties of the vessel wall. However little is known about the implications of bioresorbable vascular scaffolds (BVS) on the vessel wall strain. *Methods* Patients ($n = 53$) implanted with an Absorb BVS that had palpographic evaluation at any time point [before device implantation, immediate after treatment, at short-term (6–12 months) or mid-term follow-up (24–36 months)] were included in the current analysis. The palpographic data were used to estimate the mean of the maximum strain values and the obtained measurements were classified using the Rotterdam classification (ROC) score and expressed as ROC/mm. *Results* Scaffold implantation led to a significant decrease of the vessel wall strain in the treated segment [0.35 (0.20, 0.38) vs. 0.19 (0.09, 0.29); $P = 0.005$] but it did not affect the proximal and distal edge. In patients who had serial palpographic examination the vessel wall strain continued to decrease in the scaffolded segment at short-term [0.20 (0.12, 0.29) vs. 0.14 (0.08, 0.20); $P = 0.048$] and mid-term follow-up [0.20

(0.12, 0.29) vs. 0.15 (0.10, 0.19), $P = 0.024$]. No changes were noted with time in the mechanical properties of the vessel wall at the proximal and distal edge. *Conclusions* Absorb BVS implantation results in a permanent alteration of the mechanical properties of the vessel wall in the treated segment. Long term follow-up data are needed in order to examine the clinical implications of these findings.

Keywords Bioresorbable vascular scaffold · Palpography · Vessel wall strain

Introduction

Vessel wall mechanical behavior appears to be associated with the compositional characteristics of the plaque and predict future cardiovascular events [1–4]. Several studies have shown that pharmaceutical or an interventional treatment can influence the mechanical properties of the vessel wall by altering its constituents [5–9]. Following an endoluminal device implantation (i.e., a metallic stent or a bioresorbable scaffold) the local vessel wall strain of the implanted segment is reduced and this has been attributed to the increased stiffness of the deployed device [5, 6, 9].

Recently we have reported the results of the palpographic analysis performed in segments implanted with the updated revision of the Absorb bioresorbable vascular scaffold (BVS) 1.1 [6]. We found that the vessel wall strain is reduced in the scaffolded segments immediately after device deployment but there are no further changes in the mechanical properties of the vessel wall between post-scaffold implantation and at short-term follow-up (i.e., at 6–12 months). The present analysis aims to investigate the mid-term implications (i.e., at 24–36 months) of the Absorb BVS 1.1 on the vessel wall strain.

On behalf of the Absorb Cohort B Investigators.

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Methods

Included patients and study design

The ABSORB Cohort B trial (A Clinical Evaluation of the Bioabsorbable Everolimus Eluting Coronary Stent System the Treatment of Patients with de Novo Native Coronary Artery Lesions) was a prospective multicenter single-arm study designed to investigate the safety and efficacy of the Absorb BVS 1.1 (Abbott Vascular, Santa Clara, CA, USA) [10]. One hundred one patients were included in this study and were divided in two groups (B1 and B2). The first group had invasive imaging evaluation [i.e., coronary angiography, grayscale intravascular ultrasound (IVUS), IVUS virtual histology, palpographic and optical coherence tomographic imaging] at baseline, 6 months and 2 years follow-up; while the second group had the abovementioned invasive tests at baseline, 1 year and at 3 years follow-up. Optical coherence tomographic (OCT) examination was optional and was not performed in all the studied patients. The current analysis included only the patients who had a palpographic assessment at least at one time point. The Absorb Cohort B study was sponsored and financially supported by Abbott Vascular.

The Absorb BVS 1.1 used in the ABSORB Cohort B trial, is a fully bioresorbable device with dimensions 3.0×18 mm. The composition of the device consists of poly-L-lactide (PLLA) that is covered by a thin layer of an amorphous matrix of poly-D,L-lactide (PDLLA) which contains and controls the release of the anti-proliferative drug everolimus (concentration: $100 \mu\text{g}/\text{cm}^2$). The Absorb BVS 1.1 has an in-phase zigzag hoops linked with bridges design that provides the device increased radial strength and eliminates the risk of late scaffold recoil, while the polymer of this revision has been processed in such a way so as to have a delayed degradation (by approximately 18 months comparing to the 1st revision).

The palpographic sub-study of the ABSORB Cohort B trial had pre-specified hypotheses. In particular the investigators expected that the delayed degradation in Absorb BVS 1.1 would result: either (1) in a delayed restoration of the normal, pre-scaffold implantation, strain, or (2) it would allow the built up of neointima tissue that would permanently alter the mechanical properties of the vessel wall.

IVUS acquisition and analysis

Intravascular ultrasound imaging was performed in the treated artery using an Eagle Eye 20 MHz imaging catheter (acquisition frame rate 30 frames/s, Volcano Corp, Rancho Cordova, CA, USA) that was withdrawn with the use of an automated pull-back device at a speed of 0.5 mm/s. During

IVUS examination the electrocardiogram and the aortic pressure were recorded.

The radiofrequency IVUS imaging data were acquired using a custom design workstation and were transferred to an independent clinical research organization (Cardialysis, Rotterdam, the Netherlands) for offline analysis. For each studied artery the IVUS images portraying the 5 mm proximal, the scaffolded, and the 5 mm distal segment were analyzed. The local strain was estimated from the radiofrequency IVUS data using cross correlation analysis according to a previously described methodology [11]. The measured strain values were displayed in spread-out vessel plots using a color coded map with the blue indicating low strain values and the red/yellow a high strain (range 0–2 %) [11].

The strain values were classified according to the Rotterdam classification (ROC) score to four classes (ROC I: 0–0.5 %, ROC II: 0.6–<0.9 %, ROC III: 0.9–<1.2 % and ROC IV: >1.2 %). A cross section was considered to have high strain when the measured strain was classified as ROC III–IV in an arc of $>12^\circ$. For each cross section the highest strain value was recorded and considered as the strain of this section. The mean of the maximum strain values measured in each segment was determined and used to characterize the strain of the segment. Results are presented as ROC/mm (Fig. 1).

Statistics

Continuous variables depending on their distribution are presented as mean \pm standard deviation or as median with 25th and 75th percentiles, as indicated in the tables. Categorical variables are presented as absolute values and percentages. Because of the small number of patients who had palpographic evaluation at different time points we merged the data from Cohort B1 and B2 and present our results at 4 time points: at baseline pre-scaffold implantation, immediately after scaffold implantation, at short-term (6–12 months), and at mid-term follow-up (24–36 months). Comparison between the two cohorts was done by *t* test and Chi square test, or Fisher's exact test when Cochran's rule is not met.

Changes in the strain values between two different time points were evaluated by means of paired Wilcoxon signed rank test. A *P* value <0.05 (two-tailed) was considered statistically significant. Data analysis was performed using the SAS statistical computer package (SAS 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Studied population

Fifty-three from the 101 patients who were enrolled in the Absorb Cohort B study had palpographic evaluation at

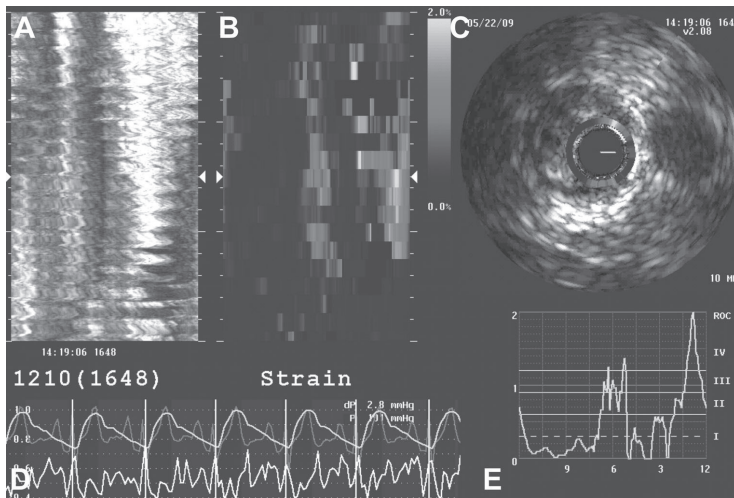


Fig. 1 Snapshot showing the palpographic evaluation of a lesion before scaffold implantation. Panel A shows a longitudinal IVUS cross-section of the studied segment while panel B a spread out plot of the measured vessel wall strain (the blue color indicates low strain and the red/yellow high strain values). An IVUS cross section with the estimated strain at the superficial plaque shown in color coding is

portrayed in panel C. Panel D shows the electrocardiogram, the measured strain, and the blood pressure changes during the cardiac cycle throughout the pull-back of the catheter, whereas panel E displays the strain values measured in the cross-section shown in panel C. High strain was noted at 1 and 6 o'clock

least at one time point and included in this analysis. The baseline characteristics of the studied population are shown in Table 1. The patients that were enrolled in the Absorb Cohort B1 group did not smoke and were more likely to suffer from hypercholesterolemia and be admitted with stable angina symptoms comparing to the subjects included in the Absorb Cohort B2 group but otherwise there were not significant differences in the baseline demographics and angiographic characteristics between the two groups.

Palpographic evaluation

Only 14 patients had palpographic evaluation before scaffold implantation, 44 patients had this investigation immediate after device deployment, 41 at short-term, and 36 at mid-term follow-up. Twenty patients had serial palpographic examination at the three time points (i.e., at baseline immediate after scaffold deployment, at short-term and mid-term follow-up).

For the entire study population ($n = 53$ patients) the strain values did not change immediate after scaffold deployment at the proximal and distal edge (Table 2). On the other hand in the treated segment the strain decreased significantly after device deployment. The vessel wall strain estimated at the proximal edge at the two follow-up time points was not different from the vessel wall strain before scaffold

deployment ($P = 0.814$ for the short-term follow-up and $P = 0.162$ for the mid-term follow-up). However, when we compared the follow-up values at the proximal edge with the strain measured immediately after scaffold deployment we found statistical significant differences (Table 2). At the distal edge the strain values did not change with time.

The strain values in the scaffolded segment at the two follow-up time points were considerably lower comparing to baseline before device implantation ($P = 0.002$ for the short-term and $P = 0.001$ for the mid-term follow-up) but they were not different from these measured immediately after scaffold deployment.

When we included in our analysis only the segments ($n = 20$ patients) that had serial palpographic examination (i.e., at baseline immediate after device deployment, at short-term, and at mid-term follow-up) we found that the strain of the proximal edge and distal edge did not change with time (Table 3; Fig. 2). On the other hand in the scaffolded segment the strain values were significantly decreased at short- and mid-term follow-up comparing to baseline.

Discussion

In this study we examined for the first time the implications of the second revision Absorb BVS on the mechanical

Table 1 Baseline demographics, angiographic characteristics and medications of the studied population

Patients' demographics	Absorb Cohort B N = 53	Absorb Cohort B1 N = 20	Absorb Cohort B2 N = 33	P
Age (years)	61.28 ± 8.41	63.84 ± 8.87	59.72 ± 7.85	0.096
Male	71.7 % (38/53)	75.0 % (15/20)	69.7 % (23/33)	0.678
Hypertension	67.3 % (35/52)	60.0 % (12/20)	71.9 % (23/32)	0.374
Hypercholesterolemia	83.0 % (44/53)	100.0 % (20/20)	72.7 % (24/33)	0.010
Diabetes	18.9 % (10/53)	15.0 % (3/20)	21.2 % (7/33)	0.725
Current smoking	15.1 % (8/53)	0.0 % (0/20)	24.2 % (8/33)	0.019
Prior PCI	22.6 % (12/53)	25.0 % (5/20)	21.2 % (7/33)	0.748
Stable angina	73.6 % (39/53)	90.0 % (18/20)	63.6 % (21/33)	0.035
Unstable angina	9.4 % (5/53)	5.0 % (1/20)	12.1 % (4/33)	0.639
Silent ischemia	1.9 % (1/53)	0.0 % (0/20)	3.0 % (1/33)	1.000
<i>Treated vessel</i>				
Left anterior descending	47.2 % (25/53)	45.0 % (9/20)	48.5 % (16/33)	0.805
Left circumflex	24.5 % (13/53)	25.0 % (5/20)	24.2 % (8/33)	1.000
Right coronary artery	28.3 % (15/53)	30.0 % (6/20)	27.3 % (9/33)	0.831
<i>QCA analysis pre-treatment</i>				
RVD (mm)	2.61 ± 0.34	2.60 ± 0.44	2.61 ± 0.28	0.949
MLD (mm)	1.04 ± 0.27	0.99 ± 0.31	1.07 ± 0.23	0.365
Diameter stenosis (%)	59.80 ± 9.96	61.25 ± 12.74	58.94 ± 7.98	0.482
<i>Medications</i>				
β-blockers	73.6 % (39)	65.0 % (13)	78.8 % (26)	0.270
RAAS inhibitors	69.8 % (37)	65.0 % (13)	72.7 % (24)	0.443
Statins	94.3 % (50)	100.0 % (20)	90.9 % (30)	0.165

PCI percutaneous coronary intervention, QCA quantitative coronary angiography, RVD reference vessel diameter, MLD minimum luminal diameter, RAAS renin angiotensin aldosterone system

Table 2 Strain values at the proximal edge, the scaffolded segment and the distal edge before device implantation, immediately after device deployment, at short-term follow-up and at mid-term follow-up

	Pre-scaffold implantation (n = 14)	Post-scaffold implantation (n = 44)	P_1	Short term follow- up (n = 41)	Mid-term follow- up (n = 36)	P_2	P_3	P_4
Proximal edge	0.19 (0.13, 0.36) (12)	0.23 (0.10, 0.35) (29)	0.793	0.17 (0.12, 0.31) (28)	0.15 (0.07, 0.20) (19)	0.989	0.022	0.043
Scaffolded segment	0.35 (0.20, 0.38) (14)	0.19 (0.09, 0.29) (44)	0.001	0.16 (0.12, 0.22) (41)	0.15 (0.10, 0.20) (36)	0.391	0.064	0.410
Distal edge	0.14 (0.08, 0.31) (9)	0.15 (0.06, 0.28) (28)	0.739	0.10 (0.04, 0.26) (29)	0.19 (0.11, 0.26) (25)	0.675	0.771	0.445

P_1 denotes the significance of difference between the strain values estimated before and immediate after device implantation; P_2 the significance of difference between the strain values at post-scaffold implantation and at short-term follow-up; P_3 the significance of difference between the strain values at post-scaffold implantation and at mid-term follow-up; and P_4 the significance of differences of the strain values at the two follow-up time points

The number in the parenthesis at the left side of each column indicates the number of segments analyzed at each time point

properties of the vessel wall. We found that in contrast to the first generation which has a transient effect on vessel wall strain, the updated revision Absorb BVS 1.1 causes a permanent decrease of the strain values at the treated segment without affecting the mechanical properties of the proximal and distal edge [5, 6].

The reduction of the vessel wall strain noted immediately after Absorb BVS 1.0 or after Absorb BVS 1.1

deployment has been attributed to the shielding effect of the device, and to fact that the foreign material is likely to interfere with the palpographic estimations due to the artifactual acoustic properties of the struts [5, 6, 12]. In the first revision Absorb BVS the change in the strain values at the treated vessel was temporary as at 6 months and 24 months follow-up the measured strain was increased and approached the strain estimated before device

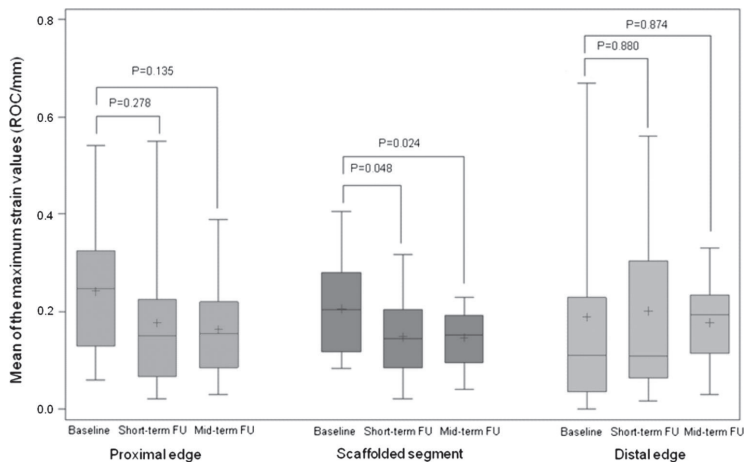
Table 3 Strain values at the proximal edge, the scaffolded segment and the distal edge before device implantation, immediately after device deployment, at short-term and at mid-term follow-up in patients who had serial palpographic examination immediate after scaffold implantation and at the two follow-up time points

	Post-scaffold implantation (n = 20)	Short term follow-up (n = 20)	Mid-term follow-up (n = 20)	P_1	P_2	P_3
Proximal edge	0.25 (0.13, 0.33) (12)	0.15 (0.07, 0.23) (12)	0.16 (0.09, 0.22) (12)	0.278	0.135	0.817
Scaffolded segment	0.20 (0.12, 0.29) (20)	0.14 (0.08, 0.20) (20)	0.15 (0.10, 0.19) (20)	0.048	0.024	0.922
Distal edge	0.11 (0.04, 0.23) (12)	0.11 (0.06, 0.31) (12)	0.20 (0.11, 0.24) (12)	0.880	0.874	0.692

P_1 denotes the significance of difference between the strain values at post-scaffold implantation and at short-term follow-up; P_2 the significance of difference between the strain values at post-scaffold implantation and at mid-term follow-up; and P_3 the significance of differences of the strain values at the two follow-up time points

The number in the parenthesis at the left side of each column indicates the number of segments analyzed at each time point

Fig. 2 Changes in vessel wall strain (ROC/mm) at the proximal edge the scaffolded segment and the distal edge in patients who had serial palpographic examination immediately after scaffold implantation at short-term and mid-term follow-up. ROC Rotterdam classification



implantation [5, 6]. These findings were attributed to the resorption process which was completed at 2 years follow-up but also to the late recoil noted in the first revision [13, 14]. The latter argument is highlighted by the findings of Tanimoto et al. [13] who showed that late scaffold recoil is more intense at 6 months follow-up in the high-strain fibro-necrotic plaques; thus it can be speculated that the late recoil of the scaffold over these plaques may allow restoration of their mechanical properties contributing to the increased strain values noted at 6 and 24 months follow-up.

On the other hand in the second revision Absorb BVS the polymer has been processed in such a way so as its degradation to delay by approximately 18 months comparing to the first revision and the scaffold has a different design which provides the device with a better radial support [14]. These modifications prolong the mechanical integrity of the scaffold resulting in a delayed restoration of vessel vasomotion at 12 months follow-up, and eliminate the risk of late recoil [15].

Furthermore, we have recently demonstrated that in Absorb BVS 1.1 a thick layer of neointimal tissue develops (mean thickness 210–220 μm at short-term follow-up) that covers the entire circumference of the vessel shielding the underlying plaque [16]. Histology studies in porcine models have shown that the neointima tissue consists of smooth muscles cells and fibrous tissue and thus the superficial plaque is anticipated to exhibit low strain values in a palpographic examination [2, 3, 17]. Indeed the strain values reported in our analysis at short- and mid-term follow-up are close to the strain measured in fibrotic plaques by Korte et al. [3] using elastography in pig models. It appears that the second revision Absorb BVS 1.1 modifies permanent the mechanical properties of the superficial plaque by altering its phenotype to a more stable form (Fig. 3). Our findings indicate that in contrast to the metallic stents, which are anticipated to have a similar effect on the mechanical properties of the vessel wall, in bioresorbable scaffolds minor changes in their design are

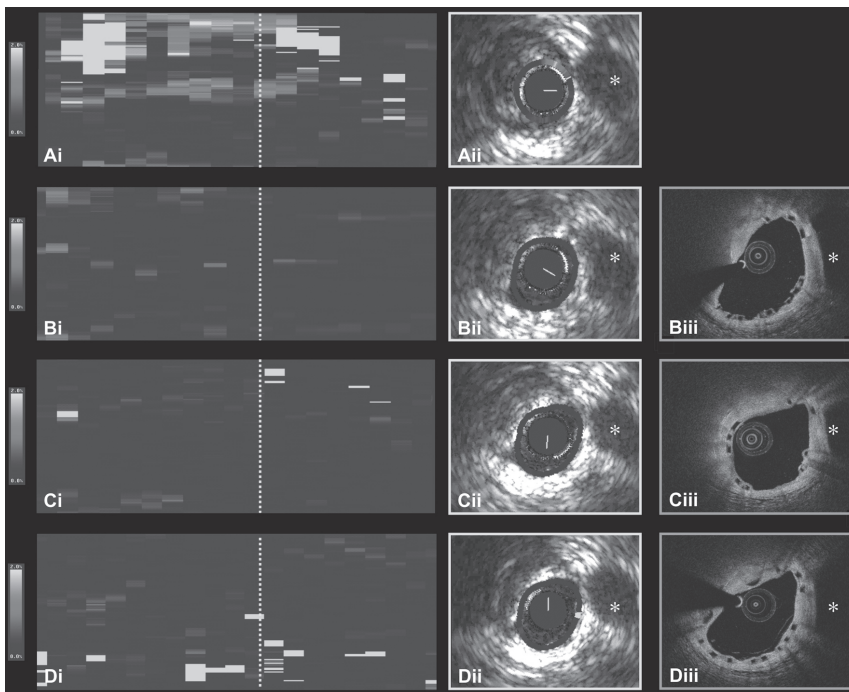


Fig. 3 Spread out plot of the vessel wall strain at baseline before Absorb BVS implantation (Ai), immediate after scaffold deployment (Bi), at short-term (Ci), and mid-term follow-up (Di). The *blue color* indicates low strain values where the *red/yellow* a high strain. It is apparent that the incidence of the high strain values decreased immediate after scaffold deployment and it is even lower at short- and mid-term follow-up. Panels Aii, Bii, Cii and Dii portray corresponding IVUS cross-sections acquired at baseline before and immediate after scaffold deployment, at short-term, and at mid-term follow-up respectively. The position of these frames in the spread-out vessel plots is indicated with a *yellow line*. High strain values are noted at the shoulders of an echolucent plaque before scaffold implantation

(Aii), however immediate after device deployment the strain values are low in the entire circumference of the lumen (Bii). OCT imaging performed after scaffold deployment this time point (Biii) indicates the presence of a lipid rich plaque (the correspondence between IVUS and OCT is shown with an *asterisk*). The strain values remain low at short- and mid-term follow-up in the IVUS cross-section (panels Cii and Dii respectively). OCT performed at the follow-up time points shows that neointima tissue has been developed that sealed the underlying plaque. The mean thickness of the neointima tissue is measured 150 μm at short-term and 220 μm at mid-term follow-up (Supplementary figure)

likely to have detrimental implications on vessel wall strain. Thus the results of this analysis cannot be extrapolated to other scaffolds even to these with a similar design and composition.

The effect of the decreased strain on vessel wall pathophysiology is yet unknown. Several studies have demonstrated that the ability of the vessel wall to expand as a response to a pulsatile cyclic strain has an athero-protective role as it stimulates eNOS gene regulation, promotes prostacyclin synthesis and maintains the contractile phenotype of the smooth muscle cells [18–20]. However, plaques exhibiting low strain such as the pathological

intimal thickening appear stable and rarely cause future events, while the plaques that demonstrate a high strain are associated with increased vulnerability [1, 4, 21]. Therefore it can be argued that the low strain estimated in stable plaques is sufficient for the stimulation of the pulsatile cyclic strain-dependent athero-protective mechanisms and for triggering the necessary mechanotransduction and pathophysiological pathways that prevent plaque progression. In Absorb BVS this argument is supported by histology studies showing that in scaffolded segments the smooth muscle cells maintain their benign contractile phenotype, and by clinical reports demonstrating

restoration of the endothelial dependent vasomotion at 1 year follow-up, suggesting a functionally normal endothelium that is capable to respond to chemical and mechanical stimuli [15, 22].

Although palpography appears unable to predict the natural history of a high risk plaque there is robust evidence to support that the mechanical properties of the vessel wall provide useful prognostic information since patients with high strain plaques are more likely to experience acute coronary events comparing to those with low strain lesions [1, 4]. Furthermore, the Integrated Biomarkers and Imaging Studies I and II have shown that an aggressive pharmaceutical treatment reduces local strain values, whereas the vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT) trial that implemented a self-expanding stent to seal high risk plaques have demonstrated a significant decrease of the strain values immediate after device deployment [7–9]. Our results are similar to what has been reported to metallic stents, showing that Absorb BVS 1.1 implantation changes permanently the mechanical properties of the vessel wall and stabilizes the plaque. However, further palpographic data after the full resorption of the BVS are needed to confirm this statement and further research and robust data from randomized control trials are required before advocating the use of these devices for the invasive sealing of vulnerable, prone-to-rupture plaques [16, 23, 24].

Limitations

A major limitation of the current study is the fact that a considerable number of patients did not have serial palpographic examination. Thus, we included all the data that were available from each patient acknowledging the fact that missing examinations can affect the reported results. To confirm the findings of our initial analysis we also performed a sub-analysis including the patients who had truly serial examinations. Although the number of patients in the sub-analysis was small the agreement noted between the results of the initial analysis and the sub-analysis with regards the scaffolded segment allows us to report these findings with some certainty. Another limitation of our analysis was the lack of a control group with serial palpographic examination that would allow us to compare the reported changes in the vessel wall stain in the scaffolded segments with these in native untreated arteries.

Unfortunately OCT was an optional examination in the ABSORB Cohort B study and thus only very few patients ($n = 4$) had serial palpographic and OCT assessment. Thus we were unable to combine these data and examine the association between the changes in the measured strain at

follow-up and the neointimal thickness as well as the effect of the different plaque characteristics (i.e., composition of the plaque, thickness of the fibrous tissue over calcific and lipid tissue, extent of the lipid and calcific tissue, plaque burden and eccentricity) on this relation [25, 26].

Conclusions

This study for the first time investigated the mid-term implications of the second revision Absorb BVS on the mechanical properties of the plaque. We found that in contrast to the first revision where the strain values of the treated segment change temporarily, in the second revision the strain of the vessel wall gradually decreases with time. Long-term clinical follow-up data and evidence from randomized studies are required in order to examine the clinical implications of these findings.

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Conflict of interest Xingyu Gao is employee of Abbott Vascular. None of the other authors have any conflict of interest to declare.

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Chapter 5.6

Impact of Everolimus-Eluting Bioresorbable Scaffold in Coronary Atherosclerosis

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ABSTRACT:

Introduction and Objectives:

Absorb BVS has shown to decrease the total plaque areas in the treated segment. However, whether the plaque size modification effect occurs only in scaffolded segments or may be extended to other coronary segments is not known.

Methods:

Absorb Cohort A is a single-arm, prospective study, with safety and imaging endpoints in which 30 patients underwent PCI with the first generation Absorb BVS. Noninvasive MSCT imaging was performed in eighteen patients at 18-month and 5-year follow-up. The present study is an intra-patient comparison of matched segments (normalized by the segment length) of the scaffolded region with non-intervened segments for: lumen volume, vessel volume, plaque volume, plaque burden and % Change in Plaque Atheroma Volume.

Results:

All 18 scaffold segments were analyzable. In the non-intervened, one of 72 segments had motion artifacts and was excluded. Serial comparison showed that the scaffolded segments did not have a significant change in the mean plaque burden, total atheroma volume, total lumen volume and vessel volume between 18 months and 5 years. Conversely, the non-treated segments had a significant increase in plaque burden ($2.7 \pm 6.5\%$; $P < 0.01$) and normalized plaque volumes ($8.0 \pm 22.8 \text{ mm}^3$, $P < 0.01$). This resulted in a significant difference in plaque burden comparison between scaffolded and non-intervened segments ($P = 0.03$).

Conclusion:

In this small series, Absorb BVS showed potential to locally reduce the progression of % plaque burden on top of pharmacological treatment. Larger studies are needed to confirm these findings.

Keywords: Absorb, atherosclerosis, computed tomography coronary angiography, coronary plaque, disease progression

INTRODUCTION

The clinical introduction of bioresorbable scaffolds (BRS) was enacted as the fourth revolution in interventional cardiology. These devices have the unique ability to provide a temporary scaffold that is necessary to maintain the patency of the vessel after intervention, and then they gradually permit the restoration of vascular physiology and integrity^[1-3]. Among the potential advantages of BRS, the atherosclerotic plaque reduction and late lumen enlargement in the treated regions^[4-6] may represent a paradigm shift in the treatment of coronary artery disease (CAD).

Pharmacological therapy has shown that, depending on patient clinical profile, it is possible to promote plaque regression^[7-9]. Therefore, plaque regression in patients treated with BRS may be related not to the device itself but due to the effect of the pharmacological therapy in a vessel that is free from its internal cage.

The aim of the present study was to perform a within-patient comparison of the natural history of coronary atherosclerosis between segments treated with poly-L-lactide-acid (PLLA) everolimus-eluting bioresorbable scaffold (Absorb BVS first generation, Abbott Vascular, Santa Clara, California) and non-intervened segments in the Absorb Cohort A trial assessed by multislice computed tomography (MSCT).

METHODS

Study Population

The design of the Absorb Cohort A trial has been previously described^[10]. In brief, it is a single-arm, prospective, open-label study,

with safety and imaging endpoints. A total of 30 patients were enrolled at 4 participating sites between March and July 2006. Patients were older than 18 years of age with a diagnosis of stable, unstable, or silent ischemia. All treated lesions (diameter stenosis >50%) were single, de novo in a native coronary artery of 3.0 mm in diameter, suitable for the 12- or 18-mm scaffold. Major exclusion criteria were patients presenting with an acute myocardial infarction (MI), unstable arrhythmias, or a left ventricular ejection fraction <30%, restenotic lesions, lesions located in the left main coronary artery, lesions involving a side branch >2 mm in diameter, and the presence of thrombus or another clinically significant stenosis in the target vessel. The ethics committees approved the protocol at the participating institutions, and the enrolled patients gave written informed consent before inclusion. Clinical endpoints were assessed at 30 days, 6 and 9 months, and 1, 2, 3, 4, and 5 years. Noninvasive MSCT imaging studies were done at 18-month and 5-year follow-up.

Study device

The study device has been described elsewhere^[10]. Briefly, the polymeric device consists of a backbone of poly-L-lactide (PLLA) coated with poly-D,L-lactide (PDLLA) that contains and controls the release of the antiproliferative drug everolimus. Absorb BVS first generation has a crossing profile of 1.4 mm in circumferential hoops of PLLA with struts 150 μ m thick either directly joined or linked by straight bridges. Both ends of the scaffold have two adjacent radio-opaque metal markers. The doses of everolimus on the Absorb BVS 1.0 are 98 μ g for a 12 mm scaffold and 153 μ g for the 18 mm scaffold.

MSCT angiography

The CT scanners used were 64-slice CT (Brilliance 64, Philips, Best, the Netherlands; CVi, GE Healthcare, Milwaukee, Wisconsin), 256-slice CT (iCT, Philips), 320-slice CT (Aquilion One, Toshiba, Nasu, Japan), 64-slice dual-source CT (Definition, Siemens AG, Forchheim, Germany), and 128-slice dual-source CT (Definition Flash, Siemens). Standard acquisition techniques were used, which included beta-blockers in patients with a fast heart rate, tube settings depending on patient size (80 to 140 kV), and axial scan protocols for patients with lower heart rates to reduce radiation doses, all at the discretion of the individual sites. Images were reconstructed using thin slices (0.5 to 0.67 mm) and medium smooth reconstruction filters, including 1 or more phases of cardiac cycle depending on the scan protocol.

MSCT analysis

The MSCT analysis followed a previously established methodology^[3, 11-13]. All datasets were transferred to an offline workstation for analysis using a semi-automated plaque analysis software (QAngioCT Research Edition version 2.1, Medis medical imaging systems b.v., Leiden, the Netherlands). The assessment of the inner lumen and outer vessel volumes was performed following a stepwise approach. First, a centreline originating from the ostium was automatically extracted. Straightened multiplanar reformatted images were generated, and the lumen and vessel borders were detected longitudinally in 4 different vessel views by the software. Cross-sectional images of these longitudinal contours were examined at 0.5-mm intervals and, if necessary, adjusted by an experienced observer. The settings for window level and width were fixed at 740 HU

and 220 HU, respectively. Gradient magnitude images, which display the degree of CT attenuation change, were used to facilitate the detection of lumen and vessel wall borders.

Only the major epicardial vessels were considered for analysis using the modified 17-segment American Heart Association model for coronary segment classification (proximal and mid segments of the right, left circumflex and left descending anterior coronary arteries)^[14]. The scaffolded regions were delimited by the presence of the radiopaque markers. In case of overlapping metallic stents (n=3), the scaffolded regions were assessed up to the regions without stent interference. The present study used as comparator for the scaffolded regions the intra-patient non-intervened native coronary vessels by assessing the first 2 proximal segments, divided in proximal or distal according to established anatomical references (Figure 1)^[14].

MSCT study imaging endpoints

Normalization for segment length provides equal weighting of each patient in the calculation of atheroma volume and also for varying segment length between the two scans^[11, 15]. The following IVUS-like parameters were calculated for the non-intervened and scaffolded segments after normalization:

Percent atheroma volume (PAV): $[(\text{total vessel volume} - \text{total lumen volume}) / \text{total vessel volume}] * 100\%$

Normalized TAV (TAVnorm): $[(\text{total vessel volume} - \text{total lumen volume}) / \text{segment length}] * \text{mean segment length in the population}$.

Normalized Percentage change in TAV (% change in TAV): $[(\text{TAVnorm at 5 years} - \text{TAVnorm at 18 months}) / \text{TAVnorm at 18 months}] * 100\%$
X mean segment length in the population

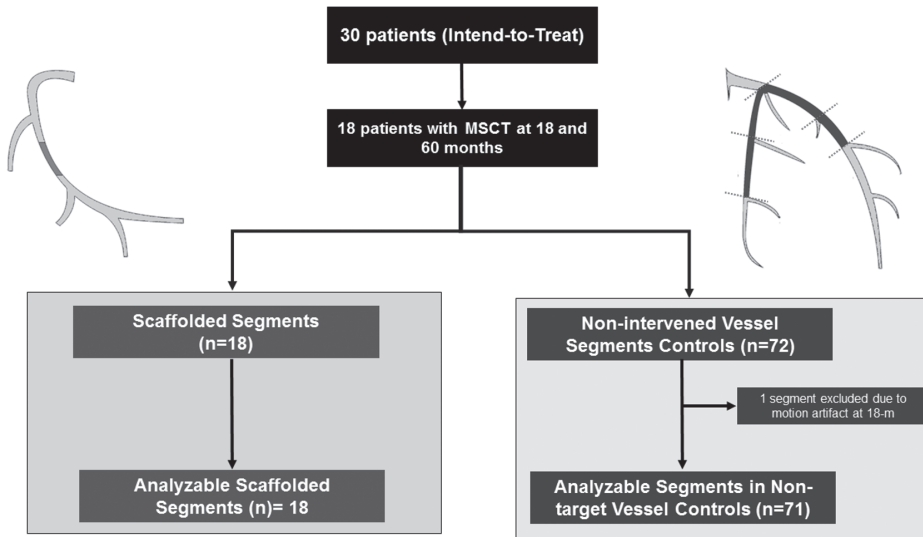


Figure 1. Flowchart of the 5-Year Serial MSCT Study. Scaffolded segments (left panel; represented in green) were matched at 18-month and 5-year follow-up for serial comparison. Non-intervened segments delimited by anatomical markers (right panel; represented in blue) were matched at 18-month and 5-year follow-up for serial comparison. One non-intervened segment had motion artifact at 18-months hindering the serial comparison and was excluded.

Statistical analysis

Continuous variables are presented as mean \pm SD and median (interquartile range [IQR]), as indicated. Categorical variables are presented as counts and percentages. Continuous variables between the 2 different time points were compared by the paired samples t test. A p value <0.05 was considered significant. Statistical analyses were performed with use of SPSS version 22.0 software (SPSS, Chicago, Illinois).

RESULTS

Patient demographic characteristics and a flow chart of the present study are shown in Table 1 and Figure 1, respectively. Of the 30 patients enrolled in the Absorb Cohort A trial, 18 underwent serial MSCT at 18-month and

5-year follow-up, and were included in the present analysis. The mean age was 62 ± 8 years old, 67% were male, 6% had diabetes mellitus and 78% had stable angina pectoris. The most frequently treated vessel was the LAD (44%) and the mean lesion length at baseline was 9.1 ± 3.6 mm.

All scaffolds (n=18) were assessable by MSCT at 18-month and 5-year follow-up. Regarding the non-intervened segments, of 72 possible analysable segments, 1 segment at 18-months was excluded due to motion artefacts (Figure 1). The mean scaffold length was 11.9 ± 1.9 mm and the mean length of the non-intervened segments was 22.6 ± 11.7 mm.

Matched Segment Serial Comparison. Between 18-month and 5-year follow-up, scaffolded segments did not show a significant change in any analysed parameters, including mean plaque burden, total atheroma volume,

Table 1. Baseline Clinical and Angiographic Characteristics

	N=18
Age, years ±SD	62.1 ± 7.8
Male gender, n(%)	12 (67)
Current tobacco use, n(%)	2 (11)
Diabetes, n(%)	1 (6)
Hypertension, n(%)	11 (61)
Hypercholesterolemia, n(%)	13 (76)
Family history of coronary artery disease, n(%)	13 (72)
Stable angina	14 (78)
Unstable angina, n(%)	4 (22)
Prior MI, n(%)	2 (11)
Target vessel , n(%)	
RCA	4 (22)
LAD	8 (44)
LCX	6 (33)
Lesion length, mm ± SD	9.1 ± 3.6
ACC/AHA lesion classification, n(%)	
B1	9 (50)
B2	9 (50)

MI= myocardial infarction; RCA=right coronary artery; LAD=left anterior descending coronary artery; LCX= left circumflex coronary artery

total lumen volume and vessel volume (Table2; Figure2). Control segments had a significant temporal increase in atherosclerotic burden as determined by the mean plaque burden (increased in 2.7±6.5%; P=0.03) and total atheroma volume (increased in 8.0±22.8mm³; P<0.01)(Table2; Figure2).

Comparison of natural history of atherosclerosis in scaffolded vs. non-intervened segments. The change in percent atheroma volume was significantly different between scaffolded regions and non-intervened segments. While in the scaffolded segments the mean plaque burden decreased by 1.2±7.7%, in the non-intervened segments it increased by 2.7±6.5% (P=0.03) (Table2; Figure2). There was also a trend to difference in the change of normalized total atheroma volume (P=0.10) and % change in total atheroma volume (P=0.09) in favour of scaffolded segments (Table 2, Figures2 and 3). The change in the vessel volume was only slightly greater in the non-intervened segments (P=0.72). Although

Table 2. MSCT IVUS-Like Analysis Results

	Scaffold (n=18)		Change	P value	Non-intervened (n=71)		Change	P value	Scaffold Vs. Non TV
	18 months	5 years			18 months	5 years			P value for changes
Percent atheroma volume, %									
Mean ±SD	49.3±10.5	48.1±8.7	-1.2±7.7	0.51	44.6±9.9	47.3±11.0	2.7±6.5	<0.01	0.03
% change in total atheroma volume									
Median (IQR)			0.6±22.0				11.9±25.6		0.09
Normalized total atheroma volume, mm³									
Mean ±SD	94.2±34.6	92.6±32.2	-1.6±18.7	0.72	95.0±33.5	103.0±36.2	8.0±22.8	<0.01	0.10
Normalized total lumen volume, mm³									
Mean ±SD	96.1±33.6	99.8±37.0	3.7±14.4	0.28	122.2±50.8	118.8±51.7	-3.4±19.83	0.16	0.16
Normalized vessel volume, mm³									
Mean ±SD	190.3±54.9	192.4±57.5	2.1±16.4	0.59	217.2±69.7	221.8±67.6	4.6±29.0	0.18	0.72

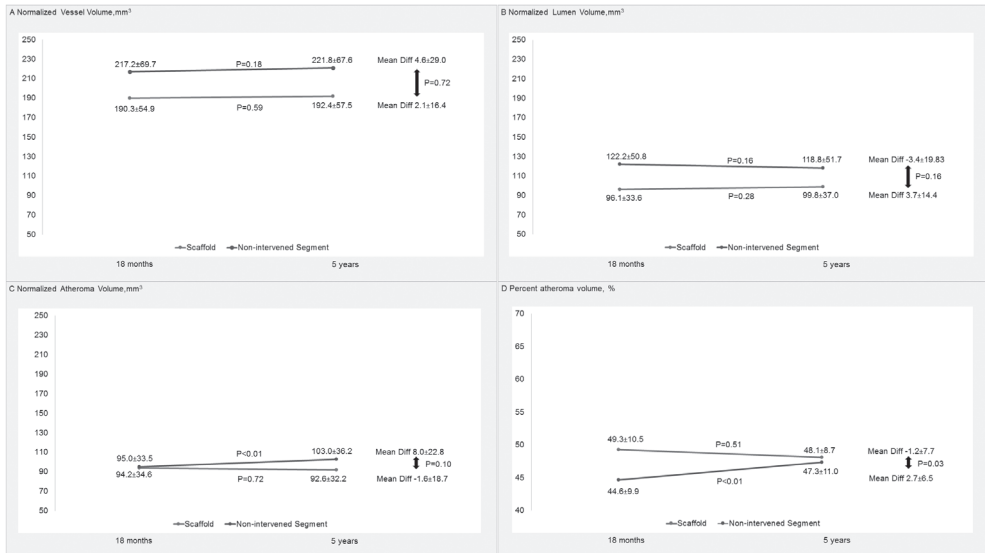


Figure 2. MSCT IVUS like parameters. Scaffold segments did not show significant temporal change in vessel, lumen and plaque volume parameters. The non-intervened segments had an increase in the plaque volume (C), representing a higher percentage of the vessel area (D).

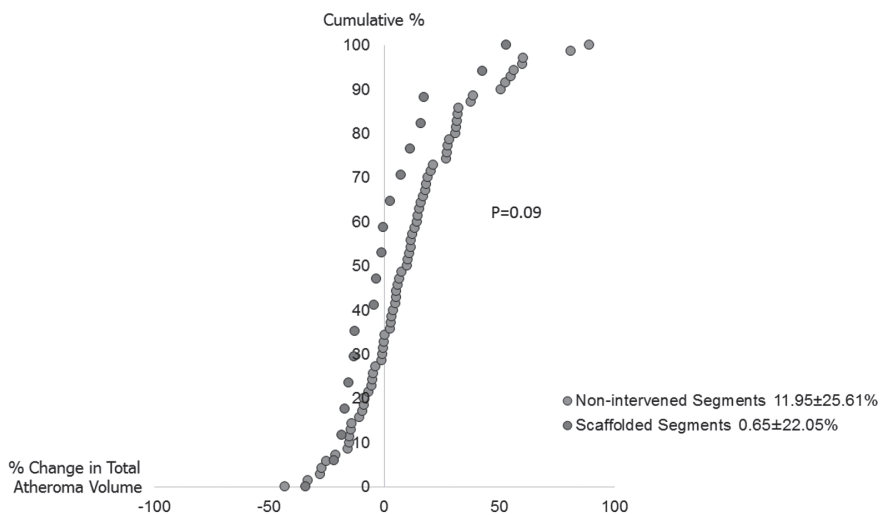


Figure 3. Percentage change in the atheroma volume in the scaffolded (green) and non-intervened vessels (blue). Each dot represents one segment. The observed shift to the left in scaffolded regions correspond to a trend towards atherosclerosis regression compared to non-intervened vessels (P=0.09).

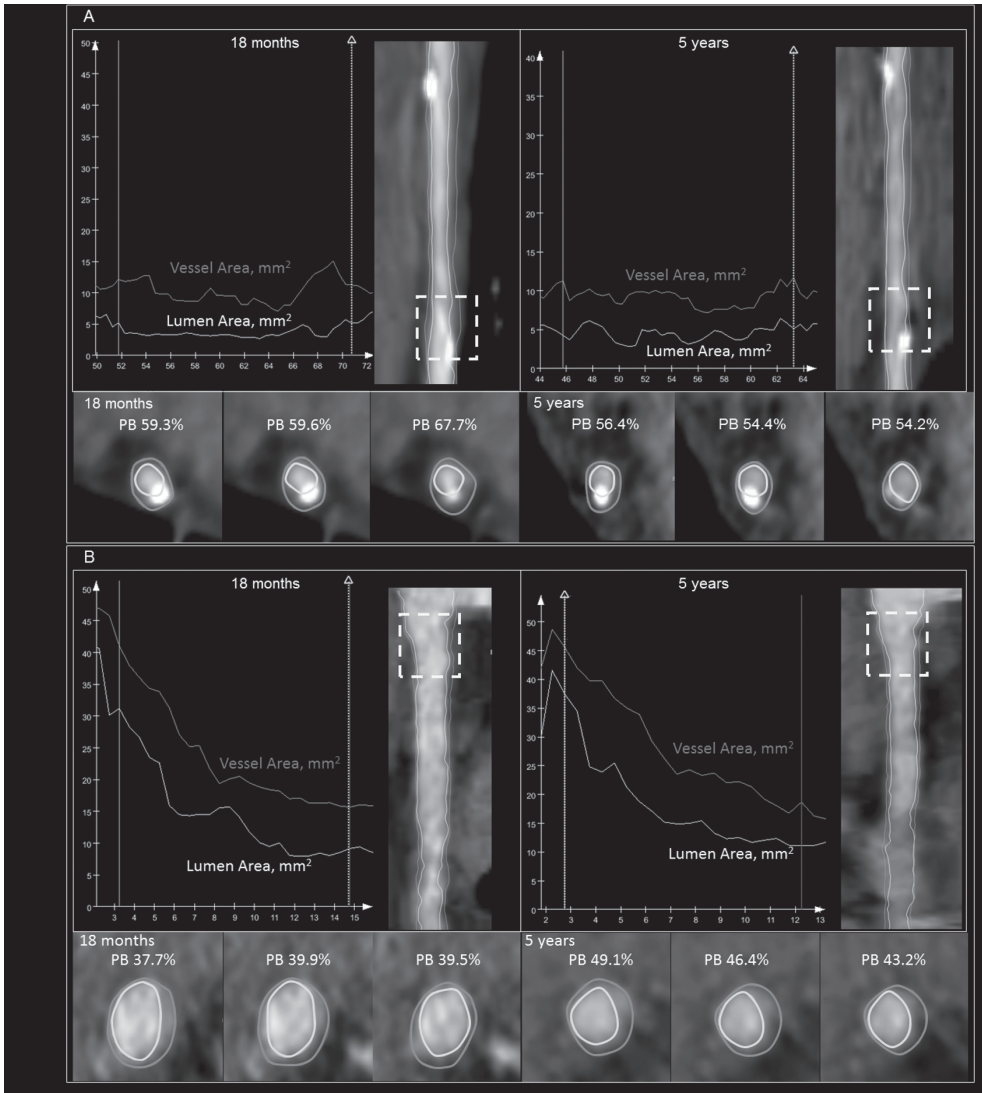


Figure 4. (A) Lumen and vessel areas of a scaffold implanted in left anterior descending coronary artery at 18 months (upper panel, left) and 5 years (upper panel, right). There is an increase in the lumen volume and decrease in the plaque burden (lower panel). (B) Lumen and vessel areas of the same patient but in the proximal right coronary artery at 18 months (upper panel, left) and 5 years (upper panel, right). There is an increase in the plaque burden (lower panel) and vessel volume with a slight increase in the lumen volume (lower panel).

the difference between groups was not significant, the bigger increase in plaque burden without proportional increase in vessel volume in the non-intervened segment resulted

in an opposite change in the lumen volume; while there was a lumen gain (increase of $3.7 \pm 14.4 \text{ mm}^3$) in the scaffold segment, a lumen loss in non-intervened segments (decrease of

3.4±19.8 mm³; P=0.16) was observed (Table 2, Figure 2 and 3). An example of intra-patient comparison of matched segments is given in Figure 4.

DISCUSSION

The main findings of the present study can be summarized as follows: (1) Segments treated with Absorb BVS 1.0 had a stabilization of the atherosclerotic process, without significant paired change in the vessel, lumen and plaque dimensions; (2) non-intervened coronary segments had a significant increase in the plaque volume and percent atheroma volume; (3) the comparison between scaffolded and non-intervened segments showed a significant benefit of the Absorb BVS scaffold in terms of plaque burden.

Coronary atherosclerosis has been challenging medical practice in terms of reversion of its chronic progressive inflammatory process and subsequent symptoms and events^[7, 9, 11, 16, 17]. As summarized in Table 3, therapeutic interventions may influence progression or regression of coronary artery disease. In addition, many individual factors may influence

the coronary plaque modification such as diabetes, waist circumference, serum CD40L, baseline diastolic blood pressure, gender and the aptitude in improving the lipid profile and C-reactive protein^[8, 18-20]. The present study, being a matched segment within-patient comparison, for the first time, assessed the long-term evolution of atherosclerosis in segments treated by a scaffold and non-intervened segments. It raises the hypothesis that local therapy with Absorb BVS could add benefit to atherosclerosis regression on top of pharmacological therapy. Importantly, the atherosclerosis progression observed in the non-intervened segments is not at variance with previous data that used the same methodology^[11] (Table 3) and did not result in coronary events^[5].

The plaque burden reduction in the Absorb BVS–implanted coronary segments has been documented previously^[4, 21]. The explanation for this finding may come from the ability of mTOR inhibitors to hinder atherosclerotic plaque formation. Rapamycin and rapalogs are potent inhibitors of vascular smooth muscle cell (SMC) proliferation. mTOR inhibitors have anti-macrophage properties through different mechanisms such as inhibition of monocyte

Table 3. Impact of therapy on atherosclerosis in recent natural progression/regression trials

Trial	Change in PAV,% Mean (95% CI)	% Change in TAV Mean (95% CI)	Follow-up
SATURN(6)			26 months
Atorvastatin 80 mg	-0.99 (-1.19 to -0.63)	-	
Rosuvastatin 40mg	-1.22 (-1.52 to -0.90)	-	
PROSPECT (MSTC sub study)(10)	-0.07 (-1.43 to 1.57)	6.7 (1.0 to 12.43)	39 months
IBIS 4(17)			13 months
Rosuvastatin 40mg	-0.9 (-1.56 to -0.25)	-13.1 (-22.5 to -3.8)	
Present study			42 months
Scaffolded segments	-1.2 (-4.8 to 2.4)	0.65 (-9.54 to 10.84)	
Non-intervened segments segments	2.6 (1.16 to 4.2)	11.9 (5.99 to 17.91)	

PAV=percent atheroma volume; TAV=total atheroma volume

chemoattractant protein-1 (MCP-1) upregulation, impaired recruitment of monocytes to the vessel and downregulation of de novo protein synthesis^[22]. mTORC inhibition also prevents lipid accumulation in the plaque due to stimulation of cholesterol efflux and downregulation of low-density lipoprotein (LDL) and scavenger receptors^[22]. It has been hypothesized that everolimus may produce a local autophagic response resulting in degradation and/or efflux of lipids via lipophagy and the loss of macrophages in the plaque^[23]. Indeed, also in animal studies, systemic administration of rapamycin or everolimus has shown to promote 7-85% plaque reduction^[22, 24, 25]. However, this process is not fully understood since the Absorb BVS elutes 80% of everolimus within 30 days and the plaque regression in patients treated with Absorb BVS occurs only after 2 years^[4, 21]. We hypothesize also that the disappearance of struts with consequent shrinking of connective tissue may result in reduction in plaque burden.

The impact of five coronary devices on plaque sizes by intravascular ultrasound have been compared previously: (Absorb bioresorbable everolimus eluting scaffold — Absorb BVS 1.0 and 1.1; everolimus eluting metallic stent — Xience V —; bare metal stent — Vision and paclitaxel-eluting metallic stent — Taxus)^[21]. At 6-month follow-up, all devices induced an increase in the total plaque area but Vision and Taxus induced larger increase as compared to other devices [Absorb BVS (1.0 and 1.1) and Xience V], ($p = 0.0002$). The comparison-at-2-year follow-up showed that Absorb BVS 1.1 had a larger increase from post procedure in total plaque compared to Absorb BVS 1.0, Xience V and Taxus ($p = 0.0499$). However, in Absorb BVS 1.1 total plaque showed a reduction of 2.2% from 1 to 3 years. Taxus showed

a 9% increase in vessel area which was much larger to that of Absorb BVS, Xience V or Vision. In addition, Haude et al. have shown that drug-eluting absorbable magnesium scaffold (DREAMS) showed a vessel area reduction at 6 months and even more between 6 months and 12 months^[26]. These observations highlight the fact that the vessel wall response varies according to the device design. At this point, it is not possible to fully understand whether it is the drug, the polymer or the constituents of the back bone (metal vs. polymer) which play the most determinant role in triggering these changes. However, permanent devices hinder any further reduction of the size of the plaque by lastingly staying in the vessel wall. On the other hand, bioresorbable scaffolds are designed to provide temporary scaffolding the coronary vessel wall, inhibit effectively neointima formation (by eluting everolimus) and also prevent late complications such as stent thrombosis by their disappearance.

In addition to the plaque burden reduction, it has been hypothesized that Absorb BVS may seal the thin-cap fibroatheromas (TCFA), which are lipid core plaques covered by a thin fibrous cap ($<65\mu\text{m}$)^[27]. An optical coherence tomography study has shown that 1-year after Absorb BVS implantation there is formation of symmetric neo-tissue with a mean thickness of $220\mu\text{m}$ ^[27]. As the device is completely degraded, this may therefore favour the use of a bioresorbable device for the treatment of TCFA. Furthermore, pre-clinical studies have demonstrated that the main component of the neointima following Absorb BVS implantation is fibrous tissue, whereas fibrin and granulomatous cells are infrequent at long-term follow-up^[28].

Finally, the present manuscript documents the longest non-invasive assessment after

Absorb BVS implantation and demonstrates the feasibility of MSCT on following patients with bioresorbable polymeric devices and quantifying the atherosclerotic burden in all coronary tree.

Limitations

The present study is a retrospective analysis that assessed patients in a first-in-humans trial including patients with low clinical and anatomical complexity. Our results should be considered as hypothesis generating given the small sample size herewith described, not permitting a definitive statement that Absorb BVS should be used as a standard therapy for plaque regression. Additionally, progression/regression studies have shown that that the larger the PAV at baseline, the higher the chance of regression. This fact may have potential to influence the more pronounced regression at scaffolded segments. The ongoing Multicentre Prospective Natural History Study Using Multimodality Imaging in Patients With Acute Coronary Syndromes (PROSPECT ABSORB trial, ClinicalTrials.gov Identifier:

NCT02171065) will examine whether the treatment of lesions with plaque burden $\geq 70\%$ with the Absorb BVS plus optimal medical therapy safely increases the minimal lumen diameter at 2 years compared with optimal medical treatment alone and may add further evidence in this regard.

CONCLUSION:

In this small series, Absorb BVS showed potential to locally reduce the progression of % plaque burden on top of pharmacological treatment. Larger studies are needed to confirm these findings.

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PART 6

Summary and Conclusions
Samenvatting en Conclusies
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SUMMARY AND CONCLUSIONS

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SUMMARY

In coronary artery disease (CAD), patients and plaque's characteristics have been scrutinized to understand how risk factors relate to the hazard of subsequent cardiovascular events. The rationale for local plaque assessment is based on the fact that the atherosclerotic plaque represents the pathological substrate for the occurrence of ischemic cardiovascular events. However, the coronary atherosclerotic disease burden is not the only factor that affect patients' prognosis. Patients with complex coronary artery disease, clinical factors beyond plaque are components of the final outcome and affects the decision-making process of coronary revascularization. Moreover, the coronary revascularization still does not represents the cure for CAD requiring adequate risk assesment, secondary prevention and development of therapeutics that are able to modify the natural history of coronary atherosclerosis. This thesis offers significant insights into these, and provides important data regarding CAD risk management.

IMAGING METHODS FOR ASSESSING CARDIOVASCULAR RISK

In chapter 1.1, we described the current histopathological definitions and state-of-the-art imaging techniques for identification of vulnerable coronary plaques. One of most widely used methods for in vivo identification of vulnerable plaques is Virtual Histology Intravascular Ultrasound (VH-IVUS). We describe in chapter 1.2 the algorithm for VH IVUS using the 45-MHz rotational IVUS catheter and the associated ex vivo validation in comparison to the gold standard histology.

In recent years, coronary Ctangiography (CCTA) has become a widely adopted technique, not only due to its high diagnostic accuracy, but also to the fact that CCTA provides a non-invasice evaluation of the total (obstructive and non-obstructive) coronary atherosclerotic burden. More recently, this technique has become mature, with a large body of evidence addressing its prognostic validation. In addition, CT angiography has moved from the field of 'imagers' and clinicians and entered the interventional cardiology arena. In chapter 1.3 we describe CCTA accuracy, prognostic value and its hability and limitations in assessing plaque characteristics.

The presence of coronary plaques with complex morphologic features in coronary angiography is the angiographic hallmark of unstable coronary syndromes. In chapter 1.4 we assessed coronary plaque features by angiography in patients with acute coronary syndrome after noncardiac surgery, patients in the emergency room with spontaneous acute coronary syndromes, and patients with stable coronary artery disease. In chapter 1.5 we assessed the distribution of angiographic thrombus-containing lesions in an all-comer population admitted with a heterogeneous clinical presentation (stable, unstable angina, or an acute coronary syndrome) and its long-term prognostic implications.

Optical coherence tomography (OCT) is an intravascular light-based imaging method with a near-histological resolution of 10-20 μm . Currently, OCT is the only technology available in the clinical setting that provides spatial resolution sufficient to assess fibrous cap thickness accurately (FCT). Coronary lesions precursors of acute events remain elusive,

since they undergo continuous changes and their temporal changes are not very well characterized. In natural history studies, optical frequency domain imaging (OFDI) has been used only to assess fibroatheromas as a two-dimensional structure and sometimes in a single frame fashion. In chapter 1.6 we described the changes of coronary fibroatheromas over a 6-month follow-up period, describing the serial volumetric modifications of the FC as determined by OCT.

INTERPLAY BETWEEN CORONARY ATHEROSCLEROSIS AND CLINICAL PROFILE

Individual risk factors and coronary plaque characteristics have been correlated in medical literature. However, the clinical and health outcomes measures assessed by the Seattle Angina Questionnaire (SAQ) have never been correlated with the characteristics of obstructive plaque determined by intravascular ultrasound (IVUS). In chapter 2.1 we discussed the impact of gender on progression/regression of coronary atherosclerosis as assessed by intravascular ultrasound. Chapter 2.2 described the largest ever description of pre-treatment intravascular ultrasound (IVUS grey scale and backscatter tissue data) findings according to patient demographics and health outcome measures as assessed by the Seattle Angina Questionnaire (SAQ). We showed that clinical characteristics still were able to differentiate the manifestation of obstructive coronary artery disease. Additionally, negative remodelling was associated with worse angina frequency by the SAQ. Patient reported physical limitation and angina stability were,

respectively, associated with necrotic core size and plaque burden.

Coronary angiography still is the gold standard method for decision making in coronary artery disease. Interventional cardiologists and surgeons in the SYNTAX (SYnergy Between PCI With TAXUS and Cardiac Surgery) trial originally used the SYNTAX score (SS) to extract objective information from the coronary angiogram on the technical challenges posed by coronary anatomy to percutaneous coronary intervention (PCI) and to facilitate discussions made by the Heart Team. Subsequently, it became apparent that the SS had a prognostic value to predict short- and long-term outcomes. In chapter 2.3 we demonstrated that the SYNTAX score assessment by clinicians had considerable difference when compared with an experienced corelab. However, the combination of clinical factors with the SYNTAX score (referred to as the SYNTAX-II score) reduced the variability, retaining its predictive performance.

Among patients' clinical characteristics, diabetes mellitus has an important role in the development of coronary artery disease and has been associated with a subsequent increase rate of death. Moreover, about a quarter of patients treated with coronary revascularization are diabetics. In chapter 2.4 we investigated whether stent thrombosis rate is different between diabetic patients and their counterparts in one of the largest randomized stent trials that was powered for stent thrombosis.

RISK STRATIFICATION IN COMPLEX CORONARY ARTERY DISEASE

In a non-emergency setting, an accurate risk estimation of patients with complex coronary

artery disease (CAD) is fundamental to determine if the patient should be treated either by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). Currently, international guidelines recommend a multidisciplinary approach referred to as the Heart Team for this decision-making process. Aiming to help the Heart Team to decide between CABG and PCI in patients with complex CAD, the SYNTAX Score II (SSII) combines 2 anatomic and 6 clinical factors and predicts long-term mortality of patients treated by either CABG or PCI. The SSII was developed in the all-comers, randomized population of the SYNTAX trial, where selection bias were minimal. The SSII also suggests a revascularization strategy (CABG or PCI) depending on the difference of estimated mortalities. The SSII recommends CABG if the difference in the predicted mortality risk is in favor of CABG with 95% confidence. The SSII recommends PCI if the difference in mortality risk predictions is in favor of PCI with 95% confidence. Conversely, the SSII recommends PCI or CABG if mortality risk predictions are within the 95% confidence interval of the difference in mortality risk predictions. In chapter 3.1 we assessed the applicability of the SSII recommendations in conjunction with the Heart Team decision-making process regarding the revascularization strategy in patients with 3-vessel coronary artery disease (CAD). The SYNTAX score II showed to be a suitable tool for guiding treatment decisions of patients with 3-vessel coronary artery disease being endorsed by the Heart Team in the vast majority (85.4%) of the patients. In chapters 3.2 and 3.3 we explored the validity of the SYNTAX score II theoretical treatment recommendation in the long-term prognosis. We found that patients who the SYNTAX score II recommendation

was CABG but were treated by PCI had worse prognosis when compared with patients that had equiposed risk between CABG and PCI or when PCI was recommended. These findings were not always related to the anatomical SYNTAX score alone.

Previously, SSII was predominantly validated in Western patients. In chapter 3.2 we validated the SSII in a Japanese population of complex coronary artery disease. Japanese have unique epidemiological characteristics. Japan has the longest life expectancy at birth worldwide and a substantially lower proportion of mortality from cardiovascular diseases, compared with Western countries. We showed a robust prognostic accuracy of the SSII, both in CABG and in PCI patient groups. Compared with the anatomical SS alone, the SSII was more accurate in stratifying patients for late mortality in a real-world complex coronary artery disease population.

We continued to study the SYNTAX score II and in chapter 3.5 explored its cost-effectiveness perspective in the SYNTAX trial. We found that in patients for whom the SYNTAX Score II favoured PCI based on lower predicted 4 year mortality, PCI was also economically dominant, whereas in those patients for whom the SYNTAX Score II favoured surgery, CABG was highly economically attractive.

The relevance of an unprotected left main coronary artery (ULMCA) stenosis was first described more than 100 years ago. James Herrick reported the story of a 55-year-old male who died in cardiogenic shock after a period of 52 hours. The autopsy found an extensive necrosis of the left ventricle associated with total occlusion of the left main

coronary artery by a thrombus overlying an area of atherosclerotic narrowing. The explanation for this massive necrosis is the large area of myocardium at risk in patients with ULMCA. It has been shown that, in a usual right dominant coronary anatomy, the left coronary artery supplies approximately 84% of the flow to the left ventricle. In chapter 3.6 we described the rationale, designs, similarities and contrasts of two large scale randomized trials of PCI versus CABG for ULMCA disease (EXCEL and Noble trials). In addition, in chapter 3.7 we, for the first time, proposed a prospective validation of the SYNTAX score II in the EXCEL trial. Based on the SYNTAX Score II, we predicted a 77.9% chance of a lower 4-year mortality in the PCI arm of the EXCEL trial, with a 40% chance that this will achieve statistical significance in favour of PCI.

POST-REVASCULARIZATION RISK ASSESSMENT AND MANAGEMENT

Coronary artery disease is, predominantly, a chronic and progressive disease. Therefore, patient's risk will not cease after coronary revascularization. In chapter 4 we studied the post-revascularization risk assessment. One of the main factors of long-term survival of these patients is the completeness of coronary revascularization. In chapter 4.1 we discussed the impact of the residual (rSS) SYNTAX score for ULMCA revascularization. The rSS was designed and validated to quantify the absolute amount of untreated CAD after percutaneous coronary intervention (PCI) revascularization. An rSS>8 was identified as a level of incomplete revascularization was associated with increased mortality and adverse ischemic events.

We continued to study the degree of coronary revascularization and in chapter 4.2 we

proposed the SYNTAX Revascularization Index (SRI), representing the proportion of treated baseline CAD (baseline SYNTAX score [bSS]; delta SYNTAX score [DSS]), to better quantify and describe the proportion of the disease treated ($SRI = DSS / bSS \cdot 100$) by PCI revascularization. In chapter 4.3 we demonstrated that the SRI to be an independent predictor of 1-year mortality in patients with nonST-elevation acute coronary syndrome and low anatomical complexity. In chapter 4.4 we validated the SRI in the population with complex CAD of the SYNTAX trial, with $SRI > 70\%$ representing a "reasonable" goal for patients with complex coronary artery disease.

Reducing risk factors after coronary revascularization has also a major role for patient survival. Cigarette smoking is a well-known risk factor for development of coronary artery disease. However, some studies have suggested a "smoker's paradox," meaning neutral or favorable outcomes in smokers who have developed CAD, especially myocardial infarction. In chapter 4.4 we examined the association of smoking status with clinical outcomes in the randomized controlled SYNTAX trial at 5-year follow-up. Smoking was associated with poor clinical outcomes after revascularization in patients with complex CAD. This placed further emphasis on efforts at smoking cessation to improve revascularization benefits.

Optimal control of dyslipidaemia improves clinical outcomes in patients with coronary artery disease. In chapter 4.5 we investigated the risk factors associated with not achieving the European Society of Cardiology recommended cholesterol levels. There was a significant drop in LDL-C levels during 1-year; nevertheless a significant proportion of pa-

tients (55% at 6-months and 58% at 1-year) remained above the target LDL-C level. We found that factors associated with not achieving target LDL levels included higher baseline LDL, prior history of myocardial infarction and lack of statin therapy.

Impact of Bioresorbable Scaffolds in the natural history of coronary atherosclerosis

The cardiovascular science community has pursued the quest to modify the natural history of coronary atherosclerosis. The clinical introduction of bioresorbable scaffolds (BRS) resulted in a revolutionary change in the application of local coronary therapies. These devices have the unique ability to provide a temporary scaffold that is necessary to maintain the patency of the vessel after intervention, releasing antiproliferative drugs. Due to the polymeric composition, bioresorbable vascular scaffolds (BVS) have unique characteristics when imaged. In chapter 5.1 we described the imaging methods for BRS, compared BRS with metallic stents, and describes the clinical relevance of BRS.

Changes in bioresorbable vascular scaffolds (BRS), design and compositions may affect their degradation and loss of biomechanical characteristics (with the risk of late recoil) and may be associated with a second wave of arterial wall inflammation. Therefore, studying the BRS degradation is crucial to fully understand this technology. Chapter 5.2 validated echogenicity (an automated and quantitative analysis of coronary tissue components scored for grey level intensity using as reference the mean level of the adventitia brightness) as a surrogate for polylactide scaffold degradation.

OCT has played a central role in understanding the short and long term BRS performance, since provides more detailed and precise morphologic information about BRS than does intravascular ultrasonography. In chapter 5.3 we reviewed the the acute and long-terms methodology and clinical application of OCT in the assessment of BRS.

Coronary plaque size modification, by either local (device) or systemic treatments, has been the target for many years. Commonly, patients receive concomitantly medical treatment and PCI and therefore the coronary vessel wall response will vary in relation to the interaction of both treatments. At follow-up, implants will be surrounded by plaque, behind (peri-stent) the struts and endoluminally (neointima). These two compartments are biologically active and will be influenced differently by the presence of a complex interaction formed by the platform (metallic/polymeric) + polymer + drug. For example, stents/scaffolds eluting everolimus will similarly affect plaque size (i.e. by clearing macrophages and inhibiting formation of neointima), but the net effect will be dissimilar since the platforms are different (metallic vs. polymeric). Thus, the effects on plaque size of this complex interplay (eluted drug/platform) can only be explored by measuring serially the size of the coronary plaque-media and neointima compartment. In chapter 5.4 we show that local devices affect coronary plaque size differently and it depends on the platform (metallic vs. polymeric) and on whether it is a bare— or drug eluting stent. Specifically, the total plaque in the sequential cohorts of Absorb BVS 1.1 increased 16.2% from baseline to 2 years while at 3 years this increase is only 5% compared to baseline.

Vessel wall mechanical behavior appears to be associated with the compositional char-

acteristics of the plaque and predict future cardiovascular events. Patients with high strain plaques are more likely to experience acute coronary events comparing to those with low strain lesions. Several studies have shown that pharmaceutical or an interventional treatment can influence the mechanical properties of the vessel wall by altering its constituents. In chapter 5.5 we found that after Absorb BVS 1.1 implantation the strain of the vessel wall gradually decreased with time.

Among the potential advantages of bioresorbable scaffolds, the atherosclerotic plaque reduction and late lumen enlargement in the treated regions may represent a paradigm shift in the treatment of coronary artery disease. However, pharmacological therapy has also shown that, depending on patient clinical profile, it is possible to promote plaque regression. Therefore, plaque regression in patients treated with bioresorbable scaffolds may be related not to the device itself but due to the effect of the pharmacological therapy in a vessel that is free from its internal cage. In chapter 5.6 we performed an intra-patient multi-slice computed tomography comparison of matched segments (normalized by the segment length) of the scaffolded region with non-intervened segments for: lumen volume, vessel volume, plaque volume, plaque burden and % change in plaque atheroma volume. Serial comparison showed that the scaffolded segments did not have a significant change in the mean plaque burden, total atheroma volume, total lumen

volume and vessel volume between 18 months and 5 years. Conversely, the non-treated segments had a significant increase in plaque burden ($2.7 \pm 6.5\%$; $P < .01$) and normalized plaque volumes ($8.0 \pm 22.8 \text{ mm}^3$, $P < .01$). This resulted in a significant difference in plaque burden comparison between scaffolded and non-intervened segments ($P = .03$).

CONCLUSIONS

This thesis comprehensively reflects the many considerations related to the risk stratification for coronary artery disease, as well as the futures perspectives for interventional cardiology. I believe this thesis is of value as it has particularly:

- offered a comprehensive guide of imaging modalities for identifying high-risk characteristics of coronary artery disease;
- provided important insights into the interplay of clinical and anatomical considerations for patients prognosis and their impacts on decision making;
- proposed for the first time an unbiased prospective validation of a risk score;
- assessed the needs and challenges of patient management post coronary revascularization;
- presented new data on the impact of bioresorbable scaffolds for modification of coronary atherosclerosis

SAMENVATTING EN CONCLUSIES

SAMENVATTING

Bij coronaire hartziekten (CHZ) is gedetailleerd onderzoek gedaan naar patiënt- en plaquekenmerken om inzicht te krijgen in de relatie tussen risicofactoren en de kans op cardio-vasculaire voorvallen. De belangrijkste reden voor lokale beoordeling van plaque berust op het feit dat de atherosclerotische plaque het pathologische substraat vormt voor het optreden van cardio-vasculaire ischemische voorvallen. De ernst van coronaire hartziekten is echter niet de enige factor die van invloed is op de prognose van de patiënt. Bij patiënten met complexe coronaire hartziekten zijn, naast plaque, ook andere klinische factoren onderdeel van de definitieve resultaten en dit heeft gevolgen voor het besluitvormingsproces bij coronaire revascularisatie. Bovendien is coronaire revascularisatie nog steeds niet de juiste behandeling voor CHZ en zijn adequate risicobeoordeling, secundaire preventie en ontwikkeling van behandelingen vereist om het natuurlijke beloop van coronaire atherosclerose te kunnen beïnvloeden. In dit proefschrift worden waardevolle inzichten gegeven in deze onderwerpen en belangrijke gegevens verstrekt over risicobeheer bij CHZ.

BEELDFORMENDE METHODEN VOOR BEOORDELING VAN CARDIOVASculaire RISICO'S

In **hoofdstuk 1.1** gaven we een beschrijving van de huidige histopathologische definities en de allernieuwste beeldvormende technieken voor het opsporen van kwetsbare coronaire plaques. Eén van de meest gebruikte methoden voor *in-vivo* identificatie van kwetsbare plaques is Virtual Histology Intra-

vascular Ultrasound (VH-IVUS). In **hoofdstuk 1.2** beschreven we het algoritme voor VH-IVUS met behulp van de 45-MHz roterende IVUS-katheter en de bijbehorende *ex-vivo* validatie in vergelijking met de gouden standaard voor histologie.

De laatste jaren is coronaire CT-angiografie (CCTA) een veelvuldig toegepaste techniek, niet alleen vanwege de hoge diagnostische nauwkeurigheid, maar ook vanwege het feit dat CCTA de mogelijkheid biedt tot een niet-invasieve beoordeling van de totale ernst van (obstructieve en niet-obstructieve) coronaire atherosclerose. Meer recentelijk heeft deze techniek een volwassen stadium bereikt en bestaat er een grote hoeveelheid bewijsmateriaal voor de prognostische validiteit ervan. Bovendien heeft CT-angiografie zich verplaatst van het terrein van de 'beeldvormers' en de klinici naar de arena van de interventionele cardiologie. In **hoofdstuk 1.3** beschreven we de nauwkeurigheid, de prognostische waarde, en het nut en de beperkingen van CCTA bij de beoordeling van plaque-eigenschappen.

Bij coronaire angiografie is de aanwezigheid van coronaire plaques met complexe morfologische kenmerken het angiografische kenmerk voor instabiele coronaire syndromen. In **hoofdstuk 1.4** beoordeelden we met behulp van angiografie de kenmerken van coronaire plaques bij patiënten met een acuut coronair syndroom na niet-cardiale chirurgie, patiënten op de afdeling voor spoedeisende hulp met een spontaan acuut coronair syndroom en patiënten met stabiele coronaire hartziekten. In **hoofdstuk 1.5** beoordeelden we de verdeling van angiografische laesies met trombus over een totale populatie die is opgenomen met heterogene klinische manifestatie (stabiele,

instabiele angina pectoris, of een acuut coronaair syndroom) en de bijbehorende implicaties voor de langetermijnprognose.

Optische Coherentie Tomografie (OCT) is een intravasculaire, op licht gebaseerde beeldvormende methode met een bijna-histologische resolutie van 10-20 μm . OCT is momenteel de enige beschikbare technologie in de klinische setting die voldoende ruimtelijke resolutie biedt voor een nauwkeurige beoordeling van de dikte van de fibreuse kap. Het blijft moeilijk coronaire laesies op te sporen die de voorbodes zijn van acute voorvallen, aangezien deze voortdurend veranderingen ondergaan en hun veranderingen in de loop van de tijd niet zeer goed zijn getypeerd. In studies naar het natuurlijke beloop is alleen gebruikgemaakt van Optical Frequency Domain Imaging (OFDI) voor de beoordeling van fibroatheromen als een tweedimensionale structuur en soms als single-frame methode. In **hoofdstuk 1.6** beschreven we de veranderingen van coronaire fibroatheromen gedurende een follow-upperiode van 6 maanden. Hierbij werden de seriële volumetrische veranderingen van de fibreuse kap beschreven die met behulp van OCT zijn gemeten.

WISSELWERKING TUSSEN CORONAIRE ATHEROSCLEROSE EN KLINISCH PROFIEL

Er is gedetailleerd onderzoek gedaan naar patiënt- en plaquekenmerken om inzicht te krijgen in de relatie tussen risicofactoren en de kans op cardiovasculaire voorvallen. De klinische en gezondheidsgerelateerde uitkomstmaten die werden beoordeeld met behulp van de Seattle Angina Questionnaire (SAQ), zijn echter nooit gecorreleerd met de kenmerken van obstructieve plaque die wordt vastgesteld met behulp van intravasculaire

echografie (IVUS). In **hoofdstuk 2.1** bespraken we de invloed van geslacht op de progressie/regressie van coronaire atherosclerose bij beoordeling met behulp van intravasculaire echografie. In **hoofdstuk 2.2** werd ingegaan op de meest uitgebreide beschrijving ooit van bevindingen vóór behandeling met intravasculaire echografie (IVUS-weefselbeelden bestaande uit grijsschaal en achterwaartse verstrooiing) aan de hand van patiëntgegevens en gezondheidsgerelateerde uitkomstmaten die werden bepaald met behulp van de Seattle Angina Questionnaire (SAQ). We lieten zien dat de manifestatie van obstructieve coronaire hartziekten nog steeds kon worden gedifferentieerd met behulp van klinische kenmerken. Bovendien werd negatieve remodelering in verband gebracht met een hogere frequentie van angina pectoris door de SAQ. Door de patiënt genoemde fysieke beperking en stabiliteit van angina pectoris werden respectievelijk in verband gebracht met de grootte van de necrotische kern en de ernst van de plaque.

Coronaire angiografie geldt nog steeds als gouden-standaardmethode voor de besluitvorming bij coronaire hartziekten. Interventiecardiologen en chirurgen in de SYNTAX (SYnergy Between PCI With TAXUS and Cardiac Surgery)-studie gebruikten de SYNTAX-score (SS) aanvankelijk om uit het coronaire angiogram objectieve gegevens te extraheren over de technische uitdagingen die de coronaire anatomie stelt aan percutane coronaire interventie (PCI) en om discussies van het 'hartteam' te ondersteunen. Vervolgens werd duidelijk dat de SS een prognostische waarde had bij het voorspellen van korte- en langetermijnresultaten. In **hoofdstuk 2.3** lieten we zien dat de beoordeling aan de hand van de SYNTAX-score door klinici een

aanzienlijk verschil opleverde wanneer we deze vergeleken met de beoordeling door een ervaren kernlaboratorium. De combinatie van klinische factoren met de SYNTAX-score (aangeduid als de SYNTAX-II-score) verminderde de variabiliteit echter, zodat de voorspellende waarde ervan behouden bleef.

Bij de klinische patiëntkenmerken speelt diabetes mellitus een belangrijke rol bij de ontwikkeling van coronaire hartziekten en is deze aandoening in verband gebracht met een stijging van het sterftecijfer. Bovendien is ongeveer één vierde van de patiënten die een coronaire revascularisatie hebben ondergaan diabeet. In **hoofdstuk 2.4** onderzochten we of er een verschil bestaat in het aantal gevallen van stenttrombose tussen diabetische en niet-diabetische patiënten in een van de grootste gerandomiseerde stentstudies die naar stenttrombose werden gedaan.

RISICOSTRATIFICATIE BIJ COMPLEXE CORONAIRE HARTZIEKTEN

In een niet-spoedeisende situatie is een nauwkeurige risico-inschatting bij patiënten met complexe coronaire hartziekten (CHZ) essentieel om te bepalen of de patiënt moet worden behandeld met een percutane coronaire interventie (PCI) of coronaire bypasschirurgie (CABG). Momenteel wordt in de internationale richtlijnen voor dit besluitvormingsproces een multidisciplinaire aanpak aanbevolen die wordt aangeduid als het 'hartteam'. De SYNTAX-II-score (SSII) is bedoeld om het hartteam te helpen beslissen tussen CABG en PCI bij patiënten met complexe CHZ. De score is een combinatie van 2 anatomische en 6 klinische factoren en voorspelt de langetermijnsterfte bij patiënten die zijn behandeld met CABG of PCI. De SSII werd ontwikkeld in de gerandomi-

seerde, totale populatie van de SYNTAX-studie, waarbij de selectievertekeningen minimaal waren. De SSII heeft ook suggestieve waarde voor een revascularisatiestrategie (CABG of PCI) die afhankelijk is van het verschil tussen de geschatte sterftecijfers. De SSII beveelt CABG aan als het verschil in het voorspelde overlijdensrisico gunstig uitvalt voor CABG met een betrouwbaarheidsinterval van 95%. De SSII beveelt PCI aan als het verschil in de voorspelling van het overlijdensrisico gunstig uitvalt voor PCI met een betrouwbaarheidsinterval van 95%. Omgekeerd beveelt de SSII PCI of CABG aan als de voorspellingen van het overlijdensrisico binnen het betrouwbaarheidsinterval van 95% liggen van het verschil tussen de voorspellingen van het overlijdensrisico. In **hoofdstuk 3.1** beoordeelden we de toepasbaarheid van de SSII-aanbevelingen in combinatie met het besluitvormingsproces van het hartteam over de revascularisatiestrategie bij patiënten met coronaire hartziekten (CHZ) van 3 vaten. De SYNTAX-II-score bleek een geschikt hulpmiddel als richtlijn bij behandelingsbeslissingen voor patiënten met coronaire hartziekten in 3 vaten, en werd voor de overgrote meerderheid (85,4%) van de patiënten onderschreven door het hartteam. In **hoofdstuk 3.2** en **3.3** onderzochten we de validiteit van de theoretische behandelingsaanbeveling uit de SYNTAX-II-score voor de langetermijnprognose. We stelden vast dat patiënten bij wie de SYNTAX-II-score de aanbeveling CABG opleverde, maar die werden behandeld met PCI, een slechtere prognose hadden dan patiënten met een even zwaar wegend risico bij CABG als bij PCI, of wanneer de aanbeveling PCI luidde. Deze bevindingen hingen niet altijd samen met enkel de anatomische SYNTAX-score.

Voorheen werd de SSII overwegend gevalideerd bij Westerse patiënten. In **hoofdstuk 3.2** valideerden we de SSII in een Japanse populatie met complexe coronaire hartziekten. Japanners hebben unieke epidemiologische kenmerken. Japan heeft wereldwijd de hoogste levensverwachting bij de geboorte en een aanzienlijk lager sterftepercentage door cardiovasculaire aandoeningen dan Westerse landen. We toonden de sterke prognostische nauwkeurigheid van de SSII aan, zowel in de CABG- als in de PCI-patiëntengroep. In vergelijking met alleen de anatomische SS was de SSII nauwkeuriger bij de stratificatie van patiënten voor late mortaliteit in een werkelijke populatie met complexe coronaire hartziekten.

We gingen verder met de studie van de SYNTAX-II-score en in **hoofdstuk 3.5** onderzochten we het kosten-batenperspectief in de SYNTAX-studie. We stelden vast dat bij patiënten bij wie de SYNTAX-II-score wees in de richting van PCI op basis van een lagere voorspelde mortaliteit na 4 jaar, PCI ook in economisch opzicht prevaleerde, terwijl bij patiënten bij wie de SYNTAX-II-score wees in de richting van een operatie, CABG in hoge mate economisch aantrekkelijk bleek.

De relevantie van een onbeschermde stenose van de linker hoofdkransslagader (ULMCA: unprotected left main coronary artery) werd meer dan 100 jaar geleden voor het eerst beschreven. James Herrick beschreef het verhaal van een 55 jaar oude man die overleed tijdens een cardiogene shock na een periode van 52 uur. Bij autopsie werd een uitgebreide necrose van het linker ventrikel aangetroffen in combinatie met totale occlusie van de linker hoofdkransslagader door een trombus die een

gebied met atherosclerotische vernauwing afsloot. De verklaring voor deze omvangrijke necrose is het grote gebied van het myocard dat risico loopt bij patiënten met een ULMCA. Er is aangetoond dat bij een normale, rechts-dominante coronaire anatomie de linker kransslagader ongeveer 84% van de bloedstroom naar het linker ventrikel verzorgt. In **hoofdstuk 3.6** beschreven we de belangrijkste redenen, opzet, punten van overeenkomst en verschil van twee grootschalige gerandomiseerde studies naar PCI versus CABG bij ULMCA (EXCEL- en Noble-studie). Bovendien deden we in **hoofdstuk 3.7** voor de eerste keer een voorstel voor een prospectieve validatie van de SYNTAX-II-score in de EXCEL-studie. Op basis van de SYNTAX-II-score voorspelden we dat er 77,9% kans bestond dat de mortaliteit na 4 jaar lager was in de PCI-arm van de EXCEL-studie, met een kans van 40% dat dit leidt tot statistische significantie ten gunste van PCI.

RISICOBEOORDELING EN -BEHEER NA REVASCULARISATIE

Coronaire hartziekten zijn, hoofdzakelijk, chronische en progressieve aandoeningen. Daarom is het risico voor de patiënt niet ten einde na een coronaire revascularisatie. In **hoofdstuk 4** bestudeerden we het risicobeheer na revascularisatie. Eén van de belangrijkste factoren voor overleving op langere termijn van deze patiënten is de volledigheid van coronaire revascularisatie. In **hoofdstuk 4.1** bespraken we de invloed van de residuele (rSS) SYNTAX-score bij ULMCA-revascularisatie. De rSS werd ontworpen en gevalideerd voor het kwantificeren van het absolute aantal onbehandelde CHZ na revascularisatie via een percutane coronaire interventie (PCI). $rSS > 8$ werd aangemerkt als een niveau voor een onvolledige revascularisatie, welke in verband

werd gebracht met een verhoogde mortaliteit en ischemische bijwerkingen.

We gingen verder met het bestuderen van de mate van coronaire revascularisatie en in **hoofdstuk 4.2** deden we een voorstel voor de SYNTAX Revascularization Index (SRI). Deze geeft de verhouding weer van behandelde CHZ in de beginfase (SYNTAX-score beginfase [bSS]; delta SYNTAX-score [DSS]) en biedt de mogelijkheid om de hoeveelheid behandelde ziektegevallen (SRI= DSS/bSS 100) met behulp van PCI-revascularisatie beter te kwantificeren en te beschrijven. In **hoofdstuk 4.3** toonden we aan dat de SRI een onafhankelijke voorspellende factor is voor de mortaliteit na 1 jaar bij patiënten met acute coronaire hartaandoeningen zonder ST-verhoging en geringe anatomische complexiteit. In **hoofdstuk 4.4** valideerden we de SRI in de populatie met complexe CHZ van de SYNTAX-studie, waarbij SRI>70% overeenkwam met een "redelijke" doelstelling voor patiënten met complexe coronaire hartziekten.

Verder speelt ook vermindering van de risicofactoren na een coronaire revascularisatie een grote rol bij de overlevingskans van patiënten. Roken is een welbekende risicofactor voor het ontstaan van coronaire hartziekten. In sommige studies bestond echter het vermoeden van een 'rokersparadox'. Dit hield in dat bij rokers met CHZ, en met name myocardinfarct, de resultaten neutraal of gunstig waren. In **hoofdstuk 4.4** bestudeerden we de combinatie van de rookstatus en de klinische resultaten in de gerandomiseerde, gecontroleerde SYNTAX-studie na een follow-upperiode van 5 jaar. Roken werd in verband gebracht met slechte klinische resultaten na revascularisatie bij patiënten met complexe CHZ. Dit onderstreepte nog eens het belang van pogingen

om te stoppen met roken om de voordelen van de revascularisatie te verhogen.

Optimale behandeling van dyslipidemie verbetert de klinische resultaten bij patiënten met coronaire hartziekten. In **hoofdstuk 4.5** onderzochten we welke risicofactoren er bestaan wanneer de door de Europese Vereniging voor Cardiologie aanbevolen cholesterolniveaus niet worden gehaald. Er bestond een significante daling van de LDL-C-niveaus gedurende 1 jaar; een significant gedeelte van de patiënten (55% na 6 maanden en 58% na 1 jaar) bleef echter boven de LDL-C-streefwaarde. We stelden vast dat o.a. de volgende factoren samenhangen met het niet bereiken van de LDL-streefwaarden: hogere LDL-niveau in de beginfase, voorgeschiedenis van myocardinfarct en ontbrekende/ontoereikende statinebehandeling.

Het effect van bioresorbeerbare scaffolds op het natuurlijke beloop van coronaire atherosclerose

In de cardiovasculaire wetenschap werd altijd gezocht naar een manier om het natuurlijke beloop van coronaire atherosclerose te beïnvloeden. De klinische introductie van bioresorbeerbare scaffolds (BRS) leidde tot een revolutionaire verandering in de toepassing van lokale behandeling van coronaire aandoeningen. Deze hulpmiddelen bezitten het unieke vermogen om te voorzien in een tijdelijke structuur die nodig is om de doorgankelijkheid van het bloedvat na een interventie te handhaven, terwijl ze een antiproliferatief middel afgeven. Vanwege hun polymere samenstelling hebben bioresorbeerbare vasculaire scaffolds (BVS) unieke eigenschappen bij beeldvormend onderzoek. In **hoofdstuk 5.1** beschreven we de beeldvormende methoden

voor BRS, vergeleken we BRS met metalen stents en beschreven we de klinische relevantie van BRS.

Wijzigingen aan het ontwerp en de samenstellingen van bioresorberebare vasculaire scaffolds (BRS) kunnen van invloed zijn op hun afbreekbaarheid, de biomechanische eigenschappen aantasten (met het risico op late recoil) en mogelijk in verband worden gebracht met een tweede ontstekingsgolf van de slagaderwand. Daarom is het cruciaal dat de afbreekbaarheid van BRS wordt bestudeerd om deze technologie volledig te begrijpen. In **hoofdstuk 5.2** werd de echogeniciteit gevalideerd (een geautomatiseerde en kwantitatieve analyse van coronaire weefselcomponenten; hierbij wordt de intensiteit van de grijsschaal gescoord en wordt als referentie het gemiddelde helderheidsniveau van de adventitia gebruikt) als vervanging voor de afbreekbaarheid van polylactide scaffolds.

OCT heeft een centrale rol gespeeld bij het verwerven van inzicht in de BRS-prestaties op kortere en langere termijn, aangezien deze methode meer gedetailleerde en nauwkeurige morfologische informatie oplevert over BRS dan intravasculaire echografie. In **hoofdstuk 5.3** hebben we gekeken naar de acute en langetermijnmethodologie, en de klinische toepassing van OCT bij de beoordeling van BRS.

Al vele jaren richt men zich op beïnvloeding van de omvang van coronaire plaques, ofwel via lokale (instrumentele) ofwel via systemische behandeling. Gewoonlijk worden patiënten gelijktijdig behandeld met medicatie en PCI. Daarom zal de respons van de coronaire vaatwand variëren overeenkomstig

de wisselwerking tussen beide behandelingen. Bij de follow-up zullen de implantaten zijn omgeven door plaque, namelijk achter de stentstruts ('peri-stent') en endoluminaal (neo-intima). Deze twee compartimenten zijn biologisch actief en zullen op verschillende wijze worden beïnvloed door de aanwezigheid van een complexe wisselwerking die ontstaat door het platform (metaal/polymeer) + polymeer + geneesmiddel. Zo zullen everolimus-eluerende stents/scaffolds op vergelijkbare wijze invloed uitoefenen op de plaque-omvang (d.w.z. door verwijdering van macrofagen en remming van de vorming van neo-intima). Het netto effect zal echter ongelijk zijn omdat de platformen verschillend zijn (metaal versus polymeer). Daarom kunnen de effecten die deze complexe wisselwerking (geëlueerd geneesmiddel/platform) heeft op de plaque-omvang alleen worden onderzocht door seriële meting van de omvang van het media- en neo-intimacompartiment van de coronaire plaque. In **hoofdstuk 5.4** laten we zien dat lokale hulpmiddelen een andere uitwerking op de omvang van de coronaire plaque hebben en dat dit afhankelijk is van het platform (metaal versus polymeer), en van het feit of er een kale of medicijn-eluerende stent wordt gebruikt. Met name de totale plaque-omvang nam in de sequentiële cohorten van Absorb BVS 1.1 toe met 16,2% 2 jaar vanaf de baseline, terwijl deze stijging na 3 jaar vanaf de baseline nog maar 5% bedroeg.

Het mechanisch gedrag van de vaatwand lijkt samen te hangen met de samenstellingskenmerken van de plaque en een voorspellende factor te zijn voor latere cardiovasculaire voorvallen. Patiënten met plaques met een hoge vervorming krijgen waarschijnlijk eerder te maken met acute coronaire voorvallen dan

patiënten met laesies met lage vervorming. In verschillende studies is aangetoond dat een medicinale of interventionele behandeling de mechanische eigenschappen van de vaatwand kan beïnvloeden door verandering van de componenten. In **hoofdstuk 5.5** stelden we vast dat na implantatie van Absorb BVS 1.1 de vervorming van de vaatwand na verloop van tijd geleidelijk aan afnam.

Enkele van de mogelijke voordelen van bioresorbeerbare scaffolds, namelijk vermindering van atherosclerotische plaque en late lumenvergroting in de behandelde gebieden, vormen mogelijk de aanleiding tot verschuivingen in het behandelingsparadigma voor coronaire hartziekten. Bij farmacologische behandeling is echter ook aangetoond dat het, afhankelijk van het klinische profiel van de patiënt, mogelijk is plaqueregressie te bevorderen. Daarom hangt plaqueregressie bij patiënten die zijn behandeld met bioresorbeerbare scaffolds mogelijk niet samen met dit hulpmiddel zelf, maar is dit het gevolg van het effect van de farmacologische behandeling op een vat dat is bevrijd van zijn interne 'kooi'. In **hoofdstuk 5.6** hebben we een intra-patiënt multislice-computer-tomografie vergelijking gemaakt tussen matchende segmenten (genormaliseerd door de segmentlengte) van de scaffold-regio's en niet-behandelde segmenten voor: lumenvolume, vaatvolume, plaquevolume, plaque-ernst en veranderingpercentage in het volume van de atherosclerotische plaque. Bij seriële vergelijking bleek dat de met scaffolds behandelde segmenten in de periode tussen 18 maanden en 5 jaar geen significante veranderingen vertoonden van de gemiddelde plaque-ernst, het totale atheroomvolume, het totale lumenvolume en het vaatvolume. Omgekeerd vertoonden de

niet-behandelde segmenten een significante toename van de plaque-ernst ($2,7 \pm 6,5\%$; $P < 0,01$) en genormaliseerde plaquevolumes ($8,0 \pm 22,8 \text{ mm}^3$, $P < 0,01$). Dit resulteerde in een significant verschil in plaque-ernst bij vergelijking tussen met scaffolds behandelde en niet-behandelde segmenten ($P = 0,03$).

CONCLUSIES

In dit proefschrift worden uitgebreid de talloze overwegingen weergegeven die samenhangen met de risicostratificatie voor coronaire hartziekten, evenals de toekomstperspectieven voor interventionele cardiologie. Ik ben van mening dat dit proefschrift waardevol is, met name vanwege de volgende redenen:

- Het biedt een uitgebreide richtlijn voor de beeldvormende modaliteiten bij de bepaling van hoge risicofactoren voor coronaire hartziekten;
- Het verschaft belangrijke inzichten in de wisselwerking tussen klinische en anatomische overwegingen bij de prognose van patiënten en de gevolgen van beide op de besluitvorming;
- Het biedt als eerste een onvertekende prospectieve validatie van een risicoscore;
- Het beoordeelt de behoeften en de problemen van patiëntbehandeling na een coronaire revascularisatie;
- Het presenteert nieuwe gegevens over het effect van bioresorbeerbare scaffolds voor beïnvloeding van coronaire atherosclerose.

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Later, in the beginning of 2012, Prof. Lemos came to me with the “crazy idea” to study abroad. My initial reaction was “Wow !! That would be wonderful. But no, I’m too old for this”. Then, instead of choosing other colleague (he has a brilliant team), he insisted that it would be a great opportunity for me. In April 2012 he went to the GI2 congress and met Prof. Patrick W. Serruys. Prof. Lemos talked to him and said that I was welcome for a 2 years fellowship at the famous Thoraxcenter, Rotterdam. Our following conversations were full of unprecedented support in my life: professional reliability, tips about The Netherlands and complete willingness to take even the most basic questions. I will never be able to

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DEPARTMENT OF PUBLIC HEALTH, THORAXCENTER, ERASMUS MC

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DIVISION OF IMAGE PROCESSING, LEIDEN UNIVERSITY MEDICAL CENTER

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INVESTIGATORS OF COMPLEX CAD STUDIES: SYNTAX, SYNTAX II, EXCEL, NOBLE AND CREDO-KYOTO

Patrick W Serruys, Marie-Claude Morice, Arie-Pieter Kappetein, Greg Stone, Joseph F. Sabik, Antonio Colombo, David R. Holmes, Michael J. Mack, Elisabeth Stähle, Ted E. Feldman, Marie-angèle Morel, Keith D. Dawkins, Vasim Farooq, Simon Walsh, Javier Escaned, Adrian Banning, Takeshi Kimura, Evald H Christiansen and Friedrich W. Mohr. It was a great honour to work alongside such a unique and inspirational team.

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Books

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Co-Editor: The Clinical Atlas of Transcatheter Aortic Valve Therapies. Europa Digital & Publishing. <http://www.pcronline.com/redirect/valveatlas>

Book Chapters

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