Angiographic Applications for Modern Percutaneous Coronary Intervention

Chrysafios Girasis

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Angiographic Applications for Modern Percutaneous Coronary Intervention

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To my parents

To Elina

Table of contents

PART III: Bifurcation QCA in clinical studies

PART V: Summary and conclusions

PART I

Preface

Chapter 1

General introduction and outline of the thesis

Introduction

Invasive coronary angiography is still considered a cornerstone in the diagnosis and treatment of coronary artery disease, despite its inherent limitations. Whereas visual estimates of coronary artery stenosis are highly variable even among experts, quantitative coronary angiography (QCA) has already been proven an objective and reproducible way to quantify the extent of coronary stenoses located in single-vessel segments. Angiographic measurements can be used on-line in order to help interventional cardiologists size and deploy intracoronary devices, whereas off-line they can help us evaluate the efficacy of coronary interventions as well as the progression of coronary atherosclerosis.

Two-dimensional (2-D) single-vessel analysis has long been the conventional methodology to analyze target vessel segments assuming smooth vessel tapering between adjacent bifurcations. However, this methodology fails in the analysis of bifurcation lesions, because of the relatively acute vessel tapering from the proximal main vessel (PMV) to the distal main vessel (DMV) and the side-branch (SB). By not acknowledging this fractal geometry, single-vessel analysis may result in the underestimation of proximal vessel size and stenosis severity; conversely, lesions in the distal vessel segments may be overestimated. These shortcomings call for the development of dedicated bifurcation QCA algorithms, reporting diameter derived values separately for PMV, DMV and the SB.

Beyond the diameter derived measures, another important piece of QCA derived information is the angulation between the main vessel and the SB; however, definitions and measurement methods are still at variance. The European Bifurcation Club has adopted a definition, according to which proximal and distal bifurcation angle (BA) are delineated between the PMV and the SB, and between the DMV and the SB respectively. Regarding BA quantification, until recently a binary approach was adopted; bifurcations used to be divided in T-shaped (BA≥70°) and Y-shaped ones (BA<70°) according to visual assessment or calculations using digital calipers. Therefore, automated algorithms for BA calculation have been implemented in dedicated bifurcation QCA software. Bifurcation angle has gained attention due to growing evidence that it can affect immediate procedural success and long-term outcome.

Notwithstanding the development of dedicated algorithms, optimal visualization of a bifurcation lesion, and especially the SB ostium, is equally important and increasingly challenging. However, conventional angiographic analysis is limited by the 2-D representation of 3-D coronary anatomy; resorting to operator expertise does not always help acquire the optimal projections. This difficulty is even more pronounced in the case of bifurcation lesions; vessel overlap and tortuosity interfere with angiographic analysis and can mask obstructive coronary lesions. Furthermore, out-of-plane magnification and foreshortening, often not fully appreciated, result in inaccurate estimates for vessel size and lesion length and thereby in erroneous stent sizing and deployment. Owing to flat-panel detectors and increased computational power of contemporary workstations, a spatially accurate 3-D reconstruction of the vessel lumen can be made available in real time for single-vessel and bifurcation lesions, when combining two orthogonal 2-D angiographic projections.

Single-vessel QCA algorithms were validated *in vitro* and *in vivo* versus phantom objects of known dimensions; a similar validation against a gold standard was lacking for 2-D and 3-D dedicated bifurcation QCA algorithms. The complex fractal nature of the coronary bifurcation along with the varying distribution of disease and angulation parameters posed a challenge equally for a representative design of a suitable bifurcation phantom as well as for the performance of QCA algorithms tested. Ultimately they will have to stand the test of reproducibility, precision and relevance, when used both in everyday clinical practice and in the context of large registries and randomized trials.

The SYNTAX score is a lesion-based angiographic scoring system originally devised to quantify the complexity of coronary artery disease and thereby facilitate consensus in the study of a diagnostic angiogram between surgeons and interventional cardiologists. In the randomized SYNTAX trial, it proved effective in predicting clinical outcomes after elective percutaneous coronary intervention (PCI) procedures in patients with three-vessel and/or left main coronary artery disease. The score's predictive ability for a number of clinical outcomes has subsequently been assessed in patient cohorts with a varying extent of coronary artery disease undergoing both elective and emergent PCI procedures, including but not limited to studies presented in this thesis.

Several of these studies have suggested that, being solely based on angiographic variables, the SYNTAX score cannot account for the variability related to clinical factors which are widely acknowledged to impact on long-term outcomes. Hence, integration of the patients' age, left ventricular ejection fraction and creatinine clearance with the SYNTAX score, in the Clinical SYNTAX score, has been shown to improve the predictive ability for adverse clinical outcomes after PCI. However, information regarding the very long-term performance of either SYNTAX score or Clinical SYNTAX score in an all-comers population is lacking.

Incomplete revascularization has been shown to be a surrogate marker of a greater burden and complexity of coronary disease and clinical co-morbidity, in both coronary artery bypass graft (CABG) surgery and PCI treated patients. Although the baseline SYNTAX score, calculated prior to surgical revascularization, has been shown not to have any effect on the short- to long-term prognosis after CABG, it was hypothesized that a suitably developed (post)-CABG SYNTAX score that takes into account native coronary disease anatomy, including features such as calcification, bifurcation disease and the effects of surgical revascularization on the vessel-segment weighting, may have potential clinical and research applications. Naturally, validation of this new scoring methodology is required.

Outline of the thesis

In Part 2 of this thesis, the development and validation of dedicated bifurcation QCA software is discussed. The development of a series of precision-manufactured plexiglas bifurcation phantoms, specifically designed for the validation of bifurcation QCA algorithms is presented (**Chapter 2**). Several dedicated 2-D QCA algorithms for bifurcation segmental analysis are validated *in vitro* (**Chapters 3** and **4**). Also, a novel dedicated 3-D QCA methodology for bifurcation lesions is described (**Chapter 5**), which was further developed and validated against the same precision-manufactured plexiglas bifurcation phantoms (**Chapter 6**). Finally, a number of bifurcation phantom images were used in order to investigate the adequacy of visual assessment in bifurcation lesions taking into account current bifurcation QCA software standards; the results of a survey among experts in the field of bifurcation PCI are reported (**Chapter 7**).

In Part 3 the use of bifurcation QCA in clinical studies is discussed. The long-term outcomes after the V stenting technique in *de novo* bifurcation lesions using drug-eluting stents are reported in patients from the RESEARCH and T-SEARCH registries (**Chapter 8**). The long-term clinical outcomes and independent predictors of major cardiac events in unprotected left main coronary artery disease treated by PCI with drug-eluting stents are investigated in patients from the RESEARCH and T-SEARCH registries; next to left main BA parameters, the prognostic value of SYNTAX score is explored as well (**Chapter 9**). The 3-D BA parameters of the left main coronary artery, the effect of PCI on this angulation, and the impact of 3-D BA on 1-year clinical outcomes are explored in patients randomized to left main PCI within the SYNTAX trial (**Chapter 10**). The impact of 3-D BA parameters on 5-year clinical outcomes is further investigated in this same cohort of patients randomized to left main PCI within the SYNTAX trial (**Chapter 11**). Furthermore, the acute procedural and six-month clinical outcomes after left main PCI with a dedicated bifurcation stent are reported in patients included in the TRYTON left main multicentre registry (**Chapter 12**).

In Part 4 several clinical applications of the SYNTAX score and derivative scores are discussed. Initially, the reproducibility of the SYNTAX score is reassessed in the angiograms of 100 randomly selected patients enrolled in the SYNTAX trial (**Chapter 13**). The predictive value of the SYNTAX score regarding 1-year major adverse cardiac events is evaluated in the all-comers population of the LEADERS trial (**Chapter 14**). In addition, the ability of SYNTAX score and Clinical SYNTAX score to predict very long-term outcomes in an all-comers population receiving drug-eluting stents is investigated in the SIRTAX trial population (**Chapter 15**). The rationale, development and feasibility of the newly developed CABG SYNTAX score are discussed (**Chapter 16**), whereas the 5-year outcomes from the CABG arm of the SYNTAX-LE MANS left main angiographic substudy are also reported stratified according to the CABG SYNTAX score (**Chapter 17**).

PART II

Bifurcation QCA: development and validation

Chapter 2

Novel bifurcation phantoms for validation of quantitative coronary angiography algorithms

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Girasis C, Schuurbiers JC, Onuma Y, Serruys PW, Wentzel JJ
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Novel Bifurcation Phantoms for Validation of Quantitative Coronary Angiography Algorithms

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Background: Validation is lacking for two- and three-dimensional (2D and 3D) bifurcation quantitative coronary angiography (QCA) algorithms. **Methods:** Six plexiglas phantoms were designed, each of them mimicking a coronary vessel with three successive bifurcations lesions, wherein at least one vessel segment had a percent diameter stenosis (DS) of $\geq$60%. The five most frequently occurring Medina classes (1,1,1), (1,1,0), (0,1,0), (0,1,1), and (1,0,0) were used in the design. Diameters of the daughter vessels in every bifurcation were dictated by the scaling law of Finet. Lesions were cosinus-shaped in longitudinal view and circular-shaped in cross-sectional view. At the level of the carina, lesions were becoming eccentric, favoring "plaque" at the outer bifurcation walls. Adjacent bifurcation lesions were kept distant by nontapering, stenosis-free segments of $\geq$10 mm length. The direction of the side branch relative to the main vessel was based on relevant literature. The phantoms were precision manufactured using computer-aided design and machining techniques. Because of the high drilling accuracy (within 10 μm), the 3D luminal surface description of the phantom could be used to determine the true lumen dimensions and bifurcation angle (BA) values of the final geometry. **Results:** Our series of bifurcation phantoms comprised 33 narrowed and 21 stenosis-free vessel segments with a mean true minimal lumen diameter (MLD) value of 0.98 ± 0.40 mm (range, 0.53–1.96 mm) and 2.29 ± 0.74 mm (range, 1.40–4.00 mm), respectively. Overall, the mean true values for MLD, reference diameter, and DS were 1.49 ± 0.85 mm, 2.70 ± 0.71 mm, and 40.9% ± 34.2%. The mean true values for the proximal and the distal BA were 123.6° ± 19.0° and 69.6° ± 19.9°, respectively. **Conclusions:** Six plexiglas phantoms containing a total of 18 bifurcations lesions with variable anatomy and Medina class were designed and precision manufactured to facilitate the validation of bifurcation QCA algorithms.

Key words: coronary angiography; quantitative coronary angiography; phantom; software validation; in vitro

INTRODUCTION

Current quantitative coronary angiography (QCA) algorithms, despite marked variability in performance [1,2], can provide us with reliable geometric measurements of single-vessel coronary lesions. These measurements serve either as online sizing tools [3] and help interventional cardiologists in tailoring therapy to the anatomy of a given patient, or, when measured offline, as surrogate endpoints to evaluate the efficacy of intracoronary devices [4,5] and the progression of atherosclerosis [6]. To establish their accuracy and precision, these algorithms were validated in vitro and in vivo versus phantom objects of known dimensions [1,2,7–10].

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TABLE I. Medina Class Frequency of Occurrence

	(1,0,0)	(1,1,0)	(1,0,1)	(0,0,1)	(0,1,0)	(0,1,1)	(1,1,1)
Enrico et al., *n* (%) (15)	26 (13.3)	79 (40.3)	1 (0.5)	11 (5.6)	45 (23.0)	0 (0.0)	34 (17.3)
Collins et al., *n* (%) (16)	38 (9.5)	28 (7.0)	n/a	5 (1.2)	52 (13.0)	33 (8.3)	243 (60.9)
van Mieghem et al.*, *n* (%) (17)	10 (21.7)	8 (17.4)	8 (17.4)	5 (10.9)	8 (17.4)	2 (4.3)	5 (10.9)
BBC-ONE trial, *n* (%) (18)	24 (4.8)	45 (9.0)	45 (9.0)	3 (0.6)	15 (3.0)	67 (13.5)	299 (60.0)
Cumulative, study size-adjusted, frequency of occurrence	**98 (8.6)**	**160 (14.0)**	**54 (4.7)**	**24 (2.1)**	**120 (10.5)**	**102 (9.0)**	**581 (51.0)**

n/a, nonavailable.
*Angiographic adjudication.

A similar validation is still lacking for two- and three-dimensional (2D and 3D) bifurcation QCA algorithms [11]. The complex fractal nature of the coronary bifurcation along with the varying distribution of disease and angulation parameters between the parent and the daughter vessels poses a challenge for a representative design of such a bifurcation phantom; therefore, detailed analysis and literature review of reported dimensions in the bifurcation region are required. This is exactly what has been advocated by the European Bifurcation Club to reconcile the diverse methodologies and to create a standard QCA approach for the evaluation of bifurcation lesions [11–13].

This report presents the development of a series of custom made, precision manufactured plexiglas bifurcation phantoms, based on data from relevant literature and specifically designed for the validation of bifurcation QCA algorithms.

MATERIALS AND METHODS

Six plexiglas phantoms were designed, each of them mimicking a coronary vessel with three successive bifurcations; every individual bifurcation had a lesion, wherein at least one vessel segment had a percent diameter stenosis (DS) of $\geq$60%. The Medina class [14] of the bifurcation lesions was defined by the distribution of degree of stenosis in the three vessel segments comprising the bifurcation. The anatomy of the lesion was defined by the vessel segment reference diameter, the minimal lumen diameter (MLD), the lesion length, and the angulation parameters. The selection of individual bifurcation lesion characteristics attributed to this dataset of 18 phantom bifurcations was derived from relevant literature.

Phantom Design

Medina class. The selection of the Medina classes used in the phantoms' design was based on studies done by Enrico et al. [15], Collins et al. [16], Van Mieghem et al. [17], and the British Bifurcation Coronary Study (BBC ONE) [18]. The study size-adjusted mean frequency of occurrence of the 7 Medina classes in the summed patient population of these studies (n = 1,139) is reported in Table I. The five most frequently registered Medina classes, (1,1,1), (1,1,0), (0,1,0), (0,1,1), and (1,0,0) were used in the phantom bifurcations (Fig. 1).

Vessel segment reference diameter. In every phantom, the stenosis-free diameter of the proximal main vessel (PMV) of the first bifurcation was 4 mm, reflecting the usual mean reference diameter of the left main coronary artery (LMCA) [19,20]. As the bifurcation is perceived to be an object of fractal geometry, the stenosis-free diameters of the distal main vessel (DMV) and the side branch (SB) were derived from the study by Finet et al. [21], investigating the ratio between PMV, DMV, and SB in 173 coronary bifurcations using QCA. For every PMV diameter of the 18 phantom bifurcations, the corresponding DMV diameter was determined from a table by Finet, showing five decreasing PMV diameter ranges and the corresponding mean DMV diameters. The SB diameter was then calculated by the scaling law of Finet, wherein PMV $= 0.678 * (\text{DMV} + \text{SB})$. Consequently, in every phantom, the PMV, DMV, and SB stenosis-free diameters were 4.00, 3.30, and 2.60 mm for the first, 3.30, 2.50, and 2.40 mm for the second, and 2.50, 2.30, and 1.40 mm for the third bifurcation, respectively (Fig. 1).

Stenosis-free segments outside the lesion boundaries in the PMV, DMV, and SB were not allowed to taper; they were of adequate length ($\geq$10 mm) to serve as reference segments for the calculation of DS. Because the reference diameter function in the current 2D QCA bifurcation software is at variance [11,22], and not wanting to introduce bias favoring either definition, we opted for this procedure to define the reference diameter and thus the DS values for the lesions in the respective vessel segments, very similar to the procedure adopted by Oviedo et al. [20].

MLD. The vessel segments that were affected by the bifurcation lesions were chosen to have DS values of either 40, 60, or 80%; the MLD values were derived, given the respective reference diameter. In the remaining, stenosis-free, vessel segments the MLD equaled the reference diameter.

The location of the MLD with respect to the bifurcation was investigated by Sano et al. [23] in an intravascular ultrasound (IVUS) study; of 115 LMCA lesions,

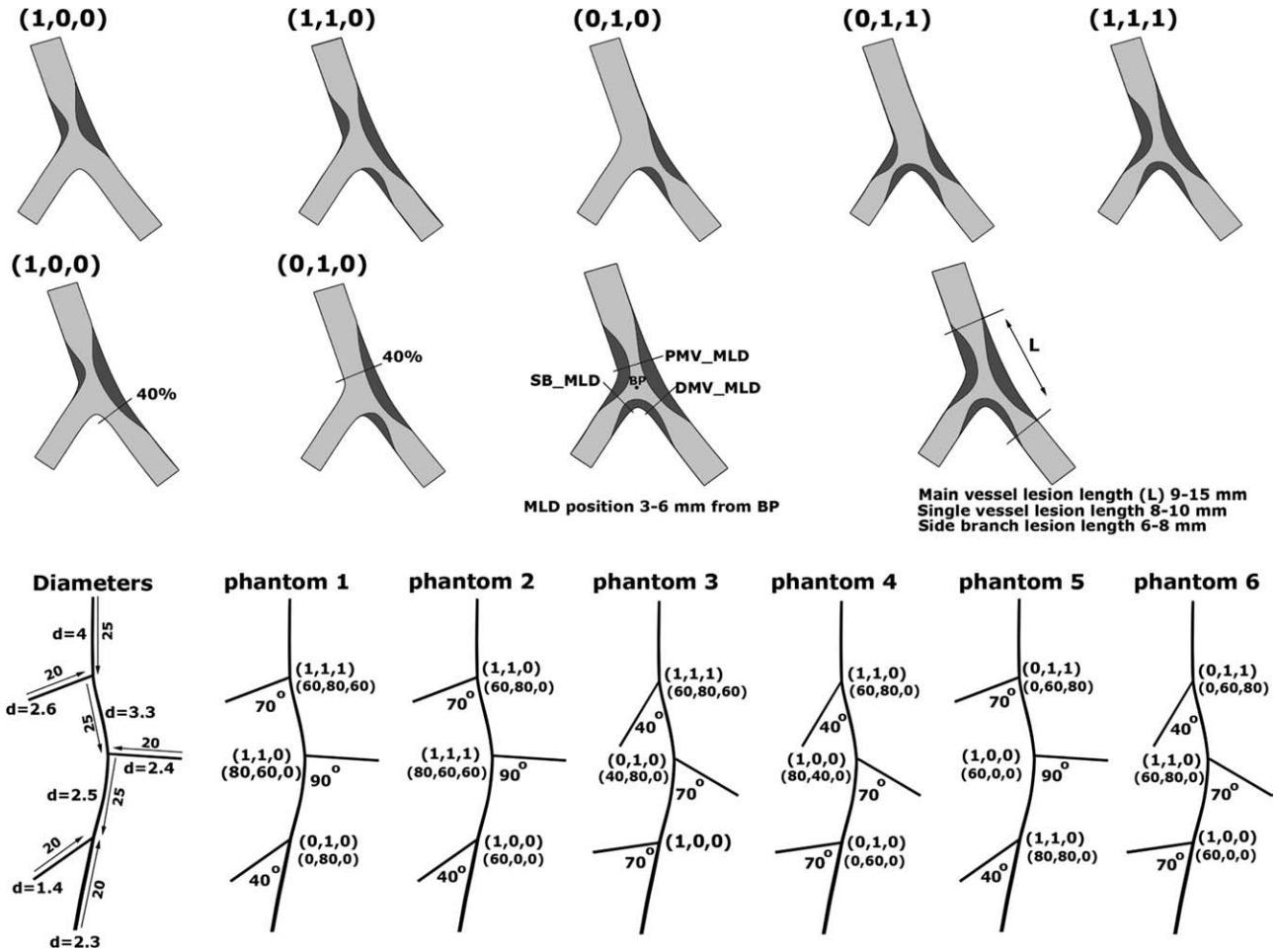

Fig. 1. Overview of the specifications of the six different bifurcation phantoms. Upper panel: schematic representation of five different Medina classes employed in the design. Middle panel: left side: two bifurcation geometries involving sites with 40% percent diameter stenosis (DS). Right side: schematic representation of the minimal lumen diameter (MLD) position and lesion length in the proximal main vessel (PMV), the distal main vessel (DMV), and the side branch (SB). Bottom panel: left side: stenosis-free diameters of the PMV, DMV, and SB and segment lengths of the bifurcation phantoms. Right side: schematic representation of all phantoms. Medina class (including DS values) and SB direction with respect to the DMV are reported for each bifurcation.

the MLD was positioned within 3 mm of the bifurcation in 65 cases. A criterion of 5 mm distance from the SB ostium or the bifurcation has been used as well [24,25]. In the phantom design, the bifurcation point was defined as the center of the largest inscribed sphere within the reference diameter contours. Taking this definition and literature data into account, we opted for an MLD position within 3–6 mm from the bifurcation point. The MLD position and the proximal and distal ends of the lesion were joined using spline interpolation.

Lesion length and shape. The length of the bifurcation lesions was based on randomized trials by Colombo et al. [26,27] and Steigen et al. [28] and large prospective registries by Di Mario et al. [29] and Collins et al. [16]. The mean lesion length in the bifurcation region in these studies varied from 10.8 $\pm$ 4.8 to 18.0 $\pm$ 8.3 for the main vessel and from 5.1 $\pm$ 4.4 to 9.2 $\pm$ 4.8 mm for the SB. Di Mario et al. [29] found mean PMV and DMV lesion lengths of 8.1 $\pm$ 5.4 and 10.1 $\pm$ 7.7, respectively.

From these data, main vessel and SB lesion length in the phantom bifurcations were chosen to vary from 9 to 15 mm and from 6 to 8 mm, respectively; lesion confined to either PMV or DMV had a length from 8 to 10 mm. Lesions were cosinus-shaped in longitudinal view, ensuring a smooth tapering length function; "plaque" was circular-shaped in cross-sectional view for design simplicity and due to manufacturing constraints. However, at the level of the carina, lesions were becoming eccentric, favoring "plaque" at the outer bifurcation walls [20,30]. Adjacent bifurcation lesions in the main

phantom vessel were kept distant by nontapering, stenosis-free segments of $\geq$10 mm length.

Angulation parameters. In the phantoms design, we had to arbitrarily define the SB direction with respect to the DMV of each bifurcation as the angle between straight lines extending from the bifurcation point through the center of 15 mm long segments into the DMV and SB segments, respectively. Values for this angle were derived from studies, where bifurcation angle (BA) calculations followed the European Bifurcation Club definitions [13]. Bifurcation QCA studies on LMCA cohorts [31,32] were combined with studies where the LMCA bifurcation was excluded [29], reporting mean distal BA values from 95.6° ± 23.6° to 58.1° ± 19.3°; in a multidetector computed tomography (MDCT) study by Pflederer et al. [33] distal BA values varied from 80° ± 27° to 46° ± 19°. From these data, we chose values of 40° ($n = 6$), 70° ($n = 9$), and 90° ($n = 3$) to be representative for the SB direction relative to the DMV (Fig. 1).

Because the available bifurcation QCA algorithms for BA definition are at variance, the true distal BA value of the final design was determined by defining branch vectors for the DMV and SB as described by Thomas et al. [34]; the BA was then defined as the angle between the projections of the branch vectors onto the bifurcation plane. Similar calculations were carried out for the proximal BA, delineated between the PMV and the SB.

Phantom Manufacturing

Taking into account the aforementioned, literature-based, specifications, the phantoms were designed using a computer-aided design program (Pro-engineer wildfire v4). In this way, a digital 3D model of the luminal surface of the three bifurcations for each phantom was created. All bifurcations of the phantom were in the same plane, which allowed splitting the 3D model into two identical longitudinal halves (Fig. 2). The geometric description of both half-luminal models were used to instruct a computer numerically controlled (CNC) milling machine (Fehlmann Picomax 60 HSC) to mill these models into 2 Perspex (Plexiglas) blocks of 110 × 40 × 10 mm after carefully flattening the surfaces to get an optimal contact between both halves of the phantom. Finally, a very thin layer of oil was applied to the surface of both halves to seal the transition layer. The two halves were put together with nylon bolds. After assembling the phantom, it was rinsed with a detergent solution to remove any redundant oil from the luminal surface. The phantom was filled with a contrast agent and closed at all SBs with nylon plugs (Fig. 2).

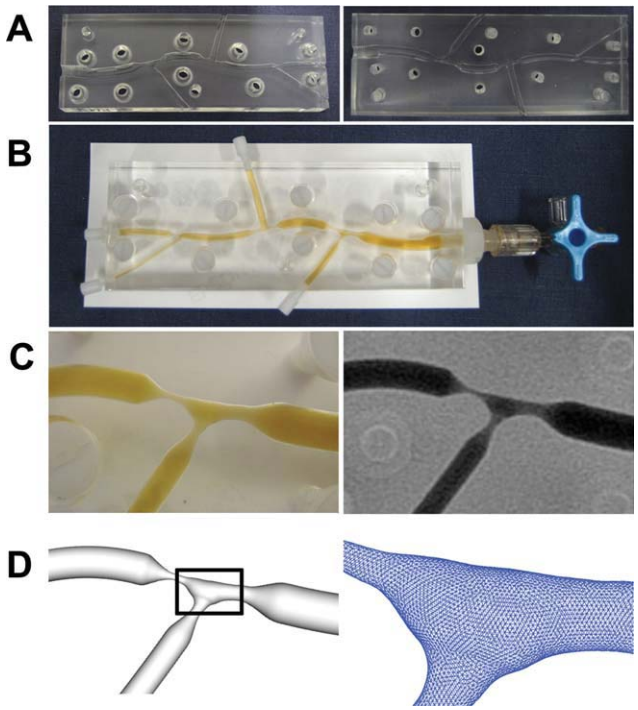

Fig. 2. Bifurcation phantom 1. A: Both half phantom parts of phantom. B: The assembled phantom filled with a colored liquid to visualize the lumen. C: Left side: a close-up of the first bifurcation. Right side: the resulting angiographic image. D: Left side: the surface rendered image of the first bifurcation. Right side: a close-up of the bifurcation area indicated by the square showing the tetrahedral surface elements.

Owing to the high accuracy of the machining process (within 10 μm), the 3D luminal surface description of the phantom, as exported from Pro-engineer in Surface Tesselation Language (STL) file format (Fig. 2), was used to determine the true lumen dimensions. Because the design process using spline interpolation allowed some freedom in lesion definition, the final anatomy of the bifurcation region, including the lesion shape, the MLD, and the BA values, was slightly deviated from the defined values. The true MLD and BA were determined from the 3D luminal surface description using VMTK (Vascular Modeling Toolkit v0.7). These values can be used as the golden standard for further validation studies.

RESULTS

The true MLD and DS values of the PMV, DMV, and SB and the true BA values in every phantom bifurcation are shown in Table II.

Our series of bifurcation phantoms comprised 33 narrowed and 21 stenosis-free vessel segments with a mean MLD value of 0.98 ± 0.40 mm (range, 0.53–1.96 mm) and 2.29 ± 0.74 mm (range, 1.40–4.00 mm), respectively. Overall, the mean values for MLD,

TABLE II. Phantom Dimensions

	Bifurcation	B1			B2			B3		
Phantom	Parameter	PMV	DMV	SB	PMV	DMV	SB	PMV	DMV	SB
P1	MLD (mm)	1.56	0.66	1.03	0.64	0.99	2.40	2.50	0.53	1.40
	DS (%)	60.9	80.0	60.3	80.5	60.6	0	0	76.9	0
	Medina		1,1,1			1,1,0			0,1,0	
	DBA (°)		84.2			97.3			40.3	
	PBA (°)		123.2			97.3			140.0	
P2	MLD (mm)	1.59	0.66	2.60	0.66	0.99	0.96	1.01	2.30	1.40
	DS (%)	60.3	80.0	0	79.9	60.3	60.1	59.4	0	0
	Medina		1,1,0			1,1,1			1,0,0	
	DBA (°)		81.1			102.9			40.3	
	PBA (°)		124.6			104.4			139.8	
P3	MLD (mm)	1.58	0.65	1.04	1.96	0.55	2.40	0.99	2.30	1.40
	DS (%)	60.6	80.2	60.0	40.7	78.1	0	60.3	0	0
	Medina		1,1,1			0,1,0			1,0,0	
	DBA (°)		47.4			82.7			67.8	
	PBA (°)		146.0			120.6			111.4	
P4	MLD (mm)	1.58	0.65	2.40	0.65	1.48	2.40	2.5	0.92	1.40
	DS (%)	60.6	80.2	0	80.2	40.6	0	0	59.9	0
	Medina		1,1,0			1,0,0			0,1,0	
	DBA (°)		53.7			82.4			68.1	
	PBA (°)		151.2			121.0			111.7	
P5	MLD (mm)	4.00	1.32	0.55	1.32	2.50	2.40	0.55	0.55	1.40
	DS (%)	0	60.1	78.7	60.0	0	0	78.0	76.1	0
	Medina		0,1,1			1,0,0			1,1,0	
	DBA (°)		70.6			89.6			54.9	
	PBA (°)		111.3			90.4			159.2	
P6	MLD (mm)	4.00	1.32	0.55	1.32	0.55	2.40	0.99	2.30	1.40
	DS (%)	0	60.1	78.7	60.1	78.1	0	60.3	0	0
	Medina		0,1,1			1,1,0			1,1,0	
	DBA (°)		39.5			82.2			67.8	
	PBA (°)		141.1			120.8			111.4	

B1–B3, bifurcation 1–bifurcation 3; P1–P6, phantom 1–phantom 6; DMV, distal main vessel; DS, percent diameter stenosis; DBA, distal bifurcation angle; PBA, proximal bifurcation angle; MLD, minimal lumen diameter; medina, medina class; PMV, proximal main vessel; SB, side branch. Distal BA, angle between DMV and SB; proximal BA, angle between PMV and SB.

reference diameter, and DS were 1.49 ± 0.85 mm, 2.70 ± 0.71 mm, and 40.9% ± 34.2%. The mean true values for the proximal and the distal BA were 123.6° ± 19.0° and 69.6° ± 19.9°, respectively.

DISCUSSION

Bifurcation lesions constitute a distinct lesion subset requiring dedicated classification, analysis, and treatment [12,13]. The multitude of studies already performed and still ongoing, evaluating different techniques and devices for bifurcation lesions, highlights the fact that consensus has not yet been reached regarding the optimum way to treat [13]. This has to some degree to do with the fact that angiography, the current golden standard to quantify outcome measures, is not yet standardized, especially when it comes to the ostium of the SB [11–13]. The obvious remedy for that was to take a step back and validate the available bifurcation QCA software packages to an object of known dimensions.

For the validation of single-vessel QCA software packages, three different series of phantoms had been developed, sharing some common features. Our group had produced a series of radiolucent plexiglas or polyamide cylinders with precision-drilled eccentric circular lumens with a diameter of 0.5–1.9 mm; these were filmed both in vitro and in vivo after inserting them in swine coronary arteries [8]. Hausleiter et al. [2] for the purpose of comparative in vitro validation of 8 QCA systems created nine stenotic and nine nonstenotic glas tubes, their inner diameter measuring 0.57–1.49 mm and 0.54–4.9 mm, respectively; after imaging, these tubes had to be cut into pieces to measure their true inner diameter. Finally, van Herck et al. [9] and Tuinenburg et al. [10] used in their studies the Medis QCA phantom (Medis medical imaging systems B.V., Leiden, The Netherlands), a plexiglas phantom consisting of 12 nonstenotic circular tubes with varying diameters from 0.51–5.00 mm. Obviously, these single-vessel phantoms were not suitable for validating bifurcation QCA algorithms owing to the complexity of the

bifurcation region; thus, a dedicated bifurcation phantom had to be designed for this purpose.

We considered several techniques to create a bifurcation phantom. Stereolithography had too low a resolution and poor sealing properties, whereas casts derived from diseased human or animal coronaries are complicated to create and it would be difficult to get a complete range of stenosis and BA values. Moreover, it would be necessary to validate the internal dimensions of these casts with another imaging modality with its inherent variability, and the material properties should match the typical characteristics of the imaging modality. Finally, casts made of gels are fragile and degrade over time and also need another imaging technique for validation.

We chose the above described computer-aided approach for its relative design and machining simplicity and for excluding the need of an additional validation of the internal dimensions of the phantom.

For the construction of the bifurcation phantoms, we selected plexiglas for its extremely high radiolucency, essentially having the same X-ray absorption coefficient as water, and its suitability for precision milling. Moreover, its transparency allowed visual inspection of the phantoms' lumen (air bubble-free filling) and the sealing quality of both halves.

MLD

A number of narrowed and stenosis-free vessel segments with varying MLD was created in order to represent the array of values encountered before interventional treatment [1,16,26–29]. A well appreciated flaw of the previously developed QCA systems was the over- and underestimation of small and large true MLD values, respectively, due to the limitations of the X-ray imaging systems [1–3,7–10]. Reiber et al. [35] provided us with cut-off values for MLD (0.66 mm), beneath which the true MLD values are significantly overestimated. Our selection of narrowed vessel segments in the bifurcation phantoms will allow us to investigate this phenomenon in the newly developed QCA systems.

Lesion Shape

A van der Giessen et al. [30], in a recent MDCT-based study, explored the spatial distribution of plaque in LMCA and non-LMCA bifurcation lesions relative to the expected wall shear–stress patterns, as can be derived from a general distribution in a bifurcation region. In that study, cross-sections 1 mm distal to the carina were studied. Plaque growth had indeed a predilection for the walls opposite the carina; however, it was reported to involve the carina in 31% of the studied cross-sections. In those cases, the plaque was always present in either of the adjacent quartiles of the vessel's circumference as well as in the outer bifurcation wall, thereby implying a circumferential growth of plaque from the low wall shear stress locations into the high wall shear stress flow-divider in the event of advanced atherosclerosis and excessive plaque burden. On the other hand, Oviedo et al. [20], in a very recent IVUS-based study on 140 patients with distal LMCA bifurcation lesions, reported that the carina was always spared of plaque growth, whereas plaque burden $\geq$40%, almost always being present in the PMV (LMCA in this situation), expanded into the DMV (left anterior descending) and the SB (left circumflex) in 90% and 66.4% of the cases, respectively. These findings were reported to be independent from BA, lesion severity, LMCA length, or remodeling. However, judging from the Medina class distribution in the bifurcation lesions of that cohort [20] by qualitative angiographic evaluation and comparing with studies such as the BBC-ONE [18], disease in the bifurcation region was apparently not excessive.

The phantom design was expected to be representative of usual lesion patterns, yet challenging the QCA software to be validated by presenting a number of lesions with excessive narrowing. Although the carina was kept free of disease, in the tightest stenoses designed, there was some disease implemented downstream the carina, however, with an eccentric lesion formation, favoring plaque presence on the opposite wall. The lesion shape was selected to be cosinus-shaped and of sufficient length to allow smooth tapering, contrary to the abrupt onset and termination of plaque in earlier phantoms [1].

Medina Class

The five most common Medina classes as derived from literature were used in the phantom design; the (1,1,0) and (0,1,0) classes could almost interchangeably be used for the ones not included, namely (1,0,1) and (0,0,1). It is just a matter of definition which branch is called the DMV and which is called the SB; analysis per se would not differ. Introducing DS values of at least 60% in the "diseased" vessel segments, we created a quantitative Medina classification, which by definition expresses more severe disease than a classification based on visual stenosis evaluation, as was the case in most clinical studies (Table I); it is well known that QCA results underestimate the severity of a lesion, compared to the angiographer's perception [36]. However, to introduce examples with lower degree of stenosis, we also included the 40% DS in our bifurcations (Fig. 1).

Angulation Parameters

BA measures have been linked both to procedural complexity and outcome measures after bifurcation stenting [13,37]. For design purpose, we defined the direction of the SB with respect to the DMV, based on straight centerlines of an arbitrary length of 15 mm. Despite the diversity in BA definition and calculations in relevant literature [29,31–33], we used the reported range of angles for the SB direction. To determine the true BA values from the 3D luminal surface, we reverted to the algorithm used by Thomas et al. [34]; this algorithm takes local vessel curvature into account and is based on the 3D vessel centerlines.

Limitations

The phantom design naturally has the inherent limitations of any artificial construction trying to mimic real life. The smooth walls of the phantoms do not resemble the jagged irregular appearance of the coronary vessel walls, especially after balloon dilation [1], nor can they reflect the bias of heart movement, being static objects. The bifurcations were constructed in a single plane, thereby permitting the placement in isocenter, lying horizontally on the flat surface of the angiographic table. Unfortunately, designing a phantom 3D bifurcation out of one plane is not permitted using the CNC method. However, in clinical practice, the optimal degree of angulation and rotation of the angiographic C-arm is selected in order to orient the X-ray beams perpendicular to the plane of a given bifurcation; thus, this limitation in design would hardly effect the applicability of our phantoms.

CONCLUSIONS

For the purpose of validating the 2D and 3D bifurcation QCA algorithms and thus standardizing the angiographic analysis of coronary bifurcation lesions, six plexiglas phantoms were designed and precision manufactured. Each phantom mimicked a coronary vessel with three successive bifurcations lesions with variable anatomy and Medina class. The selection of individual bifurcation lesion characteristics attributed to this dataset of 18 phantom bifurcations was derived from the relevant literature.

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Chapter 3

Two-dimensional quantitative coronary angiographic models for bifurcation segmental analysis: in vitro validation of CAAS against precision manufactured plexiglas phantoms

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Two-Dimensional Quantitative Coronary Angiographic Models for Bifurcation Segmental Analysis: In Vitro Validation of CAAS Against Precision Manufactured Plexiglas Phantoms

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Background: Quantitative coronary angiography (QCA) analysis for bifurcation lesions needs to be standardized. Objectives: In vitro validation of two models for bifurcation QCA segmental analysis. Methods: In the latest edition of the Cardiovascular angiography analysis system (CAAS 5v8, Pie Medical Imaging, Maastricht, The Netherlands) a 6-segment model for two-dimensional coronary bifurcation analysis was implemented next to the currently available 11-segment model. Both models were validated against 6 precision manufactured plexiglas phantoms, each of them mimicking a vessel with three successive bifurcation lesions with variable anatomy and Medina class. The phantoms were filled with 100% contrast agent and imaged with a biplane gantry. Images acquired in anteroposterior (AP) direction by either C-arm and at 30° right and left anterior oblique angulation were analyzed by two independent analysts, blinded to the actual dimensions. Manual correction of the contours was not allowed. Measurements for minimal lumen diameter (MLD), reference vessel diameter (RVD), percent diameter stenosis (DS) and bifurcation angle (BA) were compared with the true phantom dimensions. Results: In AP views the accuracy and precision (mean difference ± SD) of 11- and 6-segment model for MLD, RVD, and DS were 0.065 ± 0.128 mm vs. 0.058 ± 0.142 mm, −0.021 ± 0.032 mm vs. −0.022 ± 0.030 mm, and −2.45% ± 5.07% vs. −2.28% ± 5.29%, respectively. Phantom MLD values ≤0.7 mm were systematically overestimated; if excluded, MLD accuracy and precision became 0.015 ± 0.106 mm and 0.004 ± 0.125 mm for the 11- and 6-segment model, respectively. Accuracy and precision for BA were −2.2° ± 3.3°. Interobserver variability for MLD, RVD, DS, and BA for either model was ≤0.049 mm, ≤0.056 mm, ≤2.77%, and 1.6°, respectively. Agreement between models for MLD, RVD, and DS was ±0.079 mm, ±0.011 mm, and ±2.07%. Accuracy and precision for diameter-derived parameters were slightly decreased in angulated projections; precision for BA measurements dropped to 6.1°. Conclusions: The results of both models are highly reproducible and for phantom MLD values >0.7mm in excellent agreement with the true dimensions.

Key words: coronary angiography; phantom; software validation; in vitro; reproducibility

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INTRODUCTION

Single-vessel analysis has been the conventional methodology for quantitative coronary angiography (QCA) of coronary lesions [1–4]. However, in the analysis of bifurcation lesions, the validity of single-vessel QCA has been brought into dispute, as it fails to predict the functional significance of ostial side-branch (SB) stenosis [5]. Dedicated two-dimensional (2D) bifurcation software algorithms have been developed recently to make up for the shortcomings of 2D single-vessel QCA [6–8]. However definitions of angiographic measures, such as the reference vessel diameter (RVD), are at variance, having not yet been validated versus a golden standard [8] and thus resulting in different measures for the percent diameter stenosis (DS); moreover breaking up the reported values over an increasing number of segments could render the results too complicated for clinical use.

To meet these unanswered needs, a new simplified model for 2D bifurcation segmental analysis has been developed and integrated together with the current 11-segment bifurcation model, into the latest version of the Cardiovascular Angiography Analysis System (CAAS 5v8, Pie Medical Imaging, Maastricht, The Netherlands). This report presents the results of the validation of both models by means of a series of custom-made, precision manufactured, plexiglas phantoms, for measurements of minimal lumen diameter (MLD), RVD, DS, and bifurcation angles.

MATERIALS AND METHODS

Phantoms

Six plexiglas phantoms, each of them mimicking a vessel with three successive bifurcations, were designed in 3D and manufactured with a tolerance <10 μm [9]. Every individual bifurcation had a lesion, wherein at least one vessel segment had a DS of $\geq 60\%$, the MLD being located within 3–6 mm from the point of bifurcation; the range of diameters, lesion length, angulation, and Medina class [10] used in the design of these 18 bifurcations reflected the anatomic variation and the fractal nature of bifurcations [11] in the human coronary tree as derived from relevant literature.

Acquisition and Calibration

The digital angiograms were acquired on a biplane angiographic system (Axiom Artis™, Siemens, Forchheim, Germany). All phantoms were filled with 100% Iodixanol 320 (Visipaque™, GE Healthcare, Cork, Ireland) and imaged at 30 frames per second, in a 20-cm field, with the center of the phantom placed precisely at the isocenter. For validation purposes, images acquired in antero-posterior (AP) direction by either C-arm were analyzed. Images acquired at 30° angulation, once in right- and once in left-anterior oblique (RAO-LAO) projection, were analyzed as well, to investigate the impact of gantry angulation on the accuracy and precision of the measurements.

Calibration was performed on a 10-mm grid board acquired in AP direction by either C-arm; the recording geometry of the X-ray system obtained from the DICOM (Digital Imaging and Communications In Medicine) header and the phantom thickness were taken into account to determine the true pixel size in the phantom plane, separately for each C-arm.

Radiographic system settings, phantom arrangement, table height, and source to image intensifier distance were kept constant throughout each phantom-cm grid acquisition and were identical for all phantoms.

Quantitative Angiographic Analysis

The measurements were carried out with CAAS 5v8 2-D bifurcation software. Next to the current 11-segment model (the 10-segment model described by Ramcharitar et al [7] modified by the addition of an 11th segment reflecting the ostium of the distal main vessel) a new, simplified model was implemented, wherein the analyzed bifurcation is split into 6 segments, equally allocated to proximal main vessel (PMV), distal main vessel (DMV), and SB, separated by the point of bifurcation (Fig. 1).

Standard operator procedure for angiographic analysis consisted in the following steps: (1) The middle frame out of the total frame count of a given acquisition was consistently analyzed to avoid frame selection bias. (2) The pixel size was manually entered. (3) The bifurcation segmentation was initialized by placing one proximal and two distal delimiter points at the largest possible distance from the bifurcation to be analyzed, however not touching the adjacent bifurcation lesions or the phantom borders. (4) Contours were detected and MLD was determined with an already described methodology [7]. (5) Single point local reference obstruction analysis was applied to each vessel segment; diameters within 1.5-mm proximal and distal of each reference position were averaged to derive the corresponding RVD. The reference positions were automatically placed at a distance 5% of the vessel segment length away from the delimiter points. (6) Given the values of MLD and RVD, DS was automatically calculated. (7) Proximal and distal bifurcation angles were calculated according to the described methodology [7]; angle calculations are model independent. All aforementioned parameters for both models could be derived from the standard report capture (Fig. 1).

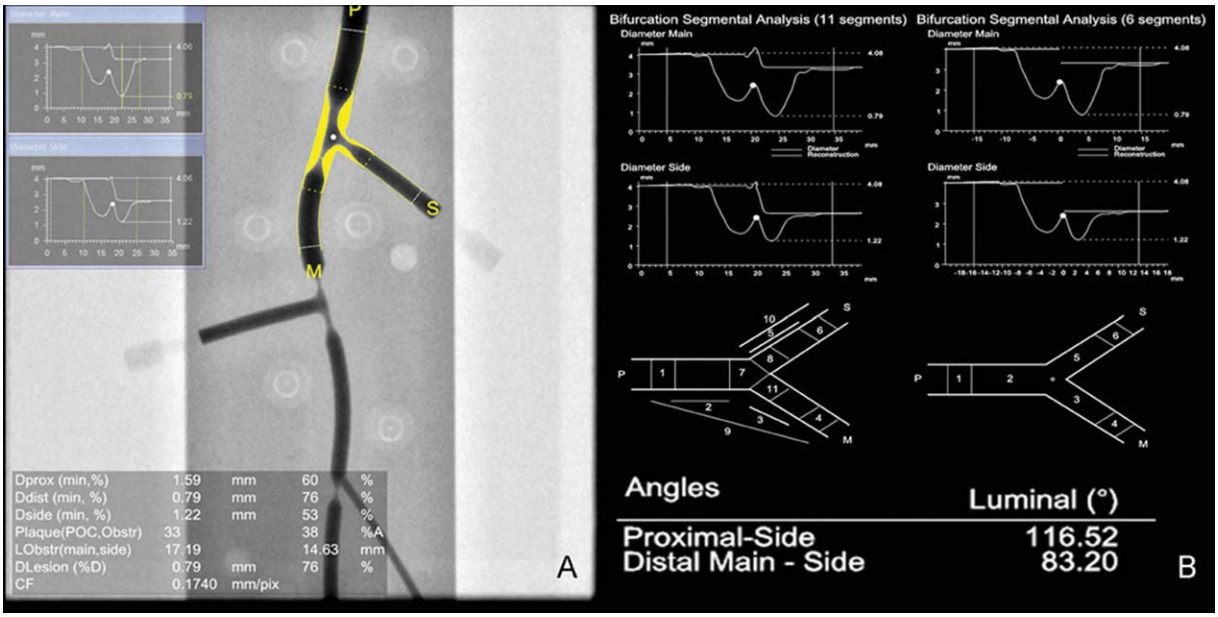

Fig. 1. Standard report of CAAS 5v8 (compilation). A. Analyzed frame highlighting the obstruction analysis (plaque in yellow) with diameter graphs and numerical results for diameter-derived parameters for 11-segment model. B. Upper panel: Diameter graphs for main vessel and side-branch for the 11- (left) and 6-segment (right) model. Middle panel: Model schematics. Lower panel: Bifurcation angle values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Validation Methodology

QCA was performed off-line by two experienced analysts (CG and YO), independent from each other, and blinded to the phantom dimensions. During the study, manual contour correction was not allowed; however, in a few cases the contour detection was adjusted by using the restriction option, an algorithm designed for excluding gross image artifacts without manually redefining the detected contours [12]. The extent of restriction applied by either analyst was meticulously reported.

MLD, RVD, and DS were reported for Segments 2, 3, and 5 (Fig. 1) of either 11- or 6-segment model, reflecting the segments, where in clinical practice the stent would be placed in the PMV, DMV, and SB, respectively; values were pooled together according to parameter. The proximal and distal BA values calculated by CAAS 5v8 were pooled together and compared to the phantom BA values.

Separate analysis of MLD, RVD, and DS was performed for phantom vessel segments with relatively larger (>0.70 mm) true MLD values. Moreover, results were stratified across distal bifurcation angles, to check for influence upon the performance of the QCA algorithm; accuracy and precision for MLD, RVD, DS, and BA measurements in bifurcations with narrow angle (40°) between SB and DMV direction [9] were compared with respective measures in wide-angled bifurcations (70° and 90°).

Statistics

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS, Chicago, IL). Continuous variables are presented as mean ± 1 standard deviation and compared with the independent- or paired-samples *t* test, as appropriate. Categorical variables are presented as counts and/or percentages. Measurements for any parameter or model derived from the two sets of images acquired in AP view were expected to be correlated (measurements of the same quantity); they were indeed preemptively checked for correlation using the Pearson coefficient, compared with a paired *t* test and then averaged, being henceforth treated as single values. The same procedure was followed for the two sets of images acquired in angulated projections.

The first analyst carried out two full rounds of measurements, with a time interval of 2 weeks, to determine intra-observer variability; the first round of measurements was compared both with the measurements of the second analyst to determine interobserver variability and with the corresponding phantom values for the purpose of the software validation. To determine the intra- and interobserver variability, we performed Bland-Altman analysis [13], wherein paired values differences were plotted against their respective average values. The mean of the paired differences and its standard deviation were calculated; the repeatability coefficient and the 95% limits of agreement were

TABLE I. Extent of Restriction Applied During the Analysis (AP Views)

	1st analyst–1st round		1st analyst–2nd round		2nd analyst	
	Bifurcations	Rate	Bifurcations	Rate	Bifurcations	Rate
Frontal C-arm	P1B3, P6B1	2/18	P1B3, P6B1	2/18	P6B1	1/18
Lateral C-arm	P5B3, P6B1	2/18	P6B1	1/18	P6B1	1/18

AP = antero-posterior, B1-B3 = Bifurcation 1-Bifurcation 3, P1-P6 = Phantom 1-Phantom 6.

TABLE II. Validation of 11-Segment Model vs. Phantom Dimensions (AP Views)

	BSM11	Phantom	Accuracy	Precision	Limits of agreement	*P*-value* BSM11 vs. phantom
MLD-all (mm)	1.55 ± 0.75	1.49 ± 0.85	0.065	0.128	±0.250	<0.001
MLD-large MLD (mm)	1.81 ± 0.70	1.80 ± 0.77	0.015	0.106	±0.208	0.39
RVD-all (mm)	2.68 ± 0.70	2.70 ± 0.71	−0.021	0.032	±0.062	<0.001
RVD-large MLD (mm)	2.62 ± 0.77	2.64 ± 0.78	−0.018	0.030	±0.058	<0.001
DS-all (%)	38.50 ± 29.75	40.94 ± 34.15	−2.45	5.07	±9.94	<0.01
DS-large MLD (%)	27.08 ± 26.13	27.63 ± 29.72	−0.55	4.30	±8.43	0.43
BA (°)	94.4 ± 33.1	96.6 ± 33.4	−2.2	3.3	±6.4	<0.001

AP = antero-posterior, BA = bifurcation angle, BSM11 = bifurcation 11-segment model, DS = percent diameter stenosis, MLD = minimal lumen diameter, RVD = reference vessel diameter.
*P significant <0.05.

TABLE III. Validation of 6-Segment Model vs. Phantom Dimensions (AP Views)

	BSM6	Phantom	Accuracy	Precision	Limits of agreement	*P*-value* BSM6 vs. phantom
MLD-all (mm)	1.55 ± 0.73	1.49 ± 0.85	0.058	0.142	±0.279	<0.01
MLD-large MLD (mm)	1.80 ± 0.68	1.80 ± 0.77	0.004	0.125	±0.244	0.83
RVD-all (mm)	2.68 ± 0.70	2.70 ± 0.71	−0.022	0.030	±0.060	<0.001
RVD-large MLD (mm)	2.61±0.77	2.64±0.78	−0.021	0.028	±0.054	<0.001
DS-all (%)	38.66 ± 29.55	40.94 ± 34.15	−2.28	5.29	±10.37	<0.01
DS-large MLD (%)	27.31 ± 25.92	27.63 ± 29.72	−0.32	4.55	±8.91	0.66
BA (°)	94.4 ± 33.1	96.6 ± 33.4	−2.2	3.3	±6.4	<0.001

AP = antero-posterior, BA = bifurcation angle, BSM6 = bifurcation 6-segment model, DS = percent diameter stenosis, MLD = minimal lumen diameter, RVD = reference vessel diameter.
*P significant <0.05.

determined. Assessment of agreement between the two bifurcation models was also performed using Bland-Altman analysis.

A paired t test was used to compare the QCA measurements by either model with the corresponding phantom values. The individual signed differences were averaged; the mean of these signed differences (bias) is a measure of accuracy; the standard deviation is a measure of precision. As the phantom values were known, we chose to plot these instead of the average values on the x-axis against the signed differences and computed the corresponding 95% limits of agreement [13]. When appropriate, signed differences were plotted on the y-axis of the plots as the percentage of the corresponding true values [14]. The same statistical approach was followed in the analysis of the vessel segments with larger true MLD values.

All statistical tests were two-sided and a P value <0.05 was considered statistically significant.

RESULTS

Analysis (Validation) in AP Views

Measurements for any parameter or model did not differ significantly between images acquired with the frontal and lateral C-arm ($P \geq 0.58$ for every parameter); values for MLD, RVD, DS, and BA were very strongly correlated between C-arms (Pearson coefficient consistently ≥ 0.99, $P < 0.001$).

The extent to which restriction was applied during the analysis is reported in Table I. The only case where restriction was consistently applied was the first bifurcation of the sixth phantom. Initial contour detection of the shallow angled side branch identified a much larger region of interest; once this was restricted, contours were adequately traced.

Accuracy and precision for MLD, RVD, DS and BA are reported in Tables II and III. MLD and DS for both models differed significantly from the phantom values ($P < 0.01$ for every parameter); however, if

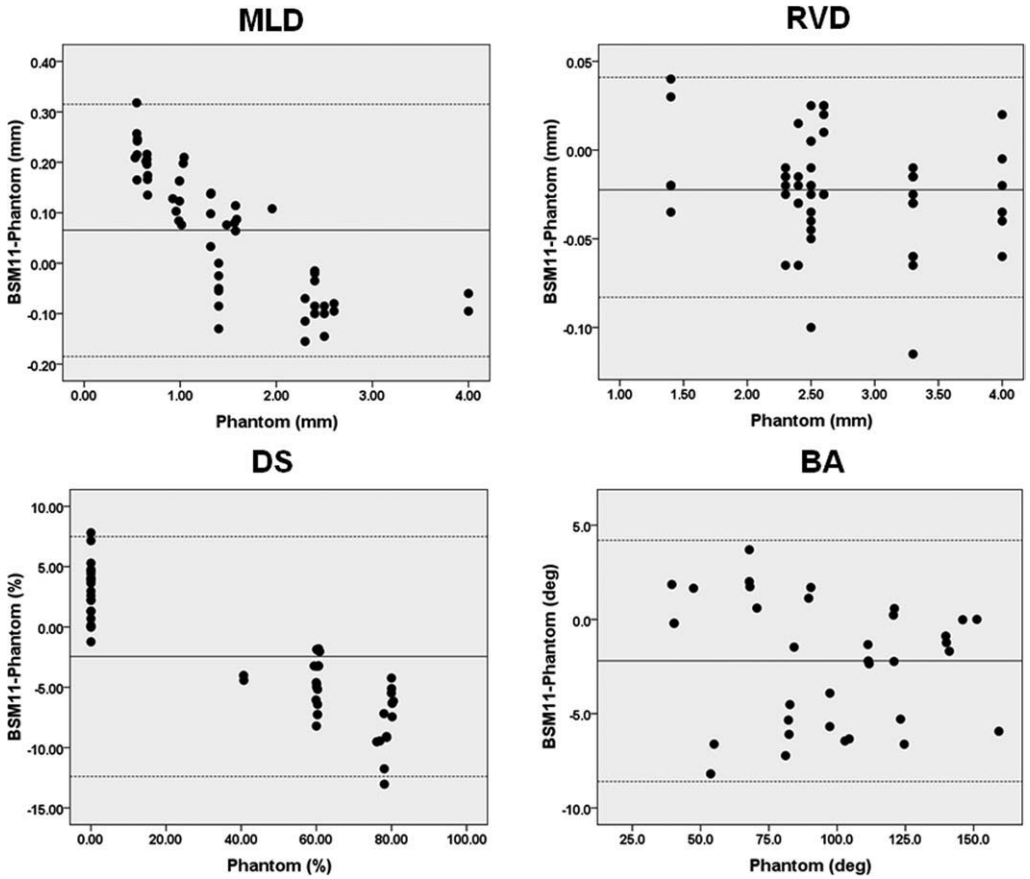

Fig. 2. Bland-Altman plots comparing 11-segment model results (54 vessel segments) to the phantom values for minimal lumen diameter (MLD), reference vessel diameter (RVD), percent diameter stenosis (DS) and bifurcation angle (BA); analysis in antero-posterior views. Solid lines represent the mean difference (bias), dotted lines represent the 95% limits of agreement (bias ± 1.96 SD). Deg = degrees.

vessel segments with larger true MLD were only considered, no statistical difference was observed anymore. MLD in vessel segments with smaller true minimal lumen diameter was systematically overestimated, whereas DS was systematically underestimated; opposite phenomena were apparent in vessel segments with larger true MLD, however to a lesser extent (Figs. 2 and 3). BA measurements underestimated on average the true phantom values ($\Delta BA = -2.2°$). There was no significant difference in accuracy and precision for MLD, RVD, DS, or BA between wide- and narrow-angled bifurcations (Table IV).

Intra- and interobserver variability. Bias, standard deviation and repeatability coefficient for either model are reported in Table V. Bias both for intra- and interobserver comparisons was equal or very close to zero for every parameter.

Intermodel agreement. Direct assessment of agreement between the two models is presented in Table VI. Limits of agreement for MLD, RVD, and DS between models were ± 0.079, ± 0.011, and $\pm 2.07\%$, respectively.

Analysis in Angulated Views

Values for MLD, RVD, DS, and BA were very strongly correlated (Pearson coefficient consistently ≥ 0.99, $P < 0.001$) and did not differ significantly between angulated views ($P \geq 0.16$ for every comparison). Accuracy and precision of measurements in angulated views are reported in Table VII. Interobserver variability for MLD, RVD, DS, and BA was ≤ 0.042mm, ≤ 0.072mm, $\leq 2.87\%$, and 2.2° for either model (not shown). Restriction was applied only once by either analyst in the angulated projections.

DISCUSSION

The main findings of this study are: (1) The new 2D QCA bifurcation software is highly accurate and

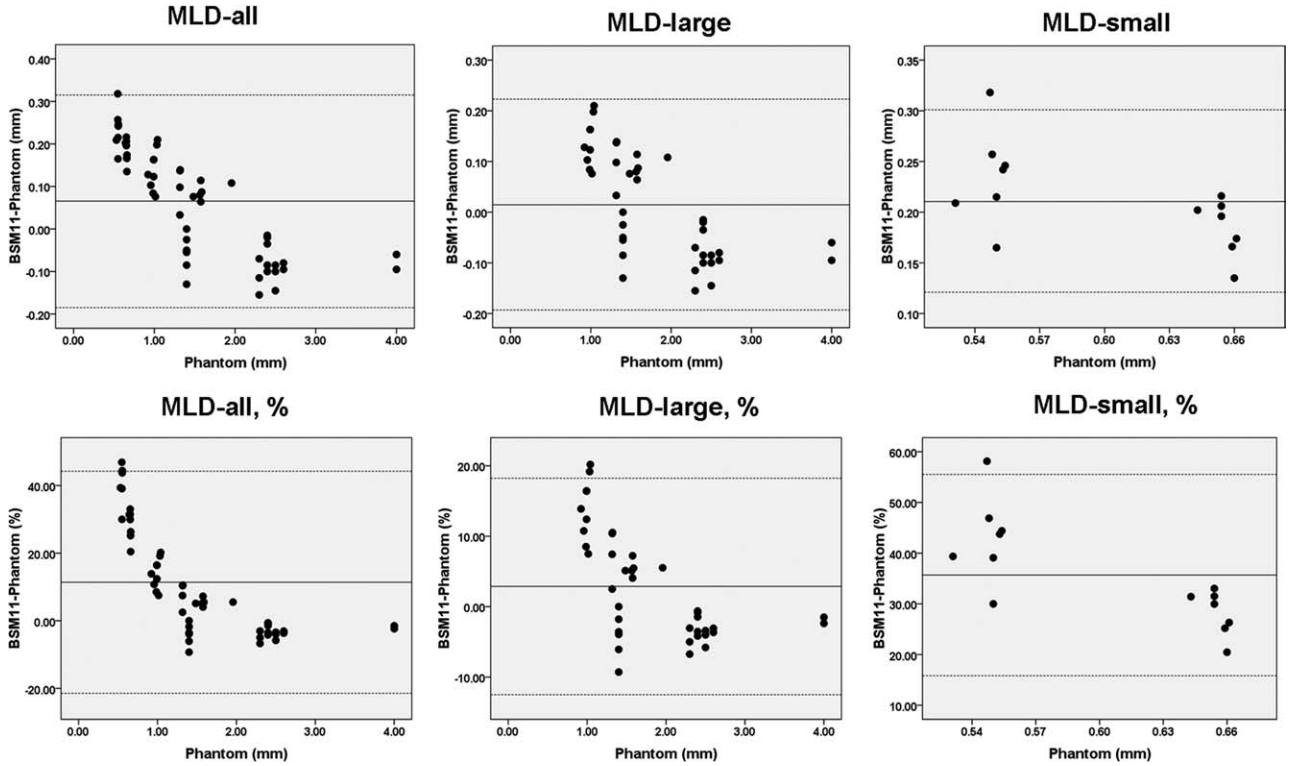

Fig. 3. Bland-Altman plots comparing 11-segment model results to the phantom values for minimal lumen diameter (MLD); analysis in antero-posterior views. Absolute (upper panel) and relative (lower panel) differences are plotted on the *Y*-axis for the entire dataset (left column), for true MLD values >0.7 mm (middle column) and for true MLD values <0.7 mm. Solid lines represent the mean difference (bias), dotted lines represent the 95% limits of agreement (bias ± 1.96 SD).

TABLE IV. Accuracy and Precision Across Distal BA Values (AP Views)

	Small distal BA			Large distal BA			
	Mean ± SD	Accuracy	Precision	Mean ± SD	Accuracy	Precision	*P*-value*
BSM11							
MLD (mm)	1.49 ± 0.82	0.068	0.129	1.58 ± 0.72	0.064	0.129	0.91 (0.64)
RVD (mm)	2.67 ± 0.83	−0.016	0.027	2.69 ± 0.64	−0.023	0.034	0.41 (0.43)
DS (%)	40.32 ± 31.21	−2.51	5.19	37.59 ± 29.39	−2.42	5.09	0.95 (0.72)
BA (°)	94.3 ± 52.7	−1.8	3.3	94.5 ± 18.4	−2.4	3.3	0.60 (0.95)
BSM6							
MLD (mm)	1.47 ± 0.77	0.049	0.166	1.58 ± 0.71	0.062	0.131	0.77 (0.71)
RVD (mm)	2.67 ± 0.83	−0.018	0.024	2.68 ± 0.64	−0.024	0.033	0.49 (0.52)
DS (%)	40.74 ± 30.68	−2.08	5.81	37.62 ± 29.35	−2.38	5.10	0.85 (0.73)
BA (°)	94.3 ± 52.7	−1.8	3.3	94.5 ± 18.4	−2.4	3.3	0.60 (0.95)

AP = antero-posterior, BA = bifurcation angle, BSM = bifurcation segment model, DS = percent diameter stenosis, MLD = minimal lumen diameter, RVD = reference vessel diameter, SD = standard deviation.

*P significant < 0.05, values relate to the comparison between accuracy measures for the small and the large BA; numbers in parentheses are derived for the respective comparison between accuracy measures relative to the true values.

precise in terms of RVD and accurate and precise in terms of MLD and DS, when compared in vitro with a series of custom-made, precision manufactured plexiglas phantoms. Optimal accuracy and a higher level of precision for MLD and DS are achieved, if vessel segments with smaller true MLD ($\leq$0.70 mm) are excluded from the analysis. The performance of the QCA algorithm does not vary significantly across distal BA values. (2) Accuracy and precision for MLD, RVD and DS in angulated projections are slightly decreased, however comparable to the respective measures in AP views. (3) Repeatability for all diameter-derived parameters and for both models is very high. (4) Agreement between the 11- and the 6-segment model is high

TABLE V. Intra- and Interobserver Repeatability for 11-Segment and 6-Segment Model (AP Views)

	INTRA-BSM11			INTRA-BSM6			INTER-BSM11			INTER-BSM6		
	Bias	SD	Repeat	Bias	SD	Repeat	Bias	SD	Repeat	Bias	SD	Repeat
MLD (mm)	0.00	0.024	0.046	0.001	0.024	0.048	−0.005	0.025	0.049	−0.004	0.025	0.048
RVD (mm)	0.009	0.028	0.054	0.008	0.028	0.055	0.005	0.028	0.055	0.004	0.029	0.056
DS (%)	0.21	1.29	2.53	0.15	1.26	2.47	0.44	1.40	2.75	0.38	1.41	2.77
BA (°)	0.2	0.8	1.5	0.2	0.8	1.5	0.0	0.8	1.6	0.0	0.8	1.6

AP = antero-posterior, BA = bifurcation angle, BSM6 = bifurcation 6-segment model, BSM11 = bifurcation 11-segment model, DS = percent diameter stenosis, MLD = minimal lumen diameter, RVD = reference vessel diameter, repeat = repeatability coefficient, SD = standard deviation.

TABLE VI. Agreement Between 11- and 6-Segment Model (AP Views)

	BSM11	BSM6	Bias	SD	LA
MLD (mm)	1.55 ± 0.75	1.55 ± 0.73	0.008	0.040	±0.079
RVD (mm)	2.68 ± 0.70	2.68 ± 0.70	0.002	0.006	±0.011
DS (%)	38.50 ± 29.75	38.66 ± 29.55	−0.16	1.05	±2.07

AP = antero-posterior, BSM6 = bifurcation 6-segment model, BSM11 = bifurcation 11-segment model, DS = percent diameter stenosis, LA = limits of agreement, MLD = minimal lumen diameter, RVD = reference vessel diameter, SD = standard deviation.

TABLE VII. Accuracy and Precision in Angulated Views

	BSM11			BSM6		
	Accuracy	Precision	AP vs. RL; *P*-value*	Accuracy	Precision	AP vs. RL; *P*-value*
MLD-all (mm)	0.097	0.141	<0.01	0.082	0.170	0.01
MLD-large MLD (mm)	0.044	0.122	<0.01	0.025	0.159	0.07
RVD-all (mm)	−0.009	0.041	0.08	−0.011	0.041	0.09
RVD-large MLD (mm)	−0.010	0.038	0.23	−0.012	0.037	0.23
DS-all (%)	−3.75	5.31	<0.01	−3.34	5.87	0.03
DS-large MLD (%)	−1.90	4.66	0.02	−1.38	5.37	0.09
BA (°)	−2.7	6.1	0.54	−2.7	6.1	0.54

AP = antero-posterior, BA = bifurcation angle, BSM = bifurcation segment model, DS = percent diameter stenosis, MLD = minimal lumen diameter, RL = right-left angulation, RVD = reference vessel diameter.
**P* significant <0.05, values relate to the comparison between accuracy measures for AP vs. RL.

for all parameters. (5) BA measurements underestimate the phantom values, whereas their repeatability is quite high. Precision of BA measurements is diminished in angulated views.

Since the early days of QCA analysis, there have been serial validation studies [2,15–22], either in vitro or in vivo, reporting on the accuracy and precision of various software algorithms compared against a phantom of known dimensions. The series of phantoms that were used for this study were specifically designed for the purpose of validation of 2D and 3D bifurcation QCA algorithms. Contrast concentration of 100% [17,19], calibration of images at isocenter [15,17,19,23] and consistent frame selection [24,25] have been employed, to acquire high quality images and high validity measurements.

Minimal Lumen Diameter

MLD is the only absolute angiographic measurement, that can serve as a marker of progression-regression of atherosclerosis and directly relates to the physiological significance of the lesion [26]. Previous phantom validation studies for the former editions of the CAAS software showed varying degrees of accuracy and precision in the analysis of single-vessel lesions: −0.03 ± 0.09 mm by Reiber et al. in vitro [2] and −0.07 ± 0.21 mm by Haase et al. in vivo [15] for CAAS I, 0.00 ± 0.11 mm in vitro and −0.01 ± 0.18 mm in vivo by Haase et al. [18] for CAAS II (obstruction diameter using a slightly different definition) and recently 0.19 ± 0.06 mm in vitro by van Herck et al. [21] for CAAS II; intra- and interobserver repeatability of obstruction diameter for either edition has been close to 0.2 mm [12].

Keane et al. [19] and Hausleiter et al. [20] explored the boundaries of the then available systems through comparative validation studies. For an array of stenotic tubes with a mean diameter of 1.12 mm (range 0.5–1.9 mm), Keane et al found varying values for accuracy (−0.01/−0.23 mm) and precision (0.07–0.28 mm) for in-vitro measurements, no system being both very

accurate and precise. Hausleiter et al. found in a series of stenotic and nonstenotic phantoms a wider range for accuracy (−0.040/0.039 mm) and precision (0.087–0.184); inclusion of stenotic tubes with MLD in the submillimeter range, limited the performance of the tested systems. In this respect, Tuinenburg et al. in a recent study, chose to exclude phantoms with an MLD <0.60 mm, because they were expected to be overestimated [22].

Our study yielded an accuracy of 0.065/0.058 mm and a precision of 0.128/0.142 mm for 11- and 6-segment model, respectively, intra- and interobserver repeatability being very high (<0.05 mm). To explore the possible impact of small phantom MLD values on the accuracy and precision of our study [20–22], we ran a separate analysis excluding 14 stenotic (DS $\geq$ 60%) vessel segments with a true MLD $\leq$ 0.7mm. Indeed analysis of the remaining vessel segments (MLD range 0.922–4.00 mm) resulted in optimal accuracy (0.015/0.004 mm) and higher precision (0.106/0.125 mm) for 11- and 6-segment model respectively being well in the range of recently suggested requirements [22]. It should be emphasized that this level of accuracy and precision is achieved by a bifurcation QCA algorithm despite the increased level of complexity, when compared to single-vessel QCA; in a single analytical process, measurements for all three bifurcation vessel segments are provided.

It is well known that small objects are overestimated due to the limitations related to the X-ray systems. Accurate assessment of small diameters suffers significantly due to the blurring effect caused by the size of the focal spot from the X-ray system [12,18]. Work is in progress to design an improved contour detection algorithm, which reduces the influence of the X-ray system limited focal spot size yielding more accurate assessment of small diameters.

Reference Vessel Diameter

Lansky et al. [8] argues that the user-defined method is prone to bias, requiring user-selection and not accounting for tapering over long vessel segments, or even the step-down phenomenon, if applied on either side of the bifurcation. Thus an iterative regression function, as already implemented in single-vessel analysis [27], would be preferred.

In our study, the RVD function was determined separately for each vessel segment of the bifurcation by means of single point local reference obstruction analysis. We followed a standardized approach of analyzing segments between successive bifurcations, which are not expected to taper if assumed healthy [28,29], assumption inherent in the RVD derivation. This argument holds even more in the situation of a multi-segmental model, wherein segments between bifurcations are subdivided into smaller ones limiting the tapering effect. Thus the reference of a given vessel segment gets extrapolated from the diameter outside the obstruction boundaries. To minimize the user-selection bias, diameter averaging over a 3-mm long segment ($\pm$1.5mm from the reference position) is applied. Moreover, in the 11-segment model, the RVD function within the polygon of confluence is still determined by the current curvature interpolation technique (Fig. 1) [7]; on the other hand, in the 6-seg model, RVD for each vessel segment is called by one straight line up until the point of bifurcation. Agreement between the models for RVD was almost optimal despite this difference in methodology; accuracy $\leq$0.022 mm and precision $\leq$0.032 mm compared to the phantom values rendered either approach valid.

Percent Diameter Stenosis

DS has been less reliable in the evaluation of percutaneous interventions [30] or the functional significance of ostial SB stenosis [5]; the application of single-vessel analysis at bifurcation sites is rather cumbersome as well [6]. Increasingly accurate, precise and repeatable MLD and RVD measurements in our study resulted in robust DS measurements, mainly in the vessel segments with larger (>0.7 mm) true MLD.

Bifurcation Angles

Recent publications from our group [31] and others [32] reinforce the suggested prognostic role [33] of bifurcation angulation parameters. CAAS is the sole 2D QCA software implementing automated algorithms for the calculation of BA [7]. The BA could be determined with an accuracy of -2.2° and a precision of 3.3°; values were remarkably repeatable thus consistent. It has to be understood that the phantom BA values were determined in a 3D space with a 3D definition [9] in contrast to the 2D definition used in the CAAS software; this fact probably accounts for the diminished agreement.

11- vs. 6-Segment Model

Segmentation of a bifurcation lesion results in the accurate localization of MLD, RVD and DS pre-, post PCI and at follow-up angiography. This way we can increase our understanding of the mechanisms that lead to post-intervention failure or success, especially at the SB ostium [8]. On the other hand simplicity is a requirement for on-line QCA; intuitive interpretation of a simplified, still all-inclusive report facilitates accurate

sizing of intracoronary devices and proper decision making.

Agreement between the two models was excellent, either of them being highly repeatable. In this respect the two models are not mutually exclusive, but could be used interchangeably according to research or clinical purpose.

Impact of Gantry Angulation on the System Performance

Similar to prior validation studies, primary analysis was performed in AP views, in order to minimize errors resulting from overlap and foreshortening [22]. In our study, angulated projections were also analyzed, in order to simulate a clinical scenario of suboptimal cineangiography. Because of the eccentric shape of the phantom bifurcation lesions analyzed, it was expected that measurements for diameter-derived parameters would be slightly less accurate and precise compared to the AP views. However, results were within the range of current standards for single-vessel QCA, especially when vessel segments with smaller true MLD were excluded. The decreased precision of the 2D BA measurements is caused by the x-ray translation effect of a 3D object into a 2D presentation. The BA is more sensitive to such spatial deformation compared to diameter-derived parameters, which are primarily effected by foreshortening.

Limitations

Our measurements were performed in vitro, probably not giving an accurate account of the system performance, when it comes to in vivo imaging. The phantoms are static objects not taking into account the movement of the coronary arteries and the inherent decrease in image quality. However, in vivo validation of a bifurcation QCA algorithm would require measurements by another imaging modality to be used as the golden standard despite their inherent variability; insertion of bifurcation phantoms in animal coronaries would be technically demanding and unsafe. Recent experience from comparative in vitro and in vivo validation studies allows us to extrapolate the in vivo performance of angiographic analysis software given its in vitro accuracy and precision; modern digital angiography systems make this extrapolation even more predictable.

Minimal user-interaction and editing of the lumen contours is a requirement for QCA studies [8], even more so for the purpose of validation. We were compelled to apply restriction in a limited number of images, where the contour of either the DMV or the SB did not follow the intuitive path-line. However, the restriction option is not a manual contour correction, but instead offers users the possibility of excluding parts of the image from the contour detection by restricting the area of interest. Moreover, in our study, selection of the restricted images was blinded, being consistently applied in only one case.

CONCLUSIONS

The latest edition of CAAS 2D QCA bifurcation software, implementing an 11-segment and a 6-segment model, was validated against a series of custom made, precision manufactured plexiglas phantoms. The software is highly accurate and precise in terms of RVD and accurate and precise in terms of MLD and DS; optimal accuracy and a higher level of precision for MLD and DS were achieved, if vessel segments with larger true MLD ($\leq$0.70 mm) were only considered. Accuracy and precision for MLD, RVD, and DS in angulated projections are comparable to the respective measures in AP views. BA measurements underestimate the phantom values, whereas their repeatability is quite high; however precision is diminished in angulated views. Both models are highly repeatable, and in excellent agreement with each other, hence they can be used interchangeably according to research or clinical purpose.

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Chapter 4

Advances in two-dimensional quantitative coronary angiographic assessment of bifurcation lesions: improved small lumen diameter detection and automatic reference vessel diameter derivation

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Advances in two-dimensional quantitative coronary angiographic assessment of bifurcation lesions: improved small lumen diameter detection and automatic reference vessel diameter derivation

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KEYWORDS

- angiography
- coronary bifurcation
- quantitative coronary angiography

Abstract

Aims: To validate a new two dimensional (2-D) bifurcation quantitative coronary angiography (QCA) software.

Methods and results: In the latest edition of the Cardiovascular Angiography Analysis System (CAAS 5.9; Pie Medical Imaging, Maastricht, The Netherlands) video-densitometric information is dynamically integrated into the edge-detection algorithm of 11- and 6-segment models to reduce overestimation of small diameters. Furthermore, automatic reference obstruction analysis was optimised. Values of the minimal lumen diameter (MLD), reference vessel diameter (RVD), percent diameter stenosis (DS) and bifurcation angle (BA) for the different bifurcation segment models were validated against precision manufactured plexiglass phantoms. In anteroposterior views, accuracy and precision (mean difference±SD) of 11- and 6-segment models for MLD were 0.013±0.082 mm vs. 0.003±0.100 mm, for RVD –0.030±0.047 mm vs. –0.029±0.045 mm and for DS –0.48±3.66% vs. –0.11±3.97%. In smaller vessel segments (true MLD <0.7 mm), MLD overestimation was reduced. Inter-observer variability for MLD, RVD and DS for either model was ≤0.052 mm, ≤0.043 mm and ≤2.24%, respectively. Agreement between models for MLD, RVD and DS was ±0.076 mm, ±0.021 mm and ±2.53%, respectively. Accuracy and precision for BA were –2.6±3.5°, and variability was ≤1.2°. Accuracy and precision for diameter-derived parameters were slightly decreased in projections with 30° rotation; BA precision dropped to 6.2°.

Conclusions: MLD quantification is improved for true MLD <0.7 mm, resulting in highly accurate and precise diameter measurements over the entire range of phantom diameters. Automatic reference obstruction analysis provides highly accurate, precise and reproducible RVD and DS measurements.

Introduction

The fundamental issue in the quantitative coronary angiography (QCA) analysis of bifurcation lesions is the calculation of the reference vessel diameter (RVD)[1,2]. It has been convincingly demonstrated that due to the step-down phenomenon, this should be calculated separately for the proximal main vessel (PMV), the distal main vessel (DMV) and the side branch (SB)[3-5]. Even so, there are two possible approaches to define the RVD values, either based on a user-defined reference position located outside the obstruction or by using an automatic regression function. The validity of the former approach for 2-D bifurcation QCA has been tested and verified during the validation process for the Cardiovascular Angiography Analysis System (CAAS; Pie Medical Imaging, Maastricht, The Netherlands)[6]. However, in true coronary cases interpolation via an automatic regression function can be of value in excessively long and/or tapered vessels[2].

Angiographic imaging of small objects is historically known to be affected by blurring due to the limitations of the X-ray systems and noise[7-11]. Notwithstanding the introduction of flat panel detectors and increased software sophistication, these phenomena are still present, as evidenced by the overestimation of lumen diameters <0.70 mm in the validation of CAAS 5.8[6] and other similar reports[12,13].

CAAS 5.9 2-D bifurcation QCA software implements both an optimised automatic reference analysis and a new small lumen detection algorithm; thus it would be expected to offer increased accuracy and precision over the entire range of lumen diameters anticipated in clinical practice. In this report we present the results of the *in vitro* validation of this software package based on a series of precision manufactured bifurcation phantoms.

Materials and methods

PHANTOMS

Six plexiglass phantoms, each of them mimicking a vessel with three successive bifurcations, were designed in 3-D and manufactured with a tolerance <10 µm[14] **(Figure 1)**. Every individual bifurcation had a lesion, wherein at least one vessel segment had a percent diameter stenosis (DS) of ≥60%, the minimum lumen diameter (MLD) being located within 3-6 mm from the point of bifurcation; the range of diameters (0.53-4.00 mm), lesion length, bifurcation angles and Medina class[15] used in the design of these 18 bifurcations reflected the anatomic variation and the fractal nature of bifurcations[3-5] in the human coronary tree.

ACQUISITION AND CALIBRATION

The digital angiograms were acquired on a biplane angiographic system (Axiom Artis™; Siemens, Forchheim, Germany). All phantoms were filled with 100% Iodixanol 320 (Visipaque™; GE Healthcare, Cork, Ireland) and imaged at 30 frames per second, in a 20 cm field of view, with the centre of the phantom placed precisely at the isocentre. For validation purposes, images acquired in anteroposterior (AP) direction by either C-arm were analysed. Images acquired at 30° rotation, once in right and once in left anterior oblique (RAO-LAO) projection, were also analysed, in order to investigate the impact of gantry angulation on the accuracy and precision of the measurements.

Calibration was performed on a 10 mm grid board and the recording geometry of the x-ray system obtained from the Digital Imaging and Communications in Medicine (DICOM) (National Electrical Manufacturers' Association, DICOM, Rosslyn, VA, USA) header and the phantom thickness were taken into account to determine the true pixel size in the phantom plane, separately for each C-arm.

Radiographic system settings, phantom position, table height and source to image intensifier distance were kept constant throughout each phantom and centimetre grid acquisition and were identical for all phantoms.

QUANTITATIVE ANGIOGRAPHIC ANALYSIS

Standard operator procedure for angiographic analysis consisted of the following steps:

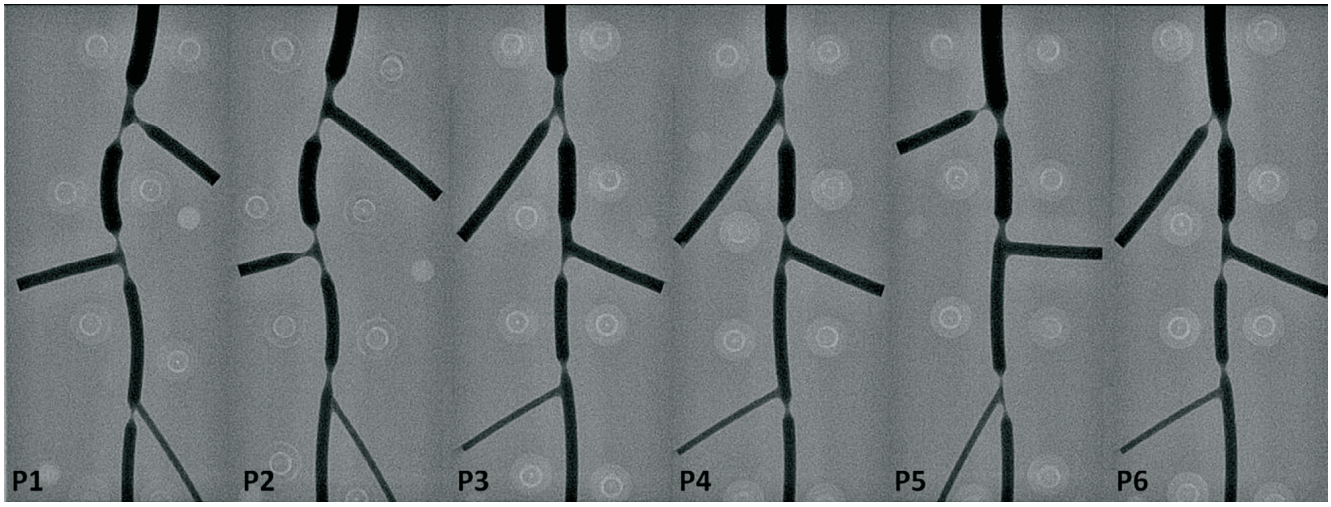

Figure 1. *Precision manufactured bifurcation phantoms. Angiographic images were acquired after filling the phantoms with contrast and were then used in the software validation; P1: phantom 1*

1) The middle frame out of the total frame count of a given acquisition was consistently analysed to avoid frame selection bias; 2) The pixel size was manually entered; 3) The bifurcation segmentation was initialised by placing one proximal and two distal delimiter points at the largest possible distance from the bifurcation to be analysed, however not touching the adjacent bifurcation lesions or the phantom borders; 4) Contours were detected using the new lumen detection algorithm and MLD was determined with an already described methodology[16]; 5) On the same contours, both single point bifurcation local reference obstruction (BLRO) analysis[6] and automatic reference obstruction (BARO) analysis were applied for the RVD calculation **(Figure 2)**; 6) Given the values of MLD and RVD, the DS was automatically calculated; 7) Proximal and distal bifurcation angles were calculated according to the described methodology[16]; angle calculations are independent of the bifurcation segment model used.

The new lumen detection algorithm is based on the method described by Ramcharitar[16]. In addition to that, it dynamically integrates video-densitometric information from the image into the segmentation algorithms thereby reducing the overestimation of the small diameters. The BARO algorithm has originally been described by Ramcharitar et al[16]. In order to improve the stability of the RVD function, this algorithm was slightly modified in the new version. In the original BARO algorithm[16], RVD outside the bifurcation region was only based on the obstruction-free parts of PMV, DMV or SB, respectively; in the CAAS 5.9, the automatic RVD function also takes into account characteristics of the bifurcation region itself. However, the BLRO algorithm was left unchanged as described in the validation paper for CAAS 5.8. Briefly, reference positions were automatically placed at a distance 5% of the vessel segment length inside the delimiter points; diameters within 1.5 mm proximal and distal of each reference position were averaged to derive the corresponding RVD. It follows, that, as illustrated in **Figure 2**, the validity of the RVD/DS measurements derived in BLRO is dependent on the definition of the reference points. On the contrary, BARO is not affected from variable positioning of the delimiter points, by fitting a reference diameter curve based on the "healthy" diameters within a given bifurcation branch.

VALIDATION METHODOLOGY

QCA was performed off-line by two experienced analysts (CG, YO), independent from each other. During the study, manual contour correction was not allowed. However, in a few cases the contour detection was adjusted by using the restriction option, therein excluding gross image artefacts without manually redefining the detected contours[17].

MLD, RVD and DS were reported for segments 2, 3 and 5 of either the 11- or 6-segment model **(Figure 3)**, reflecting the vessel segments, where in clinical practice the stent would be placed in the PMV, DMV and SB, respectively. Segment values were pooled together and analysed. The proximal and distal BA values were also pooled together and compared to the phantom BA values.

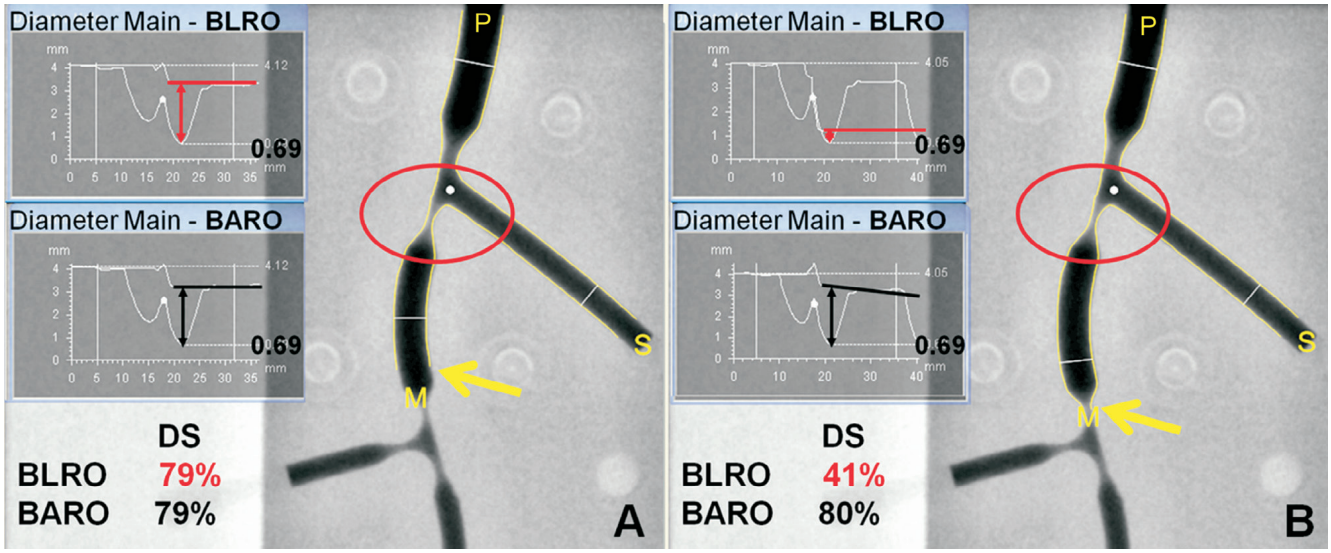

Figure 2. *Differences between automatic (BARO) and local reference obstruction (BLRO) analysis of bifurcation lesions. The first bifurcation of the second phantom was analysed twice with each method focusing on the DMV lesion (MLD=0.69 mm); the position of the distal delimiter point (indicated by the yellow arrow) shifted between analyses. A. Delimiter point is placed within the DMV. RVD is apparently equal between methods, resulting in identical DS measurements. B. Delimiter point is placed distal to the DMV, within the adjacent bifurcation lesion. Taking a severely stenosed lumen as reference for the preceding DMV segment, BLRO results in the recalibration of the reference curve (horizontal red line) and therefore in gross DS underestimation. On the contrary, in BARO, the reference curve (black line) is based on the healthy diameter values within DMV; thereby DS is almost identical to the previous analysis. DMV: distal main vessel; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter: P: proximal main vessel; M: DMV; S: side branch*

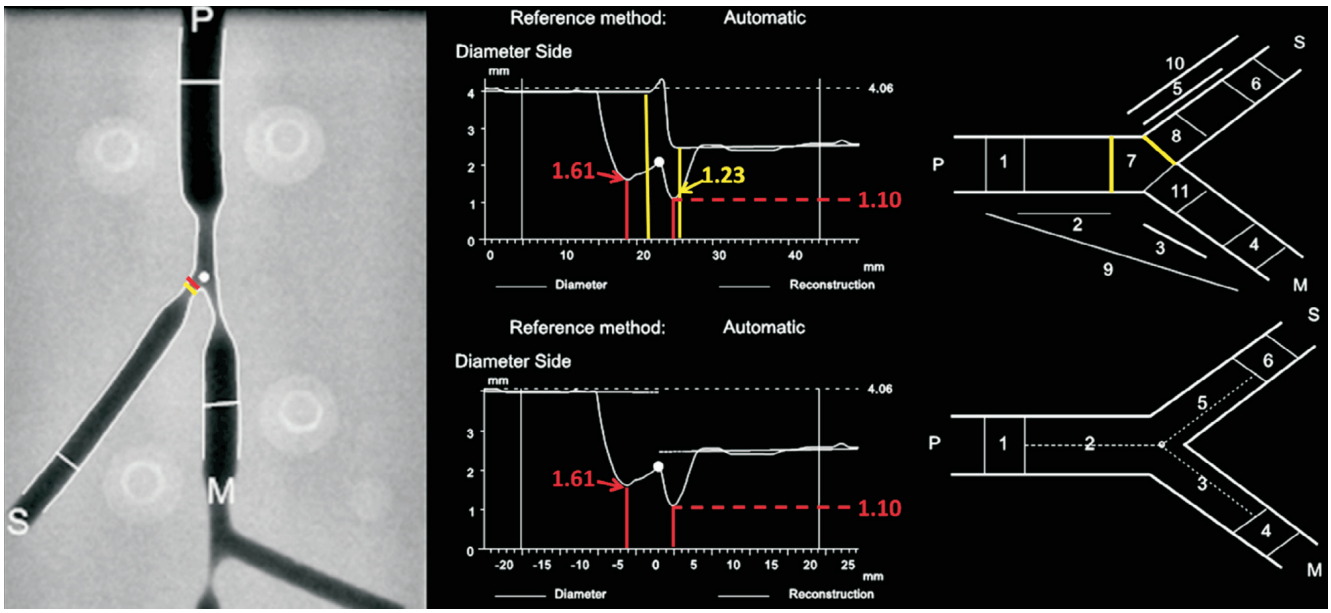

Figure 3. *Bifurcation segment models; difference in minimal lumen diameter (MLD) traced in the side branch (SB). Left: Analysed frame of a phantom bifurcation; MLD position in the 11-segment model is highlighted in yellow; in red for the 6-segment model. Right: diameter graphs and model schematics for the 11-segment (upper panel) and 6-segment models (lower panel). In the former, segments 2 (PMV) and 5 (SB) are separated by segment 7 corresponding to the polygon of confluence; proximal and distal borders thereof are highlighted in yellow on both graph and schematic. Whereas MLD value is common between models for the PMV, difference in bifurcation model definitions results in different MLD values for segment 5. PMV: proximal main vessel*

Separate analysis of MLD, RVD and DS was performed for phantom vessel segments with relatively larger (>0.70 mm) true MLD values. Moreover, results were separately analysed for BARO and BLRO algorithms and compared.

STATISTICS

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ±1 standard deviation and compared with the independent or paired samples t-test, as appropriate. Categorical variables are presented as counts and/or percentages. Measurements for any parameter or model derived from the two sets of images acquired in AP view were expected to be correlated (measurements of the same quantity). They were indeed pre-emptively checked for correlation using the Pearson coefficient, compared with a paired t-test and then averaged, being henceforth treated as single values. The same procedure was followed for the two sets of images acquired in rotated projections.

The first analyst carried out two full rounds of measurements, with a time interval of two weeks, in order to determine intra-observer variability. The first round of measurements was compared both with the measurements of the second analyst to determine inter-observer variability and with the corresponding phantom values for the purpose of validating the software against the ground truth; Bland-Altman analysis was performed for all comparisons[18]. Regarding intra- and inter-observer comparisons, the mean difference (bias) and its standard deviation were calculated; the repeatability coefficient (equal to 1.96 * standard deviation of the bias) was determined as the measure of variability. Assessment of agreement between the two bifurcation models was also performed using the Bland-Altman analysis.

A paired t-test was used to compare the QCA measurements by either model with the corresponding phantom values. The individual signed differences were averaged; the mean of these signed differences is a measure of accuracy; the standard deviation is a measure of precision. Measures of accuracy were compared between models and/or methods of obstruction analysis with the paired t-test; measures of precision/variability were compared with the F-test[12]. As the true values were known, we chose to plot these instead of the average values on the X-axis of the Bland-Altman plot against the signed differences and computed the corresponding 95% limits of agreement[18]. When appropriate, signed differences were plotted on the Y-axis of the plots as the percentage of the corresponding true values[19].

All statistical tests were two-sided and a p-value <0.05 was considered statistically significant.

Results

ANALYSIS (VALIDATION) IN AP VIEWS

The extent to which the restriction option was applied during the contour detection is reported in **Table 1**. The first analyst was consistent in his choice between the two rounds of measurements; the

Table 1. Extent of restriction applied during the analysis (AP views).

	1st analyst-1st round		1st analyst-2nd round		2nd analyst	
	Bifurcations	Rate	Bifurcations	Rate	Bifurcations	Rate
Frontal C-arm	P1B3 P6B1	2/18	P1B3 P6B1	2/18	(P6B1)*	0/18
Lateral C-arm	P6B1	1/18	P6B1	1/18	(P6B1)*	0/18

AP: anteroposterior; B1-B3: Bifurcation 1-Bifurcation 3; P1-P6: Phantom 1-Phantom 6; *: manual pathline

second analyst did in fact not apply the restriction mode but rather indicated the pathlines from the PMV into the DMV and SB, respectively by successive left mouse clicks.

Accuracy and precision for MLD, RVD and DS values are presented in **Table 2 and Table 3**. MLD values for all 54 phantom vessel segments evaluated had an accuracy and precision of 0.013±0.082 mm and 0.003±0.100 mm for the 11- and 6-segment model respectively, this not being significantly different from phantom values (p-value 0.23 and 0.81). MLD was still overestimated in vessel segments with smaller true MLD (<0.7 mm), however to a modest degree **(Figure 4)**. Because of the difference in calibre between the smaller and larger vessel segments, accuracy and precision were also expressed in percentage values in order to facilitate a comparison of respective indices. Thus, percentage accuracy and precision for the 11- and 6-segment models was 10.8±4.2% and 10.6±4.2% in smaller segments and 1.1±5.5% and 0.5±5.6% in larger segments, respectively (compare graphs in **Figure 4**).

Values for RVD and DS did not significantly differ between BARO and BLRO analysis, the latter being slightly but not significantly more precise compared to BARO **(Table 2 and Table 3)**. Finally, DS values did not differ significantly compared to phantom values either for the 11-segment (-0.48±3.66%, p=0.34 for BARO and –0.60±3.21%, p=0.17 for BLRO) or for the 6-segment model (–0.11±3.97%, p=0.84 for BARO and –0.26±3.52%, p=0.59 for BLRO).

Table 2. Validation of 11-segment model vs. phantom dimensions (AP views).

	BARO			BLRO			
	Accuracy	Precision	*p*-value BSM11 vs. phantom	Accuracy	Precision	*p*-value BSM11 vs. phantom	*p*-value* BARO vs. BLRO
MLD-all, mm	0.013	0.082	0.23	0.013	0.082	0.23	N/A
MLD-large MLD, mm	–0.005	0.087	0.73	–0.005	0.087	0.73	N/A
MLD-small MLD, mm	0.066	0.029	<0.001	0.066	0.029	<0.001	N/A
RVD-all, mm	–0.030	0.047	<0.001	–0.025	0.041	<0.001	0.49 (0.16)
DS-all, %	–0.48	3.66	0.34	–0.60	3.21	0.17	0.53 (0.17)

AP: anteroposterior; BARO: bifurcation automatic reference obstruction analysis; BLRO: bifurcation local reference obstruction analysis; BSM11: bifurcation 11-segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter; N/A: non-applicable; p-significant <0.05 *values relate to the comparison between accuracy measures; values in parentheses relate to the comparison between precision measures.

Table 3. Validation of 6-segment model vs. phantom dimensions (AP views).

	BARO			BLRO			
	Accuracy	Precision	*p*-value BSM6 vs. phantom	Accuracy	Precision	*p*-value BSM6 vs. phantom	*p*-value* BARO vs. BLRO
MLD-all, mm	0.003	0.100	0.81	0.003	0.100	0.81	N/A
MLD-large MLD, mm	–0.018	0.107	0.29	–0.018	0.107	0.29	N/A
MLD-small MLD, mm	0.064	0.029	<0.001	0.064	0.029	<0.001	N/A
RVD-all, mm	–0.029	0.045	<0.001	–0.025	0.037	<0.001	0.53 (0.08)
DS-all, %	–0.11	3.97	0.84	–0.26	3.52	0.59	0.39 (0.19)

AP: anteroposterior; BARO: bifurcation automatic reference obstruction analysis; BLRO: bifurcation local reference obstruction analysis; BSM6: bifurcation 6-segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter; N/A: non-applicable; p-significant <0.05 *values relate to the comparison between accuracy measures; values in parentheses relate to the comparison between precision measures.

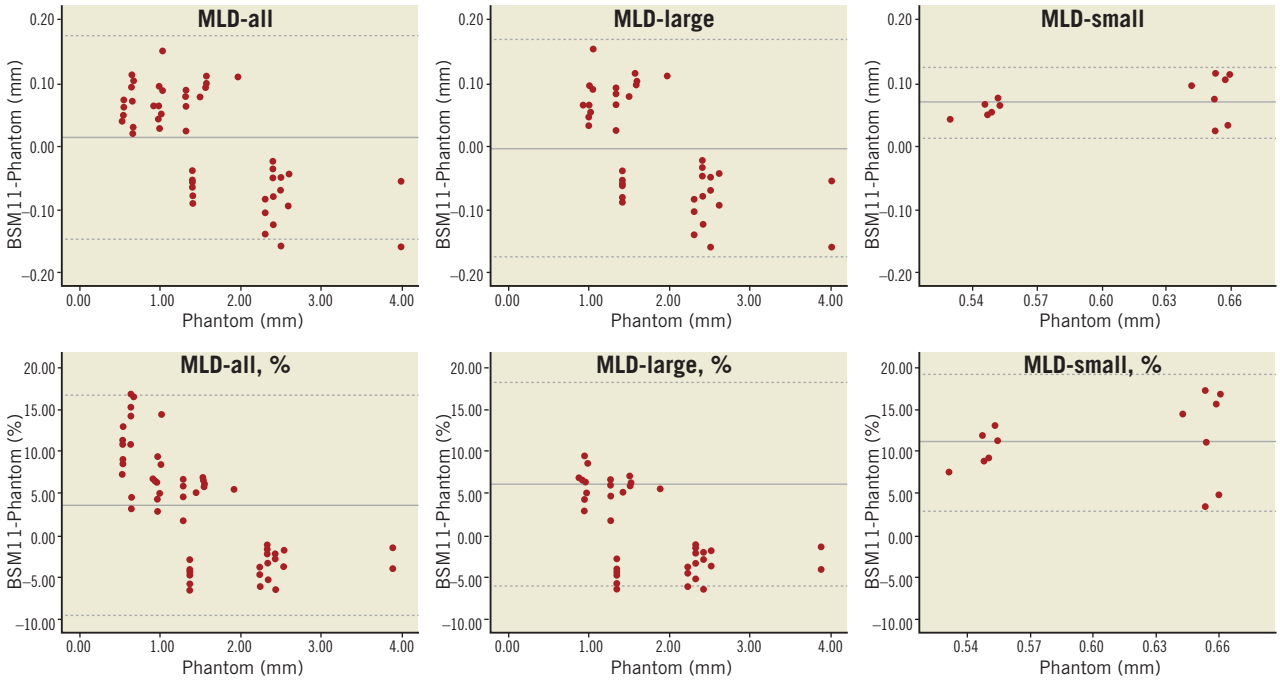

Figure 4. *Bland-Altman plots comparing the 11-segment model results to the phantom values for minimal lumen diameter (MLD); analysis in anteroposterior views. Absolute (upper panel) and relative (lower panel) differences are plotted on the Y-axis for the entire dataset (left column), for true MLD values >0.7 mm (middle column) and for true MLD values <0.7 mm (right column). Solid lines represent the mean difference; dotted lines represent the 95% limits of agreement (mean difference ±1.96 SD)*

INTRA- AND INTER-OBSERVER VARIABILITY Bias, standard deviation and repeatability coefficient for either model are reported in **Table 4**. Values for RVD derived with BARO were consistently more reproducible compared to BLRO (p<0.001 for all comparisons). DS values were also more reproducible with BARO compared to BLRO; p-value for comparisons in intra-observer analysis was 0.09 and 0.03 for the 11- and 6-segment models, respectively, whereas in inter-observer analysis it was 0.01 and 0.43, respectively.

INTER-MODEL AGREEMENT Direct assessment of agreement between the two models is presented in **Table 5**. Limits of agreement for MLD were ±0.076 mm, whereas for RVD and DS they were ±0.021 mm and ±2.53% in BARO, and ±0.035 mm and ±2.98% in BLRO analysis, respectively. Accuracy and precision measures did not differ significantly between models except for BARO derived DS values, where bias differed by 0.37% (p=0.04).

ANALYSIS IN ROTATED VIEWS

Accuracy and precision of measurements in rotated views are reported in **Table 6**. Only MLD values differed significantly from the phantom values (p=0.02). Accuracy was increased for MLD and DS measurements with the 6-segment model, however precision was comparable between models. Inter-observer variability for MLD was ≤0.088 mm, for RVD was ≤0.043 mm (BARO) and

Table 4. Intra- and inter-observer variability (AP views).

	Intra-BSM11			Intra-BSM6			Inter-BSM11			Inter-BSM6		
	Bias	SD	Repeat	Bias	SD	Repeat	Bias	SD	Repeat	Bias	SD	Repeat
MLD, mm	–0.001	0.016	0.032	0.000	0.016	0.032	–0.004	0.019	0.037	0.001	0.026	0.052
BARO												
RVD, mm	0.000	0.016	0.032	0.002	0.011	0.022	–0.002	0.022	0.043	0.002	0.020	0.040
DS, %	0.06	0.85	1.67	0.07	0.68	1.33	0.20	0.97	1.90	0.08	1.14	2.24
BLRO												
RVD, mm	0.006	0.030	0.058	0.006	0.029	0.057	0.005	0.043	0.085	0.005	0.040	0.079
DS, %	0.20	1.02	2.01	0.18	0.89	1.74	0.41	1.38	2.71	0.20	1.17	2.29

AP: anteroposterior; BARO: bifurcation automatic reference obstruction analysis; BLRO: bifurcation local reference obstruction analysis; BSM: bifurcation segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter; repeat: repeatability coefficient; SD: standard deviation

Table 5. Agreement between 11- and 6-segment model (AP views).

	BSM11-BSM6			BSM11 vs. BSM6	
	Bias	SD	95% LA	*p*-value bias	*p*-value SD
MLD, mm	0.010	0.039	±0.076	0.06	0.08
BARO					
RVD, mm	–0.001	0.011	±0.021	0.48	0.38
DS, %	–0.37	1.29	±2.53	0.04	0.28
BLRO					
RVD, mm	0.000	0.018	±0.035	0.91	0.23
DS, %	–0.34	1.52	±2.98	0.10	0.25

AP: anteroposterior; BARO: bifurcation automatic reference obstruction analysis; BLRO: bifurcation local reference obstruction analysis; BSM: bifurcation segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter; LA: limits of agreement; SD: standard deviation

≤0.088 mm (BLRO), and for DS was ≤3.39% (BARO) and ≤4.22% (BLRO) for either model (not shown). Restriction was applied by the first analyst once (1/18) per rotated projection; for the same bifurcations pathlines were manually drawn by the second observer.

BIFURCATION ANGLE

In AP views, BA was significantly underestimated, with an accuracy and precision of –2.6±3.5°, ($p<0.001$). Intra- and inter-observer bias was zero, whereas variability was 1.0° and 1.2°, respectively. In rotated views, accuracy and precision became –3.1±6.2°, whereas inter-observer variability was 1.9°; precision and reproducibility were significantly decreased compared to the AP measurements ($p<0.001$ for both).

Discussion

The main findings of this study are: 1) The new lumen detection algorithm has improved the quantification of the MLD measurements resulting in a highly accurate and precise performance across the entire range of diameter values anticipated in clinical practice; 2) The new bifurcation automatic reference obstruction analysis algorithm has comparable accuracy and precision with local reference obstruction analysis, however is more reproducible for RVD and DS measurements; 3) There is high agreement between the bifurcation segment models for all parameters, the 11-segment model being slightly less accurate but more precise compared to the 6-segment model regarding MLD values.

SMALL MLD VALUES

One can question whether analysis of diameters in the range 0.5-0.7 mm is clinically meaningful, since these are prone to induce ischaemic changes and intra-luminal thrombosis[20]. However, the accuracy and precision of the measurements impact on the calculation of the post-procedure diameter gain and the late lumen loss, still seen as surrogate angiographic markers for the evaluation of intracoronary devices[21]. Several approaches have been reported to improve the accuracy of small diameters for single vessel analysis. Generally, these approaches can be divided into two categories: either correcting the system's point spread function[10,11], or incorporating an adaptive correction function for the weighting of the first and second derivatives of the brightness profile[9,22].

In this report we presented the results of the *in vitro* validation of a new algorithm, wherein video-densitometric information is dynamically integrated in the lumen detection in order to reduce the

Table 6. Accuracy and precision in rotated views.

	BSM11			BSM6			
	Accuracy	Precision	BSM11 vs. phantom p-value	Accuracy	Precision	BSM6 vs. phantom *p*-value	BSM11 vs. BSM6 *p*-value*
MLD-all, mm	0.035	0.103	0.02	0.010	0.115	0.52	0.02 (0.21)
BARO							
RVD-all, mm	–0.004	0.041	0.49	–0.004	0.040	0.49	0.92 (0.43)
DS-all, %	–0.74	4.52	0.24	0.13	4.40	0.84	0.02 (0.42)
BLRO							
RVD-all, mm	0.001	0.049	0.91	0.000	0.046	0.94	0.88 (0.32)
DS-all, %	–0.99	4.27	0.10	–0.14	4.02	0.80	0.03 (0.33)

BARO: bifurcation automatic reference obstruction analysis; BLRO: bifurcation local reference obstruction analysis; BSM: bifurcation segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter; p-significant <0.05 *values relate to the comparison between accuracy measures; values in parentheses relate to the comparison between precision measures

overestimation of small diameters resulting from stand-alone edge detection. Thereby, this new approach benefits from the relative strengths of either technique (video-densitometry is better for small lumens whereas edge detection is better for larger lumens), by dynamically combining them as earlier suggested by Haase et al8. The algorithm takes into account that the image data produced by the angiographic system may influence the transfer function of the imaging chain while they are processed; for example, Siemens Axiom Artis™ (Siemens AG, Munich, Germany) angiographic systems might improve the image visibility by using edge enhancement and dynamic density optimisation algorithms[23]. The performance of the new algorithm for the range of phantom MLD below 0.7 mm has improved as evidenced by the decreased percentage deviation from phantom values compared to the earlier software version (10% vs. 35%, respectively, **Figure 3**)[6] and by the smaller difference in accuracy and precision between the overall values and the subgroup of vessel segments with larger MLD. Both statements hold for both 11- and 6-segment models suggesting an overall homogeneous performance of the software, without improvements in small lumen detection counteracting the software performance in the larger diameter range.

BARO VS. BLRO

Local reference analysis is based on the premise that straight vessel segments between adjacent bifurcations are not expected to taper, if assumed healthy[6]. Since the phantom vessel segments in our study had a constant calibre between bifurcations, BLRO derived RVD values at the site of the obstruction would not be expected to differ from the RVD at the respective reference positions, hence the excellent accuracy and precision for BLRO. Furthermore, in order to stabilise these BLRO derived RVD values, diameters within 1.5 mm proximal and distal to the reference positions are averaged[6]. However, notwithstanding this averaging process, an automatic regression function taking into account the whole length of the analysed straight vessel segment outside the obstruction boundaries would be expected to be more reproducible. Indeed, whereas BLRO derived RVD values were marginally but not significantly more accurate and precise compared to BARO, the latter method resulted in significantly higher (almost two-fold) reproducibility. This lower reproducibility in BLRO must have resulted from variability in placing the reference points coupled with contour irregularities; had the contours been totally free of noise, selection bias would not have made any difference.

Naturally these effects are pronounced in real coronary cases, where one could expect increased variability for BLRO derived RVD values. Operators may choose different landmarks (bifurcations) dependent on individual perception of what constitutes a true bifurcation (e.g., SB larger than 1.5 mm). Thus analysed segments may become exceedingly long and tapered, which is the case where automatic reference analysis is preferred[2]. Local reference analysis can still be beneficial in ectatic or diffusely diseased vessels, where a regression function could be severely mistaken, based on either too large or too small diameter values, respectively. Ultimately the point is that, independent of the bifurcation obstruction analysis methods (BARO or BLRO), the true reference of all vessel segments (PMV, DMV, SB) in any bifurcation lesion can be calculated simultaneously with a high accuracy and precision <0.05 mm; accurate sizing of balloons and intracoronary devices including dedicated bifurcation stents facilitates optimal deployment and final kissing ballooning resulting in optimal stent strut apposition[24-26].

Improved lumen detection coupled with refined reference obstruction analysis resulted in highly accurate, precise and reproducible DS measurements. In the context of bifurcation PCI, a precision of 3.2-3.7% (BLRO and BARO, respectively, in 11-segment model) for DS measurements at the SB ostium either pre-procedure, after ballooning or after stenting could result in closer correlation with fractional flow reserve values, and thus be included in the decision-making process[27-29].

THE 11- VS. THE 6-SEGMENT MODEL

Whereas in the 11-segment model there is a provision for segment 7 reflecting the central bifurcation region, also called the polygon of confluence (POC), in the 6-segment model there is no intervening segment; segments 2 (PMV), 3 (DMV) and 5 (SB) are separated by the point of bifurcation[6,16]. Thus in the 11-segment model there is a small chance that an obstruction located within the POC may go undetected, if we only take segments 2, 3 and 5 into consideration **(Figure 2)**. However, in this way segments 2, 3 and 5 do not become "contaminated" by contours/diameters derived by interpolation opposite the SB ostium. This difference in bifurcation segment model makes MLD detection more accurate (p=0.06) for the 6-segment model, but more precise for the 11-segment model (p=0.08) **(Table 5)**. Conclusions already made for the relative merits of BARO and BLRO analysis apply to both models. The 6-segment model BARO derived values are slightly more precise and reproducible, probably because on average they are based on longer segments. However differences are too small to make a definite statement. Lastly, one could argue that in the analysis of true coronary cases, the validity and reproducibility of the 11-segment model could be hampered by periprocedural changes in POC size. Indeed, in the original software design, POC definition was based on the luminal contours[16], which were obviously different after PCI. A relevant modification has already been integrated in CAAS 5.8, and therefore POC borders are now calculated on the reconstructed obstruction-free reference contours, thus making its size procedure independent. Naturally, the ultimate test for the two models would be the evaluation of their relative merits in the context of a large clinical registry of bifurcation PCI.

Bifurcation angle calculation algorithm did not change per se compared to the CAAS 5.8, thus accuracy and precision were not expected to vary significantly between versions. Indeed, accuracy and precision for the CAAS 5.9 2-D bifurcation QCA were –2.6° and 3.5° whereas they were –2.2° and 3.3°, respectively, for CAAS 5.8. However, calculations had a higher intra- and inter-observer reproducibility in the new version (1.0° and 1.2°, respectively,

compared to 1.5° and 1.6° in the CAAS 5.8). Minor differences in BA values must have resulted from differences in contour drawing due to the new small lumen detection algorithm. In any case, 2-D QCA derived angle values are an approximation of a 3-D structure. The widest opening of a given bifurcation and the best view of the SB ostium usually coexist in one single good 2-D image, the AP view in the phantoms' design. Declining accuracy and precision for BA calculations in the rotated views reflect this phenomenon.

Analysis in rotated views was not part of the validation study, however to a certain degree confirmed its findings. Accuracy and precision for MLD values was improved compared to the earlier version resulting in improved DS results. The 6-segment model was more accurate and precise compared to the 11-segment model. One would expect that a 3-D reconstruction combining these rotated views may have provided even better results compared to either the RAO or the LAO projection, eliminating the effect of overlap[30].

Finally, it should be stressed that *in vitro* validation does not take into account the movement of the coronary arteries and the inherent decrease in image quality from beam scattering and periprocedural thrombus and dissection flaps. However, it is a useful means to objectify software performance and gain insight into the strengths and weaknesses of the software evaluated.

Conclusions

The new lumen detection algorithm integrated into the latest version of the CAAS 2-D bifurcation QCA software improved MLD quantification for true MLD <0.7 mm resulting in highly accurate and precise diameter measurements over the entire range of diameter values anticipated in clinical practice. Furthermore, the optimised algorithm for automatic reference obstruction analysis provides highly accurate, precise and reproducible RVD and DS measurements, which may facilitate device sizing and periprocedural strategy in bifurcation PCI.

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Conflict of interest statement

J.P. Aben and B. Weijers are employees of Pie Medical Imaging. However, none of them were involved in the analysis and interpretation of data, but merely in the description of methodology. The other authors have no conflict of interest to declare.

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Chapter 5

A novel dedicated 3-dimensional quantitative coronary analysis methodology for bifurcation lesions

EuroIntervention; 7(5):629-635.

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A novel dedicated 3-dimensional quantitative coronary analysis methodology for bifurcation lesions

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Background

We developed a novel and dedicated three-dimensional (3-D) quantitative coronary analysis (QCA) software (Cardiovascular Angiography Analysis System, Pie Medical Imaging, Maastricht, The Netherlands) to overcome potential limitations associated with two-dimensional (2-D) quantitative coronary analysis of bifurcation lesions (vessel overlap, foreshortening).

By combining two 2-D image data sets, the new CAAS 5, QCA 3-D bifurcation software is able to perform a 3-D reconstruction of the bifurcation and determine lesion characteristics including bifurcation angle. This is achieved in the following steps: i) Contour detection on two angiographic projections of the involved vessel segments including the bifurcation segment identification of a common image point; ii) Creation of the 3-D model and definition of the Polygon of Confluence (POC); iii) Calculation of cross-sectional area and diameter measurement; iv) Calculation of the reference area; v) Calculation of bifurcation angle.

This paper describes how the methodology is accomplished, in which the QCA 3-D bifurcation software performs a 3-D reconstruction of the bifurcation and determines lesion characteristics including bifurcation angle, with improved accuracy by reducing overlapping.

Introduction

In the percutaneous treatment of coronary artery disease, online two-dimensional (2-D) quantitative coronary angiography (QCA) is commonly used to determine lesion length and vessel size for stent implantation[1]. Two-dimensional QCA is accepted as the gold standard for reporting angiographic outcomes and has served as a surrogate endpoint for clinical events in large trials[2]. There are, however, several limitations with this 2-D technique. Depending on the angiographic view, vessel tortuosity, vessel overlap and foreshortening can result in inaccurate measurements[3]. This inaccuracy is important during percutaneous coronary intervention (PCI), because it may influence the selection of the correct size of the devices. In tortuous vessels this can lead to underestimation of the stent length required to cover the lesion[4]. To provide solutions for many of the inherent limitations associated with 2-D QCA, three-dimensional (3-D) reconstruction software algorithms, that integrate multiple single plane images, have been developed[5,6]. Briefly, the benefits of 3-D reconstruction include elimination of vessel foreshortening, out-of-plane magnification and calibration error[7].

Recent advancements in the field of PCI (e.g., introduction of drug-eluting stents) have resulted in the treatment of more complex anatomies including bifurcation lesions[8,9]. Based on the assumption

of continuous tapering of the vessel, conventional QCA calculates the reference vessel diameter (RVD) by interpolation from the diameter of the non-diseased vessel sections. Because bifurcation lesions are associated with relatively acute tapering of the vessel (from the proximal main vessel to the distal vessel, "step-down"), analysis of bifurcation lesions may lead to (1) underestimation of the RVD and percent diameter stenosis (%DS) in the proximal vessel and (2) overestimation of the RVD and %DS in the distal vessel[10]. Several 2-D QCA software algorithms have attempted to address this issue by calculating the RVDs in the proximal main (PMV) and distal main vessel (DMV) and side branch (SB) separately[5,10]. However, the inherent limitations in 2-D QCA call for dedicated 3-D QCA software, in order to provide more accurate measurements for the bifurcation lesions. This paper describes a novel methodology for true quantitative 3-D bifurcation analysis implemented in the new Cardiovascular Angiography Analysis System (CAAS) 5, 3-D software (Pie Medical Imaging, Maastricht, The Netherlands), wherein two 2-D images are combined into reconstructed 3-D images to determine lesion dimensions and characteristics as well as bifurcation angle.

CAAS 5 QCA 3-D bifurcation methodology

The CAAS 5 3-D quantitative analysis of bifurcation vessels is accomplished in six steps:

1. Contour detection on two angiographic projections of the involved vessel segments including the bifurcation segment.
2. Identification of a common image point.
3. Creation of the 3-D model and definition of the Polygon of Confluence (POC).
4. Calculation of the cross-sectional area and diameter measurement.
5. Calculation of the reference area.
6. Calculation of the bifurcation angle.

The average analysis time of all steps is around two seconds with use of a 2.33-GHz Dual Core Intel CPU.

CONTOUR DETECTION

In two 2-D image projections, being at least 30 degree apart, obtained either from a biplane or two monoplane acquisitions, the bifurcated vessel is detected. The bifurcation contour detection is performed using a semi-automated process that employs either a manually drawn initial pathline, or an automatic pathline initiated by mean of three user-defined points; one at the proximal side of the main vessel and two at both distal ends of the bifurcated branches. The automatic pathline is calculated by a wave propagation algorithm[11]. The contours are detected by using the well established minimal cost algorithm[12], wherein the bifurcated vessel is considered to be a single entity[10]. After the automatic contour detection is applied on the first 2-D image projection, automatically a region of interest in the second 2-D image projection is indicated in order to assist the user in selecting the correct vessel segment within the second projection.

IDENTIFICATION OF A COMMON IMAGE POINT

To obtain an accurate and robust 3-D reconstruction of the bifurcated vessel it is required to correct for the system distortion introduced by the isocentre offset. This correction is performed by identifying a common image point (CIP) representing corresponding anatomical landmarks between the selected projections. Using densitometry, the CAAS software automatically locates the CIP, by performing a correlation algorithm between the densitometric intensity obtained from the detected bifurcated vessel of the two images. The analyst can manually redefine the automatic CIP if necessary **(Figure 1)**.

CREATION OF 3-D MODEL AND DEFINITION OF THE POLYGON OF CONFLUENCE (POC)

A 3-D model of the bifurcated vessel is constructed, based on the two 2-D angiographic segmented bifurcation and the geometric data of the acquisitions provided through the DICOM headers;

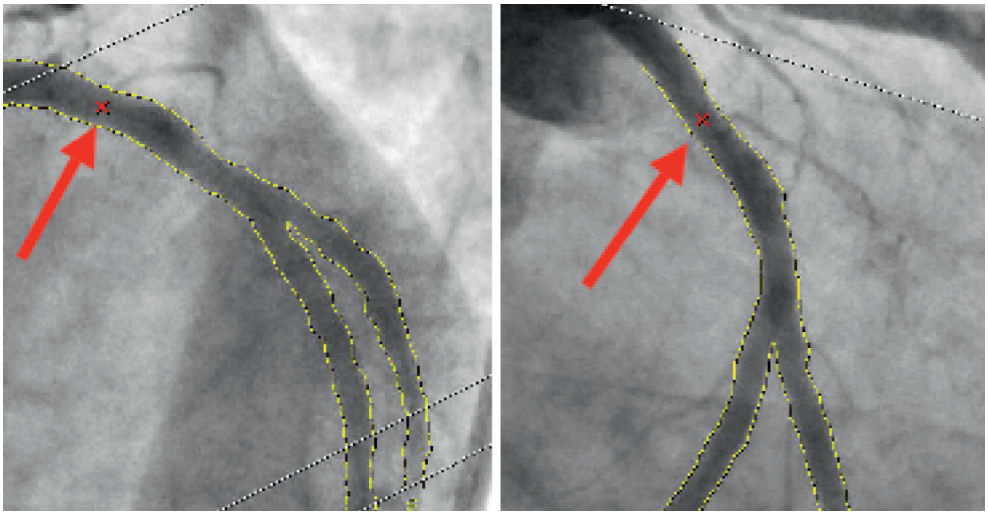

Figure 1. *Automatic selection of common imaging points (CIP, red crosses indicated with red arrows) in two different projections. The analysis can optimise the position of CIP manually if necessary.*

these are combined by means of the CIP merging point in order to correct for the distortion introduced by the isocentre offset. First the centre line of the main vessel, defined from the proximal edge of the PMV up to the distal edge of the DMV, is reconstructed in 3-D. Next the centre line of the side branch is reconstructed in 3-D, starting at the origin of bifurcation as obtained in the 2-D projections up to the distal end of the SB. In both steps the 3-D centre line reconstruction is performed by means of an adaptive 3-D epipolar geometry algorithm. The first possible epipolar mismatch is detected, by comparing the angle between the direction of the vessel and the viewing direction of the system. Within regions where no epipolar mismatch is detected, the 3-D centre line reconstruction is based on epipolar geometry. Next, within regions with possible epipolar mismatch, an iterative reduction of the cumulative difference of the 2-D centre line and the 3-D back-projected centreline is performed. The 3-D centre line of the central bifurcation area can not be directly extracted from the 2-D information, since the information obtained from these 2-D images are hampered by foreshortening and missing information due to overlap in the main vessel and the side branch. Therefore the 3-D centre line within the estimated bifurcation area, defined as the union of both POC from the 2-D projections, is adjusted by fitting a 3-D parametric curve through the estimated bifurcation based on the 3-D centre line just outside the estimated bifurcation area. During the fitting process the location of the detected bifurcation in each 2-D projection is taken into account to assure correct definition of the 3-D centre line. Based on the 3-D centre line combined with the contour information of each 2-D projection, a 3-D model of the bifurcated vessel assuming an elliptical cross-section shape is constructed. In order to correctly reconstruct the central bifurcation area into 3-D, we have to take into account the fact that the contour information obtained from the 2-D projections may contain vessel overlap, since the bifurcated vessel might be partly obscured in one or both of the image projections. To overcome this problem the 3-D cross-section shape is created by using virtual vessel contours within each 2-D POC. These virtual vessel contours are derived in each 2-D projection from the edge information outside the POC. First the centre line covering the POC is redefined using a parametric interpolation technique known as Catmull-Rom splines[13] and guided by control nodes extracted just outside the POC **(Figure 2)**. Next, the virtual edge is positioned perpendicular to the new centre line at a distance defined by a linear radius function across the POC.

The central bifurcation area, described as the polygon of confluence (POC) is specifically defined for further analysis. In the previously reported method for 2-D bifurcation software, the point of bifurcation (POB) was defined as a centre of the circle touching the three contours while the POC was defined as the area delineated by the lines perpendicular to the centre line crossing this circle[10]. Extending the previous reported method to 3-D would suggest using a sphere as a mathematical object to define the POB and POC. However, the central bifurcation area in 3-D shows a "peanut" shape; hence a new method is introduced for defining the POB and POC.

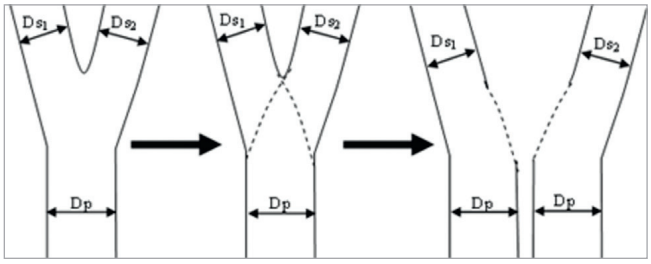

Figure 2. *Two virtual vessel contours (i. from the proximal main branch [Dp] to the distal main branch [Ds1], ii. from the proximal main branch [Dp] to the side branch [Ds2]) are created by using a parametric interpolation technique of catmull-row splines.*

The POC region in 3-D begins at the position where the 3-D centre line bifurcates (red line in **Figure 3**) and ends where the main and side branches stop coinciding with each other (green lines in **Figure 3**). In this new definition of the POC in current 3-D analysis, the location of the bifurcation carina is precisely adjusted with minimal overlap, based on the reconstructed 3-D model.

CALCULATION OF CROSS-SECTIONAL AREA AND DIAMETER VALUES

Cross-sectional areas are calculated on the assumption that the vessel has an elliptical cross section based on the luminal diameters from the two different 2-D projections. Inside of the POC region,

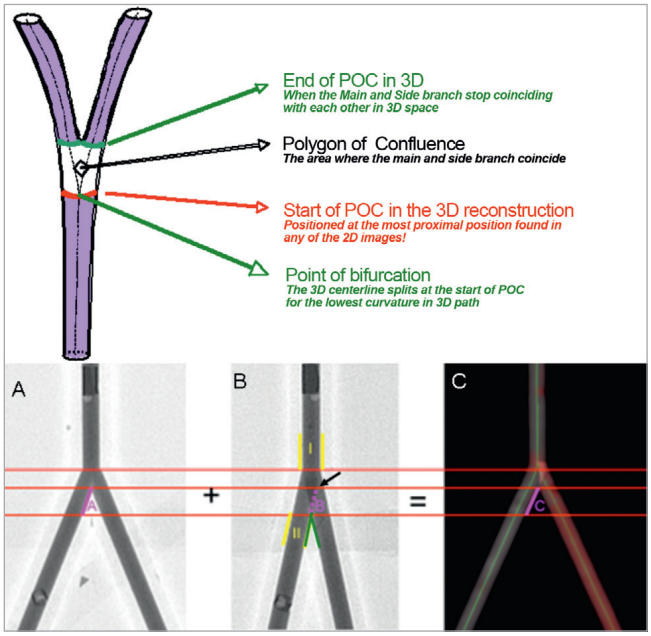

Figure 3. *Upper panel: Definition of the polygon of confluence region for optimal 3-dimensional reconstruction. Lower panel: Adjustment of bifurcation carina with minimal overlap. In a 2-D projection (B), the carina looks more distal (green lines) to the actual position (black arrow) due to overlap. After 3-D reconstruction (C), the correct location of bifurcation carina is applied in the projection B.*

the cross-sectional area shows a so-called "peanut" shape. To define in the POC the "bifurcating" cross-sectional areas of the two daughter branches, the POC area is divided into two elliptical shapes along the two centre lines based on the virtual vessel contours.

Figure 4 shows in red (continuous line) one of the cross-sectional areas located in the POC region, the black dotted line indicates the projected diameters (2-D length) obtained in each angiographic view. The missing points in blue (A and B) are the two cross-points between the 2-D diameters obtained in each angiographic view and are based on the virtual vessel contours of the distal main vessel.

In the 3-D reconstruction, the elliptical cross-sectional area is the primary measured parameter. Next to this cross-sectional area, the equivalent luminal diameter, minimum luminal diameter and maximal luminal diameter curves are calculated based on circularity assumption **(Figure 5)**. The minimum diameter represents the maximum circle that fits through the 3-D reconstruction while the maximum diameter represents the minimum circle that encloses the 3-D reconstruction; both are based on the virtual vessel contour when considering the POC.

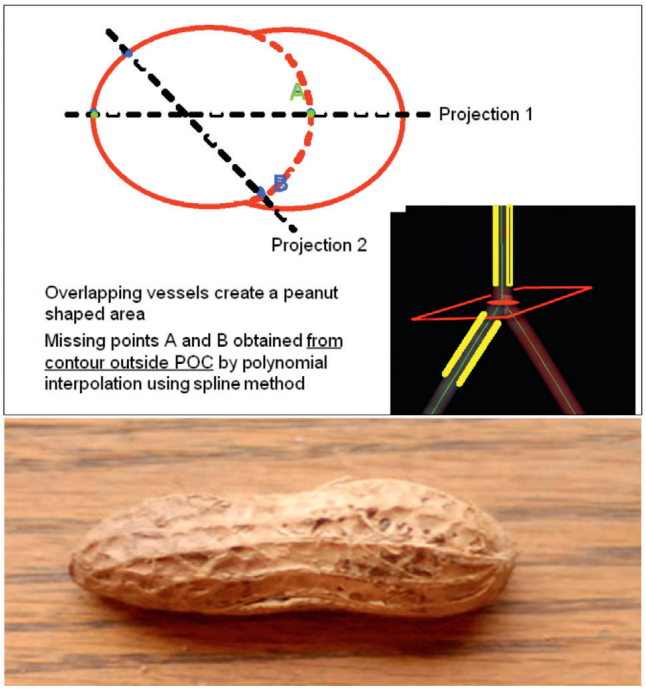

Figure 4. *Upper panel shows area measurement inside a polygon of confluence. Since overlapping vessels create peanut-shaped area (lower panel), the points A and B are calculated from contours outside POC by polynominal interpolation to create a virtual ellipsoid area (dotted red line), which is used for area measurement. Lower panel: photograph of a peanut.*

CALCULATION OF REFERENCE AREA

For the reference cross-sectional area function, a reconstruction of the "healthy" part of the cross-sectional area function is made based on the 3-D reconstructed model for each of the branches connected at the POC. For this a 3-D equivalent as used in the CAAS single vessel software is used[12]. These results in a reference function for each of the three vessel branches connected at the POC. These three reference functions are used in the 2-D healthy bifurcation reconstruction algorithm in order to create the 2-D healthy reconstructions as described by Ramcharitar et al[10]. Ramcharitar described a method to calculate the reference diameter within the POC using a curvature of a circle passing through the termination of reference vessel lines of the proximal and distal vessels at the entrance of POC where the centre of the circle is located outside the vessel, on the line perpendicular to the middle of the line connecting these termination points.

Within the current method, the reference vessel lines up to the entrance of the POC in the 2-D projections, are based on the back-projected 3-D reference area as described before. The "healthy" reconstructed 2-D measurements are then combined into 3-D measurements using a similar approach as described for the cross-sectional area calculation.

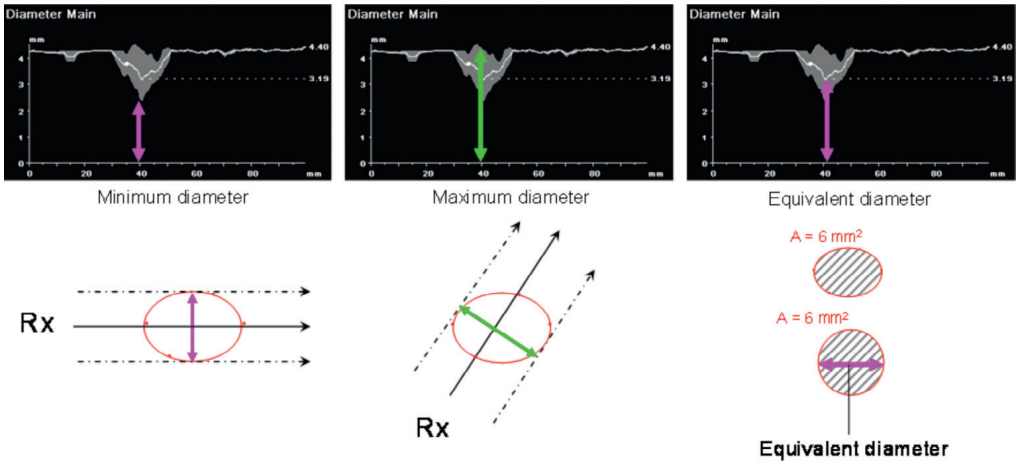

Figure 5. *Measurement of diameters. The measured cross-sectional area is converted to a circle with similar cross-sectional area. The diameter of such circle is called an "equivalent diameter".*

CALCULATION OF BIFURCATION ANGLE

Two bifurcation angles are computed between the PMV and the SB (proximal angle), and between the DMV and the SB (distal angle); they are derived from the 3-D vector of the centre line in the PMV at the start of POC (directed from distal to proximal) and the 3-D vectors of centre line in the DMV and SB at distal ends of POC (directed from proximal to distal). The size of the vector, which can influence the angle, is half the size of the equivalent luminal diameter at the start and end of the POC. This is based on the assumption that the curvature of the vessel is less than its radius. Bifurcation angles are calculated in 3-D space without overlap, and theoretically are more precise than 2-D QCA.

Discussion

Coronary bifurcation lesions are a challenging area in interventional cardiology. The European Bifurcation Club has been established to clarify some of this challenge.[14-16] Contemporary studies using drug-eluting stents (vs. bare-metal stents) have shown a reduction of restenosis of the main vessel. Residual stenosis and restenosis at the ostium of the side branch, however, still remains a concern. In addition to the provisional one-stent and two-stent strategy approach using the drug-eluting stents, dedicated bifurcation stents have been designed to specifically address this challenging issues[17-23]. To adequately determine the application and angiographic outcome of such stents, characterisation of bifurcation lesion pre-procedure and assessment of luminal diameter post-procedure and at follow-up is mandatory by means of quantitative coronary angiography. Because two-dimensional QCA in bifurcation lesion is limited by foreshortening and overlap, there has been recent interest in 3-D QCA for bifurcation lesions. Although there are multiple software programs dedicated for 3-dimensional quantitative coronary angiographic analysis, there are only two software packages dedicated for bifurcated 3-D QCA (Paieon and Pie Medical). So far, there is no direct comparison between these two QCA bifurcation software packages (Paieon vs. Pie), both of which reconstruct 3-D from two projections.

Over the years many techniques have been published describing methods for 3-D coronary reconstruction based on monoplane angiography, biplane angiography and more recently, 3-D reconstructions from rotational angiography[24-28]. Three-dimensional coronary reconstruction was introduced in the mid 80's and was mostly restricted by using angiography biplane systems. One of the limitations was the need for a geometric calibration procedure to assess the 3-D system geometry[29,30]. In addition, 3-D reconstruction was inaccurate due to the distortion introduced by the conventional X-ray image intensifier systems[31]. With the introduction of the digital flat panel (DFP) technology this geometric distortion was eliminated and the new storage capabilities with the introduction of the Digital Imaging in Communication in Medicine (DICOM) standard eliminated the need for 3-D system calibration. The DICOM standard provides the necessary X-ray system information needed to perform a 3-D reconstruction. Coronary 3-D reconstruction algorithms purely based on the 3-D system information, the so-called epipolar geometry reconstruction technique, provide only accurate reconstructions in those cases, where the vessel is roughly perpendicular to the X-ray beam[29]. In the case where the vessel morphology is roughly parallel with the X-ray beam, the epipolar reconstruction technique fails due to multiple 3-D solutions. Another restriction of this technique is the erroneous assumption that the projected coronary artery from the acquired views is spatially identical[31,32]. In practice this assumption is untenable, due to (relatively large) respiratory motions and cardiac contraction motions. Even when using a biplane system, there is a short time delay between the lateral and frontal C-arm detector, which is enough to generate inaccurate 3-D coronary reconstructions. The CAAS 5 3-D bifurcation software, incorporates an alternative new epipolar reconstruction technique for reconstructing a bifurcated vessel, combined with correcting for the system distortion introduced by the isocentre offset.

In single vessel analyses, 3-D QCA has been shown to be more accurate than 2-D QCA regarding measurement of lesion length. In a sub-study of the ABSORB cohort A trial by Bruining et al[33], the length of bioresorbable scaffold made of polylactide (12 mm) was measured in multiple modality images (3-D QCA, 2-D QCA, IVUS and MSCT) using two metallic markers as landmarks, which are located in the both ends of the scaffold. The length of the 12 mm scaffold was measured as 9.89±0.93 mm, 12.24±0.55, 12.51±0.85 and 11.89±0.20 mm with 2-D QCA, 3-D QCA, QCU and QMSCT-CTA, respectively. Two-dimensional QCA apparently underestimated the scaffold length, while 3-D QCA and QCU had similar results, very close to the actual length of 12 mm. In clinical settings, measuring the lesion length with 3-D QCA compared to 2-D QCA might be therefore more useful.

One of possible benefits of using 3-D QCA analysis is to predict outcomes of bifurcation treatment. The bifurcation angle has been shown to relate not only to the difficulty level of the procedure but is also associated with intermediate outcomes. Dzavik et al reported that a bifurcation angle over 50º was an independent predictor of MACE at one year after bifurcation crush stenting in 133 patients[34]. In 132 patients receiving Cypher stent in bifurcations excluding left main lesions, Adriaenssens et al reported that increasing bifurcation angles is an independent predictor of binary restenosis (HR 1.53 [1.04–2.23] per 10 degree increase in angulation) after culotte stenting[35]. Recently, in the sub-study of the Syntax study, Girasis et al reported that the bifurcation angles utilising 3-D QCA software have a slight but non-significant correlation with 1-year outcomes. When 2-stent techniques were employed, the result was a trend towards higher event rates for patients with wider angled LM bifurcations.

In the CAAS 5 3-D bifurcation software, bifurcation angle measurements are more accurate and robust due to the knowledge of the true 3-D vessels' morphology obtained from the 3-D model. In 2-D QCA analysis, optimal assessment of bifurcation angles necessitates three planes that involve two branches (e.g., PMB+DMB, DMB+SB, PMB+SB), to avoid potential underestimation or overestimation of bifurcation angles. For example, one 2-D projection can be taken without any overlap / foreshortening for the distal main branch and side branch, however this projection may not necessarily be the opti-

mal projection to separate the proximal main and side branch, or the proximal main and distal main branch. Three-dimensional QCA definitely addresses this issue by reconstructing a 3-D model and calculating the vectors of 3-vessels (e.g., the proximal main, distal main and side branch) in 3- dimensions without overlap. The system uses the 3-D model in combination with the method of quantitative bifurcation lesion analysis as introduced in the previous paper to obtain bifurcation lesion characteristics[10]. The basic concepts introduced in the previous paper are projected to the current 3-D methodology, resulting in a quantitative analysis of the 3-D bifurcation as a single entity.

To use this software in clinical practice, it is of importance during a procedure to take two separate images with the least overlap. However, in reality, such images are not frequently available. In a study aiming at measuring the bifurcation angle of the left main with 3-D QCA software[36], the two separate images were available in only 50% of the angiographic acquisitions. The operator should bear in mind that two separate images are at least necessary to enable optimal assessment of bifurcated lesions with 3-D software.

The current methodology suffers from several limitations. Since 3-D reconstruction consists of two projections, the issue of overlapping vessels in tortuous bifurcation lesions may still be a problem. Taking into consideration the complexity of bifurcated lesions and the difficulty to take cineangiograms without overlap, one can speculate that reconstruction utilising more than two projections may yield optimal 3-D images, at the expense of the increasing complexity of analytical software. Further developments towards using multiple projections are in progress. Furthermore, reproducibility and accuracy, and the potential clinical benefits of using 3-D QCA for bifurcation lesions should be the focus of future studies.

Conflict of interest statement

J.P. Aben and C. Lokkerbol are employees of Pie Medical Imaging BV. M.A. Morel is an employee of Cardialysis BV. The other authors have no conflicts of interest to declare.

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Chapter 6

Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation

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Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation

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KEYWORDS

- angiography
- coronary bifurcation
- quantitative coronary angiography
- three-dimensional

Abstract

Aims: Validation of new three-dimensional (3-D) bifurcation quantitative coronary angiography (QCA) software.

Methods and results: Cardiovascular Angiography Analysis System (CAAS 5v10) allows 3-D angiographic reconstructions based on two or more 2-D projection images. Measurements for minimal lumen diameter (MLD), reference vessel diameter (RVD), percent diameter stenosis (DS) and bifurcation angle (BA) were validated against precision manufactured phantom bifurcations. Length measurements were validated against angiographic measurement catheters inserted into a plexiglas bifurcation phantom. In 3-D reconstructions based on two 2-D images, acquired at variable rotation and angulation, accuracy and precision (mean difference ± SD) of the 11-segment model for MLD, RVD and DS were 0.013±0.131 mm, –0.052±0.039 mm and –1.08±5.13%, respectively; inter-observer variability was 0.141 mm, 0.058 mm and 5.42%, respectively. Adding the antero-posterior (optimal) projection to these basic reconstructions resulted in reduced variability (0.101 mm, 0.041 mm and 3.93% for MLD, RVD and DS, $p<0.01$ for all) and showed a trend towards improved precision (0.109 mm, 0.031 mm and 4.26%, respectively, $p>0.05$ for all). In basic reconstructions, accuracy and precision for BA was –1.3±5.0°, whereas inter-observer variability was 7.5°; respective measures for length were 0.15±0.26 mm and 0.54 mm. Adding the antero-posterior projection resulted in decreased precision (0.47 mm, $p<0.01$) and increased variability (1.03 mm, $p<0.01$) for length measurements; precision (5.4°) and variability (7.9°) for BA did not change significantly ($p>0.30$).

Conclusions: Advances in the methodology of 3-D reconstruction and quantitative analysis for bifurcation lesions translated into highly accurate, precise and reproducible measures of diameter, length and BA.

Introduction

Percutaneous coronary interventions (PCIs) for the treatment of coronary bifurcation lesions require optimal angiographic analysis[1]; whereas visual assessment of lesion severity is still highly variable even among experts in this field[2], quantitative coronary angiography (QCA) analysis has seen improvements in performance. Dedicated two-dimensional (2-D) bifurcation QCA software acknowledges the "step-down" in vessel calibre from the proximal main vessel into the distal main vessel and the side branch[3] by determining reference vessel diameter (RVD) based on each of the three branches separately[4,5]. Thereby, higher precision in RVD and percent diameter stenosis (DS) values are attained, facilitating accurate balloon and stent sizing. In addition, reporting results over an increased number of bifurcation vessel segments facilitates accurate disease localisation and consistency in serial angiographic studies[1].

Nevertheless, the validity of 2-D QCA is dependent on the angiographic view analysed and can be affected by foreshortening and variable magnification; tortuous and/or overlapping coronary structures could impose further limitations[6]. By eliminating these potential sources of error, 3-D QCA algorithms have been shown to provide accurate, precise and reproducible diameter, area and length measurements[7-10] for single-vessel lesions in real time. Experience with 3-D bifurcation reconstructions has been reported comparing results with 2-D analysis[11,12]; however, accuracy and precision of 3-D bifurcation QCA measurements has not been established compared to a gold standard.

Dedicated 3-D bifurcation QCA software incorporated in the latest version of Cardiovascular Angiography Analysis System (CAAS 5v10; Pie Medical Imaging, Maastricht, The Netherlands) adopts algorithms already validated in the 2-D software[4,13] and applies them to the 3-D reconstructions. Furthermore, the methodology has been revised compared to the previous version[14], in order to allow reconstructions of more than two 2-D projections. In this report we present the theoretical provisions of this software and the results of *in vitro* validation for measures of diameter, length and bifurcation angle (BA).

Materials and methods

THEORETICAL PROVISIONS

A 3-D reconstruction requires at least two angiographic images separated by a viewing angle ≥30°; up to four images acquired by a biplane, monoplane or a rotational angiographic system can be combined. Analysis is initiated by demarcating the bifurcation to be analysed on the first selected angiographic image. Subsequently, automatic contour detection is performed via a validated algorithm featuring improved analysis for small vessel lumens[13]. The region of interest is automatically indicated in the other selected image(s), thereby assisting the analyst in correctly placing the delimiter points around the bifurcation, which is then contoured with the same algorithm.

3-D RECONSTRUCTION

The acquisition geometry of the projection images provided through the DICOM (Digital Imaging and Communications in Medicine) headers of the angiographic system is not sufficient to obtain an accurate 3-D reconstruction due to the isocentre offset of the gantry. The isocentre offset is the spatial difference between the centres of rotation (isocentres) of the frontal and lateral C-arms in a biplane gantry, attributable mainly to the imperfect alignment of both C-arms but also to gravity; even in a monoplane system active gantry rotation could result in a significant shift of its isocentre. In order to correct for this system distortion, a common image point (CIP) is determined by correlating the videodensitometric information obtained from the 2-D images. Subsequently, the 3-D centrelines for the bifurcation branches are reconstructed by means of an adaptive 3-D epipolar geometry algorithm[14]. Respective 3-D cross-sections are constructed assuming an elliptical model, by using the luminal diameters of the corresponding 2-D cross-sections and their spatial orientations to define the ellipse axes. In cases where >2 projections are used, already existing cross-sections are modified by integrating contour information from each additional 2-D image, while retaining an elliptical shape. In this fitting process, axes between adjacent cross-sections are kept aligned, in order to prevent the 3-D model from twisting along its centreline. For true 3-D quantitative analysis the elliptical model is then converted into a 3-D triangular surface mesh by means of a marching cubes algorithm[15].

3-D QUANTITATIVE ANALYSIS

Analogous to previous publications on bifurcation QCA analysis[14-16], the polygon of confluence (POC) is defined as the central bifurcation region which behaves differently from a single-vessel segment. Outside the POC, the cross-sectional area is defined perpendicular to the centre of the lumen; within the POC, the cross-sectional area is defined by using the "minimum energy" cross-section, i.e., the smoothest possible surface that spans the lumen at each centre line position. This "minimisation" is performed by using a level set algorithm[17] and will result in curved cross-sections within the central bifurcation region **(Figure 1)**.

Automatic calculation of reference cross-sectional area adopts the methodology described for 2-D bifurcation QCA and applies it to the 3-D reconstructed model. Outside the POC, a 3-D equivalent of the algorithm used in single-vessel segments is employed[13,18]. Within the POC, the reference area is derived by applying an interpolation technique between the "healthy" reconstructed 3-D branches. Based on the respective cross-sectional areas, lumen diameter and RVD are defined as the equivalent diameters based on the assumption of circularity. Finally, proximal and distal BA values are derived according to the methodology already described[14].

The CAAS 5v10 analysis software has no restriction regarding the number of bifurcations the 3-D model consists of: it is possible to reconstruct and analyse a vascular tree which consists of multiple bifurcations. We chose to focus on 3-D reconstructions of one bifurcation at a time, in order to mimic routine angiographic practice. Analysis regarding full-tree reconstructions of bifurcation phantoms is presented in an **Online appendix**.

VALIDATION

DIAMETER AND BA

Six precision-manufactured plexiglas phantoms, each mimicking a vessel with three successive bifurcations lesions, were used for

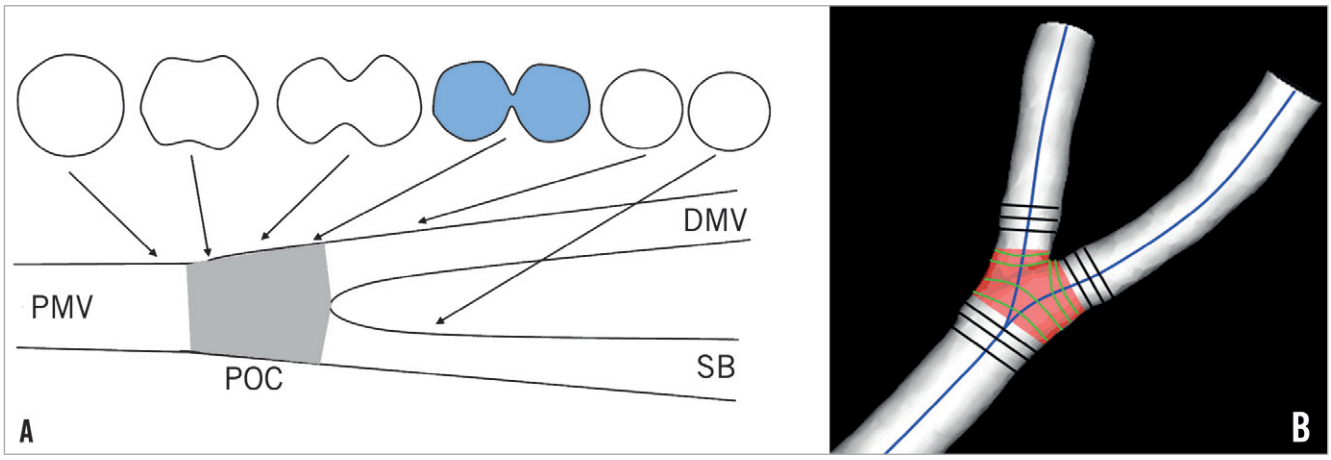

Figure 1. *Definition of polygon of confluence (POC). A) Within POC (grey) the vessel is slowly widening, but at the same time the top and bottom are slowly collapsing towards a single point (figure-of-eight shape, in blue) after which we have two "normal"-shaped vessels. B) The start of the POC (in red) is defined as the position where plane cross-sections give way to curved ones; exactly the opposite marks the end of the POC. DMV: distal main vessel; PMV: proximal main vessel; SB: side branch*

the validation of minimal lumen diameter (MLD), RVD, DS and BA measurements. Their design has already been described in detail[19]. In total, 54 phantom vessel segments of reference diameter 1.40-4.00 mm were evaluated; 33 of them had a stenosis within 3-5 mm of the bifurcation (DS 40.6-80.5%; MLD 0.53-1.96 mm), whereas the rest were free of stenoses (MLD 1.40-4.00 mm). Proximal and distal BA range was 90.4-159° and 39.5-102.9°, respectively. Digital angiograms were acquired on a biplane angiographic system (Axiom Artis™; Siemens, Forchheim, Germany); all phantoms were filled with 100% Iodixanol 320 (Visipaque™; GE Healthcare, Cork, Ireland) and imaged at 30 frames per second in a 20 cm field of view. Multiple projections were acquired for variable degrees of gantry rotation and angulation. For validation purposes, five 2-D projections including the anteroposterior (AP) projection were employed in multiple combinations. Our reconstruction protocol is shown in **Figure 2**.

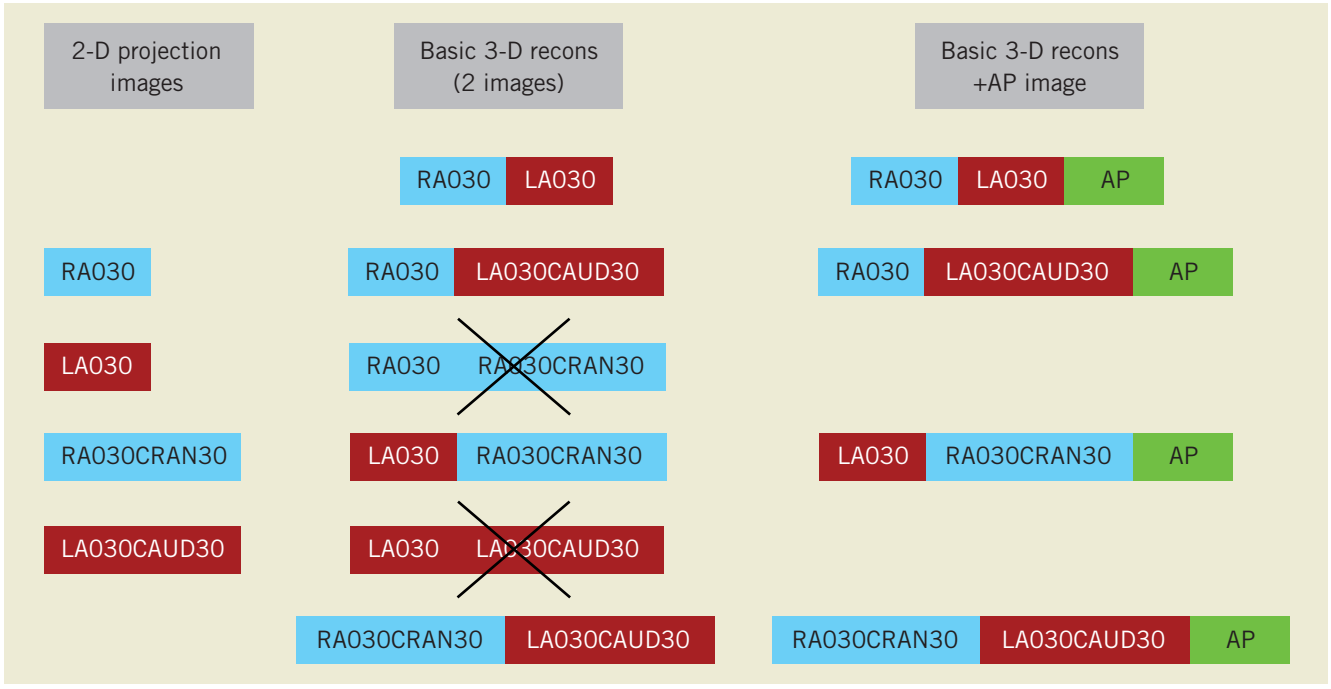

Figure 2. *3-D reconstruction protocol. For every phantom bifurcation, four 2-D projection images were combined into four separate 3-D reconstructions using two 2-D images at a time. Two potential combinations were a priori excluded, on the basis of providing limited information. The anteroposterior image (AP) was added to every one of these basic reconstructions, creating a second set of replicate 3-D QCA measurements. RAO/LAO: right/left anterior oblique (rotation); CRAN/CAUD: cranial/caudal angulation*

A standard operator procedure for angiographic analysis was followed, wherein: 1) analysis was performed on the middle frame of every angiographic image acquisition; 2) delimiter points were placed at the furthest possible distance from the bifurcation to be analysed, but not touching the adjacent bifurcation lesions or the phantom borders; 3) manual contour correction was not allowed; however, contour detection could be adjusted by using the "restriction" option, thereby excluding gross image artefacts without manually redefining the detected contours[18]; 4) if the location of the automatically defined CIP differed between images, the user could manually reposition it to an easily identifiable landmark, preferably the centre of the bifurcation.

Reconstruction resulted in a 3-D representation of the analysed bifurcation, displayed in the optimal projection, which was defined as the projection where mean foreshortening of the bifurcated vessels was minimised; quantitative analysis was reported according to the validated 11- and 6-segment models **(Figure 3)**[4,13]. Segments 2, 3 and 5 of either model reflect the segments, where in clinical practice the stent would be placed in the proximal main vessel, distal main vessel and side branch, respectively. MLD, RVD and DS values for these segments were pooled together and compared to the phantom values. Angle calculations are independent of the bifurcation segment model used. Proximal and distal BA values were pooled together and compared to the phantom angles.

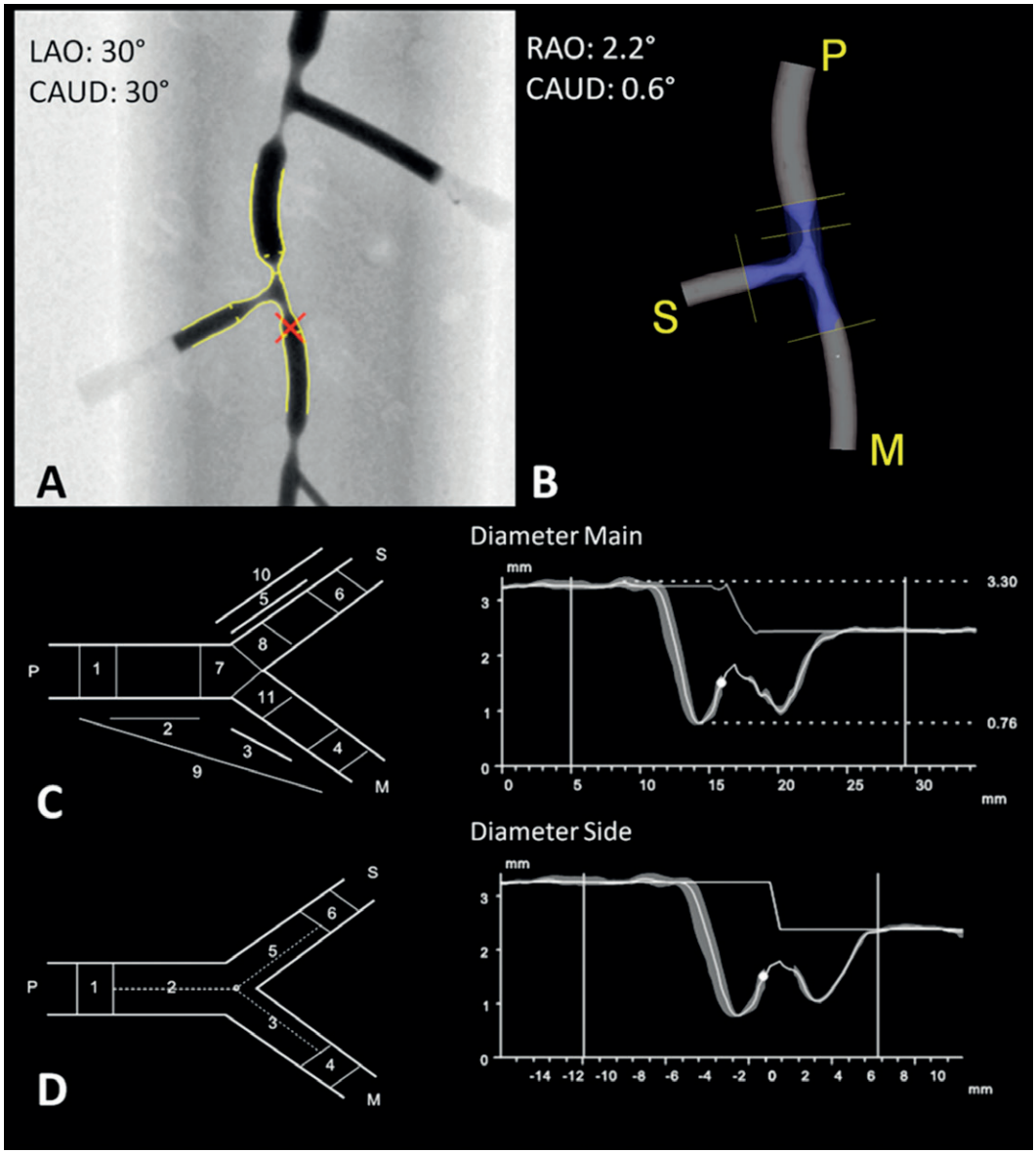

Figure 3. *3-D reconstruction and quantitative analysis (compilation). Phantom 2, bifurcation 2 was analysed in two projection images, one acquired at LAO30CAUD30 (A) and one at RAO30CRAN30 (not shown); the red cross indicates the common image point (CIP). B) 3-D reconstruction is shown in the optimal projection; P, M and S stand for PMV, DMV and SB. C) 11-segment model. Left: schematic; right: diameter graph with RVD curve for PMV into DMV. D) 6-segment model. Left: schematic; right: diameter graph with RVD curve for PMV into SB. RVD function is independent of segment model used. In both graphs, automatic reference analysis was applied. RAO/LAO: right/left anterior oblique (rotation); CRAN/CAUD: cranial/caudal angulation*

LENGTH

Due to the lack of reproducibly identifiable markers on the aforementioned bifurcation phantoms, we used a different experimental set-up for the validation of length measurements **(Figure 4)**. Two 5 Fr Cook measurement catheters (Cook Medical, Bloomington, IN, USA) with a marker distance of 10 mm were inserted into a hollow plexiglas bifurcation phantom with an inner diameter of 4.3 mm. Measurement catheters were aligned in the proximal main vessel, one extending into the distal main vessel, the second one extending into the side branch. In order to distinguish between the two branches, a copper marker was mounted on the distal main vessel. The phantom was imaged on the same angiographic system at 30 frames per second in a 25 cm field of view, and the same reconstructions protocol was followed. Within each 3-D reconstruction, 18 inter-marker segments of variable length (ranging from 20 mm up to 80 mm) were measured from leading edge to leading edge, all of these segments covering the central bifurcation region.

All QCA analyses were performed off-line by two experienced analysts (CG, TM), independently from each other.

STATISTICS

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± 1 standard deviation and compared with the paired-samples t-test; categorical variables are presented as counts. Replicate measurements reflecting multiple 3-D reconstructions of the same bifurcation were averaged separately for each analyst. The within-segment deviation of these replicate measurements was reported as the measurement error[20] and was integrated in the calculation of the final precision/variability estimates following Bland-Altman methodology[21].

The first analyst carried out two full rounds of measurements with a time interval of two weeks, in order to determine intra-observer variability. The first round of measurements was compared both with the measurements of the second analyst to determine inter-observer variability and with the corresponding true values for the purpose of validating the software against the ground truth. Bland-Altman analysis was performed for all comparisons[22].

Regarding intra- and inter-observer comparisons, the mean difference (bias) and its standard deviation were calculated; the repeatability coefficient (1.96×standard deviation) was determined as the measure of variability. For validation purposes, the signed differences between QCA measurements and the true values were averaged: the mean of these signed differences is a measure of accuracy, and the standard deviation is a measure of precision. Measures of accuracy were compared with the paired t-test; measures of precision/variability were compared with the F-test. As the true values were known, we chose to plot these on the X-axis of the Bland-Altman plot against the signed differences and computed the corresponding 95% limits of agreement[22].

All statistical tests were two-sided and a p-value <0.05 was considered statistically significant.

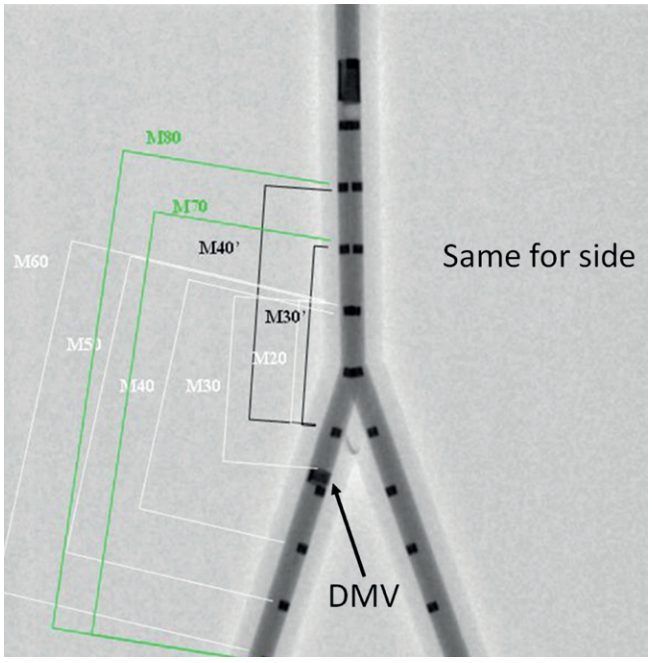

Figure 4. *Experimental set-up for validation of length measurements. Measurement catheters aligned in a plexiglas bifurcation phantom, one extending into the DMV, the second one extending into the side branch; DMV is identified by a copper marker on the catheter (arrow). Inter-marker segments of variable length are indicated on the DMV side, all of them covering the central bifurcation region. The same segments were defined and measured on the second catheter as well. DMV: distal main vessel*

Results

MLD-RVD-DS

Accuracy and precision for 3-D reconstructions of individual phantom bifurcations are shown in **Table 1**. MLD values for 3-D reconstructions of two projections (basic reconstructions) had an accuracy and precision of 0.013±0.131 mm and -0.024±0.150 mm for the 11- and 6-segment models, respectively, not being significantly different from phantom values (p-value 0.44 and 0.24). The reference size of phantom vessels was underestimated by an average 0.05 mm in both models, whereas DS estimates did not differ significantly from true values, precision being in the order of 5%. Adding the AP projection to the basic reconstructions resulted in improved precision for MLD, RVD and DS values for the 11-segment model (0.109 mm, 0.031 mm and 4.26%, respectively) **(Figure 5)**; however, improvement did not reach statistical significance for any parameter (p>0.05).

VARIABILITY

Bias, standard deviation and repeatability coefficient for the basic reconstructions are reported in **Table 2**. Adding the AP projection to the basic reconstructions resulted in increased inter-observer reproducibility for the 11-segment model, the repeatability coefficient being 0.101 mm for MLD, 0.041 mm for RVD and 3.93% for DS (p≤0.01 for every parameter). On the contrary, variability did not change significantly for the 6-segment model (p>0.05 for every parameter).

Table 1. Validation of segment models vs. phantom dimensions (3-D reconstructions of individual bifurcations).

		2 images (basic)			3 images			*p*-value		
		Accuracy	Measurement error	Precision	Accuracy	Measurement error	Precision	Basic vs. phantom	3 images vs. phantom	Basic vs. 3 images*
BSM11	MLD, mm	0.013	0.044	0.131	0.003	0.039	0.109	0.44	0.84	0.07 (0.09)
	RVD, mm	–0.052	0.023	0.039	–0.055	0.016	0.031	<0.001	<0.001	0.07 (0.06)
	DS, %	–1.08	1.68	5.13	–0.79	1.46	4.26	0.11	0.16	0.18 (0.09)
	BA, °	–1.3	3.0	5.0	–1.9	3.1	5.4	0.09	0.02	0.15 (0.33)
BSM6	MLD, mm	–0.024	0.041	0.150	–0.031	0.041	0.159	0.24	0.15	0.09 (0.34)
	RVD, mm	–0.051	0.024	0.039	–0.054	0.016	0.032	<0.001	<0.001	0.06 (0.08)
	DS, %	0.22	1.52	4.85	0.37	1.62	5.04	0.73	0.58	0.41 (0.39)
	BA, °	–1.3	3.0	5.0	–1.9	3.1	5.4	0.09	0.02	0.15 (0.33)

BA: bifurcation angle; BSM: bifurcation segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter. * values relate to the comparison between accuracy measures, values in parentheses relate to the comparison between precision measures.

Table 2. Intra- and inter-observer variability in basic 3-D reconstructions of individual bifurcations.

	Intra-BSM11			Intra-BSM6			Inter-BSM11			Inter-BSM6		
	bias	SD	repeat	bias	SD	repeat	bias	SD	repeat	bias	SD	repeat
MLD, mm	0.002	0.062	0.121	0	0.053	0.104	0.006	0.072	0.141	–0.002	0.058	0.114
RVD, mm	0	0.029	0.056	0	0.029	0.057	0.004	0.030	0.058	0.004	0.028	0.054
DS, %	–0.08	2.36	4.64	–0.01	1.96	3.84	–0.18	2.76	5.42	0.10	2.08	4.07
BA, °	0.0	4.0	7.8	0.0	4.0	7.8	0.1	3.8	7.5	0.1	3.8	7.5

BA: bifurcation angle; BSM: bifurcation segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; repeat: repeatability coefficient; RVD: reference vessel diameter; SD: standard deviation

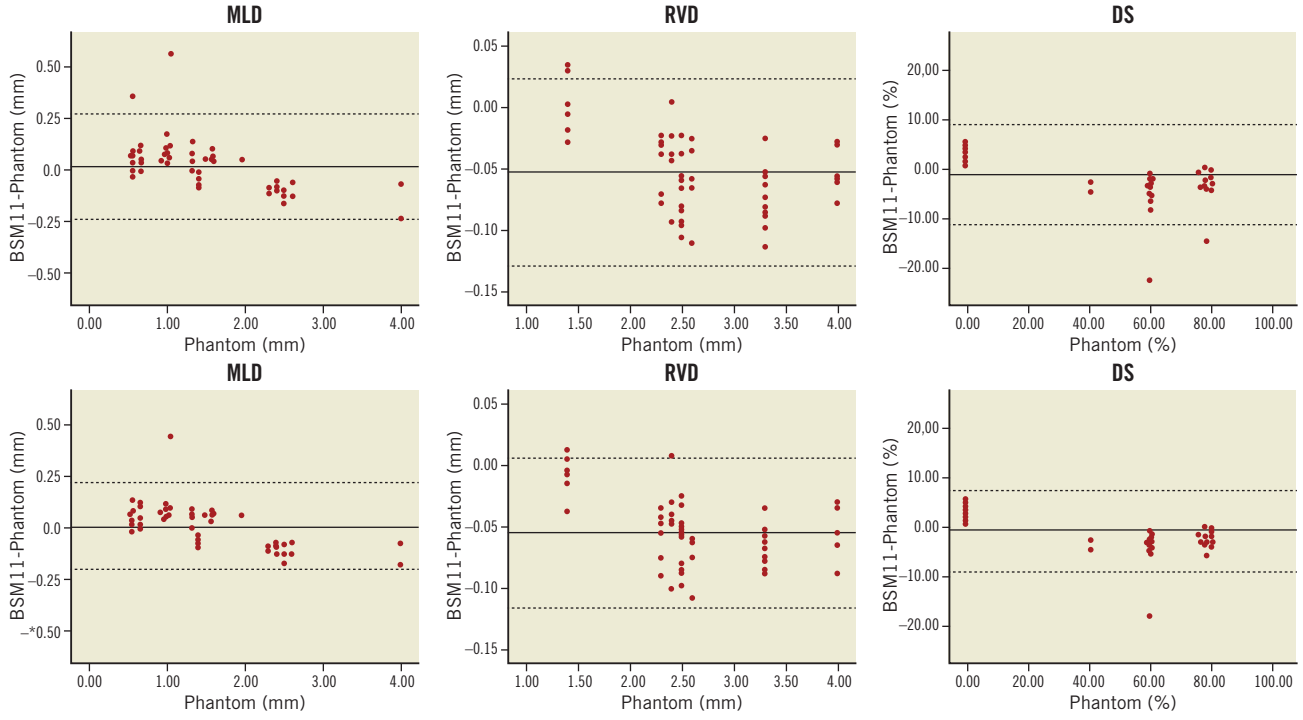

Figure 5. *Bland-Altman plots comparing 11-segment model results to the phantom values. 3-D reconstructions combining two (upper panel) or three 2-D images (lower panel) were validated for measures of minimal lumen diameter (MLD), reference vessel diameter (RVD) and percent diameter stenosis (DS). Automatic reference obstruction analysis was always used. Solid lines represent the mean difference; dotted lines represent the 95% limits of agreement (±1.96 SD). BSM11: 11-segment model*

INTER-MODEL AGREEMENT

In basic reconstructions, the 11-segment model provided significantly larger (p=0.02) and slightly more precise (p=0.16) MLD values compared to the 6-segment model; as expected, DS estimates were significantly smaller (p=0.02) and also more precise (p=0.34). However, the 6-segment model had a higher inter-observer reproducibility for DS and MLD (p-value 0.02 and 0.11, respectively). Adding the AP projection augmented the difference in precision in favour of the 11-segment model for MLD (p<0.01) and DS (p=0.11) values; there was also a trend towards higher reproducibility compared to the 6-segment model (p>0.05 for both MLD and DS).

BA

Basic 3-D reconstructions underestimated BA by 1.3° (p=0.09) having a precision of 5.0° **(Table 2)**. Intra- and inter-observer bias was close to zero, whereas the repeatability coefficient was 7.8° and 7.5°, respectively. Adding the AP projection resulted in a larger underestimation (–1.9°, p=0.02) and slightly reduced precision (5.4°, p=0.33) **(Figure 6)**, whereas inter-observer variability was 7.9° (p=0.38).

During the analysis the rates of applying restriction were uniformly low, namely 3.9% for reconstructions using either two or three images. The rates of CIP relocation were low for basic 3-D reconstructions (11.1%), whereas they were higher for reconstructions of three projections (31.0%). The CIP had to be relocated most frequently in reconstructions using angulated views.

LENGTH MEASUREMENTS

Compared to true inter-marker distances (46.67±19.40 mm), basic reconstructions showed an accuracy and precision of 0.15±0.26 mm and a measurement error of 0.23 mm; inter-observer bias was 0.07 mm, whereas variability was 0.54 mm. Adding the AP projection resulted in an accuracy and precision of 0.04±0.47 mm (p<0.01 for precision) and a measurement error of 0.50 mm; inter-observer variability was increased (1.03 mm, p<0.01). Relatively large variability between replicate measurements compared to the overall precision estimates resulted in apparently wide limits of agreement around the averaged length values **(Figure 6)**. Nevertheless, both precision and measurement error were negligible when compared with true inter-marker distances.

Discussion

The main findings of this study are: 1) the new 3-D bifurcation QCA algorithm is highly accurate, precise and reproducible in terms of RVD; 2) in terms of MLD and DS, 3-D reconstructions using two 2-D projections are highly accurate and quite precise and reproducible; when adding a third projection, a higher level of precision and reproducibility is achieved; 3) BA measurements slightly

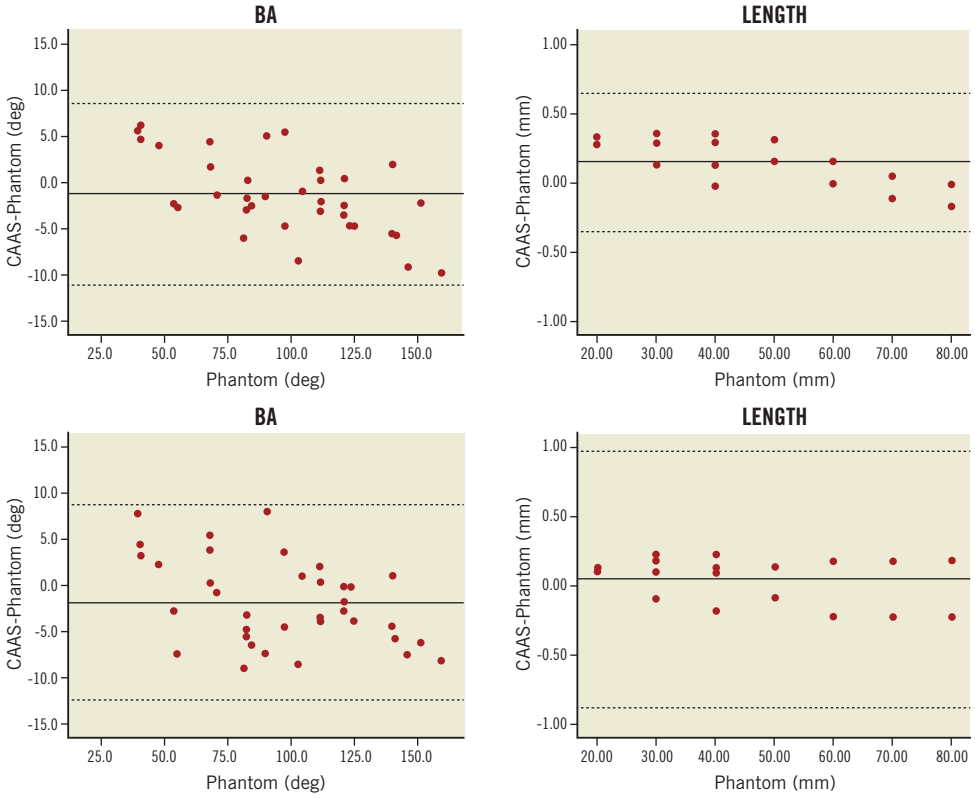

Figure 6. *Bland-Altman plots for BA values and length measurements. 3-D reconstructions combining two (upper panel) or three 2-D images (lower panel) were employed. Solid lines represent the mean difference; dotted lines represent the 95% limits of agreement (±1.96 SD). Apparently wide limits of agreement for length measurements resulted from the relatively large variability between replicate measurements compared to the overall precision.*

underestimate the true values, though precision and reproducibility are quite high and relatively unaffected by adding a third projection; 4) length measurements have excellent accuracy and precision and high reproducibility.

A number of major randomised trials are under way in the field of bifurcation PCI. The EXCEL trial will evaluate the effectiveness of left main coronary artery revascularisation comparing PCI using second-generation drug-eluting stents to coronary artery bypass grafting. Bifurcation lesions are expected to represent the largest category of lesions treated[23]. On the other hand, TRYTON will evaluate the safety and effectiveness of a dedicated bifurcation stent in the treatment of *de novo* bifurcation lesions. Whereas workhorse angiographic analysis is going to be based on 2-D QCA, 3-D QCA is involved in the evaluation of a sizeable number of patients. Hence, validation of the software's performance is imperative.

DIAMETER-DERIVED PARAMETERS

Earlier versions of 3-D reconstruction software were validated for measures of vessel diameter in the late 1990s; full coronary tree reconstruction, however, came at the cost of fair accuracy (3%-7% relative error in calculation) and increased time requirements (several hours down to 10 minutes)[24,25]. Next-generation algorithms focused on the reconstruction of single-vessel segments rather than entire coronary arteries, thereby enabling reliable results to be available in real time[7-10,26].

Achieving similar results in the 3-D reconstruction of coronary bifurcations is not a trivial task. For any given bifurcation there is usually one single optimal projection[1]. It follows that in any other projection certain parts of the anatomy, usually the ostia of the daughter branches, are obscured due to overlap. The new algorithm can retrieve missing information even from a combination of suboptimal views[14]; however, a reconstruction including the optimal 2-D projection would be expected to be even more robust.

In our study, the basic 3-D reconstructions did not include the AP view, which was the optimal 2-D view due to the phantoms' orientation. Nevertheless, compared to analysis performed on the same phantom bifurcations using 2-D CAAS , 3-D software showed similar accuracy and precision: in images acquired at 30° rotation respective 2-D measures were 0.035±0.10 mm for MLD, –0.004±0.041 mm for RVD and –0.74±4.52% for DS[13]. Moreover, since the same contour detection algorithm was used, the extent of overestimation for small true MLD values (≤0.70 mm) was uniformly limited in both 2-D and 3-D analysis. However, whereas full automatic calibration was readily available in 3-D QCA, for the purpose of 2-D validation the pixel size had to be derived off-line based on geometric calibration. Contrary to our phantoms, the course of coronary vessels does not usually lie on a single plane inside the human thorax. Hence, vessel segments analysed on a 2-D angiographic image are subject to errors from variable magnification, since an automatically derived pixel size can be valid on only one plane[10]. Naturally the same phenomenon applies to catheter calibration as well.

Adding the AP view to the basic 3-D reconstructions resulted in improved precision and reproducibility for all diameter-derived parameters in our study. One may argue that combining more than two 2-D images is rarely feasible at any stage during a procedure, at least not retrospectively, as there are simply not enough images available which are also suitable for a 3-D reconstruction[27]. However, when used on-line, this innovation can be clinically relevant. Even if the optimal view is not among the images initially acquired, it can be suggested by a 3-D reconstruction based on two suboptimal views; time requirements (<10 sec for reconstruction of two images, <60 sec for three images) should not be an issue. However, limitations imposed by patient anatomy (vessel overlap) or proximity between the gantry and the patient/table may make it difficult to acquire the optimal view exactly as suggested[10].

RVD-DS

Highly accurate, precise and reproducible RVD measurements were achieved by combining a validated algorithm for automatic RVD derivation in bifurcation lesions with genuine 3-D calculations. Thereby, instead of performing a tedious and arbitrary single-vessel analysis for all three branches separately, RVD and DS values can be derived in the time of a single analysis, having at the same time all the advantages of the 3-D reconstruction. When applied on-line, 3-D QCA-derived information may potentially complement or even substitute invasive imaging modalities in stent sizing and deployment, thereby minimising adverse event rates.

Furthermore, 3-D QCA-derived MLD and DS values for bifurcation lesions should be expected to have a better correlation with respective fractional flow reserve (FFR) values, when compared to 2-D measures[28,29]. It is not implied that a single angiographic measure can fully reflect all anatomic and haemodynamic parameters that determine the functional significance of a lesion[30]; however, we believe that spatially accurate measurements will help improve periprocedural strategy in bifurcation PCI.

SEGMENT MODELS

Agreement between models in the new software looks diminished compared to 2-D validation; however, the difference in results for MLD and DS was largely driven by a small number of outliers in MLD detection, resulting from different segment definitions between models[13]. Cases where the MLD was located in the POC rather than segments 2, 3 or 5 resulted in overestimates for the 11-segment model. On the contrary, cases where a stenosis-free proximal main vessel impinged on a distal stenosis resulted in underestimates for the 6-segment model. Similar differences were already observed in 2-D analysis, only to be inflated in the process of 3-D reconstruction. The fact remains that the 6-segment model offers a quick overview of results during a procedure, whereas the 11-segment model is more of a research tool providing more detailed information. Nevertheless, it appears that the algorithms are not mutually interchangeable when it comes to long-term angiographic analysis: whichever algorithm is adopted for reporting results pre- and post-procedure would have to be used at follow-up as well.

BA

Angle calculations have recently gained attention due to growing evidence that wider distal BA values might lead to a worse outcome, especially with two-stent techniques[27,31,32]. To our knowledge, there

is a single validation study on 3-D derived BA reporting an underestimation of the phantom values by 2.6° and a standard error of the estimate equal to 0.77[25]. In our study, BA accuracy and precision were improved compared to the 2-D QCA software validation (–3.1±6.2° in rotated views), which was not unexpected. This difference might have been more pronounced if our phantom bifurcations had lain in more than one plane. This could also explain the lack of improvement seen following the addition of the optimal view. Currently, there is a binary approach regarding BA size: several cut-off values (50°, 70°) have been proposed; however, definitions and measurement methods are still at variance. Pending more detailed data from 3-D QCA-based computations regarding the effect of BA on outcome, precision of 5.0° is considered high.

LENGTH

One of the most acknowledged advantages of 3-D QCA is its accuracy in length derivation. Foreshortening in 2-D analysis may result in erroneous sizing and deployment of stents. This could translate either into incomplete lesion coverage and the need for additional stents or into excessive stent length, jailing of a side branch and increased restenosis rates[33]. This is why length measurements have the most comprehensive validation. Demarcated wires[8], wire phantoms[10], stent balloons[9] or stented coronary segments, identified by radio-opaque markers[34], and 3-D reconstructions based on fusion of angiography and intravascular ultrasound[26] have all been used as a gold standard. In our study, length measurements were performed on demarcated catheter segments spanning the phantom bifurcation, thereby proving that they are consistent and impervious to bifurcation region definitions. Variability, albeit negligible, is assumed to correlate with the marker placement procedure, which was not automated but relied on the analysts' visual perception.

LIMITATIONS

In vitro validation has the obvious limitation of being based on static objects, acquired under ideal angiographic conditions. In our phantom bifurcations, lesions were circular-shaped in cross-sectional view for design simplicity and due to manufacturing constraints[19]. On the contrary, more than 50% of coronary lesions are asymmetric, where 2-D analysis is known to be inaccurate[35]. Furthermore, as opposed to straight phantom vessel segments, coronary vessels usually have curved trajectories, which augment the effect of foreshortening in 2-D projection images[10,11]. Taking the calibration issues already mentioned into account, we have to assume that the incremental value of 3-D bifurcation QCA as compared to 2-D analysis may have been underestimated.

Recently, minimal lumen area and percent area stenosis were shown to have a higher power for predicting reduced FFR values, when compared to the respective diameter-derived parameters[29]. In our study only diameter-derived measures were reported. However, due to the symmetric design of the phantom bifurcation lesions and because of the circularity assumption in diameters' derivation from respective cross-sectional areas, our findings are transferable to area-derived parameters as well.

Conclusions

The new dedicated 3-D bifurcation QCA software allows angiographic reconstructions of more than two 2-D projection images, and features novel 3-D quantitative analysis of bifurcation lesions. These advances translate into accurate, precise and reproducible measures of diameter, length and bifurcation angle. There is still work to be done regarding the *in vivo* validation of this software, in order to determine the clinical relevance of these data.

Conflict of interest statement

JP. Aben and S. Soekhradjare are employees of Pie Medical Imaging. MA. Morel is an employee of Cardialyis BV. The other authors have no conflicts of interest to declare.

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Online data supplement

APPENDIX

Software validation for full-tree 3-D reconstructions of bifurcation phantoms.

Online data supplement

ONLINE APPENDIX

Software validation for full-tree 3-D reconstructions of bifurcation phantoms

This appendix complements the main manuscript "Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation" and provides the results from additional analyses.

The new three-dimensional (3-D) bifurcation quantitative coronary angiography (QCA) algorithm has no restriction regarding the number of bifurcations the 3-D model consists of; it is possible to reconstruct and analyse a vascular tree which consists of multiple bifurcations.

Methods

In order to investigate the accuracy, precision and reproducibility of this methodology, we performed full-tree 3-D reconstructions for the entire series of bifurcation phantoms[1]: images acquired at 30° rotation, in right and left anterior oblique (RAO-LAO) projection were combined. The operator procedure for angiographic analysis was amended accordingly, wherein: 1) for every given phantom, delimiter points were placed in the proximal main vessel of the proximal bifurcation, in the distal main vessel of the distal bifurcation and in a side branch of any of the three bifurcations: by default we chose to begin with the side branch of the proximal bifurcation; 2) the remaining side branches were added to the phantom tree (one at a time), by indicating the junction point with the contoured main vessel and a distal delimiter; the first two steps were then repeated in the next image; 3) reconstruction was performed for the entire phantom, and the common image point (CIP) was relocated as appropriate; 4) in the 3-D reconstructed phantoms one bifurcation was selected and analysed at a time (region of interest could be edited in order that analysis was not influenced by adjacent bifurcation lesions); 5) quantitative analysis was performed and reported for minimal lumen diameter (MLD), reference vessel diameter (RVD), percent diameter stenosis (DS) and bifurcation angles (BAs) as described in the main manuscript. Results were compared with the true phantom values and with separate 3-D reconstructions of individual bifurcations using the same combinations of images (30° RAO-LAO).

Results

MLD-RVD-DS

Accuracy and precision for full-tree and individual 3-D reconstructions are shown in **Table 1**. MLD values for full-tree reconstructions had an accuracy and precision of 0.012±0.135 mm and –0.021±0.155 mm for the 11- and 6-segment models, respectively, not being significantly different from phantom values (p-value 0.51 and 0.33). The reference size of phantom vessels was underestimated by an average 0.06 mm in both models, whereas DS estimates did not significantly differ from true values, precision being in the order of 5%. Accuracy and precision did not differ significantly between full-tree and individual reconstructions.

Inter-observer variability for 11- and 6-segment models was 0.146/0.155 mm for MLD, 0.038/0.039 mm for RVD and 5.59/5.41% for DS values.

The 11-segment model was more accurate (p=0.05) and precise (p=0.16) for MLD, while the 6-segment model was more accurate (p=0.04) for DS values; difference in DS precision was not significant (p=0.47).

BA

Full-tree 3-D reconstructions underestimated BA by 2.1° (p=0.01) having a precision of 4.7°; individual reconstructions had slightly increased accuracy (–0.9°, p=0.16) but equal precision. Inter-observer bias was 0.7°, whereas the repeatability coefficient was 8.8°.

SUMMARY

The performance of the new 3-D bifurcation QCA software in full-tree reconstructions of the bifurcation phantoms was comparable, but slightly inferior to the results attained from reconstructions performed separately for each individual phantom bifurcation.

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Table 1. Validation of segment models vs. phantom dimensions (full-tree 3-D reconstructions of bifurcation phantoms).

		Full-tree		Individual		*p*-value		
		Accuracy	Precision	Accuracy	Precision	Full-tree vs. phantom	Individual vs. phantom	Full-tree vs. individual*
BSM11	MLD, mm	0.012	0.135	0.001	0.118	0.51	0.97	0.30 (0.17)
	RVD, mm	–0.059	0.037	–0.056	0.040	<0.001	<0.001	0.29 (0.29)
	DS, %	–1.18	5.25	–0.71	4.75	0.10	0.28	0.25 (0.23)
BSM6	MLD, mm	–0.021	0.155	–0.038	0.146	0.33	0.06	0.07 (0.33)
	RVD, mm	–0.058	0.037	–0.056	0.041	<0.001	<0.001	0.27 (0.23)
	DS, %	0.04	5.20	0.67	4.80	0.96	0.31	0.12 (0.28)

BSM: bifurcation segment model; DS: percent diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter. *values relate to the comparison between accuracy measures, values in parentheses relate to the comparison between precision measures.

Chapter 7

Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club

Catheter Cardiovasc Interv; 79(3):361-368.

Girasis C, Onuma Y, Schuurbiers JC, Morel MA, van Es GA, van Geuns RJ, Wentzel JJ, Serruys PW

Validity and Variability in Visual Assessment of Stenosis Severity in Phantom Bifurcation Lesions: A Survey in Experts During the Fifth Meeting of the European Bifurcation Club

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Objectives: To investigate the adequacy of visual estimate regarding the percent diameter stenosis (DS) in bifurcation lesions. Background: Quantitative coronary angiography (QCA) is more accurate and precise compared to visual estimate in assessing stenosis severity in single-vessel lesions. Methods: Thirty-six experts in the field of bifurcation PCI visually assessed the DS in cine images of five precision manufactured phantom bifurcation lesions, experts being blinded to the true values. Expert DS estimates were compared with the true values and they were also used to define the Medina class of each individual bifurcation. Results were pooled together both for proximal main vessel (PMV), distal main vessel (DMV) and side-branch (SB) segments and for vessel segments with similar DS values. Results: Individual performance was highly variable among observers; pooled values and range of accuracy and precision were 2.79% (−6.67% to 17.33%) and 8.69% (4.31–16.25%), respectively. On average, DS was underestimated in the PMV (−1.08%, $P = 0.10$) and overestimated in the DMV (3.86% $P < 0.01$) and SB segments (5.58%, $P < 0.01$). Variability in visual estimates was significantly larger in lesions of medium severity compared to the clearly obstructive ones ($P < 0.01$); the latter were consistently overestimated. Inter-observer agreement was moderate ($\kappa = 0.55$) over the entire number of estimates. However, if the segments with true DS = 0% were excluded, agreement was diminished ($\kappa = 0.27$). Inter-observer agreement in Medina class was rather low ($\kappa = 0.21$). True bifurcation lesions were misclassified as non-true ones in 14/180 estimates. Conclusions: Visual assessment by experts is more variable and less precise in the analysis of bifurcation lesions compared to bifurcation QCA software.

Key words: angiography; QCA; bifurcation

INTRODUCTION

Visual assessment of coronary stenosis severity in single-vessel lesions is known to have considerable intra- and inter-observer variability [1–3]; quantitative coronary angiography (QCA) is more accurate and precise in evaluating the percent diameter stenosis (DS), both in everyday clinical practice [4–9] and in the context of large randomized trials [10–12].

This inaccuracy in visual assessment would be expected to be even more pronounced in bifurcation lesions, where even experienced operators can be confused by the difference in caliber between the proximal and the distal branches. However, since the validity of conventional single-vessel QCA derived DS measurements is also questionable, especially at the ostium of the side branch (SB) [13], visual assessment is still employed in the design and screening process for randomized trials evaluating bifurcation percutaneous

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Conflict of interest: Nothing to report

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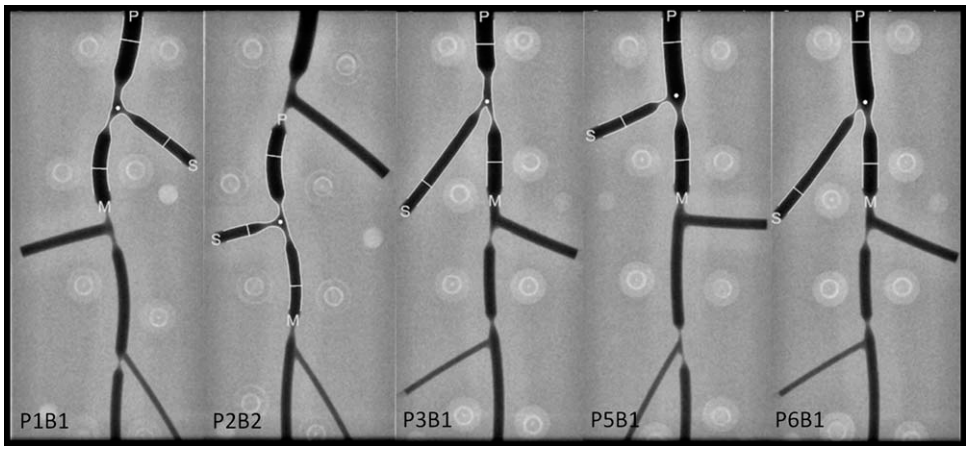

Fig. 1. Phantom bifurcations visually assessed. From left to right, cine images of five precision manufactured bifurcation phantoms acquired in antero-posterior direction. Out of every phantom a true bifurcation lesion (involving both the main vessel and the side-branch) was selected. Lesion contours presented here for illustration purposes were not made available to the observers during the survey. P1B1 reads phantom 1, bifurcation 1. P = proximal main vessel, M = main vessel, S = side-branch.

coronary intervention (PCI) strategies and dedicated bifurcation stents.

To improve the QCA-derived DS assessment in bifurcation regions, dedicated bifurcation QCA software packages were developed [14,15]. In order to validate their performance, a series of plexiglas phantoms was precision manufactured, each of them mimicking a vessel with three successive bifurcation lesions [16]. The range of diameters, lesion length, angulation, and Medina class [17] used in the phantoms' design reflected the anatomic variation and the fractal nature of bifurcations in the human coronary tree as derived from relevant literature.

These phantom images were used in order to investigate the adequacy of visual assessment in bifurcation lesions taking into account current bifurcation QCA software standards. This survey was carried out among a selected group of experts in the field of bifurcation PCI and the results are presented in this report.

TABLE I. Average Visual Estimate for Individual Phantom Bifurcation Vessel Segments Over 36 Observers

Bifurcation vessel segments	True DS (%)	Estimate mean (%)	Estimate bias (%)	Estimate SD (%)	Estimate CV
P1B1 PMV	60.88	56.25	−4.63	10.78	0.19
P1B1 DMV	80.03	85.33	5.30	8.02	0.09
P1B1 SB	60.31	66.81	6.50	10.50	0.16
P2B2 PMV	79.97	83.94	3.97	7.02	0.08
P2B2 DMV	60.32	66.97	6.65	10.02	0.15
P2B2 SB	60.13	63.19	3.07	9.79	0.15
P3B1 PMV	60.60	53.17	−7.43	10.19	0.19
P3B1 DMV	80.18	86.83	6.65	6.20	0.07
P3B1 SB	60.00	58.03	−1.97	13.04	0.22
P5B1 PMV	0.00	1.33	1.33	4.02	N/A
P5B1 DMV	60.09	60.17	0.08	9.12	0.15
P5B1 SB	78.73	89.83	11.10	5.33	0.06
P6B1 PMV	0.00	1.36	1.36	4.69	N/A
P6B1 DMV	60.09	60.69	0.60	9.47	0.16
P6B1 SB	78.69	87.89	9.20	5.92	0.07

P1B1 reads phantom 1, bifurcation 1
CV = coefficient of variation, DMV = distal main vessel, DS = percent diameter stenosis, PMV = proximal main vessel, SD = standard deviation, SB = side-branch, N/A = non-applicable.

MATERIALS AND METHODS

Material

During the fifth annual meeting of the European Bifurcation Club, held in Berlin, October 16–17, 2009, the participants were asked to fill out questionnaires, visually assessing the DS in the vessel segments comprising five bifurcation lesions out of the aforementioned series of plexiglas phantoms.

True bifurcation lesions (involving both the main vessel and the SB) were selected to be evaluated; one lesion was selected out of every phantom (Fig. 1), with the exception of phantom 4, which did not include a true bifurcation lesion [16]. The true DS values in the bifurcation lesions selected are reported in Table I.

Stop-frames of the phantom images acquired in antero-posterior direction were projected onto a high resolution screen including zoomed/magnified views of the bifurcation lesions evaluated. Each stop-frame was projected for over a minute; upon request, a given lesion was projected again on the screen to assist final decision.

Thirty-six fully filled-in questionnaires were handed in; the identity of most of the observers was stated,

however individual performance is not disclosed in the present report, since the objective of this query was not to grade the participants.

Analysis Method

In order to unveil patterns in visual assessment, rates of fair visual assessment, under- or over-estimation were derived comparing individual estimates by the experts with the true DS values. A difference of 10% in measured percent DS is described to be visually perceptible and was used in our study in order to set realistic limits of agreement [10]. Thus, estimates within $\pm 10\%$ from the true DS values were considered as fair visual assessment. Estimates exceeding the lower or upper limits of agreement were, respectively, considered to under- or over-estimate the true stenosis severity. In the vessel segments with true DS $= 0\%$, estimates between 0 and 10% were considered fair assessment; other than that true DS could only be over-estimated.

Statistical measures were calculated at an observer and a vessel segment level. Moreover, results were pooled together for the proximal main vessel (PMV), the distal main vessel (DMV) and the SB segments, and for the entire number of vessel segments evaluated. Finally, vessel segments with similar DS values were pooled together and studied separately.

Considering the fact that stenosis severity in segments with true DS value of 0% could only be overestimated, comparisons between the pooled results of PMV, DMV, and SB segments were performed with or without these segments.

Following the Medina bifurcation lesion classification, an integer of 1 was attributed to the vessel segments, when DS$\geq$50% and an integer of 0, when DS$<$50%. Vessel segments were classified according to both the true values and the visual assessment of the observers; the respective Medina class for every lesion evaluated was also derived. Agreement between the actual and the derived Medina class was investigated at the level of individual vessel segments and the entire bifurcation lesions.

Statistics

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL). Continuous variables are presented as mean $\pm$ 1 standard deviation (SD); categorical variables are presented as counts and/or percentages. Comparisons of continuous variables among groups were performed with the paired or unpaired *t*-test, as appropriate; for multiple comparisons, one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* analysis was employed. Comparisons of categorical variables among groups were performed with the chi-square test.

In order to be able to compare DS estimates for variability, coefficients of variation (CVs) were formed for every single vessel segment dividing the estimate SD by the estimate mean, thus providing a value independent measure of variability. CVs were pooled according to the root mean square method [18]; their values were squared for the purpose of comparison.

For every single observer, Bland–Altman analysis [19] was performed to compare the DS estimate for all 15 vessel segments with the corresponding true values; accuracy and precision of the estimate were calculated. The individual signed differences with the true values were averaged; the mean of these signed differences (bias) is a measure of accuracy; SD is a measure of precision. Bias was averaged over the entire number of observers; the overall precision (SD) was calculated with the root mean square method. The corresponding 95% limits of agreement were computed for every observer and for an average visual estimate (average bias with average precision).

Inter-observer agreement in visual assessment was measured using the κ statistic. The intra-class correlation coefficient was calculated in SPSS, as this is mathematically equal to the average of weighted κ values [20] for all possible pairwise comparisons between multiple observers [21]. The qualitative classification of the κ values used to interpret the degree of agreement beyond the level of chance is shown in Table II.

All statistical tests were two-sided and a P value <0.05 was considered statistically significant.

RESULTS

The mean $\pm$ 1SD, the bias, and the CV of the visual estimate for DS in every vessel segment are reported in Table I.

Bland–Altman Analysis

Individual performance was highly variable among the observers; range for accuracy and precision were

TABLE II. Quantitative Classification of Kappa Values as a Degree of Agreement Beyond the Level of Chance

Kappa value	Degree of agreement beyond chance
0	None
$0.0< \kappa \leq 0.2$	Slight
$0.2< \kappa \leq 0.4$	Fair
$0.4< \kappa \leq 0.6$	Moderate
$0.6< \kappa \leq 0.8$	Substantial
$0.8< \kappa \leq 1.0$	Almost perfect

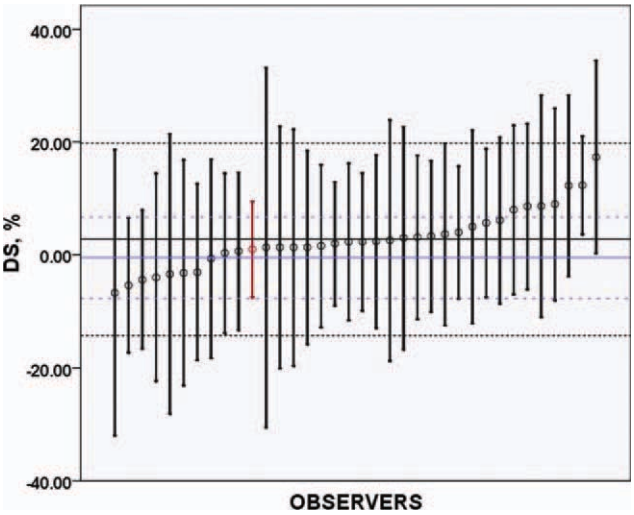

Fig. 2. Accuracy and precision of visual estimates for percent diameter stenosis (DS) among experts. Error bars indicate the 95% limits of agreement for every individual observer, circle marks the mean intra-observer bias. The error bar in red identifies the most precise estimate among observers. Solid black line indicates bias averaged over all observers; dotted black lines indicate the respective 95% limits of agreement for this average estimate. Solid and dotted blue lines indicate the respective measures for CAAS 5.9 bifurcation QCA software for the purpose of comparison. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

−6.67% to 17.33% and 4.31%–16.25%, respectively. Pooled accuracy and precision were 2.79% and 8.69%; 95% limits of agreement of this pooled estimate with the true DS values were −14.24% to 19.82% (Fig. 2). However the distribution of accuracy and precision measures among the observers was not always uniform; higher accuracy could coincide with diminished precision and vice versa.

Accuracy and Precision in Subgroups

Visual assessment of stenosis severity in PMV segments underestimated the true DS values (−1.08%, $P = 0.10$); bias was larger when segments with true DS = 0% were not considered (−2.69%, $P < 0.01$). On the contrary, in DMV and SB segments, DS was overestimated (bias 3.86% and 5.58%, respectively, $P < 0.01$ for both). There was no significant difference in variability of the DS estimates ($P = 0.68$) between the pooled PMV (true DS>0%), DMV, and SB vessel segments (Table III). Visual estimate in segments with true DS ∼60% did not differ on average from the true values ($P = 0.59$), whereas segments with true DS ∼80% were consistently overestimated (7.25%, $P < 0.01$). However, there was a significantly larger variability ($P < 0.01$) for the DS estimate in the former compared to the latter (Table III).

TABLE III. Visual Estimate for Pooled Phantom Bifurcation Vessel Segments

Vessel segments	Pooled bias (%)	Pooled SD (%)	Pooled CV
PMV	−1.08	7.84	N/A
PMV>0%	−2.69	9.48	0.164
DMV	3.86	8.67	0.129
SB	5.58	9.38	0.146
True DS ∼60%	0.36	10.42	0.174
True DS ∼80%	7.25	6.56	0.076
True DS>0%	3.01	9.14	0.144
All segments	2.79	8.69	N/A

CV = coefficient of variation, DMV = distal main vessel, DS = percent diameter stenosis, PMV = proximal main vessel, SD = standard deviation, SB = side-branch; N/A = non-applicable

Semiquantitative Visual Assessment of Stenosis Severity in Vessel Segments

Rates of wrong assessment (either over- or underestimation) of stenosis severity were significantly higher in SB compared to PMV segments (50.6% vs. 33.9%, $P < 0.01$); this difference was no longer significant ($P = 0.63$), when PMV segments with true DS = 0% were excluded. Within the wrong assessments, the SB was more often over-estimated compared to the PMV segments (78.0% vs. 37.7%, $P < 0.01$). Rates of wrong assessment were higher in SB compared with DMV segments (50.6% vs. 26.7%, $P < 0.01$); there was also more frequent DS over-estimation in SB compared with DMV (78.0% vs. 58.3%, $P = 0.02$) (Fig. 3).

Rates of wrong assessment did not differ between segments with true DS ∼60% compared to the ones with true DS ∼80% (43.1% vs. 40.6%, $P = 0.63$). However, within these wrong assessments, DS was almost always overestimated in the latter segments (97.3%), but more frequently underestimated in the former (61.3%); difference in distribution of wrong assessments was significant ($P < 0.01$) (Fig. 4). Overall, in 20% of the cases, a lesion with true DS ∼80% was estimated by the observers to have a stenosis >90%.

Inter-observer agreement following this visual assessment classification (fair, over- or underestimation) was moderate ($\kappa = 0.55$) over the entire number of estimates (Table IV). However, if the segments with true DS = 0% were excluded, agreement was diminished ($\kappa = 0.27$).

Medina Classification

At the vessel segment level, there were 25/540 false negative estimates (integer 0 instead of 1), all of them in segments with true DS ∼60% with no difference in frequency between PMV, DMV, and SB (P value=0.58); inter-observer agreement was high ($\kappa = 0.74$). However, if the segments with true DS = 0% were excluded, inter-observer agreement was barely higher than the level

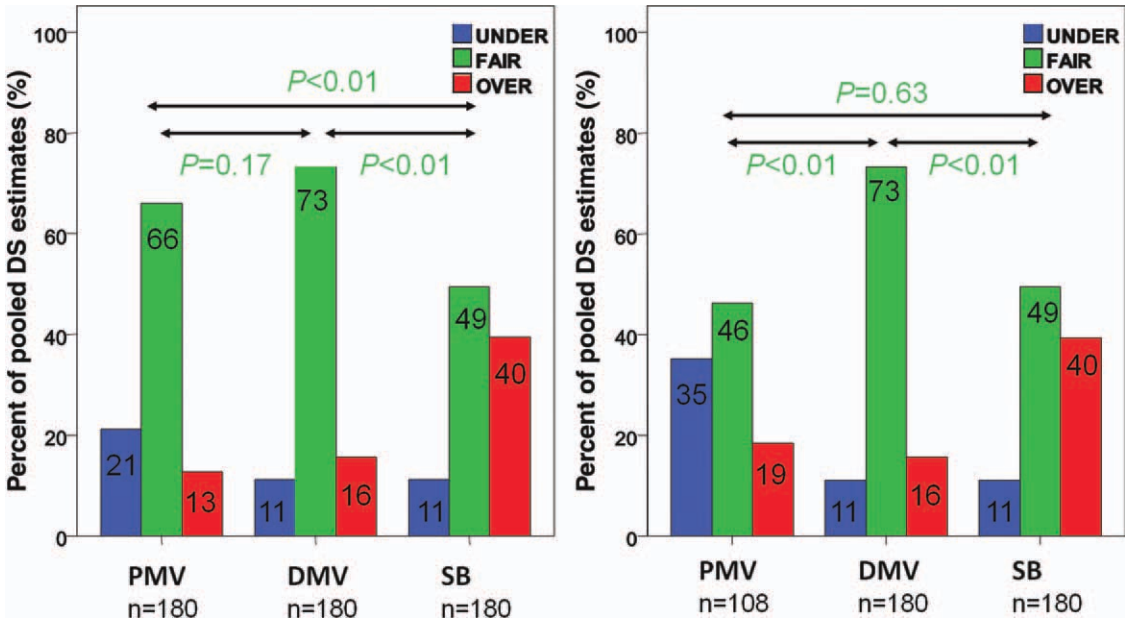

Fig. 3. Visual estimates for proximal main vessel (PMV), distal main vessel (DMV), and side-branch (SB) segments pooled over the 36 observers. Left side: All segments assessed; there are significantly less fair estimates but more over-estimates (*P*-value not shown) for the SB. Right side: Segments with true percent diameter stenosis 0% were removed; fair estimates in the PMV segments are decreased, under-estimates are increased. Wrong estimates in DMV segments are rather limited and balanced. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

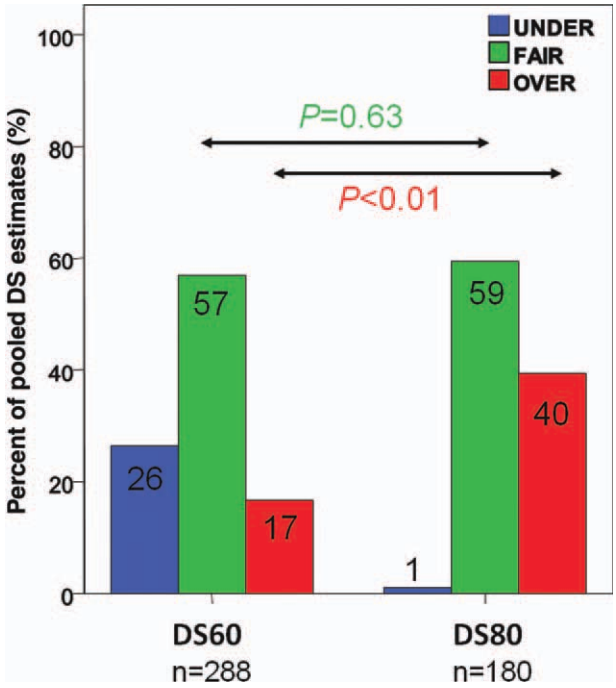

Fig. 4. Visual estimates for segments with true percent diameter stenosis 60% (DS60) or 80% (DS80) pooled over the 36 observers. Fair estimates do not differ significantly, however for DS80 segments over-estimates are significantly more and under-estimates very limited. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of chance ($\kappa = 0.08$) (Table IV). In regard to the derived Medina class, inter-observer agreement was rather low ($\kappa = 0.21$). In total, errors in single vessel segments resulted in the derivation of a false Medina class in 22/180 estimates; in 14 (7.8%) of them the derived Medina class corresponded to a non-true bifurcation lesion.

DISCUSSION

The main findings of this study are: (1) Accuracy and precision in visual assessment of the stenosis severity in bifurcation lesions was highly variable among experts in bifurcation PCI. On average, stenosis severity was underestimated in the PMV and overestimated in the DMV and SB segments. (2) Variability of visual estimate was significantly larger in lesions of medium severity compared to the clearly obstructive ones, which on the other hand were consistently overestimated. (3) Inter-observer agreement in derived Medina class was rather poor; true bifurcation lesions were misclassified as non-true ones in 14/180 estimates.

Visual Assessment vs. QCA

Already in the early 80s Serruys et al. [4] had reported a discrepancy between visual and QCA

TABLE IV. Inter-Observer Agreement (in Kappa) Applying the Fair-Over-Under or the MEDINA Classification on Individual Vessel Segments

Vessel segments	Fair-over-under	Medina
PMV	0.35	0.84
PMV>0%	0.39	0.06
DMV	0.06	0.01
SB	0.26	0.17
True DS ~60%	0.13	0.05
True DS ~80%	0.26	N/A
True DS>0%	0.27	0.08
All segments	0.55	0.74

DMV = distal main vessel, DS = percent diameter stenosis, N/A = non-applicable, PMV = proximal main vessel, QCA = quantitative coronary angiography, SB = side-branch.

estimates of DS values in single-vessel lesions, visual estimate systematically overestimating severe QCA-assessed stenoses by almost 10%; similar studies corroborated this finding [22,23]. On the other hand, the large intra- and inter-observer variability of visual estimate (SD up to 18%) has been a consistent finding since the late 70s [1–3].

The extent of inaccuracy and variability in visual assessment in our study possibly represents an additive effect between these well known shortcomings of visual estimates and the particularities in bifurcation lesion interpretation, especially when it comes to the interpretation of the SB ostium [14,24]. The vessel segments distal to the bifurcation carina taper in size, their reference diameter being dictated by laws of fractal geometry [25]. However, the intuitive way, in which even experienced operators interpret stenosis severity at or close to the ostium of distal bifurcation branches, is by referring to the PMV segment, thus resulting in overestimated DS values. Conversely, yet to a lesser extent, lesions in the PMV may be underestimated [26].

These phenomena are also reflected in the way single-vessel QCA analysis has been applied in the bifurcation lesions. Manual extension of vessel contours from the SB into the PMV and reference vessel size interpolations across the carina often resulted in invalid DS measurements that failed to predict the functional significance of ostial SB stenoses [13]. In order to make up for these shortcomings, dedicated 2-D bifurcation QCA algorithms have been developed; the Cardiovascular Angiography Analysis System (CAAS, Pie Medical Imaging, Maastricht, The Netherlands) [15,27] and QAngio XA (Medis medical imaging systems, Leiden, The Netherlands) [14,28] have been validated against the entire series of plexiglas phantom bifurcations already mentioned and rendered excellent accuracy and precision for DS measurements, 0.5 ± 3.7% for CAAS and 0.6 ± 4.2% for QAngio XA respectively (Girasis, 6th meeting of the European Bifurcation Club, Budapest, 2010).

These algorithms outperform average visual assessment among experts in our study almost by a factor of three. Actually, only one out of 36 participants could match the QCA software accuracy and precision; for the rest higher accuracy could coincide with diminished precision and vice versa. Furthermore, average bias was negative for the pooled PMV segments, whereas positive for both DMV and SB segments. Because these pooled accuracy measures derived over the 36 participants could obscure patterns in visual assessment, individual estimates were semi-quantitatively classified applying ±10% limits of agreement and a stratified analysis was performed. Indeed, there was a consistent trend for underestimation of stenosis severity in the PMV and overestimation in the SB; wrong estimates in DMV segments were rather limited and balanced.

Variability of Assessment for Varying Stenosis Severity

There have been varying reports on the extent of change in DS before and immediately after PCI and at follow-up angiography [5,7,8]. Nonetheless, they all seem to agree that in equivocal stenoses visual estimates are highly variable showing a bimodal distribution [7,8], as opposed to the Gaussian distribution of QCA derived DS values [29]; small true DS values are underestimated, large true DS values are overestimated, when visually assessed. Following this pattern, in our study, variability of visual assessment compared to the true DS values was significantly larger in the vessel segments with true DS ~60%, that is where it matters the most in clinical practice. Inter-observer agreement was limited, especially when registering visual estimate according to the 50% criterion (Medina classification). On the other hand, in clearly obstructive lesions (true DS ~80%), DS values were almost always overestimated, estimates in excess of 90% not being rare. However, such high degrees of luminal restriction are unlikely to occur in human coronaries, being prone to intraluminal thrombosis and obstruction [4].

Inter-Observer Agreement–Medina Classification

The current consensus in bifurcation lesion classification is the one proposed by Medina. Lesions with Medina class (1,1,1), (1,0,1) and (0,1,1), where both the main vessel and the SB display significant stenosis, are designated as "true" bifurcation lesions, where a two-stents strategy is still debatable. Whereas Medina class derivation in upcoming randomized bifurcation PCI trials, such as EXCEL, Tryton and EBC TWO

will still be based on visual assessment, a more rigorous approach would be suggested by the findings of this study. Marked inter-observer variability in visual assessment among experts participating in our study resulted in relatively poor agreement in the derived Medina classification. Low levels of inter-observer agreement have been reported before and were attributed either to variable operator experience [3,30], or to a lesion location in the distal coronary segments having smaller caliber and inadequate opacification [1,3]. Employing a consensus decision among $\geq$3 observers [6] or a 70% DS criterion for angiographic significance [3,30] is known to have improved visual assessment on occasion. Lastly, one cannot rule out variability in clinical expertise, even among experts in the field; however the extent of variability reported in this selected group of interventional cardiologists has apparent implications for the recruitment strategy in major bifurcation studies and everyday clinical practice. If resorting to the Core Laboratory to determine the eligibility of a patient/lesion for a given trial is deemed cumbersome, online bifurcation QCA could aid patient inclusion and/or procedure strategy being accurate, reproducible and time efficient at the same time.

Limitations

The lesions evaluated in our study had all the advantages and limitations of phantoms. Angiographic evaluation was free of technical difficulties regarding acquisition, opacification, and orientation of SB ostium. Vessel segments had sufficiently large caliber and did not display diffuse/ectatic reference segments or post-PTCA haziness [4]; in short an optimal clinical scenario. However, this study provided us with measurable indices and helps us understand how visual assessment by experts relates to current bifurcation QCA standards.

Lesions with true DS values of 0%, 60%, or 80% were scored; admittedly a larger number of lesions with 30–50% DS could have been included. The rationale behind the phantoms' design has already been detailed elsewhere [16]. In short, 0% was selected as the lowest possible degree of stenosis (instead of a possible 25%) due to manufacturing constraints; additionally, vessel segments with true DS of 40% were included as well in that series of phantoms. However, during this survey we purposely used only true bifurcations lesions of the largest possible phantom vessel caliber, in order to test our hypothesis on inter-observer agreement on Medina class, thereby simulating the enrolment phase of a bifurcation study. Due to this selection process, lesions with 40% true DS were left out. Nevertheless, visual assessment is most variable in medium severity lesions; thus our findings in the lesions with 60% true DS can quite safely be extrapolated to this medium-low part (25–40%) of the lesion severity spectrum.

CONCLUSIONS

In a survey among experts in the field of bifurcation PCI, accuracy and precision of visual estimates of DS in phantom bifurcation lesions was highly variable compared to current bifurcation QCA standards. Large variability of visual estimate in equivocal stenoses and low inter-observer agreement in derived Medina classification may justify the inclusion of online bifurcation QCA in the decision making process.

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PART III

Bifurcation QCA in clinical studies

Chapter 8

Long-term outcome after the V stenting technique in de novo bifurcation lesions using drug-eluting stents

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Long-term outcome after the V stenting technique in *de novo* bifurcation lesions using drug-eluting stents

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KEYWORDS
Angioplasty, drug eluting stent, stent thrombosis

Abstract

Aims: To report long-term outcome data on the V technique using drug-eluting stents.

Methods and results: From April 2002 to December 2006, 31 consecutive patients were successfully treated with V stenting of a *de novo* bifurcation lesion. The technique involves the deployment of two stents in the two branches of a bifurcation, the proximal edges of the stents just touching one another. Patients exclusively received either sirolimus- (10), paclitaxel- (20) or biolimus-eluting (one) stents. On average, 1.5±0.8 stents with a total length of 26.6±17.2 mm and 1.1±0.4 stents with a total length of 18.3±7.6 mm were deployed in the distal main vessel and side branch respectively. Mean duration of follow-up was 853±553 days. Within 30 days, three patients died; two other patients had definite stent thrombosis involving the V stents, both requiring re-PCI. Beyond 30 days and within one year, there was one death and three cases of target vessel revascularisation, including one target lesion revascularisation. There were a further three deaths (one cardiac) beyond one year. Eleven patients (35.5%) had angiographic follow-up, exhibiting a binary restenosis rate of 9.1% at 203±33 days.

Conclusions: In this real-world cohort, late clinical events stand in accord with studies on competitive techniques, but early outcome was less encouraging, probably due to the baseline risks.

Introduction

The optimal technique for treating bifurcation lesions with percutaneous coronary intervention (PCI) has not been clearly established. There is particularly little outcome data on V stenting in the current drug-eluting stent (DES) era. The V stenting technique scaffolds both distal limbs of a bifurcation lesion from the carina onwards and is only suitable when the lesion spares the proximal main vessel (PMV)[1]. In treating bifurcation lesions, optimal coverage without any un-stented gaps is essential for optimal scaffolding and drug delivery to mitigate the restenotic process[2-4]. Recently, various groups have described the Simultaneous Kissing Stents (SKS) technique – the simultaneous deployment of the distal main vessel (DMV) and side branch (SB) stents so that the new apposing struts from the two adjacent stents extended proximally from the carina[5-7] for 8±5 mm[5] or 8.9±2.5 mm[6]. Preliminary angiographic[6] and histologic[7] results showed that a new carinal membrane developed on these struts. While this technique can handle proximal disease close to the carina, the PMV receiving the two stents is often over-dilatated with its attendant risks[5]. A newer approach is to implant in the PMV a conical self-expandable Axxess (Devax, Irvine, CA, USA) stent with a "flared" distal part covering the outer rim of the bifurcation and two stents distally with V technique to scaffold the inner rim. To facilitate progress in this field, noting the possible dreaded complication of late stent thrombosis[8], we reviewed the long-term outcome of V stenting using DES from April 2002[9] to December 2006.

Methods

Study population

On April 16, 2002, our institution began to use sirolimus-eluting stents (SES, Cypher, Cordis Corporation, Warren, NJ, USA) as the default strategy for every PCI, until Feb 16, 2003 when paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA, USA) became our default strategy. Data were recorded in the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry[10] and the Taxus Stent Evaluated AT Rotterdam Cardiology Hospital (T-SEARCH) registry[11]. From April 2002 to December 2006, 656 procedures involving treatment of *de novo* bifurcation lesions were performed in 638 patients. Out of this cohort, and after reviewing the angiographic films, we identified 31 consecutive patients, who had one bifurcation lesion successfully treated with V stenting; none of them had a second procedure involving this technique. Written informed consent was obtained from all patients prior to the procedure.

Procedure

V stenting is defined as the delivery and implantation of two stents in the two branches of a bifurcation; one stent is deployed in the DMV and the other one in the SB[12]. The stents can be deployed either concurrently or in a successive mode[13]. The latter is presumably an acceptable alternative, provided that the second stent is deployed concurrently with a balloon inflated in the first stent, to protect this from being crushed; systematic post-dilation with kissing balloons should be performed. To differentiate from the SKS technique, we defined V stenting as the proximal edges of the stents just touching one another without any significant overlap, protruding into the PMV by no more than 5 mm[12] (Figure 1).

All procedures were performed according to current interventional standards at the time. The use of predilation, post-procedure kissing balloon inflation and the use of glycoprotein IIb/IIIa inhibitors was left to the operators' discretion. During the procedure, intravenous heparin was administered, in order to maintain an activated clotting time above 250 seconds. All patients were prescribed 80 mg of aspirin lifelong and were pretreated with 300 mg clopidogrel followed by 75 mg clopidogrel for at least six months.

Clinical definitions and follow-up

Angiographic success was defined as residual stenosis <30% by visual estimation in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. Clinical success was defined as angiographic success without the occurrence of death, myocardial infarction or repeat revascularisation of the target lesion during the hospital stay. Myocardial infarction was diagnosed by an increase in creatine kinase-MB fraction of three times the upper limit of normal, according to American Heart Association / American College of Cardiology guidelines[14]. Target lesion revascularisation (TLR) and target vessel revascularisation (TVR) were defined according to the Academic Research Consortium (ARC) recommendations[15]; they were adjudicated as clinically indicated, only if driven by symptoms/objective signs of ischaemia and a percent diameter stenosis exceeding 50% on follow-up angiography. Clinical events were recorded in two ways: firstly, as composite major adverse cardiac events (MACE), including all-cause death, nonfatal myocardial infarction and TVR and secondly, in the form of the ARC recommended device-oriented composite, including cardiac death, myocardial infarction (not clearly attributable to a non-target vessel) and TLR.

We applied ARC recommendations to adjudicate stent thrombosis. Angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow-limiting thrombus accompanied by acute symptoms was considered as definite stent thrombosis. Unexplained death was adjudicated as probable stent thrombosis if occurring within 30 days, and as possible stent thrombosis if after 30 days[15]. Stent thrombosis was further categorised according to the timing of the event into acute (within 24 hours), subacute (24 hours-30 days), late (30 days-1 year) and very late (beyond one year). We retrieved electrocardiographic (ECG) information on patients with myocardial infarction for adjudication.

Data sources for both registries included municipal civil registries for survival status, information from health questionnaires, medical records, and information from local physicians on repeat coronary interventions (surgical or PCI), myocardial infarction and medication usage [10, 11].

Angiographic evaluation

The bifurcation lesions were adjudicated according to the Medina classification[16] after reviewing the pre-procedure images. Quantitative coronary angiographic (QCA) analysis was performed by means of dedicated bifurcation QCA software (CAAS 5.4,

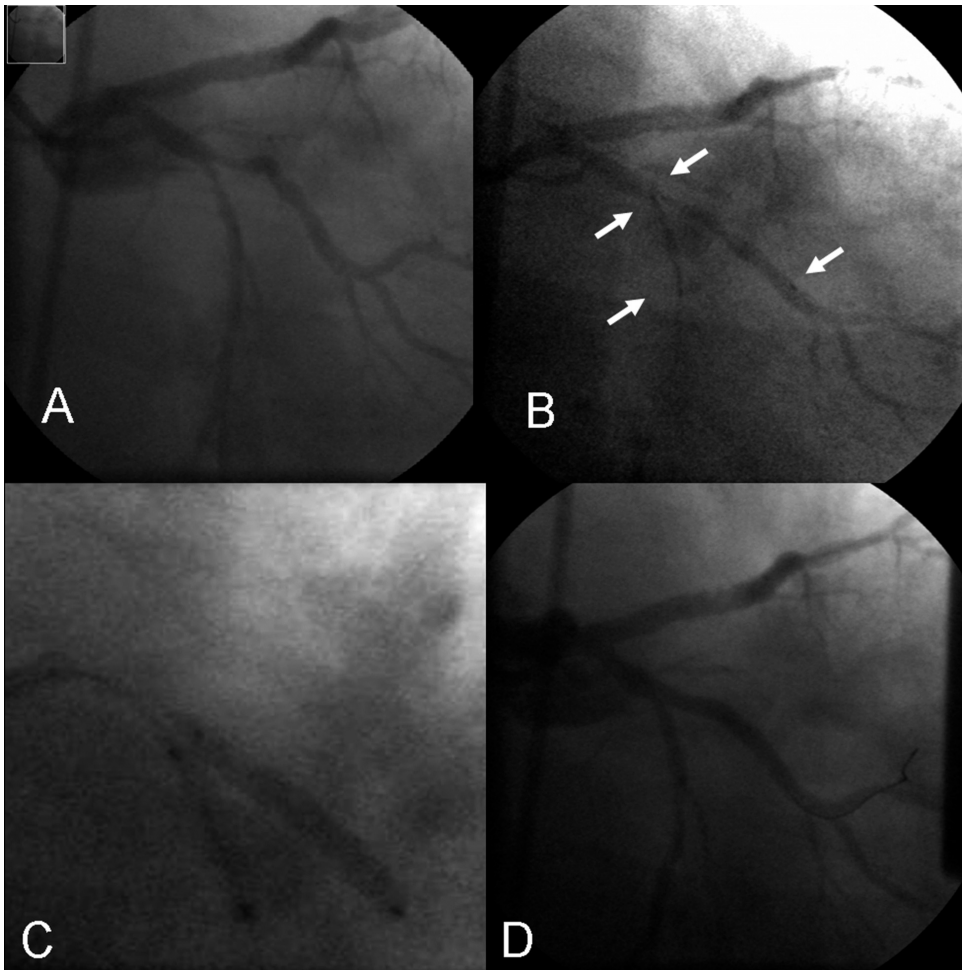

Figure 1. Illustration of V stenting technique. A. Typical 0,1,1 bifurcation lesion involving the left circumflex (LCX) and the obtuse marginal (OM) branch (distal main vessel). B. Two sirolimus-eluting, Cypher, stents have been advanced into position. The 3.0 x 23 mm stent is in the OM, the 2.5 x 13 mm stent is in the LCX. Arrows point at the stents' markers; the proximal markers barely touch each other, not protruding into the proximal main vessel. C. Both stents are simultaneously deployed. D. Final result.

Maastricht, PIE Medical software, The Netherlands) (Figure 2); the relevant methodology employing a ten-segment model for the bifurcation lesion has already been described[17]. Angiographic parameters, namely minimal lumen diameter (MLD), interpolated reference vessel diameter (RVD) and percentage diameter stenosis (DS), were independently determined both within the stent(s) and within the segment(s). These parameters were measured pre-procedure, post-procedure and, when available, at follow-up. In the case of a chronic total occlusion (CTO), the MLD equals 0 mm, %DS equals 100% and RVD cannot be determined. Late lumen loss (LLL) was calculated as the difference in MLD between post-procedure and follow-up. Angles between the PMV and SB (proximal bifurcation angle) and between DMV and SB (distal bifurcation angle) were automatically determined. Binary angiographic restenosis was defined as DS ≥50% at follow-up.

Statistical analysis

Categorical variables are presented as counts and percentages, whereas continuous variables are expressed as mean ± standard deviation. A comparison of angiographic variables both between pre and post and between post and follow-up was performed with a Wilcoxon signed rank test. A p- value of <0.05 was considered significant. Statistical analysis was performed using commercially available software (SPSS 12.0 for Windows, SPSS, Chicago, IL, USA).

Results

The baseline demographics and procedural characteristics in the 31 patients are reported in Tables 1 and 2. PCI was performed in 20 (64.5%) patients for an acute coronary syndrome (22.6% with ST elevation myocardial infarction and 41.9% with unstable angina or non-ST elevation myocardial infarction). Twenty-three patients (74.2%) had multivessel disease and 12 of them (38.7%) had interventions to at least one additional major epicardial vessel beyond the target vessels. All patients received exclusively one type of DES; Taxus and Cypher stents were implanted in 20 and 10 cases respectively. There was a single patient who received exclusively biolimus-eluting stents (BES, Biomatrix, Biosensors, Singapore); he was recruited in a research study and had no clinical event during the follow-up period. The average number of stents was 3.5±1.5 per patient with a total stent length 64.1±32.6 mm. However, regarding

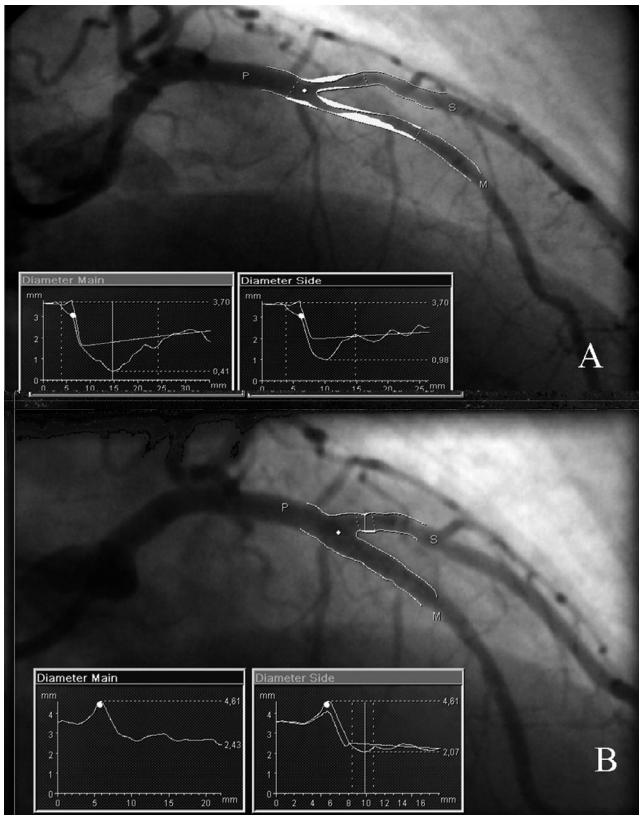

Figure 2. Quantitative coronary angiography of a bifurcation lesion involving the left anterior descending (LAD) and the diagonal branch (side branch). Automatic contour detection pre-procedure (A) and post-procedure (B). Images include the corresponding diameter plots for the main branch and the side branch (CAAS 5.4, Maastricht, PIE Medical software, The Netherlands).

the bifurcation lesion itself, 1.5±0.8 stents with a mean total length of 26.6±17.2 mm and 1.1±0.4 stents with a mean total length of 18.3±7.6 mm were deployed in the DMV and SB respectively. All patients had Medina bifurcation lesion classification of 0,1,1 for the lesion receiving V stenting. The left main bifurcation was the location of the lesion in the majority of the cases (16 cases-51.6%); the lesion involved the left anterior descending (LAD)/diagonal bifurcation in eight cases, the left circumflex (LCX)/obtuse marginal bifurcation in six cases and the distal right coronary artery (RCA) bifurcation in one case. Stents were deployed simultaneously at all times, whereas post-dilation with kissing balloons was performed in 10 cases (32.3%); glycoprotein IIb/IIIa inhibition was employed in 13 cases (41.9%).

Thirty-day outcome

Within 30 days, three patients died (patients 1, 2 and 3 in Table 3). The first death was regarded as non-cardiovascular, since the patient succumbed to hospital acquired pneumonia after a stroke, whereas patient 2 was adjudicated to have probable stent thrombosis. Patient 3 could not be saved despite a rescue procedure for cardiogenic shock after failed thrombolysis, and died of heart failure. Two other patients had definite stent thrombosis and required emergency PCI, one on day 0 and one on Day 5. The latter (patient 4 in Table 3), a 78-year old man suffering a heart attack five days after a prostate operation, had a cerebral haemorrhage on day 4 and therefore aspirin and clopidogrel were discontinued; the stents occluded the very next day. Finally, another patient who had the V stents placed at the left main bifurcation, and also had intervention on a sub-totally occluded venous graft to his right coronary artery, had a myocardial infarction on the same day; ECG changes pointed to the treated graft as the culprit.

Table 1. Patient demographics and clinical characteristics (n = 31).

Age (years)	65.9±11.4
Male gender (%)	22 (70.9)
Diabetes mellitus (%) -all NIDDM	5 (16.1)
Hypertension (%)	10 (32.3)
Hypercholesterolaemia (%)	15 (48.4)
Current smoker (%)	6 (19.4)
Previous myocardial infarction (%)	12 (38.7)
Previous PCI (%)	4 (12.9)
Previous CABG (%)	2 (6.5)
Clinical presentation	
Stable angina (%)	11 (35.5)
Unstable angina or non-ST elevation myocardial infarction (%)	13 (41.9)
ST elevation myocardial infarction (%)	7 (22.6)
Glycoprotein IIb/IIIa inhibitors periprocedural usage (%)	13 (41.9)

NIDDM: non insulin dependent diabetes mellitus; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery

Table 2. Baseline angiographic and procedural characteristics (n = 31).

Multivessel disease (%)	23 (74.2)
Multivessel intervention (%)	21 (67.7)
Angiographic success (%)	31 (100)
Clinical success (%)	25 (80.6)
Target bifurcation lesion location	
LMS (%)	16 (51.6)
LAD / diagonal (%)	8 (25.8)
LCX / obtuse marginal (%)	6 (19.4)
RCA bifurcation (%)	1 (3.2)
CTO within the target bifurcation lesion	5 (16.1)
In the distal main vessel	4 (12.9)
In the side branch	1 (3.2)
Mean number of stents per patient	3.5±1.5
Mean total length of stents (mm)	64.1±32.6
Mean number of stents in the main vessel	1.5±0.8
Mean total length of stents in the main vessel (mm)	26.6±17.2
Mean number of stents in the side branch	1.1±0.4
Mean total length of stents in the side branch (mm)	18.3±7.6
DES implanted	
Patients receiving SES (%)	10 (32.3)
Patients receiving PES (%)	20 (64.5)
Patients receiving BES (%)	1 (3.2)
Post-dilation with kissing balloons (%)	10 (32.3)

LMS: left main stem; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; CTO: chronic total occlusion; DES, SES, PES, BES: drug-, sirolimus, paclitaxel and biolimus- eluting stents respectively

Table 3. All-cause death: patient characteristics and procedural details.

Patient	Gender/Age	Index PCI indication	Treated vessels	V stents location	Stent type	GP IIb/IIIa Inhibitor use	Kissing balloon inflation	Stent thrombosis by ARC definitions	Time to TLR/TVR, days	Time to Death, days	Remarks
1	M/64 yrs	Unstable angina	LCX, intermediate	LCX-intermediate	PES	Yes	Yes	No	No	11	Stroke on day 4, died of hospital acquired pneumonia
2	F/63 yrs	Unstable angina	LAD, LCX	LAD-LCX	PES	Yes	Yes	Probable	No	11	Pulmonary embolism, hence anti-coagulated. Sudden death preceded by generalised convulsion
3	M/78 yrs	ST elevation myocardial infarction	LAD, LCX	LAD-LCX	SES	No	No	No	No	14	Index PCI was rescue procedure for cardiogenic shock. Died of heart failure
4	M/78yrs	ST elevation myocardial infarction	LAD, diagonal	LAD-diagonal	PES	No	No	Definite	LAD stent thrombosis Day 5	42	Cerebral haemorrhage on day 4; cessation of aspirin and clopidogrel on the same day; LAD and LM stented on re-PCI with moderate result Sudden death during recovery
5	F/80yrs	Unstable angina	LAD, LCX, OM	LCX-OM	SES	No	No	No	No	450	Sepsis after amputation
6	M/74yrs	Unstable angina	LAD, LCX	LAD-LCX	SES	No	No	No	Ostial LCX restenosis Day 189	1058	Ischaemia-driven TLR, day 189. Succumbed to end-stage heart failure
7	M/66yrs	Stable angina	LAD, LCX	LAD-LCX	SES	Yes	No	No	No	1206	Sepsis due to pneumonia

PCI: Percutaneous coronary intervention; TLR: Target lesion revascularisation; TVR: Target vessel revascularisation; ARC: Academic Research Consortium; LCX: Left circumflex; LAD: Left anterior descending; OM: Obtuse Marginal branch; LM: Left Main coronary artery; SES/PES: sirolimus-/paclitaxel-eluting stents

Late clinical outcome

Survival status was available in every patient for ≥ 12 months after the initial PCI. The mean duration to the last follow-up or to death was 853±553 days. Beyond 30 days, and within a year, there was one more death (Table 4). Patient number 4 in Table 3 died on day 42 while recovering from the cerebral haemorrhage; this sudden death was adjudicated as possible stent thrombosis. Three patients required a target vessel revascularisation, but in only two were the bifurcation V stents the targets for re-intervention. One patient underwent repeat coronary angiography and subsequently reintervention on day 160 upon referral for unstable angina. He had a mid-LAD in-stent restenosis of 70% and a borderline 50% (by visual estimation) ostial LAD restenosis, involving the V stents implanted at the LAD-LCX bifurcation. The former lesion was deemed the culprit lesion and was re-stented with a DES, whereas the latter was also treated with a DES deployed in the distal left main into the proximal LAD, fenestrated to the LCX; the procedure was completed with a kissing balloon inflation. However, QCA analysis ascribed a 43.9% stenosis to the ostial LAD restenotic lesion; thus this was not adjudicated as an ischaemia-driven revascularisation. Another patient with LAD-LCX V stents, had a re-study on day 189 revealing ostial LCX in-stent restenosis, which was treated with balloon dilatation. No patients had reinfarction beyond 30 days (Table 4). There were a further three deaths on days 450, 1058, 1206; the causes of death were respectively sepsis, end-stage heart failure and sepsis and none was adjudicated as having stent thrombosis (Table 3). The patient who died of heart failure was actually the single ischaemia-driven TLR case. The overall rates of mortality and other clinical endpoints within 30 days and 1-year (cumulative) are summarily reported in Table 4.

Quantitative angiographic analysis

Analysis of the baseline procedure could be done for 30 out of the 31 patients (Table 5); we could not retrieve post-procedure images for one case. Out of the 30 baseline procedures analysed, there were five cases involving a CTO, therefore the preprocedure RVD and the bifurcation angulation parameters could not be determined. In 11 cases, there was minimal stent protrusion into the PMV (2.23±0.72 mm), however never exceeding 5 mm or the respective RVD of the PMV; in three cases the protrusion was actually less than half the respective RVD. Angiographic follow-up (at a period of 203±33 days) was available for 11 patients (35.5%); data are presented in Table 6. Out of this group, eight patients underwent routine control coronary angiography and presented no binary angiographic restenosis of the target bifurcation lesion; out of the three patients who were referred for anginal symptoms (two with stable angina and one with unstable angina), one patient had binary in-stent restenosis. Thus, this cohort exhibited a restenosis rate of 9.1% (1/11). The LLL in the DMV and SB was 0.17±0.53 mm and

Table 4. Clinical outcome over the follow-up period.

	Within 30 days	At one year (cumulative)
All-cause mortality	3 (9.7%)	4 (12.9%)
Cardiac mortality	2 (6.5%)	3 (9.7%)
Non-cardiovascular mortality	1 (3.2%)	1 (3.2%)
Non-fatal myocardial infarction	2 (6.5%)	2 (6.5%)
Target lesion revascularisation (ischaemia driven)	2 (6.5%)	3 (9.7%)
Target vessel revascularisation (ischaemia driven)	2 (6.5%)	5 (16.1%)
MACE-Mortality or non-fatal ST elevation myocardial infarction or target vessel revascularisation	6 (19.4%)	9 (29.0%)
Device oriented composite-cardiac mortality or target vessel related myocardial infarction or target lesion revascularisation	4 (12.9%)	5 (16.1%)
Stent thrombosis according to Academic Research Consortium definitions	Acute	Subacute / Late
Definite	1 (3.2%)	1 (3.2%) / 0 (0%)
Probable	0 (0%)	1 (3.2%) / 0 (0%)
Possible	0 (0%)	0 (0%) / 1 (3.2%)

MACE: Major Adverse Cardiac Events

Table 5. Angiographic parameters for the baseline procedure (n=30).

	Pre	Post	P-value
Proximal main vessel			
MLD (mm)	1.73±0.55	2.45±0.46	<0.01
RVD (mm)	2.69±0.92	2.90±0.65	0.73
%DS	26.2±16.0	13.8±6.8	<0.01
Distal main vessel			
In segment			
MLD (mm)	0.96±0.59	2.13±0.43	<0.01
RVD (mm)*	2.10±0.47	2.69±0.46	<0.01
%DS	54.8±25.9	19.5±10.1	<0.01
In stent			
MLD (mm)	0.96±0.59	2.39±0.37	<0.01
RVD (mm)*	2.10±0.47	2.70±0.45	<0.01
%DS	54.8±25.9	11.0±7.9	<0.01
Side branch			
In segment			
MLD (mm)	0.99±0.41	1.91±0.47	<0.01
RVD (mm)**	2.04±0.49	2.41±0.44	<0.01
%DS	50.3±19.1	21.6±10.5	<0.01
In stent			
MLD (mm)	0.99±0.41	2.10±0.43	<0.01
RVD (mm)**	2.04±0.49	2.45±0.44	<0.01
%DS	50.3±19.1	14.4±6.0	<0.01
Distal bifurcation angle (degrees)	60.7±21.0	51.1±18.3	0.01

MLD: minimal lumen diameter; RVD: reference vessel diameter; DS: diameter stenosis. * 26 patients (4 pre-procedure chronic total occlusions). ** 29 patients (1 pre-procedure chronic total occlusion).

Table 6. Angiographic parameters from the patients having angiographic follow-up (n=11).

	Post	Follow-up	P-value
Proximal main vessel			
MLD (mm)	2.56±0.48	2.29±0.38	0.09
RVD (mm)	3.03±0.53	2.85±0.36	0.16
%DS	15.9±7.1	19.7±8.2	0.42
LLL (mm)		0.27±0.44	
BAR		0	
Distal main vessel			
In segment			
MLD (mm)	2.24±0.46	2.07±0.44	0.35
RVD (mm)	2.74±0.51	2.65±0.41	0.37
%DS	1.6±1.0	23.0±9.5	<0.01
LLL (mm)		0.17±0.53	
BAR		0	
In stent			
MLD (mm)	2.39±0.41	2.08±0.45	0.04
RVD (mm)	2.74±0.54	2.66±0.42	0.45
%DS	12.1±8.4	22.0±10.3	0.03
LLL (mm)		0.31±0.43	
BAR		0	
Side branch			
In segment			
MLD (mm)	1.96±0.46	1.78±0.49	0.33
RVD (mm)	2.42±0.49	2.44±0.59	0.65
%DS	19.0±7.4	27.1±14.0	0.11
LLL (mm)		0.18±0.60	
BAR		0	
In stent			
MLD (mm)	2.12±0.55	1.83±0.49	0.16
RVD (mm)	2.46±0.50	2.46±0.55	0.79
%DS	14.8±5.9	25.9±14.5	0.04
LLL (mm)		0.29±0.57	
BAR		1 (9.1%)	
Distal bifurcation angle (degrees)	45.6±13.2	50.9±17.7	0.29

MLD: minimal lumen diameter; RVD: reference vessel diameter; DS: diameter stenosis; LLL: late lumen loss; BAR: binary angiographic restenosis

0.18±0.60 mm in-segment and 0.31±0.43 mm and 0.29±0.57 mm in-stent respectively. Sixteen cases exhibited a Y anatomical configuration regarding the bifurcation treated, whereas nine were T-shaped; the distal bifurcation angle was smaller than 70 degrees in the former and larger in the latter.

Discussion

This paper reports a real-world experience on V stenting technique using DES. The paucity of outcome data after V stenting reflects that this technique is rarely performed[9]; the current series of 31 patients were collected over nearly five years. A percentage of 13.7% has been reported[18] regarding the frequency of the type 4 bifurcation lesion according to the ICPS classification system, which is the equivalent of the 0,1,1 lesion in the Medina classification. Even if this is per definition, the ideal lesion configuration for the implementation of V stenting, similar techniques such as Simultaneous Kissing Stents claim a great share of those procedures, accounting for the rarity of V stenting.

Many techniques have been described to treat bifurcations, reflecting the lack of a perfect solution. Although the proposed strategy would be stenting the main branch with provisional stenting of the side branch, this would not apply in this setting; a bifurcation lesion involving a large side branch with a long stenosis certainly calls for a two-stent strategy. With the Crush technique, bench studies revealed that stent deployment even after kissing balloon inflation is often suboptimal and associated with malapposition[4,19], findings corroborated by intravascular ultrasound studies[20]. Stent under-expansion could predispose to higher restenosis rate and thrombotic risk[21,22]. Less data has accumulated for Culotte stenting in the current DES era, but this technique has attracted renewed attention[23,24].

Early outcome

The admittedly less than desirable early outcome (MACE rate of 19.4%) should be interpreted in the context of unstable clinical presentation, extensive coronary disease and a multitude of aggravating factors. This series bears the highest rate (64.5%) of acute coronary syndrome as the clinical presentation compared to other relevant studies in the DES era (13.3-62.0%)[2,3,6,7,24,25]; moreover the rates of multivessel disease (74.2%), multivessel intervention (67.7%), intervention on additional major epicardial vessels beyond the target vessels (38.7%) and the rate of left main stem stenting (51.6%) rank high among the corresponding studies. Out of the three deaths occurring within 30 days, none was clearly attributable to the PCI itself, even though two of them were adjudicated as cardiac. One was due to cardiogenic shock, not reversed by a rescue procedure after failed thrombolysis, and the other one had to be adjudicated as probable stent thrombosis, recent pulmonary embolism notwithstanding; an autopsy was not performed.

As to the two definite stent thrombosis cases, both of them presented with ST elevation myocardial infarction; neither of them was treated with glycoprotein IIb/IIIa inhibitors at index procedure, most probably due to old age; cessation of both antiplatelet agents in the second case was undoubtedly the major contributor to the stent thrombosis within 24 hours. Interestingly, in these two cases, stent protrusion by QCA was either trivial on non-existent. The remaining case of myocardial infarction was related to the concomitant intervention on the sub-totally occluded saphenous vein graft. Applying the ARC recommended device-oriented composite, the event rate substantially drops (12.9%), not adjusting however for the aforementioned circumstances.

Late outcome

Contrary to the early outcome, event rates at one year excluding the first 30 days, are close to the corresponding values reported in the vast majority of the relevant literature. As a matter of fact, cumulative 1-year TVR and TLR rates (16.1% and 9.7% respectively) compare favourably to DES studies employing Crush (11.0% TVR and 9.7% TLR at nine months)[25], Culotte (11.1% TVR and 8.9% TLR at nine months)[24], T stenting (TVR and TLR 27.3% at nine months)[24], SKS (TLR 4.0-13.9%)[5,6] and mixed cohorts (TLR 4.3-9.5 at six months)[2,3,9]. Equally amenable are the angiographic features (low LLL in both branches and low binary restenosis rate), despite the increased average number of stents and total stent length implanted. Of note, in the RESEARCH and T-SEARCH registries[10,11], the average stent length was 38.7±23.7 mm and 42.9±31.2 mm respectively. The Nordic Bifurcation Study stands out due to its strikingly low rates of events (3.4% MACE and 1.0% TLR at six months in the two stent arm); however, this is offset by leaving the much higher angiographic restenosis (16.0%) unattended[26]. Over an average of 853 days of follow-up, there was only one case of possible late stent thrombosis.

Unlike the Crush or Culotte techniques, the V stenting technique does not deform conventional tubular stents. It allows the operator to preserve access to both branches throughout the procedure, without the need to rewire. However, this has to be traded against the possibility of using a smaller guiding catheter, since a guiding catheter of at least 7 Fr for the Taxus stent or even 8 Fr for the Cypher stent, is required for simultaneous stent deployment[12]. Moreover, great precision is required for accurate positioning of the stents, in order to avoid geographic miss or protrusion into the PMV. When the PMV is also involved (i.e. Medina classification 1,1,1), usage of dedicated devices such as the Devax stent to deal with the proximal lesion in the main vessel combined with V stenting of the bifurcation should provide full coverage of the lesion with minimal overlapping of the stent struts. The recent multicentre Axxess Plus trial[27] on 139 patients receiving the Axxess (Devax) stent, reported satisfactory outcome at 6-months with a TLR rate of 7.5% and angiographic in-stent LLL of 0.09 mm. However, only 77.7% of patients were regarded as having "true" bifurcation lesions involving both the PMV and SB and only 41.9% had stenting of both DMV and SB[27]. Future studies with V stenting, plus a proximal dedicated device for more challenging bifurcation lesions, are eagerly awaited.

Limitations

An obvious limitation to this analysis is the small number of patients involved. This precluded us from performing any kind of subgroup analysis; we could not compare events in the DMV and the SB or study the influence of variables, such as the type of DES, the clinical indication, the number of stents and total stented length, the location of the bifurcation lesion and last, but not least, the impact of angulation on the short- and long-term outcome. Even more limited was the rate of angiographic follow-up (35.5%), which was not routinely acquired. Regrettably, IVUS images were not available; in this setting they would have verified complete and accurate lesion coverage and adequate stent struts apposition. Finally, this is a retrospective, single-centre study, with no control arm. This does not allow us to favour or discredit the technique at hand.

Conclusions

We provided long-term outcome data on an unselected cohort who had V stenting of *de novo* bifurcation lesions with drug-eluting stents. It is a technique dedicated to a distinct anatomic dataset. Early outcome looks less than encouraging, but on closer scrutiny could appear circumstantial and endpoint-dependent; late outcome, on the other hand, stands in accord with competitive techniques and merits further evaluation.

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Chapter 9

Long-term clinical results following stenting of the left main stem: insights from RESEARCH and T-SEARCH Registries

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Long-Term Clinical Results Following Stenting of the Left Main Stem

Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries

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Objectives We investigated the long-term clinical outcomes and independent predictors of major cardiac events in unprotected left main coronary artery disease (ULMCA) patients treated by percutaneous coronary intervention with drug-eluting stent (DES).

Background There is limited information on long-term (>3 years) outcomes after DES implantation for ULMCA. Furthermore, bifurcation angle and SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score are emerging as parameters for patient risk stratification, and their prognostic implications have still to be elucidated.

Methods One hundred forty-eight patients with ULMCA treated with DES were analyzed and compared with a historical cohort of 79 patients who received bare-metal stents for the treatment of ULMCA. Patient-oriented composite end point was defined as the occurrence of all-cause death, any myocardial infarction, or any revascularization.

Results The 4-year cumulative incidence of all-cause death, any myocardial infarction, any revascularization, and patient-oriented composite were 35.6%, 3.8%, 25.2%, and 54.4%, respectively. These end points had relatively increased from 1 year to 4 years by Δ70%, Δ5%, Δ50%, and Δ68%, respectively. When compared with a historical cohort who received bare-metal stents for ULMCA treatment, landmark analysis performed after the first 2 years of follow-up demonstrated that the DES cohort had significantly higher patient-oriented composite end point over the last 2 years of follow-up (26% vs. 8%, $p = 0.02$). EuroSCORE (European System for Cardiac Operative Risk Evaluation), cardiogenic shock, and SYNTAX score were identified as independent predictors for the 4-year patient-oriented composite, whereas bifurcation angle was not.

Conclusions Late increase in patient-oriented composite end points after DES implantation for ULMCA warrants careful and long-term follow-up. SYNTAX score and EuroSCORE appear to have a significant prognostic value in long-term patient risk. (J Am Coll Cardiol Intv 2010;3:584–94)

The prevalence of left main disease in patients with coronary artery atherosclerosis varies from 2.5% to 10% (1). Coronary artery bypass graft (CABG) remains the treatment of choice in patients with unprotected left main coronary artery disease (ULMCA) (2,3). Although percutaneous coronary intervention (PCI) using bare-metal stent (BMS) in patients having 2- or 3-vessel disease is associated with no significant difference in long-term mortality compared with CABG, restenosis and need for repeat revascularization remain major limitations of this mode of revascularization. These latter limitations have precluded the widespread use of PCI, not only in multivessel disease, but also in LM disease (4). Reduction of restenosis with drug-eluting stents (DES), however, has raised the possibility of their use for multivessel treatment as well as LM treatment. So far, several registries and randomized trials have investigated the short- and mid-term clinical outcomes of PCI using DES for ULMCA treatment (5–14), but little is known about its long-term safety and efficacy beyond 3 years (15). In addition, the rate of potentially fatal consequences of stent thrombosis or in-stent restenosis in this patient subset has not fully been investigated (16,17).

See page 642

Several clinical and angiographic parameters for risk stratification after PCI are emerging. Recently, EuroSCORE (European System for Cardiac Operative Risk Evaluation), a typically surgical risk stratification score, has been applied to the PCI population (18). As angiographic analysis, the angle between bifurcated branches has been recognized as a significant prognostic factor for immediate procedural outcomes as well as for intermediate-term outcomes (19–21). In addition, a comprehensive, angiographic scoring system, the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score (22,23) based on morphology and location of coronary artery stenoses in the coronary tree has been proven to predict clinical outcomes in high-risk patients (9,24,25).

The main aim of this study was to report the long-term clinical outcomes of patients receiving DES for unprotected LM lesions in a daily practice of a tertiary medical center. In addition, we assessed the prognostic value of recently emerging predictors of adverse outcomes for PCI treatment of multivessel disease and ULMCA, such as EuroSCORE, the bifurcation angle, and SYNTAX score.

Methods

Study design and patient population. Between April 2002 and December 31, 2005, 210 consecutive patients underwent PCI for LM stenting (7,8). Sixty-two patients with a history of CABG were not retained in this analysis. The remaining 148 patients are the subject of the present investigation. On April 16, 2002, our institution adopted the use of sirolimus-eluting stents (Cypher, Cordis, Warren, New Jersey) as the default strategy for all coronary interventions, as part of RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry (26). On February 16, 2003, sirolimus-eluting stents were replaced by paclitaxel-eluting stents (Taxus Express2, Boston Scientific, Natick, Massachusetts) as the default stent, as part of the T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registry (27). For evaluation of long-term outcomes, this DES group was compared with a historical cohort who received BMS in the unprotected LM trunk before April 2002 (n = 79).

In this study, the decision to intervene in the patients with PCI was based on a consensus reached during a multidisciplinary medical surgical conference (the so-called heart-team conference) involving surgeon, interventionalist, and referring physician (28), except for patients who presented with ST-segment elevation myocardial infarction (STEMI), considering the emergent character of the clinical presentation. All procedures were performed according to standard clinical guidelines at the time. All patients were pretreated with 300 mg of clopidogrel. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for at least 3 months for patients with DES. Life-long aspirin therapy was recommended in all patients.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
LM = left main
MACCE = major adverse cerebrovascular cardiac event
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization
ULMCA = unprotected left main coronary artery disease

QCA analysis. To assess the bifurcation angle between the left anterior descending and left circumflex arteries, 3-dimensional quantitative coronary angiography (QCA) analyses were performed by 2 observers blinded to the patient data and clinical outcomes. A validated program was used to reconstruct 3-dimensional images from 2 different projections at least 30° apart from each other (CardiOp-B system version 2.1.0.151, Paieon Medical Ltd., Park Afek, Israel) (29–31). Separate 3-dimensional angiographic images were constructed for systolic and diastolic phases. The bifurcation angle was defined as the angle between the left anterior descending and left circumflex arteries (32). In cases where the separate projections were not available, 2-dimensional bifurcation software (CAAS version 5.6, Pie Medical, Maastricht, the Netherlands) was used to calculate bifurcation angle (33). In primary PCI cases where TIMI (Thrombolysis In Myocardial

Infarction) flow grade was 0 or 1 pre-procedure, the cineangiography following the first balloon angioplasty was analyzed for the determination of the angle.

SYNTAX score. Two analysts blinded to patient characteristics and clinical outcomes reviewed the angiograms to calculate the SYNTAX score (22,23). In case of disagreement, the opinion of a third observer was obtained and the final decision was made by consensus. Each coronary lesion producing >50% luminal obstruction in vessels >1.5 mm was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the following: 1) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (34); and 2) the morphologic features of each single lesion (35,36). The reproducibility of the SYNTAX score was recently reported (22).

Clinical follow-up. Survival data for all patients were obtained from municipal civil registries on a yearly basis. A questionnaire was subsequently sent to all living patients with specific enquiries on rehospitalization and major adverse cardiac events (MACE). As the principal regional cardiac referral center, most repeat revascularization (either percutaneous or surgical) is normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary. Causes of death were obtained from medical records when they happened during hospitalization, and otherwise from the Central Bureau of Statistics, The Hague, the Netherlands (37,38). Causes of death were classified according to the International Classification of Diseases and Related Health Problems-10th Revision. For the present analysis, death from ischemic heart disease (I-20 to I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were considered to be cardiac. Death from cancer was defined as any death from malignant neoplasm (C-009 to C-97). All the remaining deaths were classified as being due to other causes, and no further distinction was made. In this study, there was no mandatory angiographic follow-up.

End point definitions. The primary end point was a patient-oriented composite defined as all-cause death or any myocardial infarction (MI) or any revascularization (all surgical and percutaneous, target lesion, target vessel, and non–target vessel revascularization) according to the Academic Research Consortium definitions (39). The secondary end point was the device-oriented composite end point defined as cardiac death, MI in the target vessel territory, or a target lesion revascularization. In addition, each individual component end point was analyzed in a nonhierarchical way. Definite stent thrombosis was also considered as a separate secondary end point.

Myocardial infarction included periprocedural MI (diagnosed by a rise in creatine kinase-myocardial band fraction of 3 times the upper limit of normal), reinfarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes following stable or decreasing values), or spontaneous MI (diagnosed by any rise in creatine kinase-myocardial band fraction above the upper limit of normal) (40). Target lesion revascularization was defined as a repeat revascularization of in-stent or within 5 mm proximal or distal to the stent implanted in the index procedure (41). Target vessel revascularization (TVR) was defined as any revascularization in the same epicardial vessel treated in the index procedure. Definite stent thrombosis was defined as TIMI flow grade 0 or 1 or the presence of a flow-limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention (42). The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year), or very late (more than 1 year) (39).

Statistical analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentages. Comparisons among groups were performed by the independent *t* test for continuous variables and Pearson chi-square test for categorical variables. All statistical tests were 2-tailed, and p value of <0.05 was considered as statistically significant. The incidence of events over time was studied with the use of the Kaplan-Meier method, whereas log-rank tests were applied to evaluate differences between the current cohort and the historical control. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression models were built to elucidate independent predictors of clinical end points. Significant variables in univariate analysis ($p < 0.1$) were selected to put in the multivariate model. The following pre-procedural variables were included in the initial univariate analysis: gender, diabetes, current smoking habit, hypertension, hypercholesterolemia, age, previous history of myocardial infarction or PCI, SYNTAX score, EuroSCORE, shock at entry, clinical presentation, and bifurcation angle. Clinical presentation (STEMI, unstable angina or non-STEMI, and stable angina) was coded as a categorical variable. Bifurcation angle was partitioned according to tertiles (lowest tertile as a reference). The results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI). Statistical analysis was performed with SPSS version 16 for windows (SPSS Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics. The baseline and procedural characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
Demographics			
Age, yrs	64.9 ± 12.1	65.1 ± 11.2	0.96
Men	108 (73)	49 (62)	0.10
Diabetes	24 (16.2)	15 (19)	0.59
Hypertension	61 (41)	34 (43)	0.89
Hypercholesterolemia	80 (54)	34 (43)	0.13
Family history of coronary artery disease	47 (32)	15 (19)	0.04
Current smoking	27 (18)	14 (18)	1.00
Previous PCI	32 (22)	25 (32)	0.11
Previous MI	49 (33)	24 (30)	0.77
Additive EuroSCORE	4.26 ± 3.54	4.37 ± 3.57	0.82
SYNTAX score	39.4 ± 22.9	36.8 ± 24.6	0.96
LVEF, %	45.3 ± 13.6	41.8 ± 16.9	0.48
Presentation			
STEMI	36 (24.3)	22 (27.8)	0.64
Stable angina	60 (40.5)	30 (33.3)	0.78
Unstable angina/non-STEMI	52 (35.1)	27 (34.2)	1.00
Shock at entry	13 (8.8)	6 (7.6)	1.00
Pre-procedural quantitative angiographic analysis			
Bifurcation angle in diastole, °	94.1 ± 25.5	89.5 ± 25.3	0.29
Bifurcation angle in systole, °	84.9 ± 26.6	81.42 ± 23.8	0.42
Minimal lumen diameter, mm	1.09 ± 0.32	1.08 ± 0.27	0.92
Reference vessel diameter, mm	3.35 ± 2.49	3.31 ± 0.36	0.69
Procedural characteristics			
Number of implanted stents	3.08 ± 0.37	2.85 ± 0.47	<0.0001
Total stented length per patient	59.9 ± 40.4	42.4 ± 28.4	<0.0001
Average stent diameter	3.08 ± 0.37	3.52 ± 0.47	<0.0001
Clopidogrel duration in month	7.53 ± 5.32	5.27 ± 4.86	0.01
IVUS use	48 (32)	34 (43)	0.15
Stenting strategy			
Provisional	114 (77)	70 (89)	0.07
Culotte	13 (9)	1 (1)	
T-stenting	15 (10)	8 (10)	
Crush stenting	4 (3)	0	
Kissing technique	2 (1)	0	
Post-procedural bifurcation angle			
Bifurcation angle in diastole, °	85.1 ± 24.8	84.2 ± 25.9	0.83
Bifurcation angle in systole, °	80.0 ± 23.7	76.7 ± 21.2	0.38

Values are expressed as n (%) or mean ± SD.

BMS = bare-metal stents; DES = drug-eluting stents; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

The mean age of the patients was 64.9 years old, 16.2% of the patients had diabetes, and 33% had previous history of MI. Approximately one-quarter of patients presented with STEMI, and 8% presented with severe hemodynamic compromise at entry. The average additive EuroSCORE and SYNTAX score was 4.26 and 39.4, respectively.

Clinical outcomes. Clinical follow-up was available in all patients, with a median duration of follow-up of 1,473 days (interquartile range: 1,182 to 1,848 days) for patients alive at follow-up. Hierarchical count of adverse events is shown in Table 2. Patient-oriented composite increases from 32.4% at 1 year to 51.4% at 4 years (Δ58%), which was mainly driven by an increase in all-cause mortality from 19.6% at 1 year to 33.1% at 4 years, a relative increase of 68%. There was 1 case of definite late stent thrombosis at 1 year, and there was 1 case of definite very late stent thrombosis at 4 years.

Kaplan-Meier estimates of clinical end points are presented in Figures 1A to 1C. At 4 years, the cumulative

Table 2. Hierarchical Count of Patient-Oriented Composite After DES Implantation Compared With the Historical Cohort With BMS

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
1 yr			
All-cause death	29 (19.6)	23 (29.1)	0.14
Any MI	2 (1.4)	1 (1.3)	1.00
Any revascularization	17 (11.5)	10 (12.7)	1.00
Patient-oriented composite	48 (32.4)	34 (43)	0.15
2 yrs			
All-cause death	35 (23.6)	27 (34.2)	0.11
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	19 (12.8)	11 (13.9)	0.84
Patient-oriented composite	57 (38.5)	39 (49.4)	0.12
3 yrs			
All-cause death	41 (27.7)	29 (36.7)	0.18
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	23 (15.5)	11 (13.9)	0.85
Patient-oriented composite	67 (45.3)	41 (51.9)	0.4
4 yrs			
All-cause death	49 (33.1)	30 (38)	0.47
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	24 (16.2)	11 (13.9)	0.7
Patient-oriented composite	76 (51.4)	42 (53.2)	0.9

Event rates were calculated as number of events divided by total number of patients and therefore differ from those in the figures, where event rates were calculated by Kaplan-Meier methods. In this table, comparison was made with the chi-square or Fisher exact test.

Abbreviations as in Table 1.

incidence of all-cause death, MI, any revascularization, and patient-oriented composite were 35.6% (95% CI: 27.3% to 43.8%), 3.8% (95% CI: 0.5% to 7.1%), 25.2% (95% CI: 16.9% to 33.6%), and 54.4% (95% CI: 45.8% to 63.1%), respectively. Cardiac mortality, all-cause mortality, and any revascularization rate relatively increased from 1 year to 4 years by Δ68%, Δ82%, and Δ49%, respectively, whereas the changes in target lesion revascularization and MI was less increased from 1 year to 4 years (Δ5% and Δ28%, respectively) (Figs. 1A and 1B). In summary, the device-oriented and patient-oriented composite increased from 1 year to 4 years by Δ56% and Δ68%, respectively (Fig. 1C). If stratified by the presentation with STEMI versus others (non-STEMI, unstable angina, and stable angina), the patient-oriented composite was higher in STEMI patients (68.6%) than the others (49%, $p < 0.001$), also the device-oriented composite, all-cause death, and cardiac death were higher in the STEMI patients than the others (53% vs. 30%, $p < 0001$; 55% vs. 29%, $p < 0.001$; 48% vs. 16%, $p < 0.001$) (Fig. 2A). With stratification according to the tertiles of EuroSCORE (<2, ≥2 and <5, ≥5), the patient-oriented composite was higher in the high tertile (76.8%) than in the low (41.2%, log-rank $p < 0.001$) or intermediate tertiles (51.8%, log-rank $p < 0.001$) (Fig. 2B). If stratified according to type of DES (Cypher and Taxus), the patient-oriented composite was

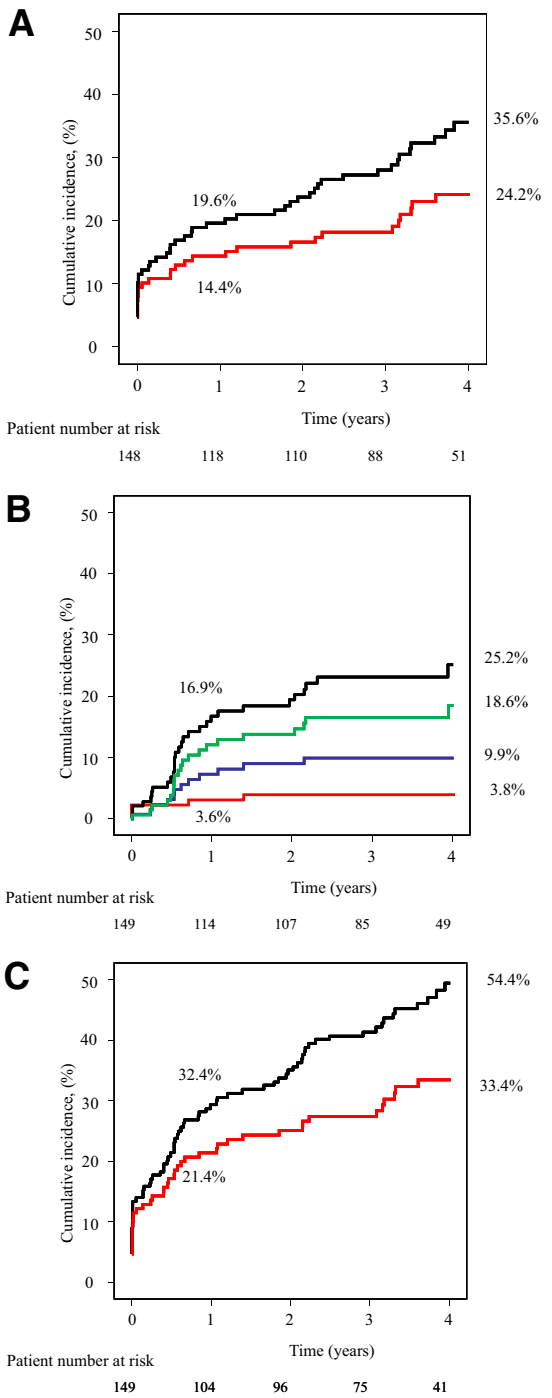

Figure 1. Kaplan-Meier Estimates After Implantation of DES

(A) Kaplan-Meier estimates demonstrate all-cause mortality **(black line)** and cardiac mortality **(red line)**. **(B)** Kaplan-Meier estimates present the end points of any myocardial infarction **(red line)**, target lesion revascularization **(blue line)**, target vessel revascularization **(green)**, and any revascularization including target and non–target vessel revascularization **(black line)**. **(C)** Kaplan-Meier estimates show the composite end point **(red line)** of cardiac mortality, myocardial infarction in the stented vessel territory, or target lesion revascularization and the composite end point **(black line)** of all-cause mortality, any myocardial infarction, or any revascularization. DES = drug-eluting stent.

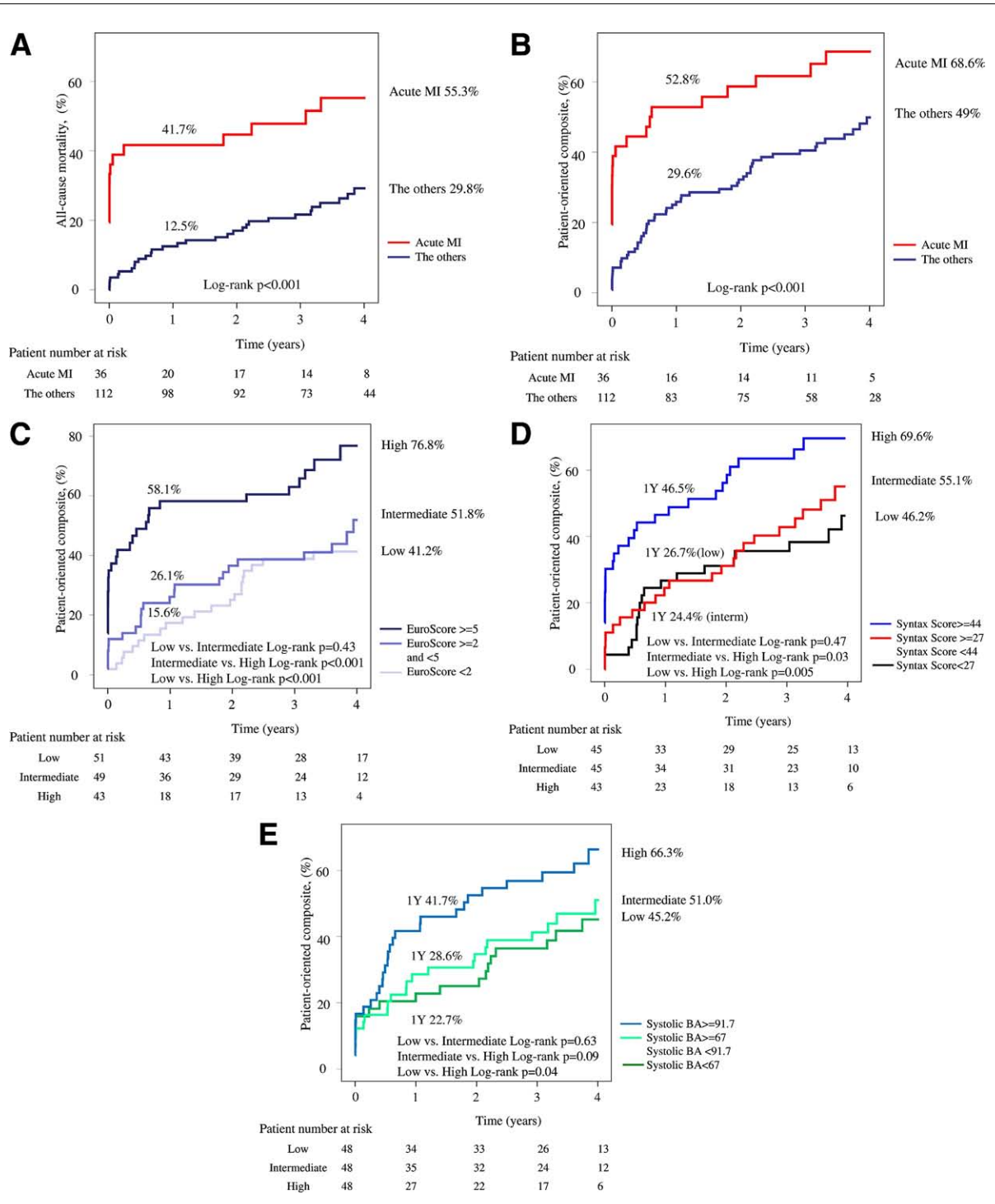

Figure 2. Kaplan-Meier Estimates After Implantation of DES With Stratification of Subgroups

(A) All-cause mortality and **(B)** patient-oriented composite end point (all-cause mortality, any myocardial infarction [MI]), or any revascularization) according to a presentation of ST-segment elevation myocardial infarction or the others (stable angina, non–ST-segment elevation myocardial infarction, or unstable angina). Patient-oriented composite end point stratified by **(C)** tertile division of EuroSCORE (European System for Cardiac Operative Risk Evaluation) with cutoff values of 2 and 5 and **(D)** tertiles of SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score of the current cohort (cutoff values of 27 and 44). **(E)** The patient-oriented composite end points were classified according to tertiles of bifurcation angle (BA) between the left anterior descending and circumflex arteries (cutoff values of 67 and 91.7). Abbreviations as in Figure 1.

53.8% in Cypher and 54.8% in paclitaxel-eluting stent (p = 0.83), whereas the all-cause mortality was 30.8% versus 36.5%, respectively (p = 0.56).

Comparison with historical cohort. Patient demographics in the historical control (n = 79) were similar to the current cohort except for a lower frequency of family history of coronary artery disease (32% vs. 19%, p = 0.04), reflecting that the changes in clinical practice, number of implanted stents, stent length, stent diameter, and clopidogrel duration are higher in the current cohort than in the historical control group.

Figure 3 shows the Kaplan-Meier estimates of all-cause mortality and the patient-oriented composite end point of the current cohort with DES and the historical control with BMS. At 1 year, the rate of all-cause death (current cohort 19.6% vs. historical cohort 29.1%) and patient-oriented composite (32.4% vs. 43.0%) was lower in the current cohort than in the historical cohort (Figs. 3A and 3B). At 4 years the events rate, however, became comparable between the 2 groups (all-cause mortality: 38.0 vs. 35.6%, p = 0.48; patient-oriented composite: 54.4 vs. 53.2%, p = 0.64) as a result from a late increase of events in the current cohort. Kaplan-Meier estimate before 2 years yielded a numerically higher patient-oriented composite end point in the historical cohort (log-rank p = 0.1), whereas landmark analysis (Fig. 3B) after the second year demonstrated a significantly higher event rate in the current cohort than the historical cohort (log-rank p = 0.02).

SYNTAX score. In the current cohort, the SYNTAX score ranged from 7 to 104 with median of 33.0. If the SYNTAX score is divided into tertiles, the cutoff values were 27.0 and 44.0. The Kaplan-Meier curves of device-oriented composite stratified by these tertiles of SYNTAX score are presented in Figure 2C. The 4-year event rates were 46.2%, 55.1%, and 69.6% in low, intermediate, and high tertile groups, respectively. High tertile group demonstrated significantly higher event rates than intermediate tertile (log-rank p = 0.03) and low tertile (log-rank p = 0.005) groups did.

Three-dimensional QCA analysis. Three-dimensional QCA analysis was feasible in only 50.7% of patients due to the unavailability of 2 separate angiographic views of more than 30° that is a prerequisite for 3-dimensional QCA; in the remaining patients, 2-dimensional QCA was performed. The results are shown in Table 1. In the patient receiving DES, the Kaplan-Meier curves of patient-oriented composite were separated according to the tertiles of systolic bifurcation angle (high >91.7, intermediate ≤91.7 and >67, low ≤67) as shown in Figure 2E. High tertile group demonstrated higher patient-oriented composite at 4 years (66.3%) than the intermediate (51.0%) and the low (45.2%) groups did (log-rank high vs. low: p = 0.04; high vs. intermediate: p = 0.09).

Predictor of adverse events. Table 3 shows the results of the univariate and multivariate analyses to identify the predictors for all-cause mortality and for patient-oriented composite. Bifurcation angle did not remain as a significant predictor of either all-cause mortality or patient-oriented end point in the multivariate analysis.

At 1 year, multivariate analysis demonstrated that EuroSCORE, age, shock at entry, and SYNTAX score were independent predictors for all-cause mortality and patient-

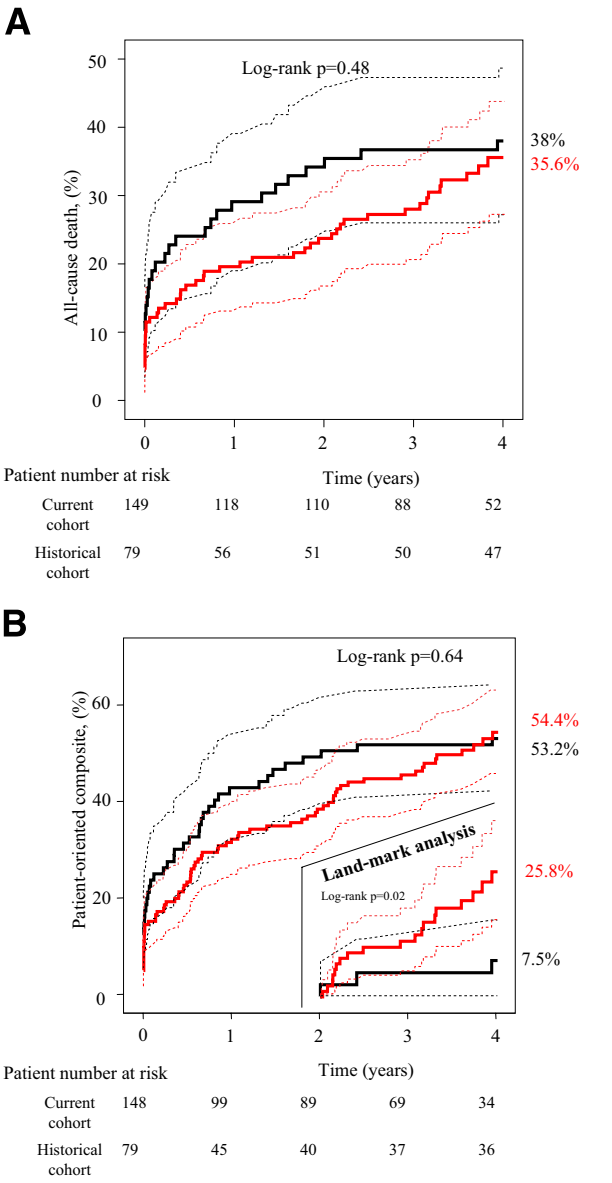

Figure 3. Kaplan-Meier Estimates of DES and BMS Cohorts

Kaplan-Meier estimates of the current cohort treated with drug-eluting stent **(red line)** or historical cohort treated with bare-metal stent **(black line).** All-cause mortality is demonstrated in **(A)**, whereas **(B)** demonstrates patient-oriented composite end point (all-cause mortality, any myocardial infarction, or any revascularization) with a landmark analysis more than 2 years after implantation. **Dotted lines** = 95% confidence interval. BMS = bare-metal stent(s); other abbreviations as in Figure 1.

Table 3. Univariate and Multivariate Analysis for Predictors of All-Cause Mortality and Patient-Oriented Composite After DES Implantation in the Left Main Trunk

	All-Cause Mortality				Patient-Oriented Composite			
	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value
1-year outcome								
EuroSCORE	1.26 (1.17–1.36)	<0.001	1.24 (1.11–1.39)	<0.001	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009
Presentation of STEMI*	6.77 (3.56–18.66)	<0.001			4.38 (2.08–9.23)	<0.001		
Age	1.06 (1.02–1.09)	0.003	1.05 (1.01–1.10)	0.03	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009
Shock at entry	8.56 (3.83–19.1)	<0.001	4.21 (1.50–1.82)	0.006	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001
SYNTAX score†	1.35 (1.17–1.56)	<0.001	1.23 (1.06–1.42)	0.006	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03
Hypercholesterolemia	0.33 (0.15–0.73)	0.006			0.43 (0.24–0.76)	0.004		
Hypertension	0.41 (0.18–0.96)	0.04	0.34 (0.13–0.88)	0.03	0.45 (0.24–0.84)	0.01		
4-year outcome								
EuroSCORE	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009	1.16 (1.09–1.24)	<0.001	1.09 (1.02–1.16)	0.02
Presentation of STEMI*	4.38 (2.08–9.23)	<0.001			3.42 (1.69–6.94)	0.001		
Age	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009	1.04 (1.01–1.070)	0.004		
Shock at entry	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001	4.61 (2.21–6.61)	<0.001	2.74 (1.30–5.80)	0.008
SYNTAX score†	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03	1.22 (1.08–1.38)	0.001	1.12 (1.01–1.24)	0.4
High bifurcation angle‡					1.99 (0.93–4.26)	0.075		

Univariate or multivariate hazard ratios were calculated by Cox regression models.

*Stable angina used as a reference. †Each 10-point increase of SYNTAX score. ‡Low tertile bifurcation angle used as a reference.

Abbreviations as in Table 1.

oriented composite. At 4 years, in the final multivariate models, age, shock at entry, the SYNTAX score and EuroSCORE remained as independent predictors for all-cause mortality, whereas EuroSCORE, shock at entry, and SYNTAX score were identified as independent predictors for patient-oriented composite.

Discussion

The main findings of the current study are the following: 1) At 4-year follow-up after DES implantation in ULMCA, patient-oriented composite end point was 51.4% with a 58% relative increase of events from 1 year to 4 years. 2) A landmark analysis of the last 2 years of follow-up indicated a higher composite end point for the current cohort with DES when compared with the historical cohort with BMS (25% vs. 8%, p = 0.02). 3) EuroSCORE and SYNTAX score were independent predictors for both all-cause mortality and the patient-oriented composite end point up to 4 years, whereas pre-procedural bifurcation angle between the left circumflex and left anterior descending arteries was not.

According to the current guidelines of the European Society of Cardiology and the American Heart Association and American College of Cardiology guidelines (40,43), the presence of a stenosis in the LMCA is a class IIB or III indication for PCI unless the patient is not eligible for CABG in presence of extreme comorbidities and STEMI. In the recent U.S. criteria for appropriateness of revascularization, percutaneous treatment of LM disease is considered "inappropriate" (2). In European daily practice, however, 4.6% of patients treated in the catheterization lab have LM stenosis, and 58% of those are treated by percutaneous means (44).

Up to now, 2 randomized trials have been performed to compare CABG and PCI using DES in patients undergoing treatment for LM disease. In the LE MANS (Left Main Coronary Artery Stenting) study by Buszman et al. (10), PCI was associated with a lower 30-day risk of major adverse cerebrovascular cardiac event (MACCE) (p = 0.03) and had comparable 1-year mortality or MACCE to surgery. In the more recent SYNTAX trial (9), which randomized 1,800 patients with 3-vessel or LM coronary artery disease to either CABG or PCI, the use of PCI at 1 year was associated with safety end points (death, cerebrovascular accident, and MI) but a higher rate of MACCE than CABG, due to a significantly higher rate of revascularization. However, in the subgroup of patients with LM disease with an average SYNTAX score of 28.1, PCI and CABG were associated with similar MACCE rates at 1 year (PCI 15.8% vs. CABG 13.6%). In the DES cohort of the present study, the 1-year all-cause mortality and revascularization rate of patients treated with DES (19.6% and 16.9%, respectively) were higher than rates reported in the LM subgroup of the randomized cohort in the SYNTAX trial (4.2% and 12.0%, respectively). This is likely due to the high-risk nature of our all-comers registry (e.g., including 24% STEMI patients with a mean EuroSCORE of 4.26 and an average SYNTAX score of 39.4).

In this analysis, we selected a patient-oriented composite end point as a primary end point, because it represents the most critical clinical approach for a population undergoing a new form of treatment. The Academic Research Consortium defined 2 methodological approaches to report clinical follow-up: 1) the device-oriented composite end point; and 2) the patient-oriented composite end point. The device-oriented approach put the accent on the efficiency and efficacy of a new device, therefore, focusing on the cardiac death, MI, and reintervention related to the device. The patient-oriented end point is a follow-up, which specifically considers the welfare of the patient, and includes all-cause death, any MI, and any revascularization.

In the current analysis, we entered only the pre-procedural parameters in the multivariate analysis and excluded the procedural variables such as angulation after stenting, technique of stenting, number of stent, length of stent, and so forth, because they are factors reflecting the treatment modalities rather than the anticipated prognosis of the treatment. Parameters describing lesion characteristics were also excluded because they were incorporated in the SYNTAX score: for example, Medina classification, chronic total occlusion, American College of Cardiology/American Heart Association lesion classification (45).

Long-term outcomes after PCI in the LM population are limited. Park et al. (46) reported the 3-year safety composite rate (death, Q-wave MI, or stroke) of 9.7% with TVR rate of 12.6%. Vaquerizo et al. (12) demonstrated the device-oriented composite end point at 2 years of 12.6% after UCLMA stenting with paclitaxel-eluting stents in 291 patients from multicenter registry. In these registries, the patients with acute MI or cardiogenic shock were excluded; whereas in our registry, such patients were included and had a negative impact on clinical outcomes. Also, frequent use of intravascular ultrasound might contribute the relatively lower mortality in the Korean registry than in our European registry (46). In one of largest "all-comer" DELFT (Drug-Eluting Stent for Left Main) registries exclusively using DES in ULMCA with 3-year complete follow-up, Meliga et al. (15) demonstrated 3-year MACE rate (a composite of cardiac mortality, MI, and TVR) of 26.5%, cardiac mortality of 9.2%, and TVR of 14.2%. If the same composite definition were applied to the present study, the 3-year MACE rate in our study (26.0%) would be similar to the DELFT registry (26.5%). Wood et al. (47) reported a long-term outcome of 100 patients with high surgical risk after PCI. All-cause mortality at 28 months was 21%; event-free survival was around 65% at 27 months (47).

In the current study, the baseline patient demographics are comparable between the current and the historical cohorts. Although the anatomical complexity reflected by SYNTAX score was comparable between the 2 cohorts (the current cohort 39.4 vs. the historical control 36.8, $p = 0.96$), the cohort with DES was more aggressively treated than the historical cohort with BMS, as indicated by a higher incidence of bifurcation stenting (48% vs. 57%, $p = 0.04$), by a larger number of stents implanted (2.85 ± 0.47 vs. 3.08 ± 0.37), and by on average a longer stented length (42.4 ± 28.4 mm vs. 59.9 ± 40.4 mm).

The source of our concerns is the increase of the patient-oriented composite in the DES group between 2 and 4 years, which was significantly higher than in the historical cohort of BMS, and the long-term safety of DES in the treatment of patients with ULMCA remains an unanswered question. One possible explanation for unfavorable follow-up could be the occurrence of occult stent thrombosis. Occlusion of the LM trunk with thrombus is likely to be lethal. Thus, patients can present with sudden and/or out-of-hospital death rather than with angiographically proven stent thrombosis. The very late stent thrombosis presenting with out-of-hospital death, however, can be undiagnosed and under-reported. The cause of death was obtained from the civil registry, and it is up to the general practitioners to classify the cause of mortality according to International Classification of Diseases and Related Health Problems-10th Revision unless the patient passed away in the hospital. Therefore, no attempt was made to impute death to possible or probable stent thrombosis.

In the large multicenter registry ($n = 731$) by Chieffo et al. (17), the cumulative incidence of stent thrombosis at 29.5 months after LM stenting was reported to be 0.95% for definite stent thrombosis and 2.7% for possible stent thrombosis. In DELFT registry (15) ($n = 358$) at ≥3-year follow-up, the incidence of definite, probable, and possible stent thrombosis were 0.6%, 1.1%, and 4.4%. In ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) trial (48) ($n = 607$), the 2-year rate of definite or probable stent thrombosis was about 0.5% to 1.0%. In a series of high surgical risk patients, Wood et al. (47) reported a 5% possible stent thrombosis presenting as sudden death. Taking into account the late increase in mortality shown in our study, follow-up extending beyond 3 years is warranted for patients receiving DES in the setting of ULMCA.

The bifurcation angle has been shown to relate not only to the difficulty level of the procedure but is also associated with intermediate outcomes. Dzavik et al. (19) reported that a bifurcation angle ≥50 was an independent predictor of MACE at 1 year after bifurcation crush stenting in 133 patients. In 132 patients receiving Cypher stents in bifurcations excluding LM lesions, Adriaenssens et al. (49) reported that increasing bifurcation angles is an independent predictor of binary restenosis (HR: 1.53 [95% CI: 1.04 to 2.23] per 10° increase in angulation) after culotte stenting. The worse outcomes in high-angulated bifurcation lesions might be the result of the adjacent presence of low and high shear stress found in bifurcation lesions. High

shear stress possibly stimulates platelet activation and aggregation, and low shear stress might enhance deposition of platelets. This mechanism can be potentially exaggerated in higher bifurcation angles. Furthermore, when bifurcation stenting is performed in high-angle lesions, the stent will likely not appose against the wall of bifurcation (50), especially in the ostium of the left circumflex artery (20). In the present study, however, we observed that the bifurcation angle between the left anterior descending and left circumflex arteries was not an independent predictor for adverse events, although there is a weak statistical association with 4-year composite end points in the univariate analysis (HR: 1.99 [95% CI: 0.93 to 4.26], p = 0.07).

Study limitations. This study has several limitations. This is a single center, observational study that included a modest number of patients. The results of this landmark analysis (reporting a higher event rate in patients treated with DES compared with BMS after 2 years) would need to be confirmed in a larger study. In addition, the low 1-year mortality rate compelled us to include only 2 or 3 independent variables in the Cox regression model, resulting in overfitting of the model. Confounding factors, such as procedural variables, might have been overlooked. Although baseline characteristics were similar in the historical BMS and current DES groups, some procedural variables were in fact different and as a result might have influenced outcomes.

Conclusions

Our study reports a late increase in adverse events up to 4 years, which warrants careful follow-up of the patient receiving DES in the LM trunk. The SYNTAX score and EuroSCORE can be considered important components of risk stratification.

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Key Words: coronary disease ■ stents ■ atherosclerosis.

Chapter 10

Three-Dimensional bifurcation angle analysis in patients with left main disease: a substudy of the SYNTAX trial

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3-Dimensional Bifurcation Angle Analysis in Patients With Left Main Disease

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

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Objectives We explore the bifurcation angle (BA) parameters of the left main coronary artery (LM), the effect of percutaneous coronary intervention (PCI) on this angulation, and the impact of BA on clinical outcome.

Background The BA is emerging as a predictor of outcome after PCI of bifurcation lesions. Three-dimensional (3D) quantitative coronary angiography (QCA) overcomes the shortcomings of 2-dimensional analysis and provides reliable data.

Methods This is a substudy of the SYNTAX (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery) trial. The cineangiograms of the 354 patients who underwent PCI of their LM stem were analyzed with 3D QCA software (CardiOp-B, Paieon Medical, Ltd., Rosh Ha'ayin, Israel). The proximal BA (between LM and left circumflex [LCX]) and the distal BA (between left anterior descending and LCX) were computed in end-diastole and end-systole, both before and after PCI. The cumulative major adverse cardiac and cardiovascular event (MACCE) rates throughout the 12-month period after randomization were stratified across pre-PCI distal BA values and compared accordingly.

Results Complete analysis was feasible in 266 (75.1%) patients. Proximal and distal BA had mean pre-PCI end-diastolic values of 105.9 $\pm$ 21.7° and 95.6 $\pm$ 23.6°, respectively, and were inversely correlated ($r = -0.75$, $p < 0.001$). During systolic motion of the heart there was an enlargement of the proximal angle and a reduction of the distal angle (ΔBA $-8.2°$ and 8.5°, respectively, $p < 0.001$ for both). The PCI resulted in a mean decrease in the distal BA (ΔBA 4.5°, $p < 0.001$). The MACCE rates did not differ across distal BA values; freedom from MACCE at 12 months was 82.8%, 85.4%, and 81.1% ($p = 0.74$) for diastolic values (first through third tertile).

Conclusions Left main BA analysis with 3D QCA is feasible. Both proximal and distal angles are affected by cardiac motion; PCI modifies the distal angle. There is no clear difference in event rates across pre-PCI distal BA values. (J Am Coll Cardiol Intv 2010;3:41–8)

The optimal treatment of left main coronary artery (LM) disease remains contentious (1,2), with much of the debate focused on the treatment of its distal part (3,4). Despite increasing data on LM interventions (5–8), the importance of anatomical parameters such as the bifurcation angle (BA) has not been fully appreciated (9).

A number of clinical (10–13) and bench (14,15) studies identify the significance of this angle in predicting the immediate procedural success or the long-term outcome. Limitations to previous studies include ambiguity in the definition of the BA and the specific stenting techniques. The most prominent limitation is that almost all relevant clinical studies rely on 2-dimensional (2D) analysis. The LM bifurcation is particularly difficult to image, because of foreshortening and vessel overlap (16); 3-dimensional (3D) quantitative coronary angiography (QCA) overcomes these shortcomings of 2D analysis and might be beneficial in this setting (16–18).

Abbreviations and Acronyms

BA = bifurcation angle

LAD = left anterior descending coronary artery

LCX = left circumflex coronary artery

LM = left main coronary artery

MACCE = major adverse cardiac and cardiovascular events

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

SB = side branch

TLR = target lesion revascularization

3D = 3-dimensional

The purpose of this study was to test the feasibility of assessment of the LM BA with a 3D QCA algorithm, describe the angulation parameters before and after PCI and evaluate their impact on the clinical outcome of the patients.

Methods

Study population. This is a substudy of the SYNTAX (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery) trial (19), which was a prospective, randomized, all-comers clinical trial with the overall goal of assessing the optimum revascularization treatment for patients with *de novo* 3-vessel disease or LM disease (either isolated or in combination with 1-, 2-, or 3-vessel disease). Patients (n = 1,800) suitable for either treatment option were randomized to PCI with polymer-based, paclitaxel-eluting TAXUS Express (Boston Scientific Corp., Natick, Massachusetts) stents or coronary artery bypass graft surgery; they were also stratified according to the presence or absence of LM disease. For the purpose of this study, we reviewed the cineangiograms of the 354 patients who underwent PCI of the LM stem. Patients with both bifurcation and nonbifurcation LM lesions were included in the study population.

This study was performed in Cardialysis BV (Rotterdam, the Netherlands) as an exploratory analysis and was not subsidized by the official sponsor of the trial, Boston Scientific Corporation. Prior permission was sought and granted by the Steering Committee to access and analyze this dataset.

Analysis method. Three-dimensional reconstruction was performed offline by 2 experienced operators (C.G. and Y.O.), blinded to individual patient data and clinical outcome, with a validated (20) program for 3D QCA (CardiOp-B system version 2.1.0.151, Paieon Medical, Ltd., Rosh Ha'ayin, Israel); the sequence of a single 3D reconstruction has already been amply described elsewhere (21–23). The software algorithm rendered an image as well as quantitative information including BA values; these were derived from images without any guidewires in place, which could modify the angle.

Two angles are presented in accordance with the European Bifurcation Club consensus document (9). Proximal Angle A is defined as the angle between the proximal main vessel and the side branch (SB), whereas distal Angle B is delineated between the distal main vessel and the SB (Fig. 1). By convention the left anterior descending coronary artery (LAD) was designated as the distal main vessel, and the left circumflex (LCX) as the SB. The LM bifurcation was designated as Y-shaped for distal BA values $<70^{\circ}$.

Study design. Three-dimensional reconstructions were performed before and after PCI. To assess the effect of the systolic-diastolic motion on the LM bifurcation angulation, separate 3D images were reconstructed for the end-diastolic and -systolic frames, both before and after the procedure. Systolic-diastolic variation of BA equals the difference of the respective end-diastolic and -systolic values.

Analysis was deemed complete, only if all 4 of the 3D images that were required were successfully reconstructed; outcome of each individual case study was categorized as partially analyzable or nonanalyzable, in cases where <4 or no images at all, respectively, were obtained.

The primary clinical end point of the trial was a composite of major adverse cardiac and cardiovascular events (MACCE) (death from any cause, stroke, myocardial infarction, or repeat revascularization) throughout the 12-month period after randomization.

Statistical analysis. Statistical analysis was performed with SPSS version 16.0 for Windows (SPSS, Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). Continuous variables are expressed as mean ± 1 SD and compared between groups by unpaired Student *t* test; paired *t* test was employed for within-group comparisons. Categorical variables are expressed as counts and/or percentages. Correlations between continuous variables were performed with the Pearson coefficient. Cumulative survival free of adverse events was calculated according to the Kaplan-Meier method and compared across the median and the tertile values of pre-PCI distal BA with the log-rank test. All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

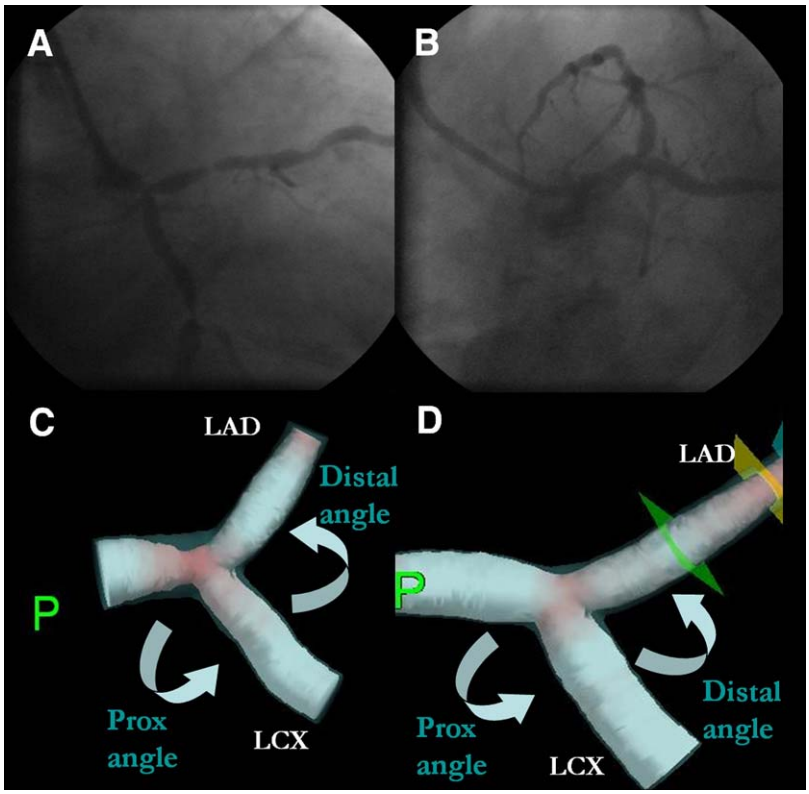

Figure 1. 3D BA Analysis

Two 2-dimensional single-plane angiographic images displaying the left main coronary artery (LM) bifurcation, one filmed in a right anterior oblique caudal view **(A)** and one in a left anterior oblique caudal view **(B)**, are post-processed; the 3-dimensional (3D) reconstructed image **(C)** is created. The proximal angle is defined between the LM stem and the left circumflex (LCX); the distal angle is defined between the left anterior descending (LAD) and LCX. After percutaneous coronary intervention **(D)** the proximal bifurcation angle (BA) is enlarged, whereas the distal BA gets narrower (CardiOp-B, Paieon Medical, Ltd., Rosh Ha'ayin, Israel).

Results

Complete 3D QCA analysis was feasible in 266 (75.1%) patients. The baseline demographic data and clinical characteristics of these patients are reported in Table 1. Total SYNTAX score (24) measured 29.9 ± 13.2. Stents were placed across the LM bifurcation in 185 cases; 1 stent was used in 75 cases, whereas ≥2 stents were used in 110 cases. Only 8.8% of all patients had isolated LM disease without additional diseased vessels.

Feasibility of analysis with 3D QCA. Beyond the 266 cases completely analyzed, another 88 could be analyzed either partly or not at all (48 and 40 cases, respectively). Less than complete analysis was attributable to 3 main reasons: 1) inadequate cineangiography and difficult anatomy in 42 cases; these cases displayed overlap and/or tortuosity of the branch vessels, particularly in their proximal segments; appropriate demarcation of the bifurcation was also compromised by a very short LM stem or a very small LCX (<1.5 mm); 2) failure to record 2 separate angiographic projections in 23 cases; in most of them, the final result of the procedure was filmed in a single projection, usually the operator's working view; and 3) 23 studies could not be processed with the 3D QCA software, mostly due to digitization in a non-DICOM (Digital Imaging and Communications in Medicine) format.

Baseline descriptives of LM BA. In the completely analyzable cohort (n = 266), distal and proximal BA had mean pre-PCI end-diastolic values of 95.6° ± 23.6° and 105.9° ± 21.7°, respectively. Distal and proximal BA values were inversely correlated ($r = -0.75$, $p < 0.001$), followed a normal distribution, and ranged from 44° to 165° and from 54° to 168°, respectively.

Effects of cardiac motion. End-systolic mean values of distal and proximal BA were 87.1° ± 22.9° and 114.0° ± 19.6°, respectively; there was a statistically significant effect of systolic motion on both parameters, a mean decrease of 8.5° ($p < 0.001$) for the distal BA, and a mean increase of 8.2° ($p < 0.001$) for the proximal BA. A similar effect was seen with post-procedural values, at the same level of statistical significance.

Table 1. Patient Demographic Data and Clinical Characteristics (n = 266)

Age (yrs)	65.2 ± 9.8
Male	73.7
BMI (kg/m^2)	28.2 ± 5.0
Diabetes mellitus	23.7
Insulin-requiring	6.0
Noninsulin-requiring	17.7
Hypertension	68.6*
Hyperlipidemia	80.5
Current smoker	20.3
Prior myocardial infarction	27.2
Unstable angina	29.7
Revascularization priority	
Emergent	3.0
Urgent	7.1
Elective	89.9
Additive EuroSCORE	3.8 ± 2.8
Total Parsonnet score	8.7 ± 7.6

Values are mean ± SD or %. *Data available in 264 patients.
BMI = body mass index; equals weight in kilograms divided by the square of the height in meters.

Effects of PCI on angulation. The effects of PCI on BA are summarized in Table 2. A PCI conferred a significant mean decrease in the distal BA (ΔBA = 4.5°, p < 0.001) (Fig. 2), whereas the proximal BA increased by a mean of 2.0° (p = 0.064). However, studying the Y-shaped LM bifurcations (13.9%) separately, the opposite phenomenon was apparent; distal BA increased after PCI by a mean of 10.3° (p = 0.001) and proximal BA decreased by 5.5° (p = 0.056). There was substantial individual variation for each angiographic study. PCI had equivalent impact on the end-systolic BA values.

Impact of BA on outcome. Outcome data to 12 months stratified and compared across pre-PCI distal BA tertiles is reported in Table 3. Freedom from MACCE was not significantly different whether diastolic or systolic values were analyzed; respective tertiles were <82°, 82° to 106°, and >107° and <77°, 77° to 96°, and >97°. Analysis with the median values (96° and 86°, respectively) as cutoff had a similar result.

Similar analysis of the subgroups where 1 stent or ≥2 stents were used in the LM bifurcation did not produce any significant differences between tertiles either (Fig. 3).

Discussion

The main findings of this study are: 1) 3D BA analysis seems feasible, even in this demanding angiographic setting; 2) there is a large variation in the angulation parameters of the LM; 3) cardiac motion modifies the bifurcation angulation; systolic motion results in a reduction of the distal and an enlargement of the proximal BA; 4) PCI treatment modifies the distal BA; overall, angles get narrower after PCI, whereas Y-shaped LM bifurcations increase their distal BA after the procedure; and 5) MACCE rates throughout 12 months after randomization did not differ across pre-PCI distal BA values.

The European Bifurcation Club has consistently been advocating the importance of BA measurements for the prediction of procedural outcome (9,25). The unique nature of the LM bifurcation requires the greatest possible accuracy in measurements, provided by 3D QCA algorithms (16–18).

Feasibility and advantages of 3D analysis. Inadequate cineangiography and difficult anatomy were the main reasons for less than optimal analysis in our study. Vessel overlap and foreshortening are well-known pitfalls of 2D analysis; resorting to operator expertise is not always the answer for acquiring the optimal projections (26). In the last 10 years evidence has accumulated that 3D angiographic reconstruction is accurate, sensitive, and reproducible (17,18,20,27–30) with a high degree of correlation for BA measurements in phantom studies (18). Reduced time requirements for a single 3D reconstruction (<60 s) with real-time analysis facilitate the choice of optimal gantry positions. Thus, we believe that, in a prospective study where operators are obtaining cineangiograms with the view to perform this kind of analysis, the number of non-analyzable cases could be limited to <10%.

Baseline angulation parameters of the LM. Upon review of relevant published reports, there is a single 2D-based angiographic study by Chen et al. (12) reporting on the BA in 37 LM patients submitted to crush stenting; distal BA had a mean value of 76° ± 24° and came up as an independent predictor of target lesion revascularization (TLR).

Three recent multislice computer tomography studies provide more than conventional angiographic data. Kawasaki et al. (31) studied the angles of the LM bifurcation in 209 patients and calculated a mean value of 72° for the distal LM angle. Pflederer et al. (32) reported an average value of 80° ± 27° for the angle between LAD and LCX, and Rodriguez-Granillo et al. (33) reported a median distal LM BA of 88.5° with an interquartile range of 68.8° to

Table 2. Pre- Versus Post-PCI Angulation Parameters (n = 266)

	Pre-PCI	Post-PCI	p Value*
Diastolic proximal BA, °	105.9 ± 21.7	107.9 ± 21.4	0.064
Systolic proximal BA, °	114.0 ± 19.6	114.5 ± 18.6	0.621
SDV-proximal BA, °	8.2 ± 13.2	6.7 ± 12.3	0.118
Diastolic distal BA, °	95.6 ± 23.6	91.1 ± 22.0	<0.001
Systolic distal BA, °	87.1 ± 22.9	83.0 ± 20.8	<0.001
SDV-distal BA, °	8.5 ± 12.5	8.1 ± 12.7	0.670

*Paired *t* test, 2-sided, p significant <0.05.
BA = bifurcation angle; PCI = Percutaneous coronary intervention, SDV = systolic-diastolic variation.

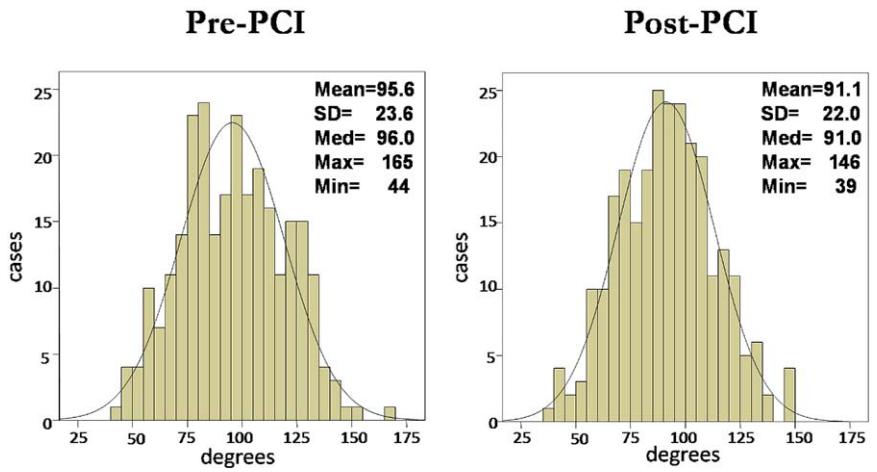

Figure 2. BA Values Distribution

Histograms of end-diastolic distal bifurcation angle (BA) values before and after percutaneous coronary intervention (PCI) with superimposed normal curves; values are in degrees. Post-PCI mean values are significantly decreased ($p < 0.001$). Descriptive statistics (mean ± SD, median, maximum, and minimum) are provided as well.

101.4°. An important finding of this study was that the more diseased individual vessels were, the wider the BA was.

Our study was based on 354 patients submitted to PCI of the LM stem; notwithstanding the increased mean distal BA values, the variation of our findings is comparable to previous studies. As a matter of fact, Kawasaki measured the angle complementary to the proximal BA, which is by definition narrower than the angle between the 3D reconstructed centerlines of the distal vessels, the one measured in our study.

Systolic-diastolic variation of BA values. The enlargement of the proximal BA and the reduction of the distal BA during systolic motion of the heart is a novel finding unaccounted for in the published data, possibly because deemed trivial or obvious. However, we feel that, from a methodological point of view, authors should define what BA values they are reporting on, because of their significant systolic-diastolic variation.

Table 3. Freedom From MACCE Across Pre-PCI Distal BA Tertiles (n = 266)

	1st Tertile	2nd Tertile	3rd Tertile	p Value*
Diastolic BA				
30 days	95.4%	95.5%	94.4%	
6 months	90.8%	89.9%	86.7%	
12 months	82.8%	85.4%	81.1%	0.74
Systolic BA				
30 days	95.4%	96.6%	93.4%	
6 months	89.7%	89.8%	87.9%	
12 months	80.5%	84.1%	84.6%	0.77

*Log-rank test between groups, p significant <0.05.

BA = bifurcation angle; MACCE = major adverse cardiac and cardiovascular events; PCI = percutaneous coronary intervention.

Impact of PCI on the angulation. Louvard et al. (34) reported that even the temporary insertion of an angioplasty guidewire is sufficient for the BA to be considerably modified. This leads us to believe that the permanent implantation of 1 or even 2 rigid metallic structures across the bifurcation would modify the angulation.

Another debatable issue is the extent and the direction of modification of the angulation parameters. As evidenced by our data, the distal BA is the primary variable modified. It seems that, overall, angles are decreased, whereas the narrowest pre-PCI angles are increased. Dvir et al. (35), with CardiOp-B software, have recently reported on the impact of PCI on the distal BA in 27 patients. Apart from provisional stenting, where the angle was not modified, every other technique or anatomy has resulted in a decrease in distal BA. Di Mario et al. (36) has also reported on single and double stent techniques and the change conferred, if any, on the BA. This was a subgroup analysis of the TRUE (TAXUS in real life usage evaluation) registry, comprising 1,069 patients and 191 bifurcations. Double stent techniques, particularly Culotte and Crush, significantly decreased the distal BA, whereas implantation of a single stent induced a nonsignificant increase. In a similar report from Kaplan et al. (37), distal BA was actually increased after T stenting yet by a modest 2°; in regard to Culotte, previous findings were reproduced.

Impact of BA on outcome. The impact of BA on immediate procedural success or long-term outcome is discussed in many studies. Dzavik et al. (10) identified high BA as an

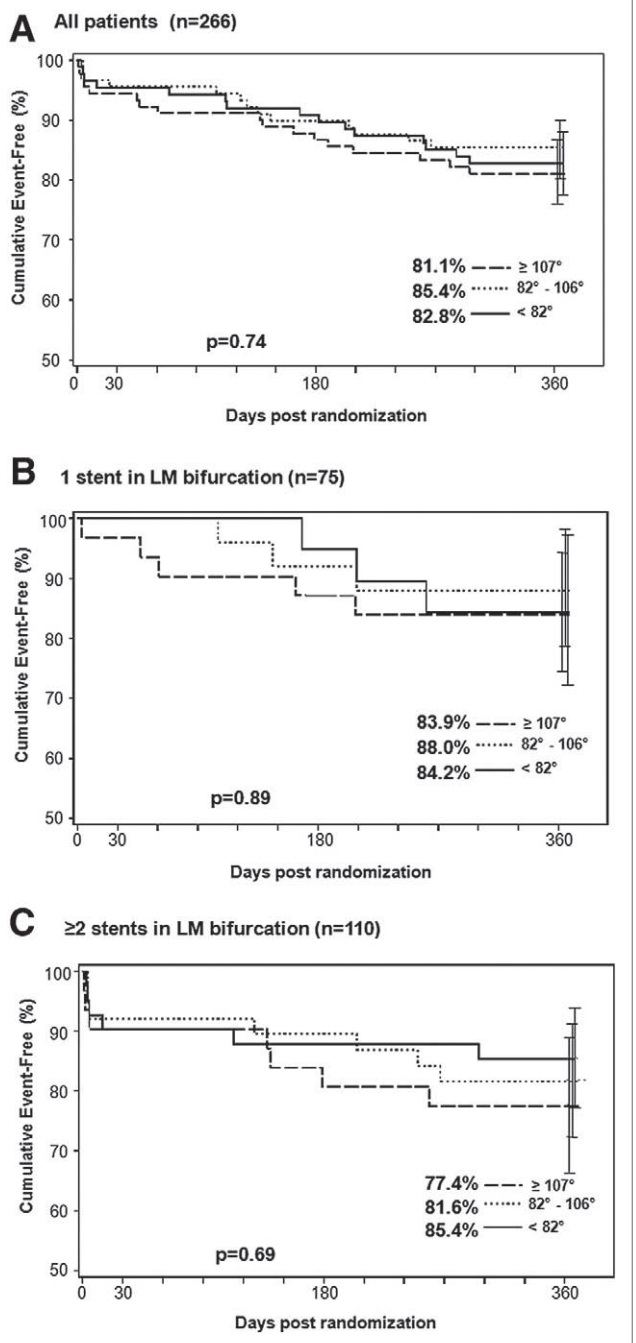

Figure 3. Freedom From MACCE to 12 Months Across Diastolic Pre-PCI Distal BA Values

Kaplan-Meier curves are shown for the entire analyzable cohort (n = 266) **(A)**, the subgroup of patients with 1 stent in the left main (LM) bifurcation (n = 75) **(B)**, and the subgroup of patients with ≥2 stents in the LM bifurcation (n = 110) **(C)**. No significant difference is calculated in any of the panels. Tertile values for diastolic distal bifurcation angle (BA) are reported. The **I bars** indicate 1.5 SE. The p values were calculated with the log-rank test. MACCE = major adverse cardiac and cardiovascular events.

independent predictor of increased major adverse cardiac events at 12 months after crush stenting of bifurcation lesions; this was not the case after main vessel stenting only (11). The study by Chen et al. (12) linked increased TLR rates to higher distal BA values in an LM cohort, whereas an association between high BA values and high restenosis rates has also been verified by Adriaenssens et al. (13) in the context of Culotte stenting, albeit excluding LM cases. However, neither Di Mario et al. (36) nor Kaplan (37) has found in their respective studies evidence that would support this hypothesis; Di Mario et al. (36), like Adriaenssens et al. (13), excluded LM cases from his study.

Ormiston et al. (14) and Murasato (15) have already proven in their bench studies that, in the context of crush stenting, a steep proximal angle and hence a larger distal angle are associated with less optimal expansion and apposition of the SB stent, especially at the site of the ostium.

In contrast, theoretical considerations lead to the conclusion that the outcome of either Crush or Culotte technique would have been adversely influenced by a narrower distal angle; this would be attributable to a more probable carina shift limiting the diameter of the SB ostium in Crush (38) and to an increased stent cell size necessary to span an oblique ostium in Culotte (39). Consequently we are led to speculate that added factors come into play to determine the long-term outcome, such as fluid biomechanics. High and low shear stress areas are supposed to exist in close proximity in steeply angulated bifurcations, thus promoting platelet activation and stasis; Dzavik et al. (10) postulate that an excess of metal in such an area would only aggravate these phenomena, possibly leading to increased rates of thrombosis and restenosis.

Our study did not corroborate the findings of several of the studies referenced. Only when separately studying the cases where ≥2 stents were implanted in the LM bifurcation was there a trend toward lower event rates for the patients with narrower diastolic pre-PCI distal BA values. However, the strength of our study consists in the very fact that the analysts were totally unaware of individual patient data and clinical outcome; thus, this could be considered as a double-blind approach. Moreover, this is the first study correlating 3D QCA-derived angulation data to long-term MACCE; superior assessment of the anatomical changes conferred by PCI will potentially unravel the interplay between geometry and clinical outcome.

Study limitations. This study was performed as an exploratory analysis blinded to individual patient data, treatment, and clinical outcome. Because analysis was independent from the Case Report Form, no relevant subgroup analysis could be performed. Consequently we also could not establish whether the systolic heart motion effect universally outweighs the relevant PCI effect. Moreover, the limited number of events precluded any detailed analysis of MACCE components and increased the probability of a

type II error. A post-hoc calculation revealed a diminished power of either overall or subgroup analysis (not >30% at a significance level of 0.05).

Angulation parameters could not be determined in 25% of patients in the study group; exclusion of one-half of these studies was ascribed to difficult anatomy and inadequate cineangiography, a major confounder being a narrow distal BA. This might have ultimately induced a bias for higher mean distal BA values. However, this was a retrospective post hoc analysis; had the angulation parameters been calculated prospectively and online, a higher rate of complete analysis could have been anticipated.

Conclusions

Three-dimensional BA analysis for the LM, before and after PCI, is feasible; LM angulation parameters vary considerably. Cardiac motion exerts a reciprocal effect on proximal and distal BA, the former being increased and the latter decreased during systole. A PCI modifies the distal BA; overall, angles are decreased, whereas the narrowest pre-PCI angles are actually increased after the procedure. Cumulative event rates throughout the first 12 months after randomization did not differ significantly, when compared across pre-PCI distal BA values. The potential long-term predictive value of these parameters and their prospective applicability during PCI merit further inquiry.

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

Chapter 11

Impact of 3-dimensional bifurcation angle on 5-year outcome of patients after percutaneous coronary intervention for left main coronary artery disease: a substudy of the SYNTAX trial

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

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

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

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

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

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

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

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

See page 1261

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

Methods

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

Abbreviations and Acronyms

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

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

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

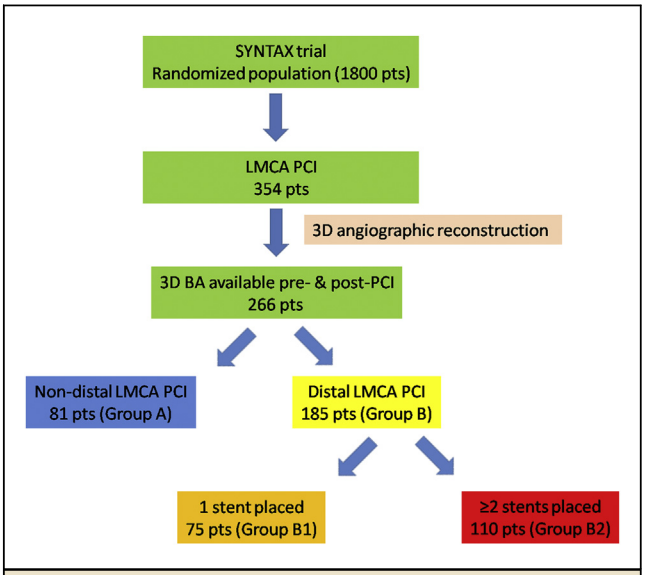

Figure 1. Flow Diagram Indicating the Entire Study Population Synthesis and Subgroups

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 3. BA Variables for Patients With LMCA Bifurcation PCI

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

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

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

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

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

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

Discussion

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

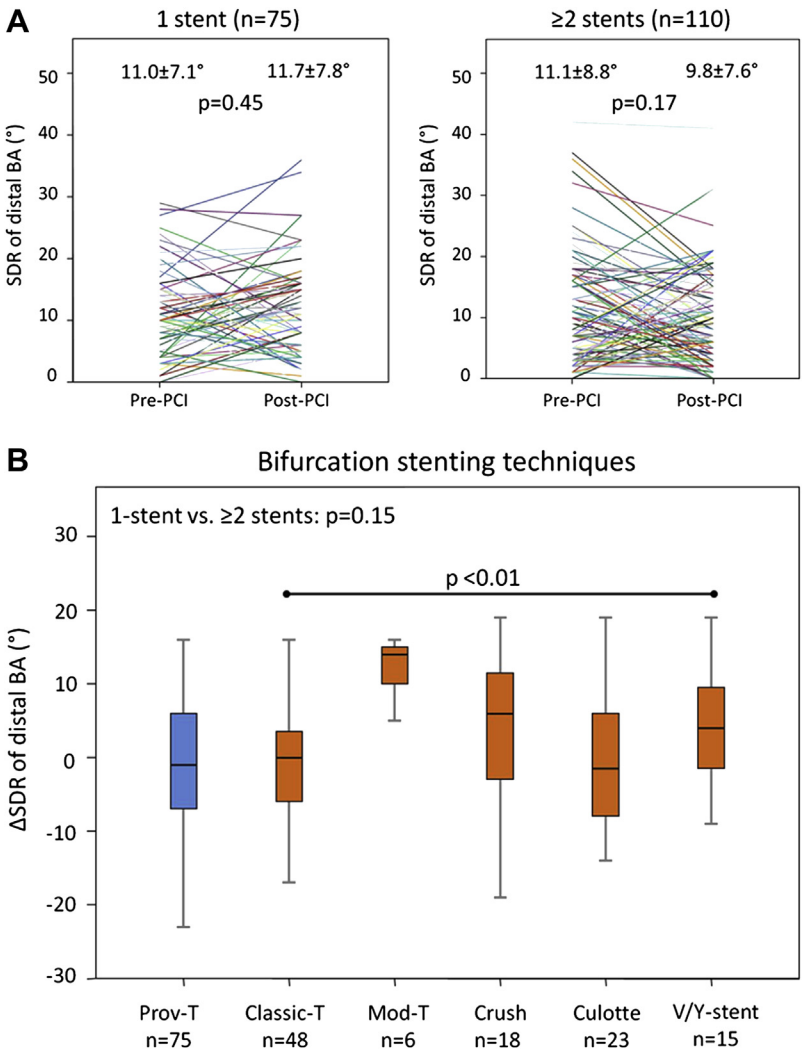

Figure 2. Effect of Bifurcation Stenting on the SDR of the Distal BA

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

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

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

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

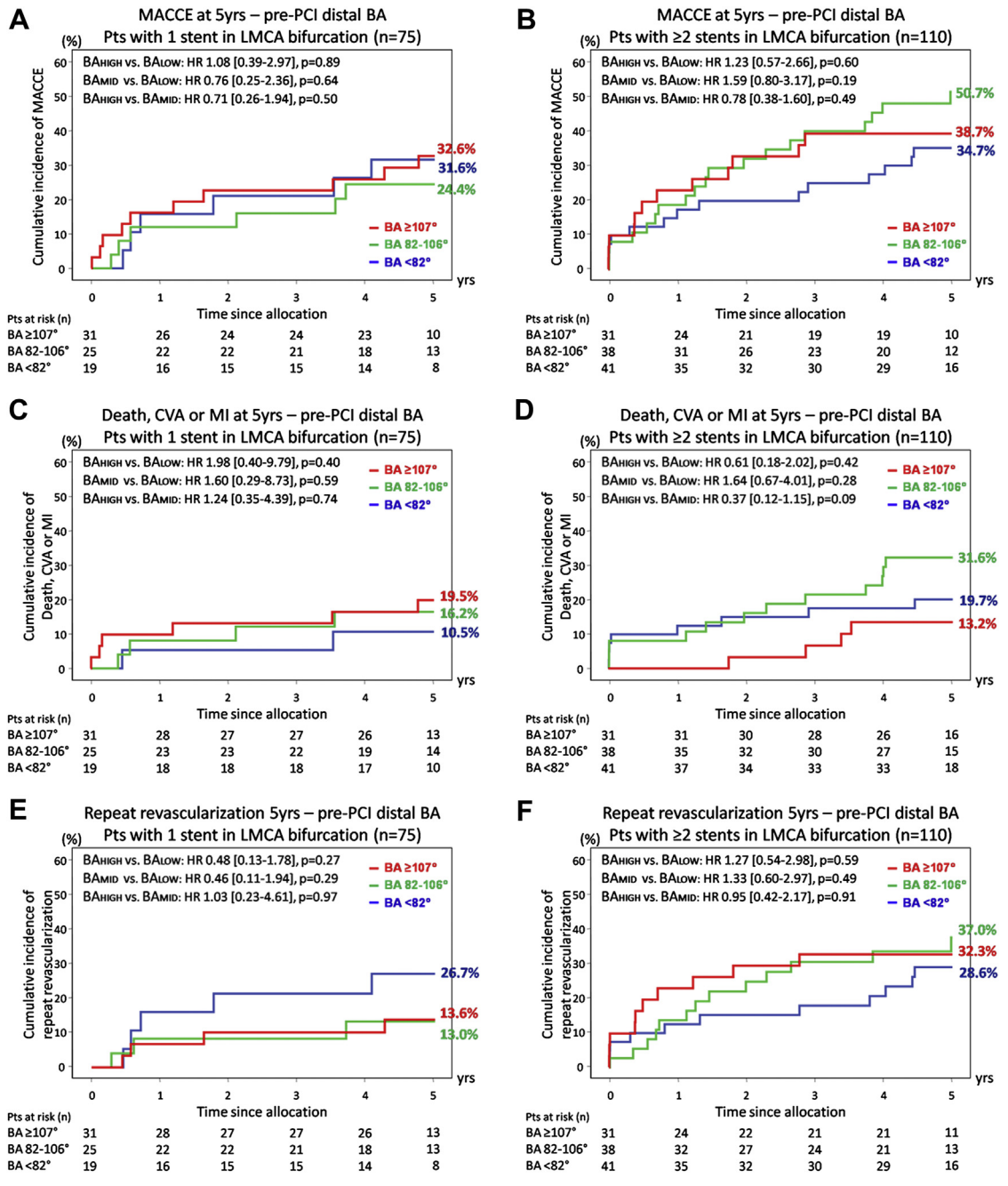

Figure 3. Impact of Pre-PCI Diastolic Distal BA on 5-Year MACCE, All-Cause Death, CVA, or MI (Safety Endpoint), and Repeat Revascularization

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

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

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

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

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

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

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

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

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

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

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

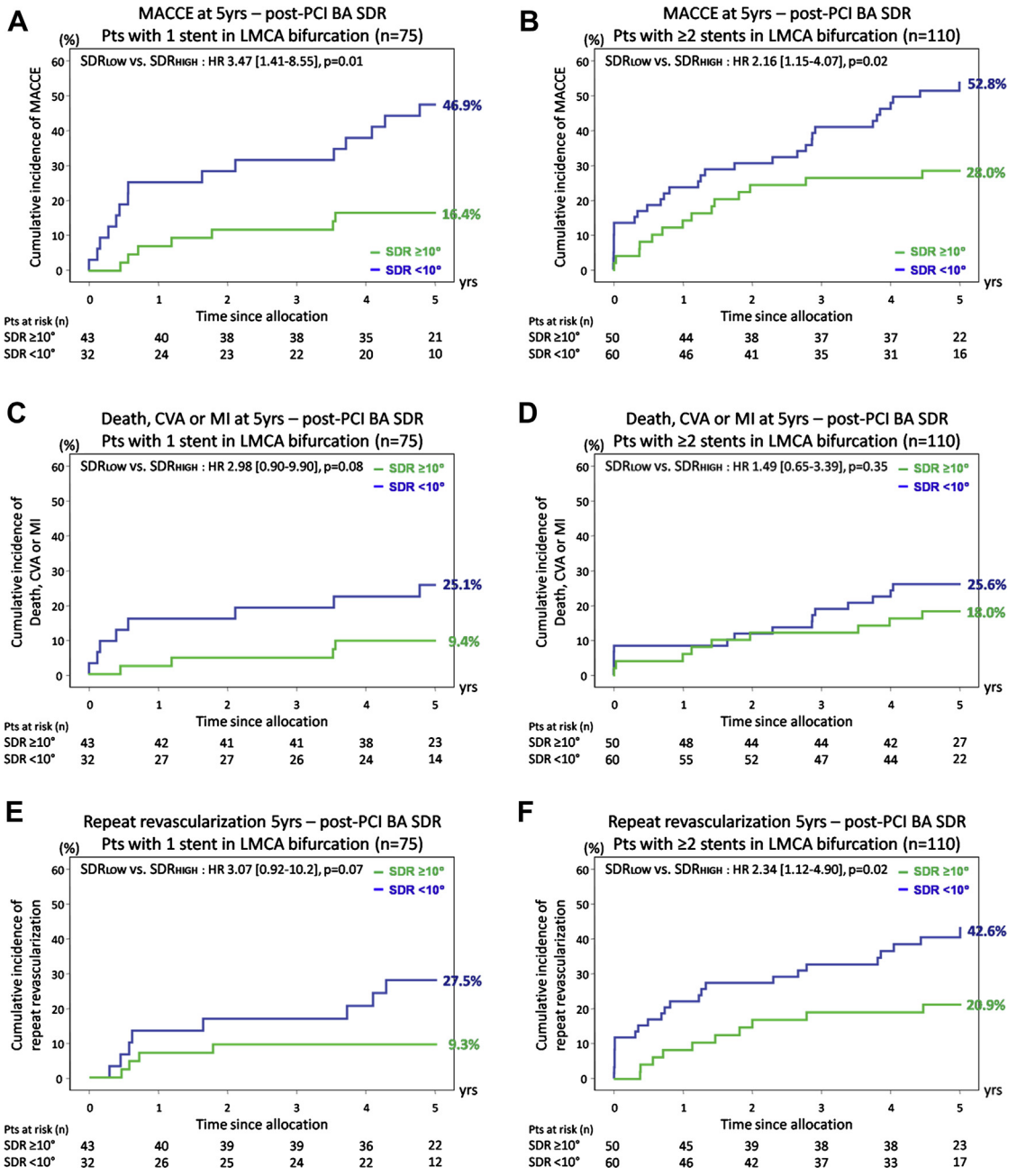

Figure 4. Impact of Post-PCI SDR of the Distal BA on 5-Year MACCE, All-Cause Death, CVA, or MI (Safety Endpoint), and Repeat Revascularization

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

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

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

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

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

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

Conclusions

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

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

Chapter 12

Acute procedural and six-month clinical outcome in patients treated with a dedicated bifurcation stent for left main stem disease: the TRYTON LM multicentre registry

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Acute procedural and six-month clinical outcome in patients treated with a dedicated bifurcation stent for left main stem disease: the TRYTON LM multicentre registry

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KEYWORDS

- 3-D quantitative coronary angiography
- dedicated bifurcation stents
- left main stem bifurcation
- procedural success
- six-month MACE

Abstract

Aims: Tryton side branch (SB) reverse culotte stenting has been employed for the treatment of left main (LM) stem bifurcations in patients at high risk for bypass surgery. The aim of this study was to assess acute angiographic results and six-month clinical outcome after implantation of the Tryton stent in the LM.

Methods and results: We studied 52 consecutive patients with LM disease treated in nine European centres. Angiographic and clinical data analysis was performed centrally. Fifty-one of 52 patients (age 68±11 yrs, 75% male, 42% unstable angina, SYNTAX score 20±8) were successfully treated with the Tryton stent. Medina class was 1,1,1 in 33 (63%), 1,0,1 in 7 (13%), 1,1,0 in 3 (6%), 0,1,1 in 8 (4%) and 0,0,1 in 1 (2%). The Tryton stent on a stepped balloon (diameter 3.5-2.5 mm) was used in 41/51 (80%) of cases. The mean main vessel stent diameter was 3.4±0.4 mm with an everolimus-eluting stent employed in 30/51 (59%) of cases. Final kissing balloon dilatation was performed in 48/51 (94%). Acute gain was 1.52±0.86 mm in the LM and 0.92±0.47 mm in the SB. The angiographic success rate was 100%; the procedural success rate reached 94%. Periprocedural MI occurred in three patients. At six-month follow-up, the TLR rate was 12%, MI 10% and cardiac death 2%. The hierarchical MACE rate at six months was 22%. No cases of definite stent thrombosis occurred.

Conclusions: The use of the Tryton stent for treatment of LM bifurcation disease in combination with a conventional drug-eluting stent is feasible and achieves an optimal angiographic result. Safety of the procedure and six-month outcome are acceptable in this high-risk lesion PCI. Further safety and efficacy studies with long-term outcome assessment of this strategy are warranted.

Introduction

Stenting of the left main (LM) stem is increasingly recognised as a valid revascularisation strategy in patients with significant disease involving this important segment of the coronary tree. Although coronary artery bypass surgery (CABG) is considered a superior treatment option for LM disease, some patient subgroups may still benefit from revascularisation by PCI. Randomised trials of LM PCI versus CABG have repeatedly revealed target vessel revascularisation (TVR) as the Achilles heel of the former[1]. However, recent studies have shown that patients with less diffuse coronary disease in low SYNTAX score tertiles have comparable outcomes with PCI and CABG[2]. Having secured at least a similar safety profile, PCI of LM stenosis has been upgraded to a class IIa or IIb indication in the current European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American College of Cardiology/American Heart Association practice guidelines[3,4].

Not all LM lesions have similar outcomes and, in fact, involvement of the LM bifurcation is associated with suboptimal short-term and long-term results when conventional stents are employed. Poor angiographic results are often obtained with the use of a provisional stenting technique in cases where the side branch (SB) is significantly diseased. Refinement of interventional techniques and the introduction of dedicated devices may improve the outcome of LM PCI. The use of a dedicated bifurcation stent – the Tryton side branch stent in conjunction with a conventional stent in a "reverse culotte" technique – facilitates stenting and may potentially improve angiographic results and clinical outcome in patients who undergo LM bifurcation intervention. Indeed, use of this dedicated stent has been increasing in the "real world" even in "off-label" anatomic locations, including the LM bifurcation[5].

The aim of the present study was to assess the acute angiographic outcome of LM bifurcation treatment with the Tryton stent (Tryton Medical, Inc., Durham, NC, USA) in conjunction with a conventional stent. The acute and mid-term clinical outcome up to six months was also investigated.

Methods

The Tryton LM registry was established by retrospective inclusion of patients treated in nine European centres by very experienced operators. Procedural and clinical data of all consecutive patients in whom treatment of the LM with a Tryton stent was attempted were collected on a purposely designed electronic case report form (CRF), which was sent to the investigators. The investigators at each centre (see authors) were responsible for filling in the forms and vouch for the integrity of the data provided centrally for analysis. Angiography films of the procedures and follow-up angiograms (when available) were collected centrally and analysed by three experienced interventional cardiologists (MM, CG, RJvG).

In this report, we present the data of the first 52 patients with LM bifurcation disease in whom the operators intended to use the Tryton stenting technique. The inclusion period spanned May 2008 to October 2011.

Prespecified primary endpoints of the study included acute gain in the three segments of the bifurcation as measured by quantitative coronary angiography (QCA) as well as procedural and six-month clinical outcome in terms of major adverse cardiac events (MACE).

Patient population

Patients included were selected by the operators and, whenever feasible, after case discussion by a heart team. In general, patients were either unfit for surgery, had previous bypass surgery, had isolated LM with low SYNTAX scores or presented as an emergency. The size of the Tryton stent available at the time of patient enrolment limited the range of vessel sizes that could be treated. The visually estimated reference diameter of the main vessel (MV) could be 2.5-5.0 mm and that of the SB in the range 2.5-2.75 mm. Also, the LM had to be ≥7 mm in length to allow an adequate landing zone of the proximal part of the stent. However, the decision to treat the bifurcation and employ a Tryton stent remained at the discretion of the treating interventional cardiologist.

Device description and deployment sequence

The Tryton stent is a balloon-expandable cobalt chromium stent with strut thickness of 84 µm. The stent is available in one standard length of 19 mm and has three distinct zones: a distal SB zone, which is 6.5 mm long, a central transition zone 4.5 mm in length, and a proximal MV zone of 8 mm. The distal zone has a standard slotted tube workhorse stent design; the central transition zone consists of three panels, while the proximal MV zone is composed of three fronds that terminate proximally in two circumferential bands (only one in the first-generation device). The stent is mounted either on a balloon with uniform diameter (straight type) or on a stepped balloon (tapered type). Stent sizes (proximal-distal) available during the study period were 2.5-2.5; 3.0-2.5; 3.5-2.5 and 3.5-3.0. The stent delivery system has four markers to delineate the proximal and distal ends of the stent as well as the proximal and distal parts of the transition zone. After optional wiring of both MV and SB for predilation, the Tryton stent is advanced over the wire into the SB and is positioned with the guidance of the two middle markers which should straddle the carina. Deployment of the stent is followed by retraction of the guidewire from the SB and repositioning it through the fronds of the transition zone into the distal MV. A standard stent is then advanced, positioned, and deployed in the MV, jailing the stented SB. Proximal optimisation technique can be employed at this time by inflating a balloon the size of the proximal MV with the distal marker at the ostium of the SB. This may facilitate wire recross into the SB for final kissing balloon (FKB) dilation. A case example is presented in **Figure 1**. Further details of the Tryton stent and deployment procedure have been described in detail elsewhere[6].

Procedure

Patients were pretreated with aspirin and clopidogrel. Intravenous heparin was administered to maintain an activated clotting time of >250 seconds. Glycoprotein IIb/IIIa inhibitor use was left to the discretion of the treating interventional cardiologist. Delivery

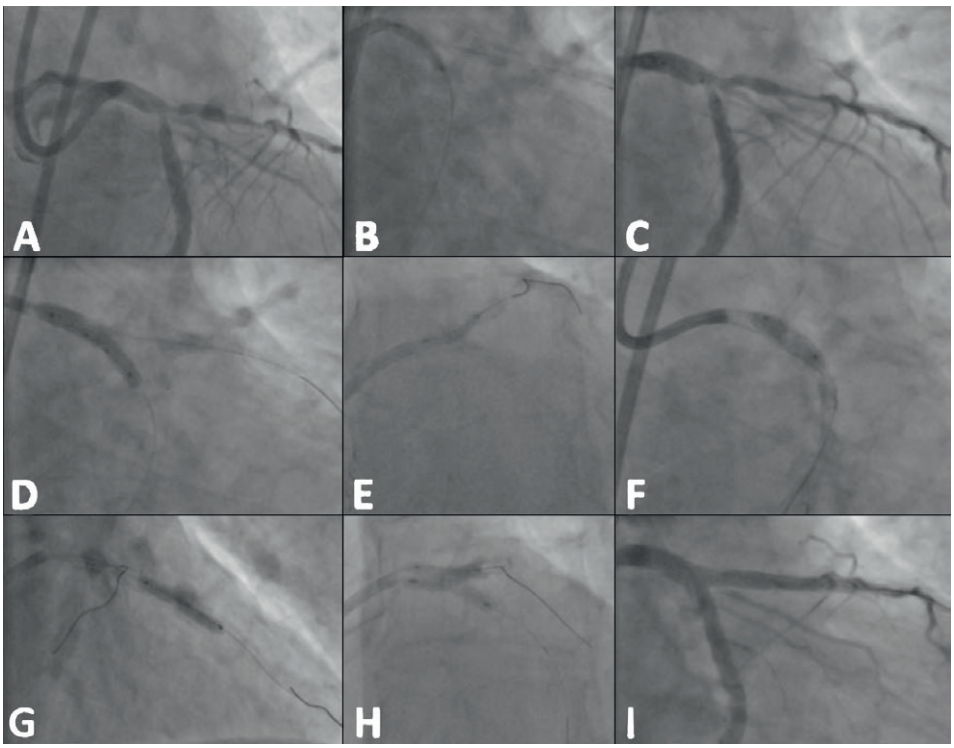

Figure 1. *Implantation sequence of the Tryton stent in the left main stem bifurcation. This 78-year-old man was deemed high risk for surgery when he presented with unstable angina pectoris. The left main (LM) stem showed a Medina class 1,1,1 bifurcation lesion and further disease in segment 6 (A). The left anterior descending (LAD) and left circumflex (LCx) coronary arteries were wired and the latter was predilated with a 2.5 mm balloon (B). A 3.5-2.5×19 mm Tryton stent was positioned with the middle markers straddling the carina (C) and subsequently implanted by inflating the stepped balloon (D). The LCx wire was then retracted to the point of bifurcation and redirected into the LAD. After removal of the jailed first LAD wire, the LAD was predilated with a balloon (E) and a 3.5×18 mm XIENCE PRIME™ stent (Abbott Vascular, Redwood City, CA, USA) was placed along the LAD and across the LCx (F). After implantation of the stent, a second overlapping stent was used to treat the stenosis in segment 6 (G). The LCx was then rewired and final kissing balloon inflations were performed (H) with a good angiographic result (I).*

failures, need for additional overlapping stents to cover the whole lesion, additional balloon dilation and procedural angiographic and clinical complications were noted. Aspirin was prescribed indefinitely while clopidogrel was prescribed for at least 12 months after the index procedure.

Clinical follow-up

In-hospital events were recorded in the patient's clinical notes. Clinical follow-up was obtained by clinical visits or phone interview during which data on hospital readmission and MACE were collected. Medical records, discharge summaries and any repeat angiography films of patients with suspected events were systematically reviewed and adjudicated by local cardiologists according to established criteria defined below.

Definitions

Device success was defined as successful deployment of the intended stent without system failure. Angiographic success was defined as <30% residual stenosis and TIMI 3 flow in both MV and SB after the procedure. Procedure success included angiographic success in the absence of in-hospital MACE, defined as a composite of cardiac death, myocardial infarction (MI) and ischaemia-driven TVR. MI was defined as clinical signs of acute ischaemia, associated with a CK-MB mass or troponin-T/troponin-I increase to ≥3 times the upper limit of normal and corresponding changes on a 12-lead electrocardiogram (ECG). TVR was defined as revascularisation of any part of the index coronary artery. Definite stent thrombosis was defined according to the Academic Research Consortium (ARC) definitions[7].

Angiographic analysis

QUANTITATIVE CORONARY ANGIOGRAPHY

QCA was performed with the Cardiovascular Angiography Analysis System (CAAS; Pie Medical Imaging, Maastricht, The Netherlands) version 5.10, by experienced analysts blinded to the clinical data. All available studies were analysed with a dedicated 2-D bifurcation QCA algorithm, using matched projections, pre- and post-procedure, and end-diastolic frames. The vessel distal to the LM bifurcation where the distal Tryton stent was implanted was defined as the SB, whereas the vessel where the conventional stent was implanted was identified as the distal main vessel (DMV). A device-oriented analysis

was performed, whereby the region of interest around the LM bifurcation was demarcated according to the stent borders as identified on the positioning/implantation cine runs. Specifically, the Tryton stent proximal and distal edges were defined as the proximal border of the proximal main vessel (PMV) and the distal SB border, respectively, whereas the distal DMV border was set at either the distal edge of the DES implanted through the Tryton stent or at the first major SB distal to the LM bifurcation in case of multiple overlapping stents. The minimal lumen diameter (MLD), reference vessel diameter (RVD) and percent diameter stenosis (DS) were quantified for the stented vessel segments and 5 mm peri-stent segments. Respective values for corresponding stent and segment were obtained from the six-segment bifurcation model (segments 1 and 2 for PMV, 3 and 4 for DMV, 5 and 6 for SB)[8]; in addition, quantitative parameters for 3 mm ostial segments were derived from the 11-segment bifurcation model (segment 11 and 8 for DMV and SB, respectively) **(Figure 2** and **Figure 3)**. Reference vessel obstruction analysis was performed with either the automatic (interpolation) method or local reference method (single point for each vessel segment). The second method was mostly reserved for diffusely diseased vessel segments prior to treatment[9]. Finally, proximal and distal bifurcation angle (BA) values were calculated.

In the cases where at least two angiographic images of the LM bifurcation separated by a viewing angle of ≥30° were available for both pre- and post-procedure, a 3-D reconstruction was also performed with a dedicated bifurcation algorithm[10]. Specifically, 2-D analysis was performed first using the 2-D angiographic image showing the best (optimal) view of the LM bifurcation. After saving the 2-D analysis results (numerical values and graphs) the vessel contours of this optimal view were imported into the 3-D analysis algorithm together with the second 2-D image, which still required contouring following the procedure already described. In the 3-D reconstructed image, segmentation of the region of interest and reporting of angiographic quantitative parameters were analogous with the 2-D analysis; thereby results from 2-D and 3-D analyses were directly comparable.

The depth of implantation of the Tryton stent was measured by QCA using the two middle markers as illustrated in **Figure 4**. The angiography film showing the positioning of the stent prior to implantation was analysed for all but 11 cases in which this was not recorded. The distances between the proximal middle marker and the carina and the distal middle marker and the carina were measured. A difference of ≥1 mm between the two measurements was identified as inappropriate implantation.

SYNTAX SCORE

SYNTAX score was calculated by an experienced analyst as previously described using the programme on the website www.syntaxscore.com[11].

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD or as median (interquartile ranges) whereas dichotomous data are summarised as counts

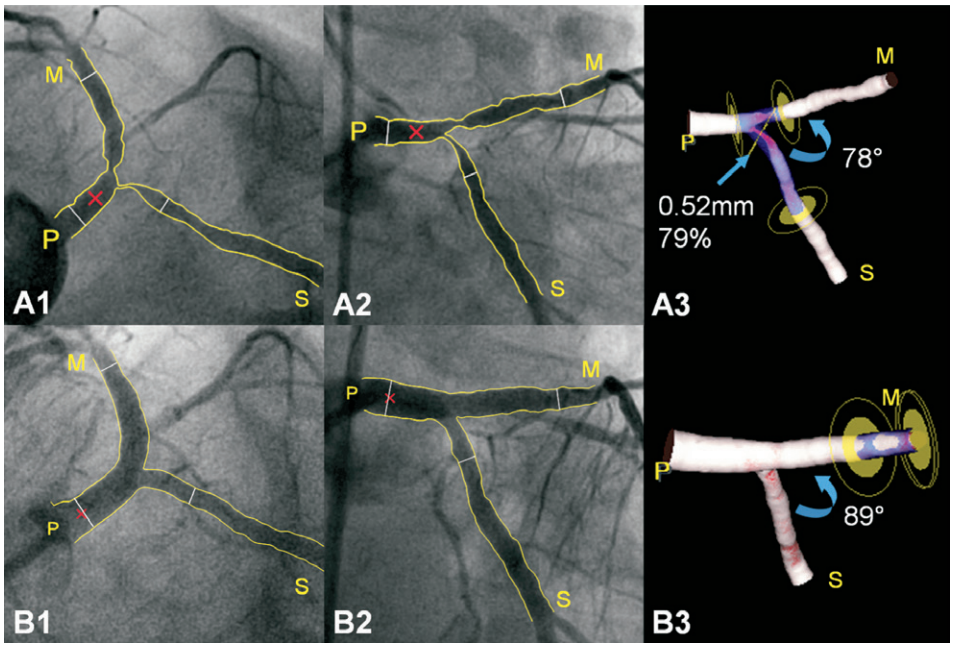

Figure 2. *Three-dimensional reconstruction pre- and post-procedure. A1-A2: A left and a right anterior oblique caudal view of a left main (0,1,1) bifurcation lesion are shown before stent placement; a Tryton stent will be placed from the proximal main vessel (P) into the side branch (S). Thin white lines demarcate the region of interest, whereas the red cross marks the common image point facilitating the 3-D reconstruction (A3); the most severe stenosis is located in the side branch ostium. B1-B3: Respective images post-procedure. Stenosis around the bifurcation is reduced, whereas minor obstruction is now located distal to the drug-eluting stent in the distal main vessel (M); PCI resulted in a slight increase in the 3-D distal bifurcation angle.*

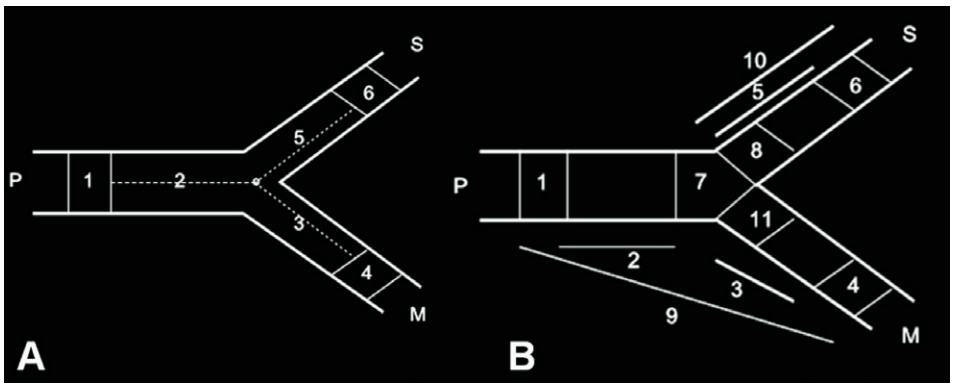

Figure 3. *Bifurcation segment models in the Cardiovascular Angiography Analysis System (CAAS). Segments 2, 3 and 5 in both models reflect the segments where the stents were placed in the proximal main vessel (P), distal main vessel (M) and side branch (S), respectively; segments 1, 4 and 6 are corresponding 5 mm-long peri-stent segments. Segments 8 and 11 in the extended model (B) reflect 3 mm-long ostial segments for the side branch and distal main vessel, respectively.*

and/or percentages. The paired t-test was employed for comparisons of quantitative parameters pre- and post-procedure and between 2-D and 3-D estimates of the same parameters. Statistical analysis was performed using SPSS software version 20 (SPSS, Chicago, IL, USA).

Results

Fifty-two LM bifurcation lesions were included in the TRYTON LM registry between May 2008 and October 2011. **Table 1** shows the baseline characteristics of the study cohort. The mean age of patients was 68.3±10.8 years and 75% were male. Fifty-eight percent of patients presented for PCI with stable angina while 25% presented with a myocardial infarction and 8% were in cardiogenic shock.

Coronary lesion characteristics are summarised in **Table 1**. The average SYNTAX score was 20±8 and 19% of patients had a previous CABG. Five patients had two bifurcation lesions that needed revascularisation. Eighty-five percent of lesions were true bifurcation lesions (1,0,1 or 1,1,1 or 0,1,1) .

The mean reference diameters for the LM stem, DMB and SB were 4.00, 2.63 and 2.48 mm, respectively. The mean DS was 39.5%, 36.2% and 41.8% for LM, DMB and SB, respectively. The mean angle between the LM and the SB was 139.4˚, while that between the DMB and the SB was 78.5˚.

All stents implanted during the procedure except for the Tryton stent were drug-eluting. Failure of delivery of the Tryton stent occurred in one patient despite repeated predilatation of a heavily calcified LM and a very tight lesion of the left circumflex (LCx) coronary artery. Eventually, a conventional drug-eluting stent (DES) was placed with a good angiographic result. For the rest of the cohort, a Tryton stent on a stepped balloon with a diameter of 3.5-2.5 mm was successfully deployed in 41/51 (80%) cases. In 11/51 (22%) cases, the distal zone of the Tryton stent was implanted in the left anterior descending (LAD) coronary artery. Six (55%) of these cases were protected by a left internal mammary artery. For the remaining five (45%), the LCx was larger in diameter than the LAD and the operator chose the latter as the "side branch". The mean MV stent diameter

Table 1. Baseline clinical and angiographic characteristics.

Baseline clinical characteristics	n=52
Age, years	68.3±10.8
Male sex	75% (39)
Hypertension	60% (31)
Diabetes	38% (20)
Hypercholesterolaemia	58% (30)
Current smoker	17% (9)
Family history of coronary artery disease	30% (16)
End stage renal failure	2% (1)
Previous percutaneous coronary intervention	35% (18)
Previous coronary artery bypass surgery	19% (10)
History of myocardial infarction	29% (15)
Clinical presentation	
Stable angina	58% (30)
Unstable angina	17% (9)
ST-segment myocardial infarction	2% (1)
Non-ST-segment myocardial infarction	23% (12)
Cardiogenic shock	8% (4)
Angiographic characteristics	
SYNTAX score	20±8
Left main stem bifurcation	
MEDINA classification	
1,1,1	63% (33)
1,1,0	6% (3)
1,0,1	13% (7)
1,0,0	0% (0)
0,1,1	8% (4)
0,0,1	2% (1)
0,1,0	0% (0)
Functional LIMA on LAD	19% (10)

LAD: left anterior descending coronary artery; LIMA: left internal mammary artery graft

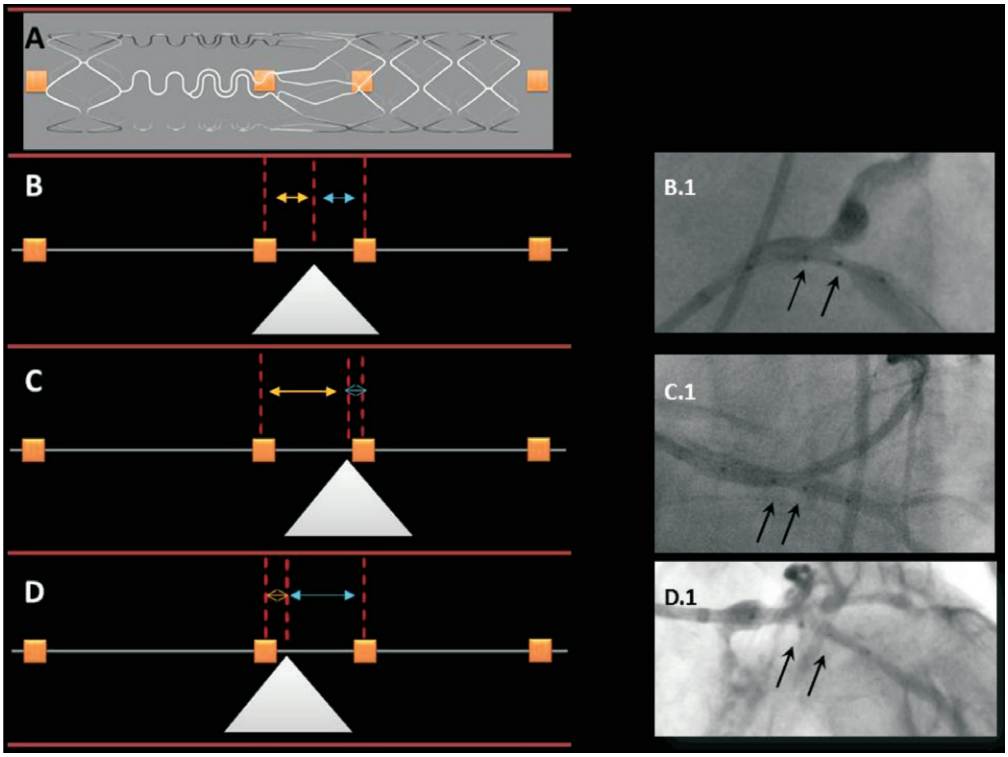

Figure 4. *Depth of implantation assessement. The Tryton stent delivery system has four markers (depicted in orange boxes): the outer markers delineate the proximal and distal ends of the stent, while the two middle markers delineate the transition zone (A). The two middle markers (black arrows on angiographic images) should straddle the carina (white triangle) during implantation. Equal distances between the proximal middle marker (yellow arrow) and the distal middle marker (blue arrow) to a line perpendicular to the carina indicate appropriate implantation depth as exemplified in B and B.1. The implantation in C and C.1 is not deep enough (yellow>blue arrow), while that in D and D.1 is too deep (yellow<blue).*

was 3.4±0.4 mm with an everolimus-eluting stent employed in 30/51 (59%) of cases. FKB dilatation was performed in 48/51 (94%) bifurcation lesions. **Table 2** summarises procedural parameters.

There were no device-related complications except for one delivery failure. Thus, the device success rate was 98%. Angiographic success was achieved in all patients (100%). One patient had a non-flow-limiting dissection in the LAD following deployment of a MV conventional stent that was used in combination with the Tryton stent for treatment of a LAD/diagonal branch bifurcation lesion. The dissection at the proximal edge of the stent was covered by placement of an additional stent and the operator went on to treat the LM bifurcation with a second Tryton stent, achieving a good result. The patient had no evidence of periprocedural infarction. A second patient also had two Tryton stents deployed to treat two bifurcation lesions during the same procedure with a good result. In total, three patients developed periprocedural MI without angiographic complications so that procedural success reached 94%.

Table 2. Procedural characteristics.

Characteristics	
Tryton implanted in LAD	22% (11/51)
Tryton implanted in intermediate artery	2% (1/51)
Main vessel stent size	
Diameter, mm	3.4±0.4
Length, mm	22.9±4.9
Main vessel stent type	
Everolimus-eluting	59% (30/51)
Biolimus-eluting	14% (7/51)
Zotarolimus-eluting	8% (4/51)
Other DES	19% (10/51)
Additional stent in the side branch	15/49 (30%)
Additional stent in the main vessel	13/49 (27%)
Final kissing balloons	94% (48/51)
Device success	51/52 (98%)
Procedural success	49/52 (94%)

DES: drug-eluting stents; LAD: left anterior descending coronary artery

QCA RESULTS

Two-dimensional analysis was performed in 46 cases. The other cases had to be excluded due to inadequate cineangiography either pre- or post-procedure (no clear view of the bifurcation, overlapping vessel segments, presence of angiographic guidewires). Results for diameter-derived parameters for the overall 2-D analysis are shown in **Table 3A**. Acute gain in the LM and in the SB was 1.52±0.86 mm and 0.92±0.47 mm, respectively.

Three-dimensional analysis was feasible in 14 cases and results for diameter-derived parameters are shown in **Table 3B**. On average, two-dimensional BA values were larger as compared to the

3-D ones, both pre- and post-procedure **(Table 4)**. However, the difference was significant for pre-PCI proximal BA values (145.1° vs. 132.4°, p=0.03) only.

From the 46 angiography films analysed with 2-D QCA, the proximal BA changed by ≥5° in 65% (28/43) of cases, while the distal BA changed by more than ≥5° in 74% (32/43) of cases. For the distal BA, most cases with a change showed a narrowing of the angle and this occurred in 54% of the QCA cohort. On the other hand, the proximal BA most commonly widened (40% of cases) or remained the same (35%).

Depth of implantation of the Tryton stent was assessable in 77% (40/52) of cases. Depth was deemed appropriate in 38% (15/40). In 43% (17/40) of those assessed, the implantation was not deep enough, while in 20% (8/40) implantation was too deep. These results are summarised in **Table 5**.

Table 3A. 2-D QCA analysis of left main bifurcation pre- and post-procedure (n=43).

	Pre-procedure			Post-procedure				
	In-stent			In-stent				
	MLD (mm)	RVD (mm)	DS (%)	MLD (mm)	RVD (mm)	DS (%)	Acute gain	*p*-value
PMV	2.42±0.98	4.00±0.77	39.5±20.2	3.94±0.75	4.50±0.82	11.9±9.9	1.52±0.86	<0.0001
DMV	1.67±0.51	2.63±0.43	36.2±17.6	2.75±0.41	3.26±0.43	15.5±8.9	1.07±0.58	<0.0001
SB	1.44±0.51	2.48±0.46	41.8±18.7	2.35±0.39	2.83±0.42	16.6±9.0	0.92±0.47	<0.0001
Tryton stent	1.62±0.78	3.34±0.90	51.7±17.5	2.78±0.86	3.51±1.14	20.1±8.7	1.16±0.97	<0.0001
Ostial DMV	1.91±0.64	2.68±0.43	28.6±19.3	3.06±0.53	3.33±0.42	8.3±9.1	0.87±0.56	<0.0001
Ostial SB	1.58±0.61	2.48±0.44	36.1±21.4	2.46±0.42	2.84±0.42	13.2±9.9	1.15±0.58	<0.0001
	In-segment			In-segment				
	MLD (mm)	RVD (mm)	DS (%)	MLD (mm)	RVD (mm)	DS (%)	Acute gain	*p*-value
PMV	2.42±0.98	4.00±0.77	39.5±20.2	3.86±0.65	4.49±0.82	13.5±8.8	1.43±0.80	<0.0001
DMV	1.65±0.50	2.62±0.43	36.9±16.9	2.52±0.48	3.26±0.45	22.6±10.8	0.87±0.53	<0.0001
SB	1.41±0.51	2.48±0.46	42.8±18.4	2.15±0.44	2.81±0.42	23.6±11.1	0.74±0.52	<0.0001
Tryton stent	1.62±0.78	3.34±0.90	51.7±17.5	2.42±0.83	3.25±1.04	25.6±10.3	0.79±0.99	<0.0001
Ostial DMV	N/A			N/A			N/A	
Ostial SB	N/A			N/A			N/A	

2-D: two-dimensional; DMV: distal main vessel; DS: percent diameter stenosis; MLD: minimal lumen diameter; N/A: non-applicable; PMV: proximal main vessel; QCA: quantitative coronary angiography; RVD: reference vessel diameter; SB: side branch

Table 3B. 2-D and 3-D QCA analysis of left main bifurcation pre- and post-procedure in 3-D analysable cases (n=14).

	Pre-procedure in-stent					
	2-D			3-D		
	MLD	RVD	DS	MLD	RVD	DS
PMV	2.61±1.08	4.05±0.73	36.41±20.72	2.82±0.99	3.83±0.67*	26.55±20.75**
DMV	1.55±0.49	2.48±0.30	37.19±18.88	1.61±0.63	2.54±0.38	37.39±18.25
SB	1.31±0.41	2.46±0.44	45.93±17.75	1.41±0.49	2.41±0.54	41.22±18.21
Tryton	1.38±0.48	3.13±0.70	55.77±12.70	1.45±0.56	2.84±0.85	48.17±15.46**
Ostial DMV	1.72±0.61	2.52±0.29	31.82±21.25	1.81±0.70	2.54±0.40	29.36±20.52
Ostial SB	1.44±0.55	2.45±0.43	40.77±22.94	1.54±0.62	2.40±0.53	35.96±23.33*
	Post-procedure in-stent					
	2-D			3-D		
	MLD	RVD	DS	MLD	RVD	DS
PMV	3.99±0.73	4.51±0.67	11.41±9.41	4.13±0.70	4.52±0.70	8.55±6.78
DMV	2.82±0.48	3.30±0.42	14.51±8.17	2.83±0.45	3.29±0.38	14.15±7.20
SB	2.38±0.39	2.86±0.50	16.70±6.86	2.42±0.35	2.78±0.46	12.55±4.82*
Tryton	2.83±0.87	3.53±1.15	19.38±6.03	2.60±0.55	3.04±0.71	13.95±4.51**
Ostial DMV	3.09±0.46	3.33±0.37	7.27±8.45	3.14±0.48	3.35±0.41	6.53±6.93
Ostial SB	2.49±0.46	2.87±0.50	13.12±8.29	2.56±0.47	2.82±0.50	9.06±7.30

2/3-D: two/three-dimensional; DMV: distal main vessel; DS: percent diameter stenosis; MLD: minimal lumen diameter; PMV: proximal main vessel; QCA: quantitative coronary angiography; RVD: reference vessel diameter; SB: side branch; *p≤0.05 compared to 2-D; ** p≤0.01 compared to 2-D

Table 4. Bifurcation angles pre and post Tryton implantation.

	Preprocedural		Postprocedural					
	LM-SB	DMB-SB	LM-SB	Angle change	*p*-value	DMB-SB	Angle change	*p*-value
2-D QCA (n=43)	139.4±34.7	78.5±32.7	142.8±29.2	3.4±18.8	0.24	75.2±27.1	–3.39±24.0	0.36
3-D QCA (n=14)	132.4±15.0	65.5±18.7	134.0±17.5	1.58±11.5	0.62	65.7±16.8	0.19±19.6	0.97

Table 5. Depth of implantation.

Tryton implantation parameters	
Tryton successfully implanted	98% (51/52)
Implantation depth assessable	77% (40/51)
Proximal middle marker to carina distance, mm	3.11±1.85
Distal middle marker to carina distance, mm	1.35±1.87
Appropriate implantation	38% (15/40)
Implantation too deep	20% (8/40)
Implantation not deep enough	43% (17/40)

CLINICAL FOLLOW-UP

At a median of six months, one patient of the entire cohort treated with the Tryton stent was lost to follow-up. The events in the rest as well as the hierarchical MACE are reported in **Table 6**. One patient died of cardiovascular complications at 83 days after the index procedure. Two other patients died of non-cardiac causes, one from septic shock and the other from a gastrointestinal bleed. Apart from the three periprocedural MIs, two other patients suffered a NSTEMI at 55 days and 92 days post procedure, respectively. In the first patient, angiography revealed no obvious restenosis or culprit lesion, whereas in the second restenosis with a hazy lesion in the SB ostium was treated with balloon angioplasty. In total, six patients had TVR, all involving the SB, with one of them being referred for CABG because of concomitant MV and SB restenosis. All cases of TVR occurred in the side branch with QCA-derived reference diameter of <2.3 mm. The depth of implantation in cases of TVR was appropriate in two, too deep in two and not deep enough in two.

On further analysis of the baseline and follow-up angiography films of cases with restenosis, the following observations were made: all cases of restenosis involved the SB ostium. Evaluation of procedural steps revealed prolonged attempts at rewiring of the SB for FKB.

No cases of definite stent thrombosis were reported.

Table 6. Acute and 6-month clinical outcome.

Periprocedural adverse events	
Procedure-related MI	6% (3/50)
Target vessel revascularisation	0 (0/50)
ARC definite stent thrombosis	0 (0/50)
Cardiac death	0 (0/50)
MACE (hierarchical)	6% (3/50)
30-day adverse events	
Myocardial infarction	6% (3/50)
Target vessel revascularisation	0% (0/50)
ARC definite stent thrombosis	0% (0/50)
All-cause death	4% (2/50)
Cardiac death	0% (0/50)
MACE (hierarchical)	6% (3/50)
6-month adverse events	
Myocardial infarction	10% (5/50)
Target vessel revascularisation	12% (6/50)
Main vessel	12% (6/50)
Side branch	2% (1/50)
ARC definite stent thrombosis	0% (0/50)
All-cause death	6% (3/50)
Cardiac death	2% (1/50)
MACE (hierarchical)	22% (11/50)

Discussion

Use of the Tryton side branch stent for treatment of LM bifurcation lesions was associated with a high rate of device and procedural success without complications in such a high-risk patient and lesion cohort. The angiographic result is excellent with optimal acute luminal gain in all three segments of the bifurcation including the distal MB and SB ostia as measured by 2-D and 3-D QCA. Although BA changes were observed to similar extents as previously described for two-stent techniques, they were not associated with adverse events at follow-up. At six months, TLR (12%) was due almost exclusively to SB ostium restenosis, an event that warrants in-depth evaluation.

Previous studies have shown that PCI of the LM has two distinct anatomical subcategories distinguished by their differential outcome in terms of restenosis. In fact, while treatment of disease limited to the shaft compares well with CABG results, that of the bifurcation is limited by excessive revascularisation rates. A LM substudy from the j-Cypher Registry found a three-year TVR rate of 3.6% for ostial lesions and significantly higher rates (17.1%) after bifurcation stenting with early-generation sirolimus-eluting stents[12]. Two-stent strategies including crush, culotte and T stenting provide better angiographic results at the expense of a more complex procedure with higher risk of complications and lack of superiority or even inferiority in terms of efficacy when compared to provisional T stenting. Reports of a 30.9% TVR rate at three years with two-stent techniques compared with a more acceptable 11.1% for provisional stenting are a matter of some concern[12]. An Italian survey also reported similar

rates at two years with a similar difference between simple and more complex techniques (TLR-free survival 87% vs. 73%)[13]. Such trends are maintained up to five-year follow-up[14]. It is worth noting that the majority of two-stent techniques employed in these studies were crush and T stenting with under-representation of culotte stenting. The latter has the potential advantage of a better scaffolding of the distal vessel ostia and at the same time may minimise the number of unopposed struts at the bifurcation. In true bifurcation lesions with significant SB involvement, these features may be particularly advantageous. The Tryton stent facilitates the reverse culotte technique and, as shown in previous reports, it simplifies the interventional technique leading to a low intraprocedural complication rate and excellent angiographic results. In our current registry, these theoretical advantages still resulted in a TLR rate of 12% at six months. Some important device-dependent and operator-dependent features have to be considered in order to understand how these may interact to affect clinical outcome.

DEPTH OF IMPLANTATION

The middle markers on the Tryton stent delivery system are essential to guide the desired depth of implantation of the device. Straddling the carina between the two markers allows correct positioning of the stent transition zone, resulting in good scaffolding of the SB ostium. This zone has a lower radial strength than the SB zone due to the design, which on the other hand allows for easier recross of wires, balloons and stents across it and along the MV. Therefore, a balance has to be sought, as implanting the device too deep will result in poor SB ostial scaffolding while too shallow an implantation will result in difficult MV rewiring. Most operators in our series preferred to keep the major part of the transition zone in the MV. This strategy probably provides better scaffolding of the SB ostium, while recrossing into the relatively large MV was not associated with any significant difficulty. Theoretically, this issue would be best explored with the use of intraprocedural intravascular ultrasound (IVUS) or optical coherence tomography (OCT). However, it should be noted that inappropriate implantation depth was not predictive of restenosis up to six months post procedure.

STENT SIZING

Small branch vessels treated with the Tryton stent were more likely to have restenoses at follow-up. Indeed, five of the seven cases with restenosis at six months occurred in vessels less than 2 mm by QCA. Introduction of a drug-eluting version of the Tryton stent may potentially overcome this problem in vessels ≤2.5 mm in diameter.

CHANGE IN BIFURCATION ANGLE AFTER TRYTON-CONVENTIONAL STENT IMPLANTATION

Cardiac motion may change BA, namely widening the angle between the LM and the LCx, and simultaneously narrowing the angle between the LAD and the LCx by about 8°[15]. PCI of the LM bifurcation also changes the angle in most instances, narrowing it by about 5°. Our study showed similar changes with the use of a dedicated bifurcation stent.

In a recent 3-D QCA study, a change of ≥5° between either the PMB and SB or DMB and SB after stenting was considered significant. Of the 102 bifurcations included in the study, 15 involved the LM. The angle between the DMB and SB changed significantly. Of note, the angle became wider with the use of complex as compared to simple bifurcation stenting techniques. However, this was not associated with adverse events. On the other hand, widening of the angle between the PMB and SB was associated with fewer events, while angle narrowing resulted in a higher rate of complications[16]. In our study, neither the angle at baseline nor a change in the angle after PCI was associated with adverse events, including restenosis. This, however, does not exclude a higher postulated risk of bifurcation restenosis with very wide angles between the DMB and SB, as scaffolding at the point of bifurcation may be reduced. Such bifurcations are under-represented in our study cohort, reflecting appropriate selection of cases based on the anatomy by the treating interventional cardiologist. Therefore, the impact of bifurcation angle change on outcome in LM intervention in appropriately selected cases certainly remains limited.

OTHER PROCEDURAL CHARACTERISTICS THAT MAY HAVE AN IMPACT ON OUTCOME

Technical strategies to ensure long-term patency include lesion preparation with rotational atherectomy if lesions are significantly calcified, balloon predilatation[17], use of cutting balloons when needed, implantation of stents at relatively high pressures, and post-dilatation with non-compliant balloons. Use of IVUS imaging[18] may be of help in assessing the need for predilatation or atherectomy, in appropriately sizing the vessel, and to evaluate the need for further post-dilatation after stenting in order to ensure good acute luminal gain. In patients undergoing bifurcation lesion PCI, FKB dilation has a positive effect on acute angiographic results, which seems to translate into better clinical outcome[19]. Indeed, the Nordic-Baltic Bifurcation Study III showed that FKB dilation reduced angiographic SB restenosis at six months in bifurcation lesions other than distal LM, especially in patients with true bifurcations (7.9% vs. 15.4% [p=0.039] for all bifurcations and 7.6% vs. 20.0% [p=0.024] for true bifurcations)[20]. Prolonged attempts at rewiring the SB for FKB were noted on detailed analysis of the Tryton cases needing revascularisation at follow-up in the current registry. We can speculate that this may be the result of passage of the wire behind the struts of the SB ostial portion of the Tryton stent (presumably at the transition zone). If that is the case, kissing inflations would crush the transition zone against the ostium, resulting in reduced carina scaffolding despite the optimal acute angiographic result and restenosis. Another possible cause of SB restenosis could be the lack of an antiproliferative drug coating on the Tryton stent implanted in a site at high risk of restenosis, such as the LCx ostium.

QCA FOR BIFURCATION ANALYSIS

The mean values for diameter stenosis established by QCA analysis in the cohort are less than 50% in all three segments of the bifurcation. This implies that such measurements were not used in isolation to

determine whether the LM bifurcation should be treated or not. Discrepancy between eyeballing and QCA (overestimation of eyeballing), use of complimentary parameters such as lesion instability, pressure drop on engagement of the LM and other physiological parameters may have instigated treatment. Angiographic derivation of the reference vessel diameter prior to intervention may underestimate the true lumen diameter, especially in diffusely diseased segments. In fact after stent implantation we observed an enlargement of the RVD. This occurs commonly with the LM since it is an end vessel and involvement starting from the ostium precludes measurement of the true RVD by angiography on the pre-treatment film. Despite these plausible reasons for the low DS in treated LM bifurcations, we still cannot exclude overtreatment, i.e., intervention of apparently non-significant lesions with the interventionalist being keen to treat if there is doubt about the significance as it is the LM.

LIMITATIONS

The present study has the intrinsic limitations of a registry. These cases are selected and therefore may not reflect use in all-comer LM lesions. In particular, the limited Tryton stent sizes available at the time of implantation may have affected the outcome. Therefore, it is more likely that the present results reflect stent performance in the range of vessel sizes treated in our cohort. There was no control group to compare the use of this dedicated bifurcation stent and stenting with other devices and techniques. Moreover, the number of patients enrolled in the registry is too limited to draw conclusions on definite and reproducible clinical outcome rates. Also, the majority of patients enrolled had no angiographic or other invasive imaging follow-up. QCA was not possible in 100% of the cohort for the reasons explained above. The use of intravascular imaging techniques (IVUS or OCT) was not available in the majority of cases and would have been useful for better evaluation of the cases of stent failure.

Conclusions

Use of the Tryton stent for treatment of LM bifurcation disease in combination with a conventional drug-eluting stent is feasible and results in optimal acute angiographic results. Safety of the procedure and six-month clinical outcome are acceptable in this high-risk lesion PCI; further prospective safety and efficacy studies with intravascular imaging as well as long-term outcomes of this strategy are warranted.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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PART IV

The SYNTAX score and other derivative scores

Chapter 13

The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility

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The SYNTAX Score Revisited: A Reassessment of the SYNTAX Score Reproducibility

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Objectives: To reassess the reproducibility of the SYNTAX score. Background: The SYNTAX score appears to have an important role to play in the evaluation of patients with complex coronary artery disease undergoing revascularisation. However, the calculation of the SYNTAX score relies on the subjective assessment of lesions using coronary angiography, and therefore is subject to intra-and inter-observer variability. Methods: The SYNTAX score was calculated in 100 patients randomly selected from the SYNTAX trial, on two occasions 8 weeks apart, by a team made up of three interventional cardiologists. The weighted kappa values were compared with values obtained 1 year previously, when core lab analysts assessed the intra-observer reproducibility amongst the same patient cohort. Results: The mean ± standard deviation difference in SYNTAX score was 2.1 ± 7.6. The respective weighted kappa values for the number of lesions, bifurcation lesions, ostial lesions, and total occlusions were 0.62, 0.36, 0.66, and 0.91 compared with 0.59, 0.41, 0.63, and 0.82 in the previous core lab assessment. The weighted kappa for the intra-observer reproducibility of the SYNTAX score grouped into deciles was 0.54, and according to the terciles ≤22, >22–≤32, >32 was 0.51 both indicating a moderate level of agreement beyond the level of chance. In the previous assessment, the comparative kappa values were 0.45 and 0.53. Conclusions: The SYNTAX score has moderate intra-observer reproducibility when assessed by a team of three interventional cardiologists, which is consistent with a prior evaluation performed by core lab analysts. The scoring of bifurcation lesions remains the main source of inconsistency.

Key words: SYNTAX score; intra-observer variability; SYNTAX trial

INTRODUCTION

Coronary artery bypass grafting (CABG) has historically been the preferred method of revascularisation in patients with complex coronary artery disease (CAD); however, recent evidence indicates that in specific groups of patients, percutaneous coronary intervention (PCI) can offer a safe and efficacious alternative treatment [1–4]. This expanding use of PCI [5] has consequently increased the importance of developing a systematic approach for risk stratifying these complex patients. The ability to objectively decide, which patients with complex CAD are suitable for PCI has gained new ground recently following the introduction of the SYNTAX score [6,7]. This lesion based scoring system cannot only quantify coronary anatomy, but studies also demonstrate that it has a role in the short and long term risk stratification of patients having percutaneous revascularisation [1,4,8–10].

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Conflicts of Interest: Nothing to report.

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The SYNTAX score is calculated using lesion assessment based on coronary angiography, however, this is subject to intra- and inter-observer variability [11–13], which may ultimately affect the overall reproducibility of the score. A poorly reproducible score will limit its clinical application, and in particular will make guideline recommendations based on specific scores of limited value. The aim of this study was to reassess the intra-observer SYNTAX score reproducibility, and compare it to previously reported values, which were obtained from an assessment by core lab analysts (Cardialysis, Rotterdam, The Netherlands) of the same patients 1 year earlier [7].

METHODS

Study Population

The study population comprised of 100 coronary angiograms, which had been randomly selected from patients who had been enrolled in the SYTNAX trial [1]. These angiograms were exactly the same as those which had been assessed in a previous intra-observer reproducibility evaluation of the SYNTAX score, which is described in full elsewhere [7].

SYNTAX Score Calculation

The SYNTAX score for each patient was calculated prospectively by a team of three interventional cardiologists who scored all coronary lesions with a diameter stenosis $\geq$50%, in vessels $\geq$1.5 mm, using the SYNTAX score algorithm, which is described in full elsewhere [6,7] and is available on the SYNTAX score website (www.syntaxscore.com) [14]. All three investigators reviewed the coronary angiogram, and decided by consensus: (i) the number of significant lesions that were present, (ii) which coronary segments were involved, and (iii) the presence of any adverse lesion characteristics. Once agreement had been reached one investigator entered the data onto a dedicated software package. The investigators were blinded to the clinical baseline characteristics, procedural data, clinical outcomes, and previously calculated SYNTAX score. Furthermore, investigators continued to remain blinded to the calculated SYNTAX score even after the all lesion variables had been recorded.

Intra-Observer Reproducibility

To assess intra-observer reproducibility, the angiograms were reanalyzed by the same team of three interventional cardiologists 8 weeks after the first analysis. The investigators remained blinded to the results of the first analysis.

TABLE I. Quantitative Classification of Kappa Values as a Degree of Agreement Beyond the Level of Chance [16]

Kappa value	Degree of agreement beyond chance
0	None
$0.0 < \text{Kappa} \leq 0.2$	Slight
$0.2 < \text{Kappa} \leq 0.4$	Fair
$0.4 < \text{Kappa} \leq 0.6$	Moderate
$0.6 < \text{Kappa} \leq 0.8$	Substantial
$0.8 < \text{Kappa} \leq 1.0$	Almost perfect

Statistics

The justification for a sample size of 100 coronary angiograms is provided elsewhere, [7] but in brief a power calculation revealed that a group size of 100 coronary angiograms would be more than sufficient to achieve a reasonable and precise kappa-value.

The extent of intra-observer agreement beyond the level of chance was measured as a percentage of the total agreement using the kappa statistic. This is routinely used to assess the level of agreement between two or more categorical observations in excess of a chance agreement [15]. The kappa value was calculated using the standard formula: [observed agreement − expected agreement]/[1 − expected agreement]. The qualitative classification of the kappa value used to interpret the degree of agreement beyond chance is shown in Table I [16]. The standard kappa does not take into account the degree of disagreement between observers and all disagreement is treated equally as total disagreement. Therefore, the Cicchetti-Allison method was used to calculate the weighted kappa to allow the relative differences between categorical variables to be appropriately quantified [17]. Those observations on the diagonal line in the table of round one *versus* round two measurements (a corresponding score in each round) were given a higher weight than observations further from the diagonal. In addition, the further the observation was away from the diagonal, the less weight it was given using a linear scale.

The weighted kappa statistic was calculated for as follows: (1) the total number lesions; (2) number of total occlusions; (3) number of bifurcation lesions; (4) number of ostial lesions; (5) total SYNTAX score in deciles (6) and SYNTAX score terciles ($\leq$22, >22–$\leq$32, >32).

All analyses were performed using SAS (Cary, NC) version 8.02 by a dedicated statistician.

RESULTS

In total 92 (92%) angiograms were included in the final analysis. Eight of the angiograms were excluded because they could not be viewed on two occasions as a result of technical problems with the angiogram disk.

TABLE II. Total number of lesions recorded during both rounds of the study

Round Two Number of Lesions	Round One Number of Lesions						
	1	2	3	4	5	6	Total
1	6	1	0	0	0	0	7
2	2	7	4	2	0	0	15
3	0	0	19	10	0	0	29
4	0	0	10	9	6	0	25
5	0	0	1	1	7	5	14
6	0	0	0	0	2	0	2
Total	8	8	34	22	15	5	92
Weighted kappa 0.62							

Shaded boxes represent concordant scores.

TABLE IV. Number of Bifurcations Lesions Recorded During Both Rounds of the Study

Round Two Number of Bifurcation Lesions	Round One Number of Bifurcation Lesions				
	0	1	2	3	Total
0	14	8	2	1	25
1	9	27	9	1	46
2	0	8	10	1	19
3	1	0	1	0	2
Total	24	43	22	3	92
Weighted kappa 0.36					

Shaded boxes represent concordant scores.

Reproducibility Assessment

The results recorded during the two rounds of the study for the total number lesions; the number of total occlusions; the number of bifurcation lesions; the number of ostial lesions; the total SYNTAX score in deciles; and the SYNTAX score in terciles are shown in Tables II–VII, together with the corresponding kappa value for the degree of agreement between both measurements beyond the level of chance. Table VIII shows the comparison of kappa values between this assessment of SYNTAX score reproducibility, and the previous assessment performed in the same population in 2008 [7].

SYNTAX Score

Figure 1 shows the SYNTAX score calculated for each patient in both rounds of the study. The majority of the values lie close to the line of concordance; however, five main outliers (highlighted) are present.

The overall mean SYNTAX score was 24.3 (range 4–54) and 26.4 (range 8–58) for rounds one and two, respectively. The mean difference (measure of precision) was 2.1 with a standard deviation of 7.6 (measure of accuracy). In the previous assessment in 2008, the respective values for the mean score in round one, mean score in round two, mean ± standard deviation of the difference were 31.3, 29.2, and 2.1 ± 9.1, respectively [7].

TABLE III. Number of Total Occlusions Recorded During Both Rounds of the Study

Round Two Number of Total Occlusions	Round One Number of Total Occlusions			
	0	1	2	Total
0	59	2	0	61
1	1	21	0	22
2	0	2	7	9
Total	60	25	7	92
Weighted kappa 0.91				

Shaded boxes represent concordant scores.

TABLE V. Number of Ostial Lesions Recorded During Both Rounds of the Study

Round Two Number of Ostial Lesions	Round One Number of Ostial Lesions		
	0	1	Total
0	74	2	76
1	6	10	16
Total	80	12	92
Weighted kappa 0.66			

Shaded boxes represent concordant scores.

TABLE VI. Total SYNTAX Score (in deciles) Calculated During Both Rounds of the Study

Round Two SYNTAX Score (deciles) \ Round One SYNTAX Score (deciles)	0-10	11-20	21-30	31-40	41-50	51-60	Total
0-10	3	2	0	0	0	0	5
11-20	1	16	10	1	2	0	30
21-30	0	5	22	7	1	0	35
31-40	0	1	4	9	2	1	17
41-50	0	0	0	2	2	0	4
51-60	0	0	0	0	0	1	1
Total	4	24	36	19	7	2	92
Weighted kappa 0.54							

Shaded boxes represent concordant scores.

DISCUSSION

The main finding from this study is that the SYNTAX score had moderate intra-observer reproducibility when assessed by a team of three interventional cardiologists, with the main source of inconsistency stemming from the evaluation of bifurcation lesions. Furthermore, these results are consistent with a previous evaluation of the score's reproducibility as performed by core lab analysts.

The Rationale for Evaluating the SYNTAX Score Reproducibility

The ability to select patients with complex CAD [triple vessel disease/left main stem disease (LMS)] who are suitable for PCI has never been as important as in the current environment where increasing numbers of patients with multiple comorbidities are being investigated, and treated for CAD [18]. These patients frequently have complex CAD, and pose a challenging clinical problem particularly as technological advances have ensured that PCI can be used to treat the majority of coronary lesions; however, this is not always the most appropriate treatment. Furthermore, the final decision regarding the method of revascularisation is also no longer simply the outcome of a discussion between physician and surgeon. Patients are becoming increasingly involved in the decision making process, and, therefore, an adequate method of risk stratification is important to enable them to make the most appropriate decision for them, as an individual [19].

The recently developed SYNTAX score [6,7] appears to have an important role to play in the evaluation of these complex patients, thereby addressing an unmet clinical need. Prospective data from the SYNTAX trial and retrospective analysis of the CUSTOMIZE registry has indicated that the SYNTAX score can reliably identify those patients with complex CAD most appropriately managed with CABG as opposed to PCI [1,4]. Moreover, evidence from prospective and retrospective analyses performed in over 4,000 patients so far suggests that the SYNTAX score can also be used to predict short and long term clinical outcomes in those undergoing PCI [1,8–10].

On the background of this increasingly complex decision making process and the positive data from trials, which have assessed the SYNTAX score's performance, it is anticipated that the SYNTAX score will be used increasingly in day-to-day clinical practice, and may will eventually be incorporated into clinical practice guidelines. The likelihood of this happening, however, is highly dependent on the demonstration of an adequately reproducible score. Importantly, this serves to improve the confidence that individual clinicians have in using the score, and also increases the probability that clinicians will adhere to suggested recommendations based on specific scores values.

TABLE VII. SYNTAX Score According to Terciles Recorded During Both Rounds of the Study

Round Two SYNTAX Score (terciles) \ Round One SYNTAX Score (terciles)	≤22	>22-≤32	>32	Total
≤22	27	9	3	39
>22-≤32	7	20	11	38
>32	1	3	11	15
Total	35	32	25	92
Weighted kappa 0.51				

Shaded boxes represent concordant scores.

TABLE VIII. Comparison of Weighted Kappa Values From 2008 and 2009 Reproducibility Assessment

Parameter	Kappa value 2008 study [7]	Kappa value 2009 study
Total number of lesions	0.59	0.62
Number of total occlusions	0.82	0.91
Number of bifurcation lesions	0.41	0.36
Number of ostial lesions	0.63	0.66
SYNTAX score (deciles)	0.45	0.54
SYNTAX score (terciles)	0.53	0.51

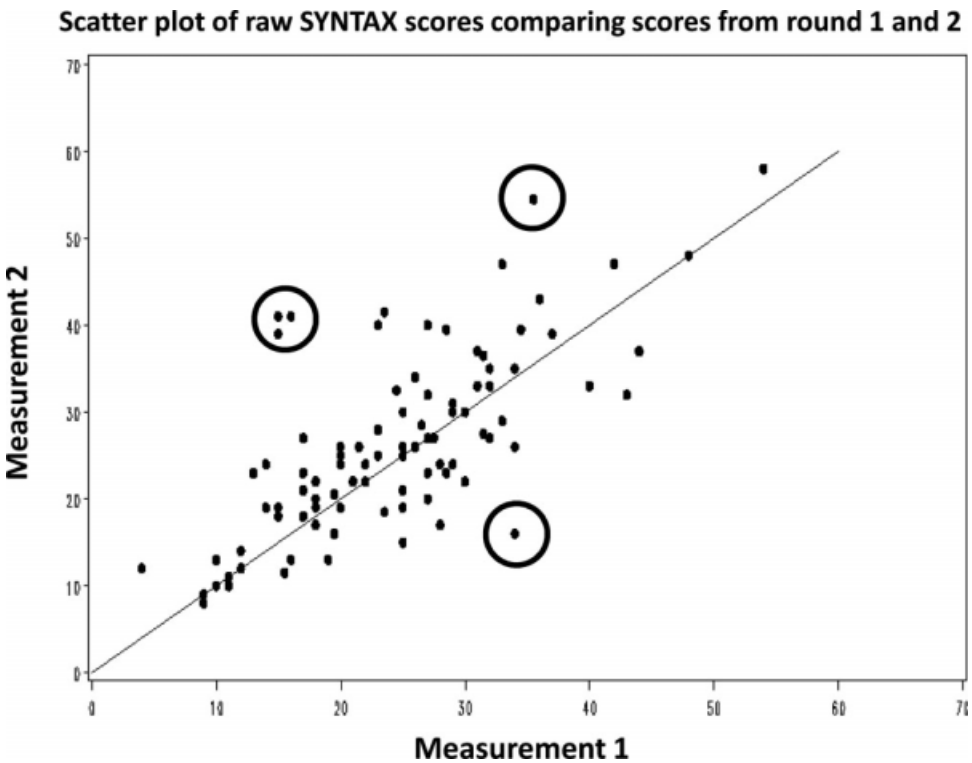

Fig. 1. Five main outliers are observed which on retrospective analysis are mainly caused by discrepancies in selecting the segments involved in bifurcation lesions, particular those involving the distal left main stem.

SYNTAX Score Reproducibility

In this study, the overall reproducibility of the SYNTAX score was moderate, with a kappa value of 0.54. To place this in the context of other subjective assessments, the interpretation of T wave changes on an exercise stress test; the assessment of regional wall motion abnormalities on echocardiography; and the previous intra-observer reproducibility of the SYNTAX score have been shown to have kappa values of 0.25, 0.41, and 0.45, respectively [7,20,21].

One of the major factors influencing the SYNTAX score's reproducibility is the use of diagnostic coronary angiography to assess lesion characteristics; however, this currently represents the ''gold-standard'' investigation for patients with suspected CAD, and is unlikely to change in the near future. It is well known that coronary angiography is subject to intra- and inter-observer variability [22] with assessment being influenced by amongst other things the quality of the diagnostic pictures, the angiographic views that are selected, lesion eccentricity, operator experience and interpretation [11–13]. Moreover, previous studies have indicated that the assessment of lesion severity based on visual estimation is inferior when compared with quantitatively derived parameters. For example, Beauman and Vogel [12] demonstrated that the visual estimation of a 50% phantom stenosis by a group of observers ranged between 30 and 95%.

Bifurcation lesions were the lesion type with the lowest reproducibility, which is consistent with the previous study [7]. Of note discrepancies in the scoring of bifurcation lesions, and in particular those involving the distal LMS, were the main culprits in the five cases with the greatest difference between round one and round two scores (range: 19–26). This inconsistency reiterates the difficulty in evaluating whether lesions involving the distal LMS extend into the ostium of the left anterior descending (LAD)/circumflex (Cx) coronary artery. Vessel foreshortening and overlap make visualization and accurate lesion assessment in this region difficult, particularly when using only coronary angiography for assessment. In fact studies demonstrate that LMS lesions are subject to the greatest degree of intra- and inter-observer variability on coronary angiography, when compared with lesions located elsewhere in the coronary tree [23,24]. In practice a suspicious lesion in this area warrants further evaluation with intra-vascular ultrasound, coronary CT, and/or functional assessment with fractional flow reserve [23,25,26]. In this study, lesion assessment was confined only to coronary angiography, however, the reproducibility in the assessment of bifurcation lesions

may well have improved if additional imaging had been available as it is in clinical practice.

Importantly, the difference in SYNTAX score between a lesion involving only the distal LMS, as compared with a distal LMS lesion extending into the ostium of the LAD/Cx is sufficiently large enough to move a patient from a low tercile score where PCI is a viable option, to the highest tercile where CABG is the standard of care. This serves to reinforce the importance of appropriate evaluation of lesions, particularly those suspected of involving the distal LMS.

Limitations

Although the kappa value is currently the accepted standard measure of intra-observer reproducibility, it is not without its limitations. By definition, it represents agreement beyond the level of chance, however, the actual level of chance agreement is variable and affected by the prevalence of the disease being studied [27]. The SYNTAX study was a multi-centre trial that enrolled patients in many different countries, and as such there is likely to be a genetic and geographic variation in the prevalence of CAD seen amongst the trial population. Nevertheless, this is not particularly relevant for the purposes of this study as investigators were blinded to clinical data. Conversely, an important factor which may have directly affected the level of chance agreement (and the resulting kappa) by acting as a surrogate for prevalence was the differences noted amongst the study population in both the quality of the diagnostic angiogram, and the angiographic views recorded. It follows that the probability of chance agreement is likely to be somewhat higher in those cases with a good quality angiogram with ample views, when compared with angiograms of poorer quality and limited views. Therefore, in those situations where the prevalence is skewed, for example as a result of an angiogram of excellent quality, a low kappa value can result from genuine poor agreement, or as a consequence of a high probability of chance agreement [28]. Unfortunately, neither the diagnostic quality nor the number of views taken per angiogram were formally assessed in this study. The effect of the angiograms' quality on the prevalence of disease can effectively be eliminated by using 100 blinded assessors scoring the same angiogram. Overall the kappa values obtained in this study should only be considered a guide, and do not reflect the reproducibility of the SYNTAX score in a different patient population with a different prevalence of CAD.

Additional limitations include the experience of the investigators in this study, who have each individually assessed the SYNTAX score in over a thousand angiograms. A repeat assessment of the same angiograms using investigators less familiar with the definitions, and less experienced in using the SYNTAX score may well provide different results.

CONCLUSIONS

This study has demonstrated moderate intra-observer reproducibility of the SYNTAX score when assessed by a team of three interventional cardiologists, which is consistent with previous evaluations by core lab analysts. The scoring of bifurcation lesions remains a source of inconsistency, which may be improved by the use of additional imaging modalities together with a review of its definition.

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Chapter 14

Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS trial

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Value of the SYNTAX Score for Risk Assessment in the All-Comers Population of the Randomized Multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) Trial

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Objectives We aimed to assess the predictive value of the SYNTAX score (SXscore) for major adverse cardiac events in the all-comers population of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial.

Background The SXscore has been shown to be an effective predictor of clinical outcomes in patients with multivessel disease undergoing percutaneous coronary intervention.

Methods The SXscore was prospectively collected in 1,397 of the 1,707 patients enrolled in the LEADERS trial (patients after surgical revascularization were excluded). Post hoc analysis was performed by stratifying clinical outcomes at 1-year follow-up, according to 1 of 3 SXscore tertiles.

Results The 1,397 patients were divided into tertiles based on the SXscore in the following fashion: SXscore ≤8 (SXlow) (n = 464), SXscore >8 and ≤16 (SXmid) (n = 472), and SXscore >16 (SXhigh) (n = 461). At 1-year follow-up, there was a significantly lower number of patients with major cardiac event–free survival in the highest tertile of SXscore (SXlow = 92.2%, SXmid = 91.1%, and SXhigh = 84.6%; p < 0.001). Death occurred in 1.5% of SXlow patients, 2.1% of SXmid patients, and 5.6% of SXhigh patients (hazard ratio [HR]: 1.97, 95% confidence interval [CI]: 1.29 to 3.01; p = 0.002). The myocardial infarction rate tended to be higher in the SXhigh group. Target vessel revascularization was 11.3% in the SXhigh group compared with 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR: 1.38, 95% CI: 1.1 to 1.75; p = 0.006). Composite of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization was 7.8%, 8.9%, and 15.4% in the SXlow, SXmid, and SXhigh groups, respectively (HR: 1.47, 95% CI: 1.19 to 1.81; p < 0.001).

Conclusions The SXscore, when applied to an all-comers patient population treated with drug-eluting stents, may allow prospective risk stratification of patients undergoing percutaneous coronary intervention. (LEADERS Trial Limus Eluted From A Durable Versus ERodable Stent Coating; NCT00389220). (J Am Coll Cardiol 2010;56:272–7)

The SYNTAX score (SXscore) is a comprehensive angiographic scoring system that is derived entirely from the coronary anatomy and lesion characteristics (1–3). It was initially designed to quantify lesion complexity; however, it is also able to predict major adverse cardiac events (MACE) after percutaneous revascularization in patients with multivessel coronary artery disease (4–6) and/or left main disease (7). More recent data indicate its ability to predict periprocedural myocardial infarction (MI) in patients undergoing elective percutaneous coronary intervention (8). In this substudy of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, in which the SXscore was collected prospectively in 1,397 all-comer patients, we assessed its prognostic value for MACE at 1-year follow-up.

Methods

Study population. LEADERS was a multicenter European noninferiority trial comparing the safety and efficacy of the BioMatrix Flex biolimus-eluting stent with a biodegradable polymer (Biosensors, Morges, Switzerland) with the Cypher Select sirolimus-eluting stent with a durable polymer (Cordis, Bridgewater, New Jersey) in 1,707 all-comer patients. Detailed study protocol can be found in the main report (9). The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent for participation in the trial.

SXscore and angiographic analysis. From the baseline diagnostic angiogram, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm was scored separately and added together to provide the overall SXscore, which was calculated prospectively using the SXscore algorithm (described in full elsewhere) (1–3). All angiographic variables pertinent to SXscore calculation were computed by blinded core laboratory analysts (Cardialysis B.V., Rotterdam, the Netherlands). The SXscore is not currently validated in patients with acute MI or previous percutaneous coronary intervention and coronary artery bypass graft. Core laboratory analysts were blinded to all clinical data, and therefore patients with occluded infarct–related arteries were scored as occlusions of unknown duration in a similar manner to any chronically occluded artery. Those patients with in-stent restenosis lesions were scored in the same manner as if the lesion was a de novo lesion.

Study end points. Definitions of all end points are provided elsewhere (9). The primary end point of this substudy was MACE, defined as the composite of cardiac death, MI, and clinically indicated target vessel revascularization (TVR) within 9 months. Secondary end points were any target lesion revascularization (both clinically and nonclinically indicated), any TVR, cardiac death, death from any cause, MI, stent thrombosis (defined according to the Academic Research Council [10]), device success, and lesion success.

The pre-specified principal outcome of the angiographic substudy was the in-stent percentage of diameter stenosis. Secondary angiographic outcomes were the in-segment percentage of diameter stenosis, minimal lumen diameter, late lumen loss, and binary restenosis.

Statistical analysis. A stratified post hoc analysis of clinical and angiographic outcomes was performed according to the tertiles of the SXscore (4,5). Dedicated software and visual coronary angiography served to determine the SXscore (1,2). All randomized patients without previous surgical revascularization (1,397 of 1,707) were included in the analysis. Angiographic outcomes were analyzed using SAS version 8 (SAS Institute, Cary, North Carolina) Proc Mixed for continuous and Proc Genmod for binominal outcomes, taking into account the within-patient correlation structure of these data. The Cox proportional hazards model was used to compare clinical outcomes among the groups. All analyses were performed using SAS version 8.02 by a dedicated statistician. All p values and confidence intervals (CIs) were 2-sided. Multivariate model included SXscore, diabetes, beta-blocker use, stent type, and the presence of acute coronary syndrome as covariates. Testing for (linear) trend was done by using generalized linear models with SYNTAX class as a covariable for continuous variables and the Cochran-Armitage test for trend in categorical data.

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
SXhigh = SYNTAX score >16
SXlow = SYNTAX score ≤8
SXmid = SYNTAX score >8 and ≤16
SXscore = SYNTAX score
TVR = target vessel revascularization

Results

SXscore and baseline characteristics. The SXscore was collected prospectively in 1,397 of the 1,707 patients (81.8%) enrolled in the LEADERS trial. The score ranged from 0 to 49, with a mean ± SD of 13.5 ± 8.7 and a median of 12 (interquartile range 7 to 19). In this post hoc analysis, the SXscore tertiles were defined as SXlow (SXscore ≤8) (n = 464), SXmid (SXscore >8 and ≤16) (n = 472), and SXhigh (SXscore >16) (n = 461). Baseline clinical and angiographic characteristics of the patients are listed in Tables 1 and 2.

1-year outcomes. The SXscore significantly predicted the rate of MACE at 360 days (Table 3, Figs. 1 to 4). There was a lower number of patients with MACE-free survival in the highest tertile of the SXscore (SXlow = 92.2%, SXmid = 91.1%, and SXhigh = 84.6%; $p < 0.001$). Death occurred in 1.5% of patients with SXlow, 2.1% of patients with SXmid, and 5.6% of patients with SXhigh (hazard ratio [HR]: 1.97, 95% CI: 1.29 to 3.01; $p = 0.002$). The rate of MI tended to be

Table 1 Baseline Clinical Characteristics

Baseline Clinical Variables	SXlow (n = 464)	SXmid (n = 472)	SXhigh (n = 461)	p Value on Trend (2-Sided)
Age >65 yrs	210 (45.3)	224 (47.5)	239 (51.8)	0.048
Male	346 (74.6)	344 (72.9)	340 (73.8)	0.79
Diabetes	93 (20.0)	117 (24.8)	111 (24.1)	0.15
Current smoking	134 (28.9)	121 (25.6)	126 (27.3)	0.61
Hypertension	353 (76.1)	353 (74.8)	324 (70.3)	0.048
Hypercholesterolemia	314 (67.7)	314 (66.5)	285 (61.8)	0.06
Family history of coronary artery disease	201 (43.3)	188 (39.8)	168 (36.4)	0.034
Renal insufficiency	17 (3.7)	21 (4.5%)	28 (6.1)	0.09
Previous MI	132 (28.5)	145 (30.7)	137 (29.7)	0.69
Previous PCI	179 (38.6)	165 (35.0)	147 (31.9)	0.036
PVD	26 (5.6)	36 (7.6)	31 (6.7)	0.51
Previous stroke	13 (2.8)	19 (4.0)	16 (3.5)	0.59
Clinical presentation				
Stable	146 (31.5)	154 (32.6)	108 (23.4)	0.008
Unstable	127 (27.4)	89 (18.9)	88 (19.1)	0.002
STEMI	46 (9.9)	90 (19.1)	128 (27.8)	<0.0001
Non-STEMI	90 (19.4)	90 (19.1)	97 (21.0)	0.54
Silent ischemia	55 (11.9)	49 (10.4)	40 (8.7)	0.12

Values shown are n (%).

MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST-segment elevation myocardial infarction; SXhigh = SYNTAX score >16; SXlow = SYNTAX score <8; SXmid = SYNTAX score >8 and ≤16.

higher in patients with SXhigh (MI HR: 1.2, 95% CI: 0.9 to 1.61; p = 0.22). TVR was 11.3% in the SXhigh group compared with 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR: 1.38, 95% CI: 1.1 to 1.75; p = 0.006). Composite of cardiac death, MI, and clinically indicated TVR was 7.8%, 8.9%, and 15.4% in the SXlow, SXmid, and SXhigh groups, respectively (HR: 1.47, 95% CI: 1.19 to 1.81; p < 0.001).

Multivariate model. In a multivariate model, SXscore remained a significant predictor of MACE and mortality. Patients in the SXhigh group had a 50% greater chance of the composite of cardiac death, MI, and clinically indicated TVR than patients in the SXmid group (p < 0.001), which was comparable to the 51% higher composite event rate among diabetic patients (p = 0.022). Use of the biolimus-eluting stent tended to reduce the composite event rate by 26% (p = 0.07).

Stent thrombosis rates. The rates of definite stent thrombosis were 0.9%, 2.1%, and 3.5% in the SXlow, SXmid, and SXhigh groups, respectively.

Table 2 Baseline Angiographic Characteristics

Angiographic Variables	SXlow	SXmid	SXhigh	p Value
No. of diseased lesions per patient (based on SYNTAX application)	1.47 ± 0.66	2.37 ± 1.00	3.45 ± 1.44	<0.001
No. of treated lesions per patient (as defined by the core laboratory)	1.2 ± 0.46	1.47 ± 0.7	1.69 ± 0.86	<0.001
Ratio of diseased to treated lesions	1.22	1.61	2.04	N/A
Coronary artery treated				
LAD	162 (34.9)	242 (51.3)	296 (64.2)	<0.001
LCX	140 (30.2)	144 (30.5)	164 (35.6)	0.079
RCA	216 (46.6)	209 (44.3)	174 (37.7)	0.007
2-vessel disease	49 (10.6)	102 (21.6)	138 (29.9)	<0.001
3-vessel disease	3 (0.7)	13 (2.8)	23 (5.0)	<0.001
Stent type				
Biolimus-eluting	229 (49.3)	235 (49.8)	239 (51.8)	0.45
Sirolimus-eluting	235 (50.7)	237 (50.2)	222 (48.2)	0.45
No. of implanted stents	1.47 ± 0.8	1.90 ± 1.12	2.33 ± 1.39	<0.001
Total stent length/patient, mm	25.9 ± 16.5	34.2 ± 21.7	42.9 ± 26.2	<0.001
Chronic total occlusion	6 (1.3)	10 (2.1)	19 (4.1)	0.006
Moderate to severe calcification	23 (5.1)	96 (20.3)	184 (39.9)	<0.001
Bifurcation lesion	57 (12.3)	161 (34.1)	184 (39.9)	<0.001
Use of glycoprotein IIb/IIIa inhibitor	80 (17.2)	113 (23.9)	154 (33.4)	<0.001

Values are mean ± SD or n (%).

LAD = left anterior descending artery; LCX = left circumflex artery; N/A = not applicable; RCA = right coronary artery; other abbreviations as in Table 1.

Table 3 Clinical Outcomes at 360 Days After Index PCI Based on Tertiles of SXscore

Type of Event	Risk Factors Used	SXlow (%)	SXmid (%)	SXhigh (%)	p Value SYNTAX	HR, SYNTAX	Lower Limit HR, SYNTAX	Upper Limit HR, SXscore
Death	SYNTAX class, DM, STEMI	1.5	2.1	5.6	0.002	1.97	1.29	3.01
Stent thrombosis	SYNTAX class, DM, STEMI	1.1	3	6.1	<0.001	2.13	1.4	3.24
MI	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	4.3	4.9	5.9	0.22	1.2	0.9	1.61
All TVR	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	6.3	7.8	11.3	0.006	1.38	1.1	1.75
All TLR	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	4.7	6.1	8.7	0.019	1.37	1.05	1.79
Composite of cardiac death, MI, clinically indicated TVR	SYNTAX class, DM, STEMI, beta-blockers, and treatment (BES vs. SES)	7.8	8.9	15.4	<0.001	1.47	1.19	1.81

BES = biolimus-eluting stent(s); DM = diabetes mellitus; HR = hazard ratio; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s); TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

Discussion

Complexity of disease and lesion characteristics are well recognized predictors of periprocedural complications (8) and long-term mortality (11–13). The SXscore was developed to comprehensively assess lesion characteristics and is based on the combination of classifications from the American Heart Association/American College of Cardiology, modified BARI classification, chronic total occlusion and bifurcation scores, and Leaman classification (1). It has previously been applied in both the SYNTAX trial and the ARTS II (Arterial Revascularization Therapies Study II), both of which demonstrated the good predictive value of the SXscore in patients with multivessel disease, with the highest tertile patients having significantly more MACE during short-term (4,5) and long-term (6) follow-up.

This study is the first to report the utility of the SXscore as a predictor of MACE, including cardiac death, in an all-comers population including patients with acute coronary syndromes. Overall, this patient population had much lower SXscores than the SYNTAX trial population; however, despite this, the SXscore still appears to have good discriminatory power for risk assessment.

Study limitations. The limitation of the SXscore is that it does not incorporate clinical patient characteristics. Patients who underwent previous coronary artery bypass graft surgery have not been included because the SXscore algorithm is only currently available for patients with de novo disease. Modifications to the SXscore for risk stratification in patients after coronary artery bypass graft surgery are currently being developed. The SXscore of patients who presented with acute MI or had previous percutaneous

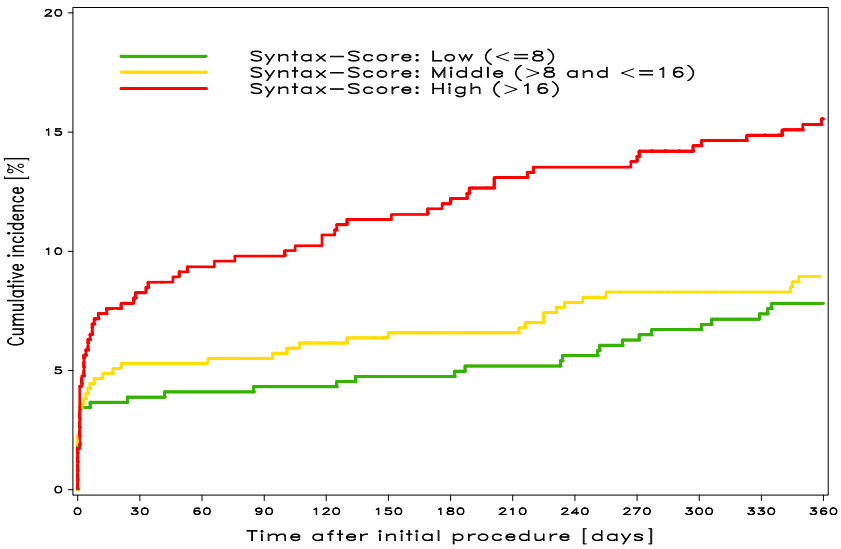

Figure 1 Kaplan-Meier Curves for MACE at 360 Days According to the SYNTAX Tertiles

Patients in the highest tertile of the SYNTAX score have an increased major adverse cardiac events (MACE) event rate (p = 0.0002).

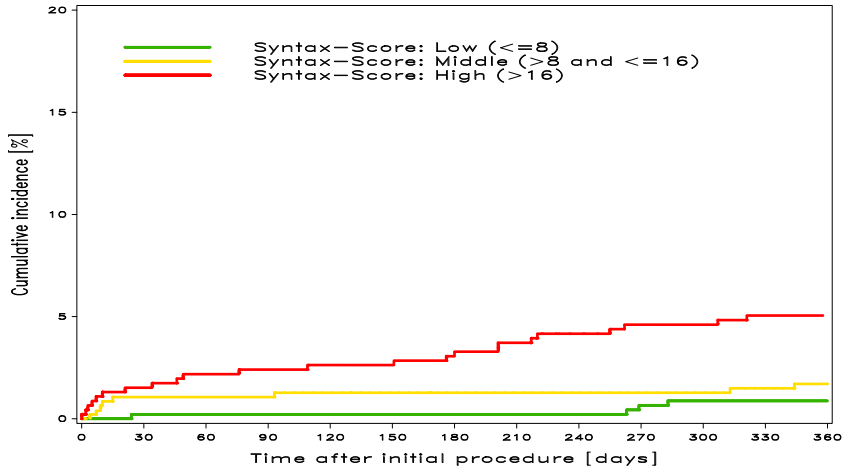

Figure 2 **Kaplan-Meier Curves for Cardiac Death at 360 Days According to the SYNTAX Score Tertiles**

Patients in the highest tertile of the SYNTAX score have a higher cardiac death rate ($p < 0.0001$).

coronary intervention were included in this analysis, despite no previous validation in these patients. Scoring of the infarct-related vessel as a chronic total occlusion may confound the results and have complex effects on the SXscore. There is the danger of overestimating the SXscore if all ST-segment elevation MIs with an occluded infarct–related vessel are taken as chronic total occlusions, particularly because the lesion is likely to be easier to treat due to the soft nature of plaque as opposed to an occlusion, which has calcified organized old thrombus and plaque (chronic occlusion). Alternatively, there is the danger of underestimating the SXscore because the underlying lesion complexity will not be accounted for because the vessel beyond the occlusion is not seen due to the occlusion. This is the subject of an ongoing study. This study may have limitations inherent to subgroup analysis (chance findings and underpowering) (14–16).

Conclusions

This study demonstrates that the prognostic value of the SXscore is valid for all patients with de novo coronary artery disease undergoing percutaneous revascularization.

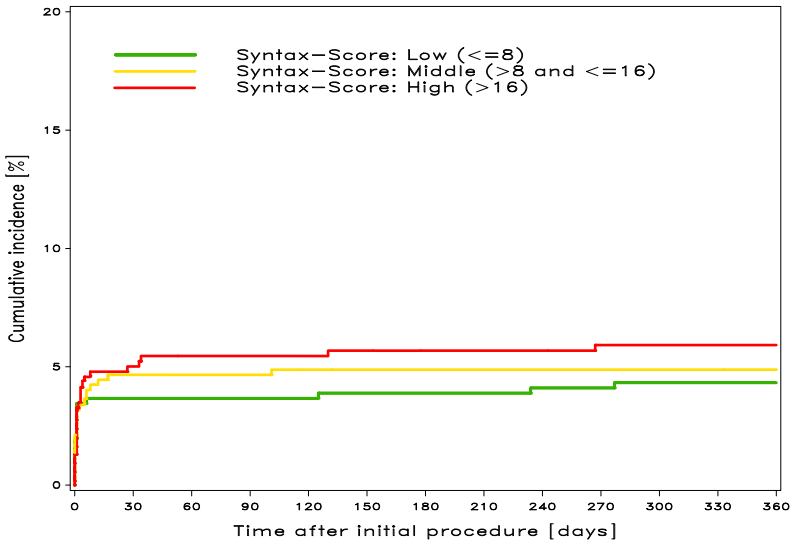

Figure 3 **Kaplan-Meier Curves for All Myocardial Infarctions at 360 Days According to the SYNTAX Score Tertiles**

There is no difference in the rate of overall myocardial infarctions across the tertiles of SYNTAX score ($p = 0.548$ [NS]).

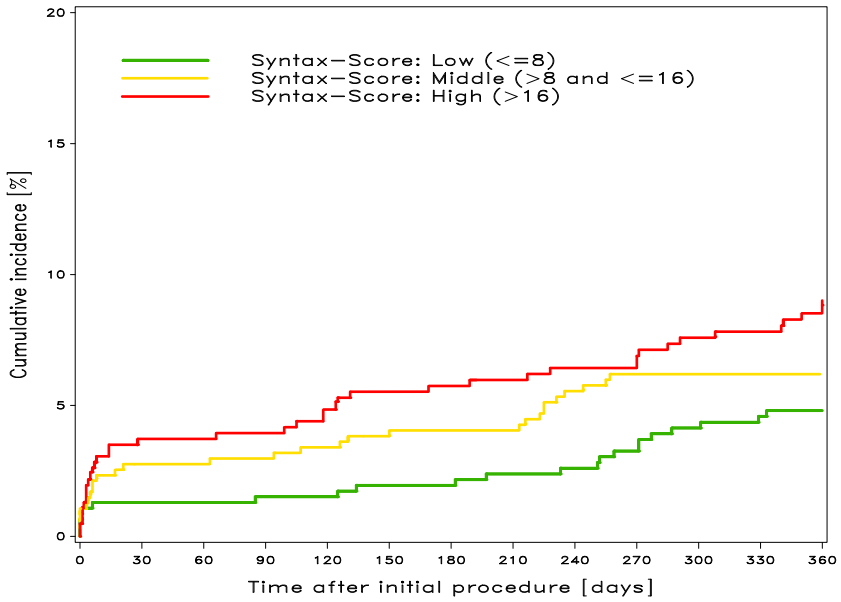

Figure 4 **Kaplan-Meier Curves for Target Lesion Revascularization at 360 Days According to the SYNTAX Score Tertiles**

Patients in the highest tertile of the SYNTAX score have an increased risk of target lesion revascularization (p = 0.036).

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Key Words: biodegradable polymer ■ biolimus-eluting stent ■ major adverse cardiac event ■ prognostic value ■ sirolimus-eluting stent ■ target vessel revascularization ■ SYNTAX score.

Chapter 15

SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRTAX trial

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SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial

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Aims To investigate the ability of SYNTAX score and Clinical SYNTAX score (CSS) to predict very long-term outcomes in an all-comers population receiving drug-eluting stents.

Methods and results The SYNTAX score was retrospectively calculated in 848 patients enrolled in the SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent for coronary revascularization (SIRTAX) trial. The CSS was calculated using age, and baseline left ventricular ejection fraction and creatinine clearance. A stratified *post hoc* comparison was performed for all-cause mortality, cardiac death, myocardial infarction (MI), ischaemia-driven target lesion revascularization (TLR), definite stent thrombosis, and major adverse cardiac events (MACE) at 1- and 5-year follow-up. Tertiles for SYNTAX score and CSS were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$ and $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17.0$ and $CSS_{HIGH} > 17.0$, respectively. Major adverse cardiac events rates were significantly higher in SS_{HIGH} compared with SS_{LOW} at 1- and 5-year follow-up, which was also seen at 5 years for all-cause mortality, cardiac death, MI, and TLR. Stratifying outcomes across CSS tertiles confirmed and augmented these results. Within CSS_{HIGH}, 5-year MACE increased with use of paclitaxel- compared with sirolimus-eluting stents (34.7 vs. 21.3%, $P = 0.008$). SYNTAX score and CSS were independent predictors of 5-year MACE; CSS was an independent predictor for 5-year mortality. Areas-under-the-curve for SYNTAX score and CSS for 5-year MACE were 0.61 (0.56–0.65) and 0.62 (0.57–0.67), for 5-year all-cause mortality 0.58 (0.51–0.65) and 0.66 (0.59–0.73) and for 5-year cardiac death 0.63 (0.54–0.72) and 0.72 (0.63–0.81), respectively.

Conclusion SYNTAX score and to a greater extent CSS were able to stratify risk for very long-term adverse clinical outcomes in an all-comers population receiving drug-eluting stents. Predictive accuracy for 5-year all-cause mortality was improved using CSS. Trial Registration Number: NCT00297661.

Keywords Percutaneous coronary intervention • Drug-eluting stents • Clinical outcome • Angiography • SYNTAX score • Clinical SYNTAX score

Introduction

The SYNTAX score is a lesion-based angiographic scoring system originally devised to grade the complexity of coronary artery disease[1] and thereby facilitate consensus in the study of a diagnostic angiogram between surgeons and interventional cardiologists. In the SYNTAX trial,[2] it proved effective in predicting clinical outcomes after elective percutaneous coronary intervention (PCI) procedures in patients with three-vessel and/or left main coronary artery disease.[3] The score's predictive ability for a number of clinical outcomes has subsequently been assessed in patient cohorts with a varying extent of coronary artery disease undergoing both elective and emergent PCI procedures.[4–13] Several of these studies have suggested that, being solely based on angiographic variables, the SYNTAX score cannot account for the variability related to clinical factors which are widely acknowledged to impact on long-term outcomes, such as a patients' age,[14] left ventricular ejection fraction,[15] and renal function.[16]

A clinical score incorporating the aforementioned variables, the ACEF score, has been retrospectively validated in patients undergoing elective coronary artery bypass grafting (CABG) operations.[17] Integration of this score, modified through the replacement of serum creatinine with creatinine clearance, with the SYNTAX score, in the Clinical SYNTAX score (CSS), has been shown to improve the predictive ability for adverse clinical outcomes after PCI.[10,11,18] However, information regarding the very long-term performance of either SYNTAX score or CSS in an all-comers population is currently lacking.

The SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent for coronary revascularization (SIRTAX) trial[19] was a prospective, observer-blind, randomized controlled study comparing the safety and efficacy of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in 1012 patients undergoing PCI for either stable angina or an acute coronary syndrome. This study design offers a convenient setting for describing the distribution of the SYNTAX score and CSS in an all-comers population. Furthermore, the availability of 5-year follow-up data permits a more robust evaluation of both scores, in order to confirm their potential to risk stratify clinical outcomes at very long-term after the implantation of drug-eluting stents.

Methods

Patient population and coronary intervention

The design of the SIRTAX trial has been previously described.[19] Patients were eligible to participate if they presented at least one lesion with percentage diameter stenosis ≥50%, in a vessel with a reference diameter between 2.25 and 4.00 mm that was suitable for stent implantation. There were no limitations on the number of lesions treated, number of vessels diseased or on the length of the lesions. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at the participating centres. Written informed consent was obtained from each patient before enrollment. There was no industry involvement in the design, conduct or analysis of the study.

Patients were randomly assigned on a 1:1 basis to treatment with SES (Cypher®; Cordis, Warren, NJ, USA) or PES (Taxus®, Boston Scientific, Natick, MA, USA). No mixture of drug-eluting stents was allowed within a given patient. All procedures were performed according to interventional standards at the time. Before or at the time of the procedure, patients received at least 100 mg of aspirin, a 300 mg loading dose of clopidogrel, and unfractionated heparin (70–100 U/kg of body weight). After the procedure, all patients were advised to maintain aspirin lifelong, and clopidogrel therapy was prescribed for 12 months irrespective of stent type.

SIRTAX endpoints and definitions

All adverse events were adjudicated by an independent clinical events committee throughout 5 years and have been reported separately.[20] The pre-specified primary endpoint was a composite of major adverse cardiac events (MACE) including death from cardiac causes, myocardial infarction (MI), and ischaemia-driven target lesion revascularization (TLR). The diagnosis of MI was based on the presence of new Q waves of at least 0.4 s duration in ≥2 contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of MI was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin I. Target lesion revascularization was defined as an intervention (either surgical or percutaneous) to treat a stenosis within the stent or within the 5-mm borders adjacent to the stent. Revascularization was considered to be driven by ischaemia, if percentage diameter stenosis was ≥50% on the basis of quantitative coronary angiography in the presence of ischaemic signs or symptoms, or ≥70% even in the absence of ischaemic signs or symptoms.

Stent thrombosis was diagnosed as an acute coronary syndrome with angiographic documentation of either target vessel occlusion or thrombus within or adjacent to the previously stented segment; applying Academic Research Consortium recommendations,[21] definite stent thrombosis was documented.

SYNTAX score and angiographic analysis

The SYNTAX score algorithm, which is described in full elsewhere and is available on the SYNTAX score website (www.syntaxscore.com), was employed to retrospectively score all coronary lesions deemed to have a percentage diameter stenosis ≥50%, in vessels ≥1.5 mm. All angiographic variables pertinent to SYNTAX score calculation were computed by two experienced interventional cardiologists (C.G., S.G.) on diagnostic angiograms obtained before the procedure. In case of disagreement, the opinion of a third analyst (G.S.) was obtained and the final decision was made by consensus. Analysts were blinded to procedural data and clinical outcome. The final score was calculated on a patient basis from the individual lesion scores, which were saved in a dedicated database, and was not made available to the analysts until after the completion of the study.

Patients with acute MIs were not included in the SYNTAX trial. In the context of our study the culprit lesions were scored using the angiographic views of the infarct-related arteries before any intervention; in the absence of flow these were scored as total occlusions of <3-months' duration.[9] Patients with prior CABG operation were excluded from the analysis; a dedicated amendment for calculating the score in the presence of grafts has not been made available yet. Finally, in-stent restenosis lesions were scored as *de novo* ones.

Clinical SYNTAX score

The modified ACEF score was retrospectively calculated,[18] based on the patients' left ventricular ejection fraction, age, and creatinine clearance derived using the Cockcroft–Gault equation.[22] Respective

methodology has been amply described elsewhere. Values for variables included in the modified ACEF score were recorded before the index PCI. Clinical SYNTAX score was calculated multiplying the value of SYNTAX score by the modified ACEF score.

Statistics

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Patient characteristics and outcome measures were stratified according to score tertiles among all patients with a calculated CSS. Continuous variables are presented as mean $\pm$ 1 standard deviation (SD) or median values (25th to 75th percentile) as appropriate; categorical variables are displayed as counts and/or percentages. Comparisons were performed with one-way analysis of variance (ANOVA) for continuous variables following a normal distribution and with the χ^2 test for categorical variables. The normality assumption was evaluated by the Kolmogorov–Smirnov test. Spearman's rank correlation coefficient was used to measure the strength of the association of SYNTAX score with CSS.

Cumulative event rates through all 5-years of follow-up were estimated by means of the Kaplan–Meier method. Testing for trends in event rates across score tertiles was done with the Cochran–Armitage test in SAS software (SAS, version 9.2, Cary, NC, USA). All-cause mortality, MACE, cardiac death, TLR, MI, and definite stent thrombosis rates were compared across SYNTAX score and CSS tertiles according to the Cox proportional-hazards model; the assumption of proportional hazards was verified by visual inspection of the log-minus-log curves. Independent predictors of 5-year MACE, all-cause mortality, and cardiac death were sought among variables significant beyond the level of $P = 0.10$ in univariable analysis. Potential predictors were checked for collinearity before entering a multivariable backward stepwise model; variables with a variance inflation factor >2.5 were disqualified. Crude and adjusted hazard ratios and corresponding 95% confidence intervals are reported for qualifying variables.

SYNTAX score, CSS, and multivariable models were also evaluated in terms of calibration and discrimination for 5-year MACE, cardiac, and all-cause mortality. Calibration was evaluated with the Hosmer–Lemeshow (H–L) goodness-of-fit test, wherein a lower χ^2 statistic and a higher corresponding *P*-value implied a better match between the estimated probabilities and the actual events. Discrimination was explored with the areas under the receiver-operating characteristics (ROC) curves; an area of 1.0 would indicate perfect discrimination, whereas an area of 0.5 indicates the total absence of discriminatory power. Areas-under-the-curves (AUCs) for SYNTAX score, CSS, and multivariable models were compared with the DeLong method[23] using MedCalc for Windows, version 11.6.0.0 (MedCalc Software, Mariakerke, Belgium). Finally, in order to formally assess, whether CSS improved the risk stratification over the SYNTAX score, a net reclassification improvement (NRI) analysis was performed.[24]

To complete our analysis, a stratified comparison of clinical outcomes between SES and PES was also performed across SYNTAX score and CSS tertiles using Cox regression analysis. To determine whether there was an interaction between treatment arm and scores' tertiles, likelihood ratio tests were used.

All statistical tests were two-sided and a *P*-value < 0.05 was considered statistically significant.

Results

Analysis was performed for 848 patients (1792 lesions). Scores were not evaluable in 91 cases due to prior CABG; another 57 angiograms were either not available or not fully evaluable in the acquired views. Finally in 16 cases, data on creatinine clearance could not be retrieved, consequently CSS could not be calculated; clinical outcomes of these 164 patients excluded from the analysis are shown in Supplementary material online, *Table S1*.

The SYNTAX score ranged from 1 to 42, with a mean $\pm$ SD of 11.7 $\pm$ 7.3, and a median of 10 (6.0–16.0). The CSS ranged from 0.7 to 272.2, with a mean + SD of 17.4 $\pm$ 20.5, and a median of 11.6 (6.4–21.2); expectedly, there was a strong correlation between the two scores ($r = 0.87$, $P < 0.001$). Both scores were non-parametric and their distribution was skewed to the right (*Figure 1*). Tertiles for SYNTAX score and CSS were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$ and $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17.0$ and $CSS_{HIGH} > 17.0$, respectively.

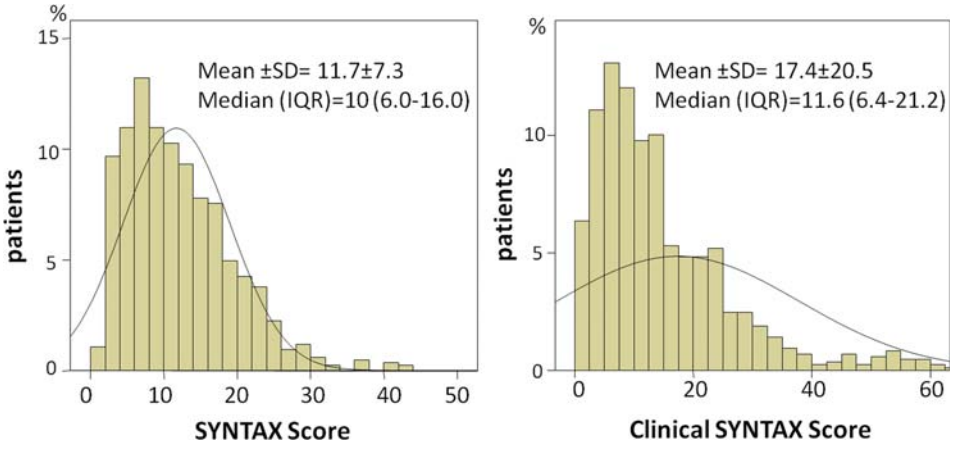

Figure 1 Scores' distribution in the SIRTAX trial population. Histograms of SYNTAX score (left side) and Clinical SYNTAX score (right side) with superimposed normal curves; in both cases the distribution is skewed to the right. Histogram for Clinical SYNTAX score is truncated at the 98th percentile value. Mean $\pm$ SD values and median values plus inter-quartile range (IQR) are reported.

Table 1 Baseline clinical characteristics and risk factors

Characteristic	SS ≤7 (*n* = 293)	7< SS ≤14 (*n* = 287)	SS >14 (*n* = 268)	*P*-value
Age (years ± SD)	60.7 ± 10.6	61.4 ± 11.2	63.7 ± 11.3	0.004
Male gender, *n* (%)	218 (74.4)	219 (76.3)	211 (78.7)	0.48
Body mass index ± SD	27.4 ± 4.2	27.4 ± 4.0	27.0 ± 3.8	0.41
Diabetes mellitus, *n* (%)	45 (15.4)	50 (17.4)	66 (24.6)	0.04
Hypertension, *n* (%)	171 (58.4)	175 (61.0)	160 (59.7)	0.85
Hyperlipidaemia, *n* (%)	176 (60.1)	159 (55.4)	146 (54.5)	0.66
Current smoking, *n* (%)	124 (42.3)	100 (34.8)	93 (34.7)	0.41
Previous MI, *n* (%)	73 (24.9)	78 (27.2)	73 (27.2)	0.56
Previous PCI, *n* (%)	51 (17.4)	51 (17.8)	48 (17.9)	0.94
Peripheral vascular disease, *n* (%)	19 (6.5)	17 (5.9)	13 (4.9)	0.84
Stable angina pectoris, *n* (%)	163 (55.6)	115 (40.1)	108 (40.3)	<0.001
Acute coronary syndromes, *n* (%)	130 (44.4)	172 (59.9)	160 (59.7)	<0.001
Unstable angina, *n* (%)	14 (4.8)	23 (8.0)	12 (4.5)	
Non ST-segment elevation MI, *n* (%)	74 (25.3)	61 (21.3)	63 (23.5)	
ST-segment elevation MI, *n* (%)	42 (14.3)	88 (30.7)	85 (31.7)	
Multi-vessel coronary artery disease, *n* (%)	96 (32.8)	107 (58.2)	209 (78.0)	<0.001
Left ventricular ejection fraction (% ± SD)	60.2 ± 9.4	56.8 ± 11.4	53.3 ± 12.6	<0.001
Serum creatinine (mg/dL ± SD)	0.93 ± 0.33	0.95 ± 0.54	1.02 ± 0.83	0.14
Creatinine clearance (mL/min/1.73 m^2 ± SD)	98.6 ± 34.9	99.5 ± 35.8	91.6 ± 34.8	0.02

MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; SS, SYNTAX score.

Table 2 Procedural characteristics and lesions adjudicated in SYNTAX score

Characteristics per patient	SS ≤7 (*n* = 293)	7 <SS ≤14 (*n* = 287)	SS >14 (*n* = 268)	*P*-value
Mean number of lesions ± SD	1.4 ± 0.6	2.1 ± 0.9	2.9 ± 1.2	<0.001
Bifurcation-trifurcation lesions ± SD	0.1 ± 0.3	0.6 ± 0.6	0.9 ± 0.8	<0.001
Total occlusions ± SD	0.1 ± 0.3	0.3 ± 0.5	0.6 ± 0.6	<0.001
Lesions treated ± SD	1.2 ± 0.5	1.4 ± 0.6	1.5 ± 0.6	<0.001
One lesion treated, *n* (%)	237 (80.9)	180 (62.7)	150 (56.0)	<0.001
Two lesions treated, *n* (%)	49 (16.7)	91 (31.7)	99 (36.9)	
Three lesions treated, *n* (%)	7 (2.4)	16 (5.6)	19 (7.1)	
Mean number of stents ± SD	1.1 ± 0.3	1.2 ± 0.4	1.2 ± 0.6	<0.001
Total stent length ± SD	20.5 ± 11.4	26.9 ± 14.8	30.0 ± 16.8	<0.001
SES usage, *n* (%)	139 (47.4)	150 (52.3)	137 (51.1)	0.48
PES usage, *n* (%)	154 (52.6)	137 (47.7)	131 (48.9)	0.48

PES, paclitaxel-eluting stents; SD, standard deviation; SES, sirolimus-eluting stents; SS, SYNTAX score.

Baseline characteristics and risk factors stratified across SYNTAX score tertiles are reported in *Table 1* and data pertinent to the procedure and the score calculation are reported in *Table 2*.

Stratified clinical outcomes

One-year outcomes across SYNTAX score tertiles are reported in Supplementary material online, *Table S2*; 5-year outcomes across SYNTAX score tertiles are shown in *Figure 2*. Five-year MACE rates were significantly higher in SS_{HIGH} compared with SS_{LOW} [24.2 vs. 12.5%, HR: 2.10 (1.40–3.16), $P < 0.01$], which was also the case for 5-year all-cause mortality, cardiac death, MI, and TLR rates; for all these endpoints there was a significant trend ($P \leq 0.03$) for higher event rates with increasing SYNTAX score tertiles.

Stratifying outcomes across CSS tertiles (*Table 3* and see Supplementary material online, *Table S3*) led to similar results for the comparisons between high and low score tertiles. However, in contrast to the SYNTAX score analysis, event rates for MACE and TLR were significantly higher in CSS_{HIGH} compared with both CSS_{MID} and CSS_{LOW} at 1- and 5-year follow-up; this held

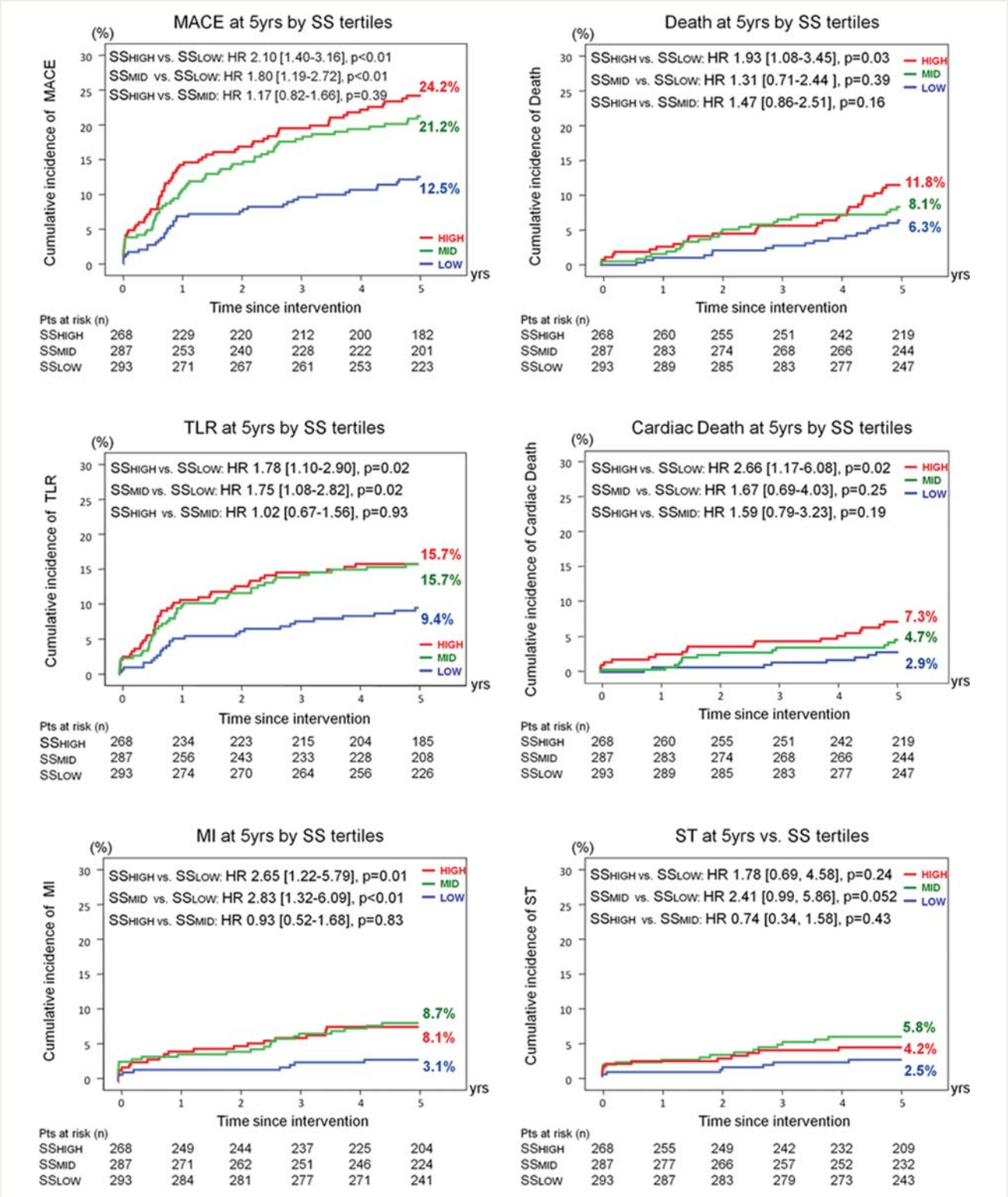

Figure 2 Clinical outcomes at 5-year follow-up stratified across SYNTAX score tertiles. Kaplan–Meier curves are presented for major adverse cardiac events, ischaemia-driven target lesion revascularization, myocardial infarction, all-cause mortality (death), cardiac death and definite stent thrombosis. Tertiles for SYNTAX score were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$. Pairwise comparison results are presented as hazard ratios plus 95% confidence intervals and respective *P*-values.

Table 3 Clinical outcomes at 5-year follow-up stratified across CSS tertiles (univariable analysis)

	CSS_{LOW}, $n = 282$, %	CSS_{MID}, $n = 283$, %	CSS_{HIGH}, $n = 283$, %	HR (95% CI) CSS_{HIGH} vs. CSS_{LOW}	*P*-value	HR (95% CI) CSS_{MID} vs. CSS_{LOW}	*P*-value	HR (95% CI) CSS_{HIGH} vs. CSS_{MID}	*P*-value	*P*-value trend*
Death	5.8	4.6	15.5	2.82 (1.59–5.00)	<0.001	0.80 (0.39–1.67)	0.56	3.51 (1.89–6.54)	<0.001	<0.001
Cardiac death	2.2	2.5	10.0	4.71 (1.94–11.40)	0.001	1.15 (0.39–3.43)	0.80	4.08 (1.78–9.35)	0.001	<0.001
MI	5.1	4.7	9.9	2.02 (1.06–3.85)	0.03	0.93 (0.44–1.97)	0.85	2.18 (1.12–4.22)	0.02	0.03
TLR (ID)	11.3	11.4	17.9	1.71 (1.09–2.67)	0.02	1.03 (0.63–1.69)	0.90	1.65 (1.06–2.58)	0.03	0.03
MACE	14.1	15.3	28.0	2.18 (1.48–3.20)	<0.001	1.10 (0.72–1.70)	0.66	1.97 (1.36–2.87)	<0.001	<0.001
Stent thrombosis (definite)	3.6	3.2	5.5	1.56 (0.70–3.48)	0.27	0.90 (0.37–2.21)	0.82	1.74 (0.76–3.97)	0.19	0.29

CI, confidence interval; CSS, Clinical SYNTAX score; HR, hazard ratio; ID, ischaemia driven; MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization.
CSS tertiles defined as $CSS_{LOW} < 8.0$, $8.0 < CSS_{MID} \leq 17.0$, $CSS_{HIGH} > 17.0$.
*Cochran-Armitage trend test.

also for all-cause mortality, cardiac death, and MI at 5 years. Definite stent thrombosis rates were directionally but not significantly higher in CSS_{HIGH} compared with both CSS_{MID} and CSS_{LOW} at 1-and 5-year follow-up.

SYNTAX Score vs. Clinical SYNTAX score

The ROC curves for MACE, all-cause mortality, and cardiac death at 5-year follow-up are shown in *Figure 3*. The AUC for CSS was significantly larger compared with the one for SYNTAX score regarding cardiac death [0.72 (0.63–0.81) vs. 0.63 (0.54–0.72), $P = 0.002$] and all-cause mortality [0.66 (0.59–0.73) vs. 0.58 (0.51–0.65), $P < 0.001$]. The AUC for MACE was decreased for both scores, being not significantly larger for CSS [0.62 (0.57–0.67) vs. 0.61 (0.56–0.65), $P = 0.24$].

In terms of calibration, CSS was more robust compared with SYNTAX score for all-cause mortality ($\chi^2 = 6.148$, $P = 0.63$ vs. $\chi^2 = 7.674$, $P = 0.36$) and slightly less robust for cardiac death ($\chi^2 = 9.695$, $P = 0.29$ vs. $\chi^2 = 7.377$, $P = 0.39$). Similar to discrimination, calibration for MACE was worse for SYNTAX score and CSS when compared with that for mortality ($\chi^2 = 9.968$, $P = 0.19$ and $\chi^2 = 15.619$, $P = 0.05$).

When reclassifying patients with all-cause mortality from SS into CSS tertiles, 14/72 (19.5%) patients with events were moved to higher risk categories (upward) and 3/72 (4.2%) to lower risk categories (downward), thus resulting in a net gain of 15.3% (*Table 4*). In patients without events, 95 were moved downward and 99 upward, on aggregate a net loss of 0.5%; consequently the NRI was 14.7% ($z = 2.46$, $P = 0.014$). Following the same procedure, NRI for cardiac mortality was more pronounced 19.1% ($z = 2.36$, $P = 0.018$); on the other hand, NRI for patients with MACE was negligible (0.6%, $P = 0.88$) (see Supplementary material online, *Tables S4* and *S5*).

Multivariable analysis

Independent predictors for MACE, all-cause mortality and cardiac death at 5-year follow-up are reported in *Tables 5* and *6*. Because of the strong correlation between SYNTAX score and CSS, each score was entered separately in the multivariable analysis together with other variables significant in univariable analysis. There were no collinearity issues among potential predictors, even when CSS was tested together with left ventricular ejection fraction, age, and creatinine clearance (variance inflation factor <1.76 for all parameters). Nevertheless, the latter three variables being components of ACEF and hence of CSS, were left out of models including CSS, in order to minimize collinearity.

Both scores were independent predictors of MACE (in separate models) next to the number of treated lesions. Addition of diabetes did not significantly impact discrimination for either the CSS ($P = 0.68$) or the SYNTAX score model ($P = 0.88$); calibration improved for the former but got worse for the latter. Regarding all-cause mortality, CSS was an independent predictor next to diabetes. Addition of diabetes to CSS resulted in a model with larger AUC ($P = 0.36$) but worse calibration compared with stand-alone CSS. Similar to all-cause mortality, CSS was an independent predictor for cardiac death next to diabetes. Addition

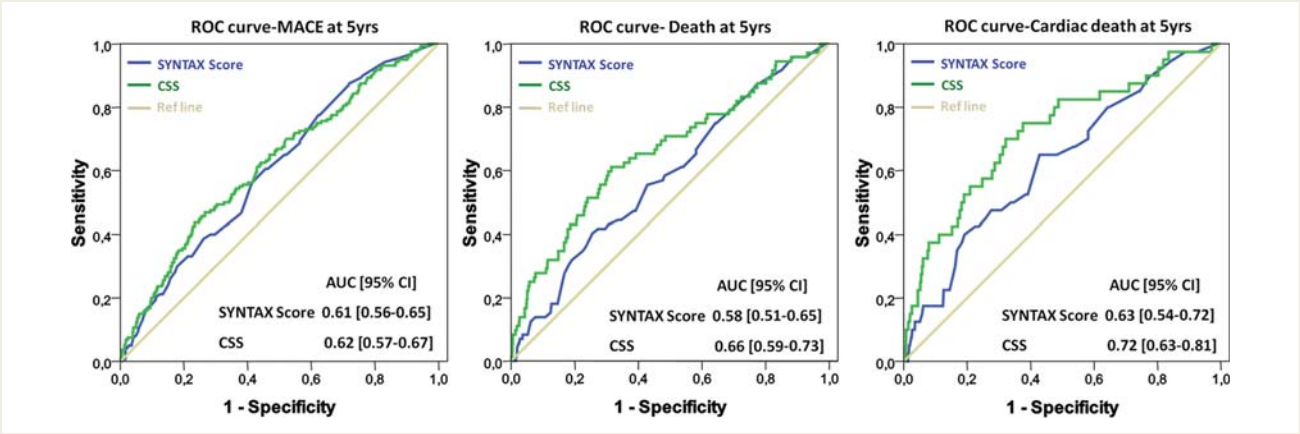

Figure 3 Receiver operating characteristic (ROC) curves for SYNTAX score and Clinical SYNTAX score. Left: 5-year major adverse cardiac events. Middle: 5-year all-cause mortality (death). Right: 5-year cardiac death. AUC, area-under-the-curve, CI, confidence interval, CSS, Clinical SYNTAX score.

Table 4 Five-year all-cause mortality reclassification into CSS tertiles

		CSS tertiles			
		CSS_{LOW}	CSS_{MID}	CSS_{HIGH}	Total
Patients with events					
SS tertiles	SS_{LOW}	14	**1**	**3**	18
	SS_{MID}	**2**	11	**10**	23
	SS_{HIGH}	**0**	**1**	30	31
	Total	16	13	43	72
Patients without events					
SS tertiles	SS_{LOW}	227	**40**	**8**	275
	SS_{MID}	**39**	174	**51**	264
	SS_{HIGH}	**0**	**56**	181	237
	Total	266	270	240	776

SS, Clinical SYNTAX score; SS, SYNTAX score.
Score tertiles as defined in text.
Patients indicated in bold were moved to higher risk (above the diagonal) and lower risk (below the diagonal) categories respectively, when reclassified.

of diabetes to CSS resulted in a model with slightly larger AUC ($P = 0.52$) and better calibration compared with stand-alone CSS.

Stratified analysis of drug-eluting stents performance

Overall adverse clinical event rates for each treatment arm are reported in *Table 7* for the 848 patients included in this substudy. Stratified comparisons of PES vs. SES across CSS tertiles for clinical outcome measures at 1- and 5-year follow-up are shown in *Figures 4* and *5*, respectively. Among patients in the higher CSS tertile, there was an increase in MACE rates with PES compared with SES at 1-year follow-up [23.9 vs. 8.6%, HR: 3.02 (1.56–5.83), $P = 0.001$], which was mainly driven by increased TLR rates in the PES arm [18.1 vs. 6.5%, HR: 2.91 (1.36–6.25), $P = 0.004$]. Higher MACE rates for the PES arm persisted at 5 years [34.7 vs. 21.3% for SES, HR: 1.85 (1.17–2.93), $P = 0.008$], whereas differences in TLR rates were no longer significant [22.0 vs. 14.0%, HR: 1.70 (0.96–3.02), $P = 0.07$]. The interaction term between treatment arm and CSS tertiles for 5-year MACE had a $P = 0.050$, suggesting a genuine effect, whereas for 1-year MACE, $P = 0.10$. Interaction term *P*-values for all-cause mortality, MI and TLR were 0.76, 0.26, 0.29 at 1-year and 0.43, 0.18, 0.39 at 5-year follow-up, respectively.

Stratifying outcome across SYNTAX score tertiles led to similar results regarding the performance of PES vs. SES (see Supplementary material online, *Figures S1* and *S2*). However, the interaction term between treatment arm and SYNTAX score tertiles for all endpoints at 1- and 5-year follow-up had a *P*-value consistently >0.05; thus conclusions drawn from these results should be interpreted with caution.

Discussion

The main findings of this study indicate that the SYNTAX score, and to a greater extent the CSS, have an important role to play in the risk stratification of very long-term clinical outcomes in an all-comers population receiving drug-eluting stents. Both scores were identified as independent predictors of 5-year MACE, nevertheless having modest discriminatory power and calibration for this endpoint. Clinical SYNTAX score was also an independent predictor of 5-year all-cause mortality and cardiac death; its superior discriminatory power and calibration compared with SYNTAX score resulted in a significant improvement in risk stratification. An additional potential role of the CSS in the assessment of stent performance was also identified.

Although the current study employed comparable inclusion criteria to the two most recent all-comers studies, the mean SYNTAX score of 11.7 was lower than the 13.5 and 14.6 seen in the LEADERS and RESOLUTE studies, respectively[7,11]; similarly CSS tertile values in our study were lower compared with the

Table 5 Independent predictors of adverse events at 5-year follow-up (models including SYNTAX score)

Variables	HR (95% CI)[a]	*P*-value	AUC (95% CI)[c]	H–L χ^2 (*P*-value)[c]
MACE				
SYNTAX score[b]	1.03 (1.01–1.05)	0.003	0.63 (0.58–0.68)	7.78 (0.46)
Number of lesions treated	1.54 (1.21–1.96)	<0.001		
All-cause mortality				
Age[b]	1.06 (1.04–1.09)	<0.001	0.71 (0.65–0.78)	10.967 (0.20)
Diabetes mellitus	2.14 (1.32–3.46)	0.002		
Cardiac death				
Age[b]	1.07 (1.03–1.11)	<0.001	0.75 (0.67–0.83)	5.425 (0.71)
Diabetes mellitus	2.01 (1.05–3.85)	0.04		
LVEF[b]	0.97 (0.94–0.99)	0.006		

AUC, area under the curve; CI, confidence interval; H–L, Hosmer–Lemeshow; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.
[a]After adjustment for confounding factors.
[b]Per unit increase.
[c]For the entire model.

Table 6 Independent predictors of adverse events at 5-year follow-up (models including CSS)

Variables	HR (95% CI)[a]	*P*-value	AUC (95% CI)[c]	H–L χ^2 (*P*-value)[c]
MACE				
CSS[b]	1.009 (1.005–1.013)	<0.001	0.65 (0.60–0.69)	10.214 (0.25)
Number of lesions treated	1.58 (1.24–2.01)	<0.001		
All-cause mortality				
CSS[b]	1.011 (1.006–1.015)	<0.001	0.68 (0.61–0.75)	7.576 (0.48)
Diabetes mellitus	2.21 (1.34–3.66)	0.002		
Cardiac death				
CSS[b]	1.012 (1.006–1.018)	<0.001	0.74 (0.65–0.82)	5.614 (0.69)
Diabetes mellitus	2.23 (1.13–4.39)	0.02		

AUC, area under the curve; CI, confidence interval; CSS, Clinical SYNTAX score; H–L, Hosmer–Lemeshow; HR, hazard ratio; MACE, major adverse cardiac events.
[a]After adjustment for confounding factors.
[b]Per unit increase.
[c]For the entire model.

RESOLUTE (0–11.2, >11.2–24.7, >24.7). This observation is not surprising considering the differing time periods when patients were enrolled in the three studies (SIRTAX 2003–2004, LEADERS 2006–2007, RESOLUTE 2008), and the increasing number of co-morbidities now seen in patients presenting for revascularization. On the other hand, the ARTS II trial enrolled patients during a similar time to the SIRTAX study; however, inclusion criteria required patients to have at least two-vessel coronary artery disease.[25] The prevalence of multi-vessel disease in SIRTAX was close to 60%,[19] and therefore the lower mean and tertile cut-off values, seen for the SYNTAX score and CSS in the current study are entirely expected.

As mean SYNTAX score values decrease in patient cohorts with less complex disease compared with the seminal SYNTAX trial, one would hypothesize that differences in clinical outcomes between individuals would go increasingly undetected by a score solely based on angiographic parameters; clinical variables may therefore compensate for this possible decrease in sensitivity of the SYNTAX score. This hypothesis has been explored in diverse patient populations by integrating clinical information together with angiographic parameters into hybrid risk scores, such as the CSS,[11,18] the Global risk classification (GRC)[10,26] and the New Risk Stratification (NERS).[27] In our study, we chose CSS as the most parsimonious of these hybrid scores to assess the incremental value of clinical data in risk stratification over stand-alone SYNTAX score; thereby we tried to limit statistical over-fitting and multiple collinearity between potential predictors.[28]

The discriminatory power for MACE was similar for SYNTAX score and CSS in our study; *C*-statistics were comparable with the findings for 5-year MACE in the ARTS II (AUC: 0.57 and 0.62)[18] and for 1-year MACE in the RESOLUTE (AUC: 0.59 and

Table 7 Clinical outcomes at 1- and 5-year follow-up by treatment arm (univariable analysis)

	PES, $n = 422$, %	SES, $n = 426$, %	HR (95% CI) PES vs. SES	*P*-value
1-year outcome				
Death	2.1	1.4	1.53 (0.54–4.29)	0.42
Cardiac death	1.4	0.9	1.52 (0.43–5.40)	0.51
Myocardial infarction	4.1	2.8	1.44 (0.69–3.02)	0.33
TLR (ID)	10.8	5.7	1.95 (1.19–3.20)	0.008
MACE	13.6	7.5	1.86 (1.20–2.86)	0.005
Stent thrombosis (definite)	1.7	1.9	0.88 (0.32–2.44)	0.81
5-year outcome				
Death	8.4	8.8	0.97 (0.61–1.54)	0.89
Cardiac death	5.1	4.6	1.13 (0.61–2.10)	0.70
Myocardial infarction	7.3	5.8	1.28 (0.75–2.20)	0.36
TLR (ID)	14.8	12.3	1.26 (0.87–1.82)	0.23
MACE	20.7	17.7	1.22 (0.90–1.67)	0.20
Stent thrombosis (definite)	4.2	4.1	1.02 (0.52–2.00)	0.96

CI, confidence interval; HR, hazard ratio; ID, ischaemia driven; MACE, major adverse cardiac events; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; TLR, target lesion revascularization.

0.62)[11] and better compared with the CUSTOMIZE registry left main PCI population (AUC for 2-year MACE 0.52 and 0.50 for SYNTAX score and CSS, respectively).[10] Nevertheless, risk stratification was not very well balanced between score tertiles; specifically, CSS showed diminished ability to discriminate between patients at low and intermediate risk, reflecting findings of earlier studies.[10,18] SYNTAX score was recently shown to have higher discriminatory power for repeat revascularization[11]; since MACE rates were mainly driven by TLR rates in our study, the lack in reclassification improvement with CSS can be explained.

On the other hand, for harder endpoints, such as the all-cause and cardiac mortality, significantly better discrimination and equivalent or better calibration compared with SYNTAX score translated into more refined risk stratification with the CSS. Interestingly, whereas *C*-statistics for both scores regarding mortality were comparable with respective measures in the ARTS II and CUSTOMIZE populations, calibration measures were improved in our study. This refinement in stratification resulted in CSS being an independent predictor for mortality, contrary to SYNTAX score, as also demonstrated in similar studies.[11,13] Very long-term mortality is expected to be dependent on well-known predictors of outcome after PCI, such as age and diabetes mellitus; age is included in the CSS, while diabetes mellitus is known to impact on renal function. Similarly, the EuroSCORE,[29,30] which has also been shown to be effective in risk stratifying patients, either as a stand-alone score or integrated in GRC,[10,26] does not include assessment of diabetic status, but renal function. Diabetes was an independent predictor for all-cause and cardiac mortality next to CSS in our study; nevertheless a model incorporating CSS and diabetes did not significantly improve discrimination or calibration for these outcomes. We may assume that to a certain extent the effect of diabetes has translated into higher angiographic complexity and diminished creatinine clearance.

An added finding of our study is the differential performance of PES and SES for patients in the highest SYNTAX score and CSS tertiles. In the original SIRTAX trial publication,[19] there was a significant increase in the primary endpoint at 9-month follow-up in patients allocated to PES compared with SES; this difference in MACE was mainly driven by the increased TLR rates in the PES treatment arm and was attributed to increased angiographic or procedural complexity. In successive reports from the same group, similarly significant differences in 2-year MACE have been reported between PES and SES, when implanted in vessels with a reference size <2.75 mm,[31] or when studied separately in diabetic patients.[32] In both analyses, differences in MACE were driven by significantly decreased TLR rates with SES. Not unexpectedly, in our study, significantly increased MACE rates with PES were observed within the subgroup of patients with increased angiographic complexity. It has already been suggested in the LEADERS[33] and the RESOLUTE[11] trials, that SYNTAX score could identify a subgroup of patients, where there is a difference in clinical outcomes between devices. Nevertheless, in our study respective hazard ratios were inflated, when MACE was stratified across the CSS tertiles; more importantly, the respective interaction term between treatment arm and CSS tertiles reached statistical significance for 5-year MACE, indicating a potential role of CSS-based stratification in device selection. However, it should be recognized that this was a subgroup analysis, not pre-specified in the original study, thus the superiority seen with SES could be the result of a type I error.

Limitations

The current study is limited by its *post hoc* nature. As the cardiologists adjudicating the diagnostic angiograms were blinded to procedural data, and taking into account the modest reproducibility of SYNTAX score even among experienced cardiologists,[34] a discrepancy in results cannot be ruled out, would the scores have been

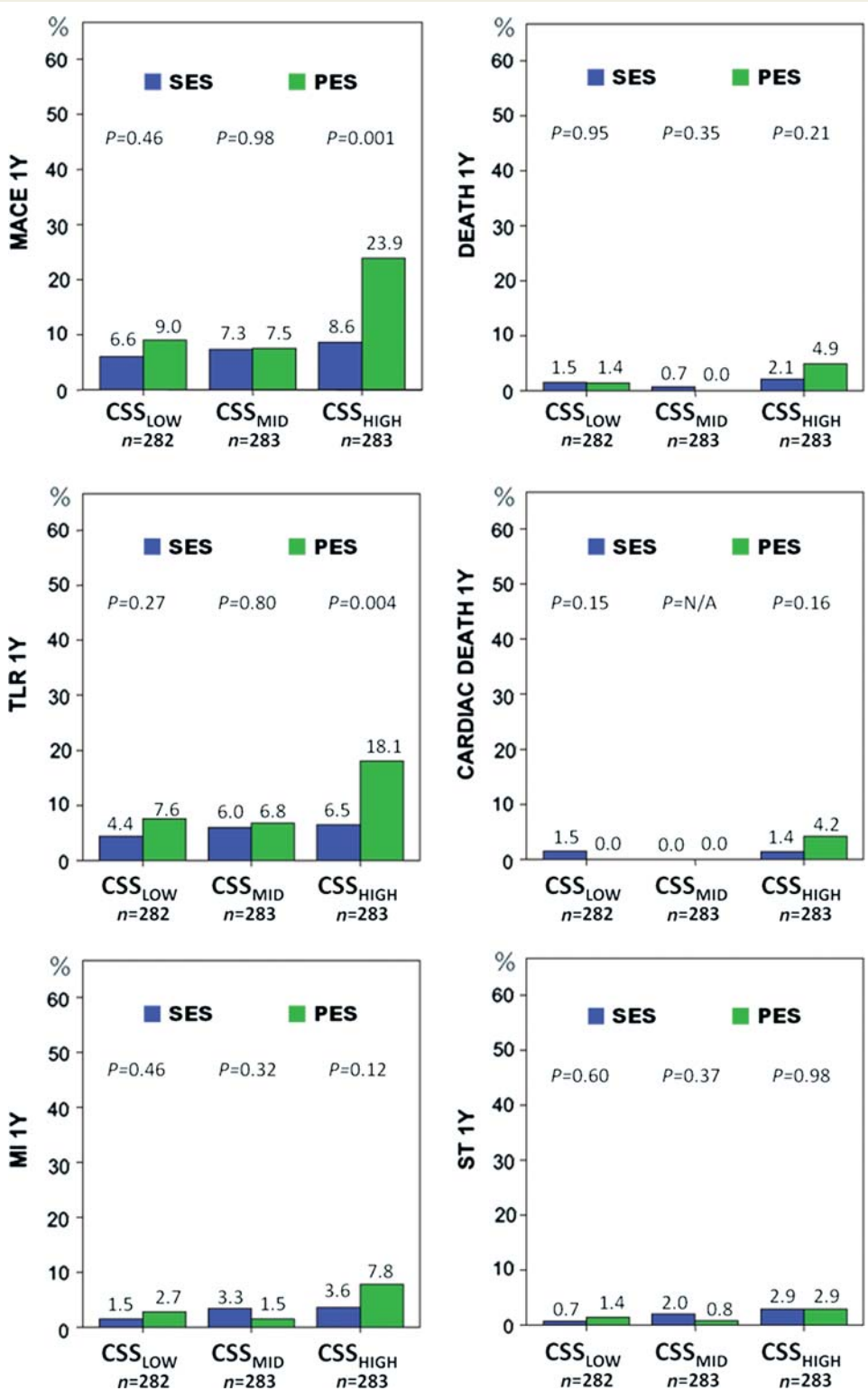

Figure 4 Stratified comparison between treatment arms for clinical outcomes at 1-year follow-up. Events are stratified across Clinical SYNTAX score tertiles defined as $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17.0$, $CSS_{HIGH} > 17.0$. Clinical outcomes' abbreviations as defined in text. PES, paclitaxel-eluting stents, SES, sirolimus-eluting stents, N/A, non-applicable.

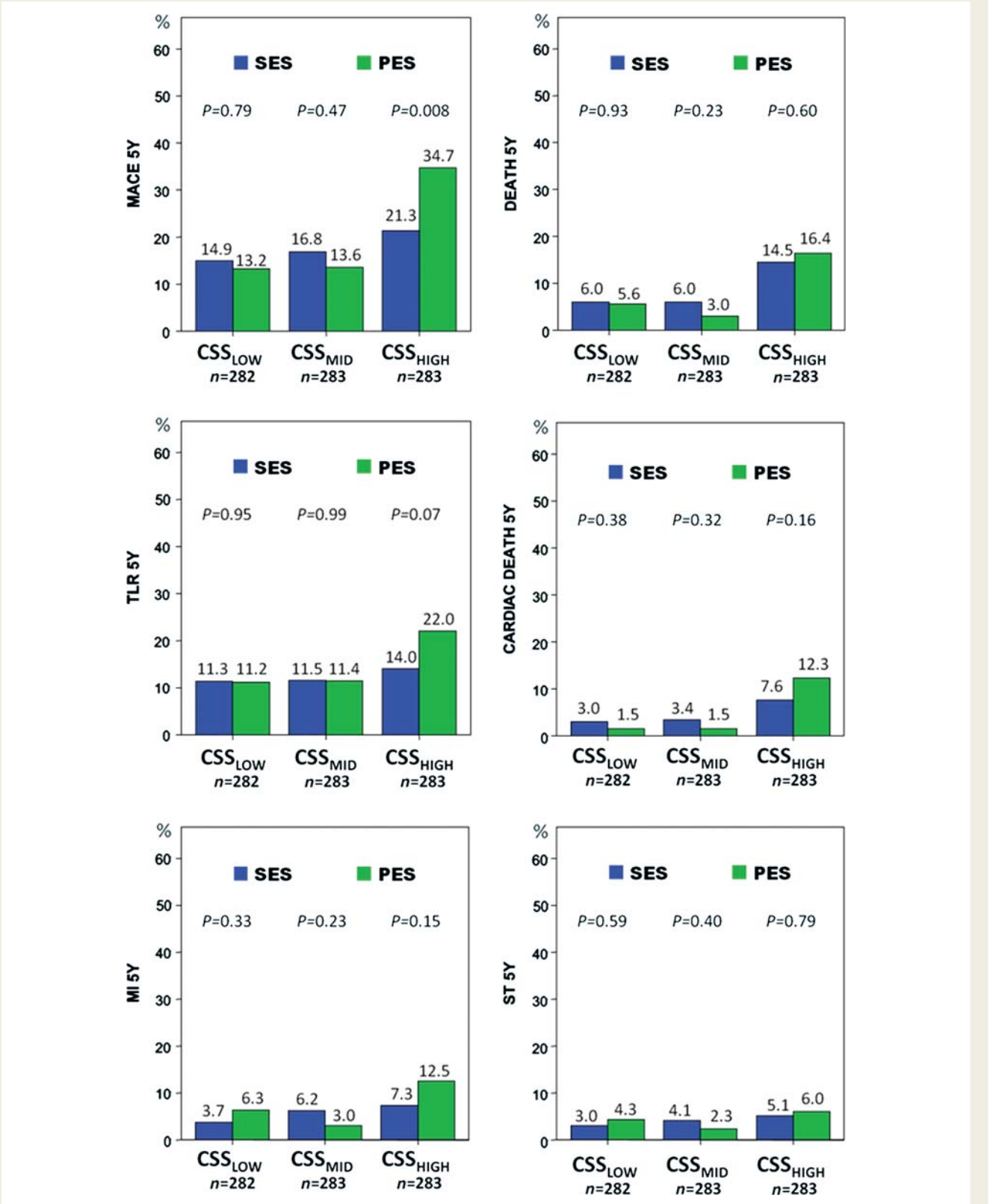

Figure 5 Stratified comparison between treatment arms for clinical outcomes at 5-year follow-up. Events are stratified across Clinical SYNTAX score tertiles defined as $CSS_{LOW} < 8.0$, $8.0 < CSS_{MID} \leq 17.0$, $CSS_{HIGH} > 17.0$. Clinical outcomes' abbreviations as defined in text. PES, paclitaxel-eluting stents, SES, sirolimus-eluting stents.

collected prospectively. However, in the case of the SIRTAX trial, this is purely hypothetical, as the SYNTAX score algorithm had not been developed at the time of patient enrolment.

Well-known limitations of the SYNTAX score should also be acknowledged. Patients with prior CABG had to be excluded from the study; moreover, scoring acute coronary occlusions as total occlusions may have resulted in an inflation of the individual scores overestimating the complexity of recanalization. However, it has been recently shown that SYNTAX score values derived after the instrumentation of the infarct-related artery and therefore probably lower compared with the values derived with the standard method, could have resulted in an erroneous risk stratification; it should not be overlooked that the absence of flow itself holds an adverse impact on long-term outcome.[9] Moreover, irrespective of the method used, SYNTAX score for acute MI patients was proven to improve the discriminatory power of models solely based on clinical variables, such as the TIMI risk score.[35] Lastly, in our study, multivariable analysis adjusted for clinical presentation, rendering SYNTAX score and CSS as independent predictors of MACE and CSS as independent predictor of mortality.

Conclusions

The SYNTAX score and to a greater extent the CSS were able to stratify risk for very long-term adverse clinical outcomes in an all-comers population receiving drug-eluting stents. Predictive accuracy for 5-year mortality was improved using the CSS. Within the highest score tertiles 5-year MACE increased with use of paclitaxel- compared with sirolimus-eluting stents. This study is yet another step to map the performance of SYNTAX score and CSS in the entire range of coronary artery disease seen in daily clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Chapter 16

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

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

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

KEYWORDS

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

Abstract

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

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

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

Introduction

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

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

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

Methods

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

CABG SYNTAX SCORE ANALYSIS

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

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

CABG SYNTAX SCORE

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

SYNTAX SCORE

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

LEAMAN SCORE

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

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

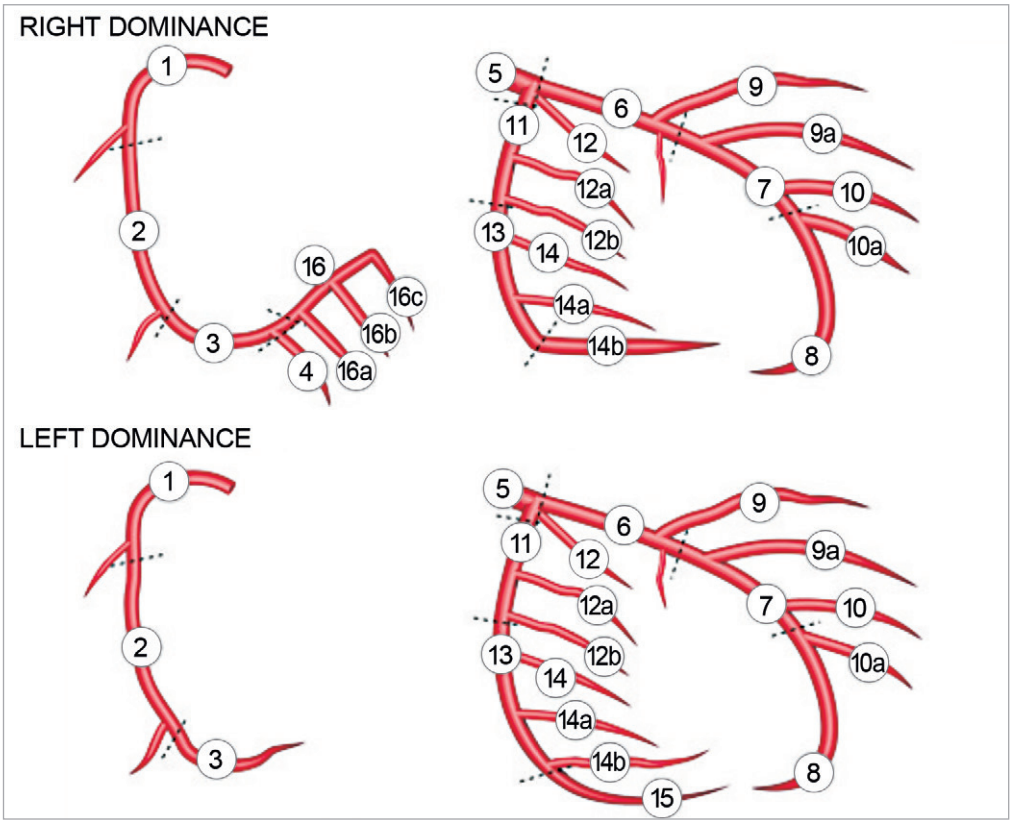

Figure 1. *The effect of right and left arterial dominance on the segment numbering – refer to Table 1 for the segment-weighting for the respective arterial segments. Anatomical description of the segment numbers has previously been described[2] and is included in the supplementary appendix.*

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

CALCULATION OF THE CABG SYNTAX SCORE

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

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

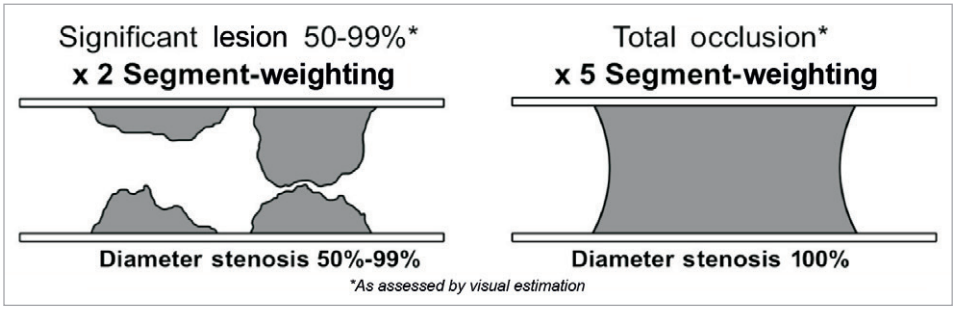

Figure 2. *Segment-weighting multiplication factors utilised in the SYNTAX Score – used to calculate the points required to deduct from the "native SXscore" to calculate the CABG SYNTAX Score.*

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

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

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

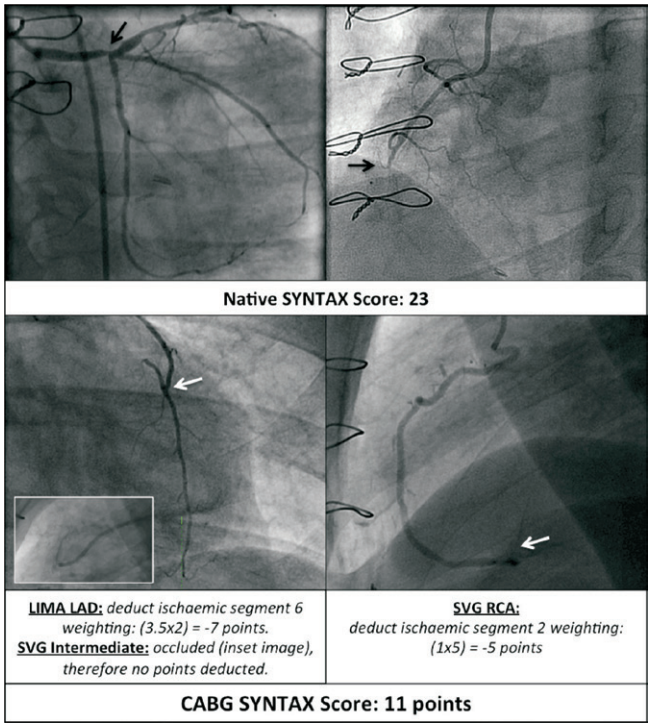

Figure 3. *Example of the calculation of the CABG SXscore in a patient with distal left main trifurcation disease and an occluded mid RCA. The native SXscore was 23 (upper images). A patent LIMA to the LAD with no intervening obstructive coronary disease (lower left image) led to the deduction of 3.5×2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

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

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

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

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

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

4. Any further native coronary disease clearly identified through the angiograms of the bypass grafts were added to the native SXscore. Lesions ≥3 reference vessel diameters were viewed as two separate lesions and within this distance as one lesion.

5. If an obstructive coronary lesion interferes with the blood flow to the vessel being protected by the bypass graft, then the points deducted were for the segment weighting of the lesion only **(Figure 5)**.

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

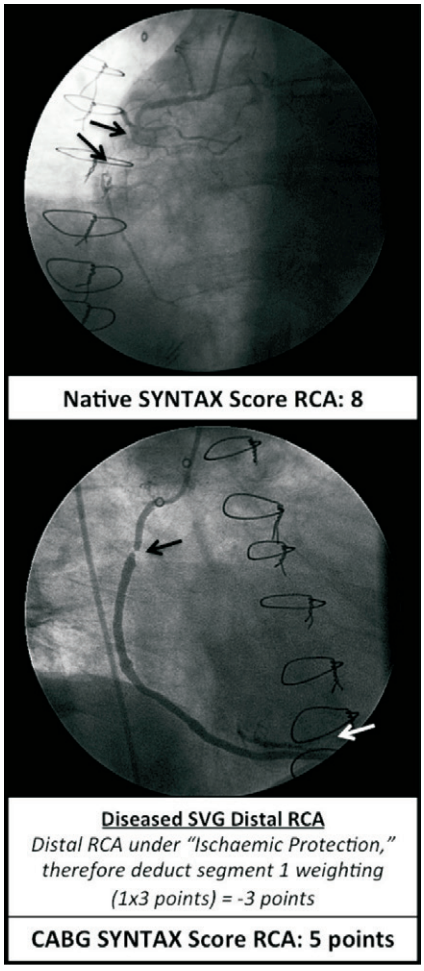

Figure 4. *Principle of "ischaemic protection" in the CABG SXscore. Upper image: occluded mid RCA (segment 2 - black arrows) with bridging collaterals: native SXscore for the RCA is 8. Lower image: SVG anastomosed to distal RCA (white arrow). If the SVG was free of obstructive disease then the CABG SXscore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

STATISTICAL ANALYSIS

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

Results

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

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

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

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

REPRODUCIBILITY ANALYSES

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

CLINICAL OUTCOMES

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

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

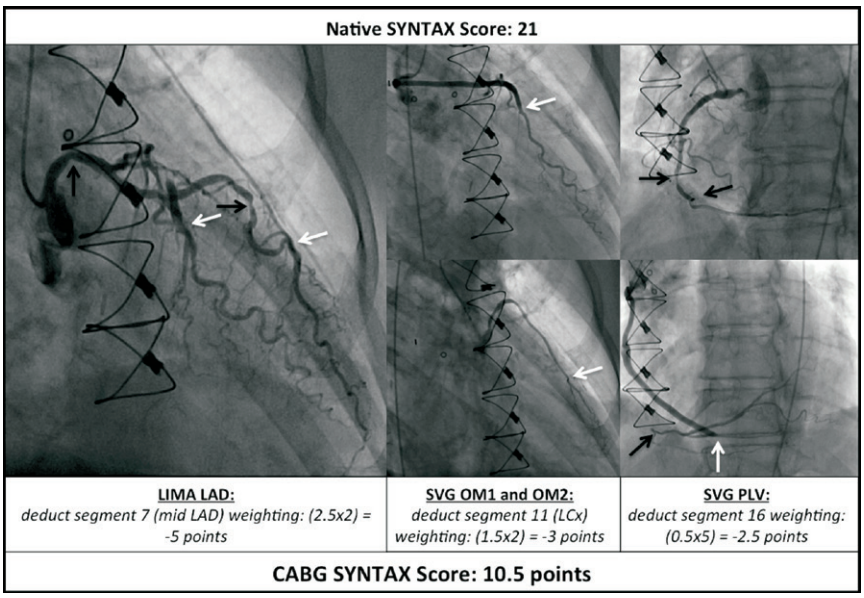

Figure 5. *Example of the calculation of the CABG SXscore in a patient with mid left main and two-vessel coronary disease. Native SXscore was 21. A patent LIMA anastomosed to the mid LAD, with upstream native mid LAD disease, and led to the segment-weighting (2.5×2 points) of the mid LAD (segment 7)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

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

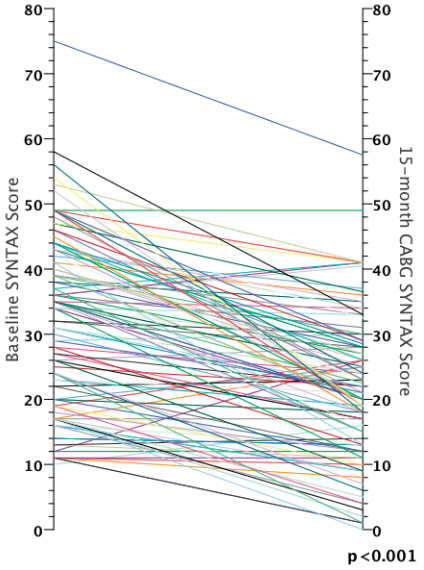

Figure 6. *Reduction in the CABG SYNTAX Score at scheduled coronary angiography at 15 months, compared to the baseline SYNTAX Score (n=113).*

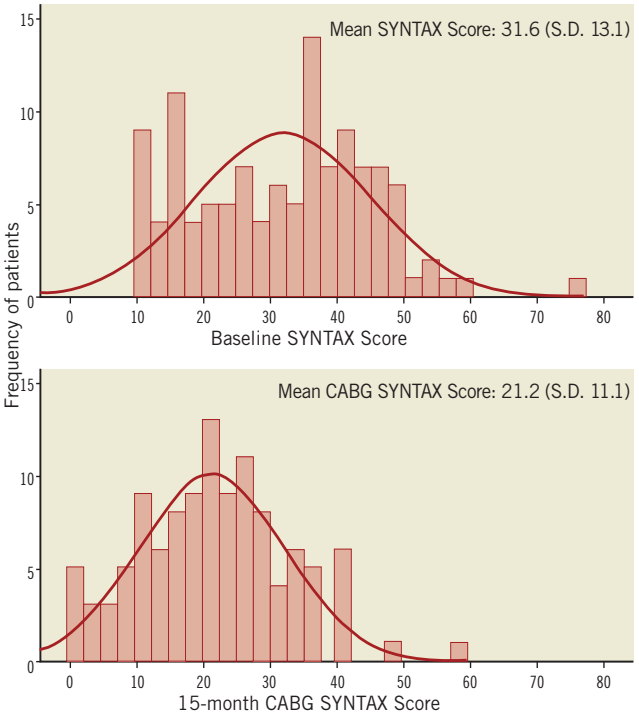

Figure 7. *Distribution of the baseline SYNTAX Scores and the 15-month CABG SYNTAX Scores (n=113). Note the significant decrease in the mean CABG SYNTAX Score compared to the mean baseline SYNTAX Score (p<0.001). SD: standard deviation.*

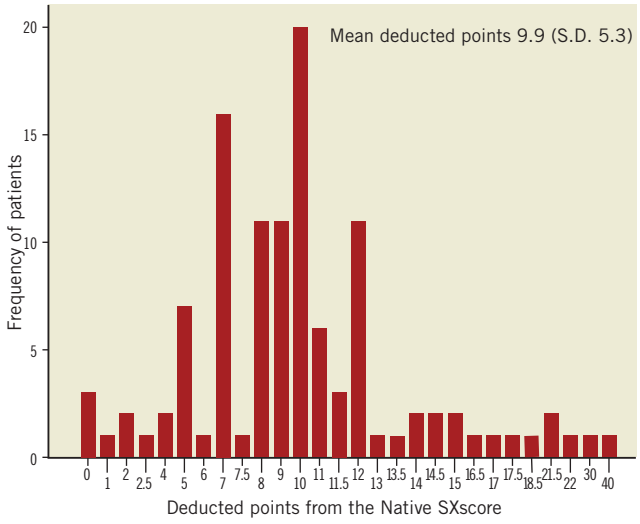

Figure 8. *Distribution of the deducted points from the native SXscore to calculate the CABG SXscore (n=113). SD: standard deviation.*

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

Discussion

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

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

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

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

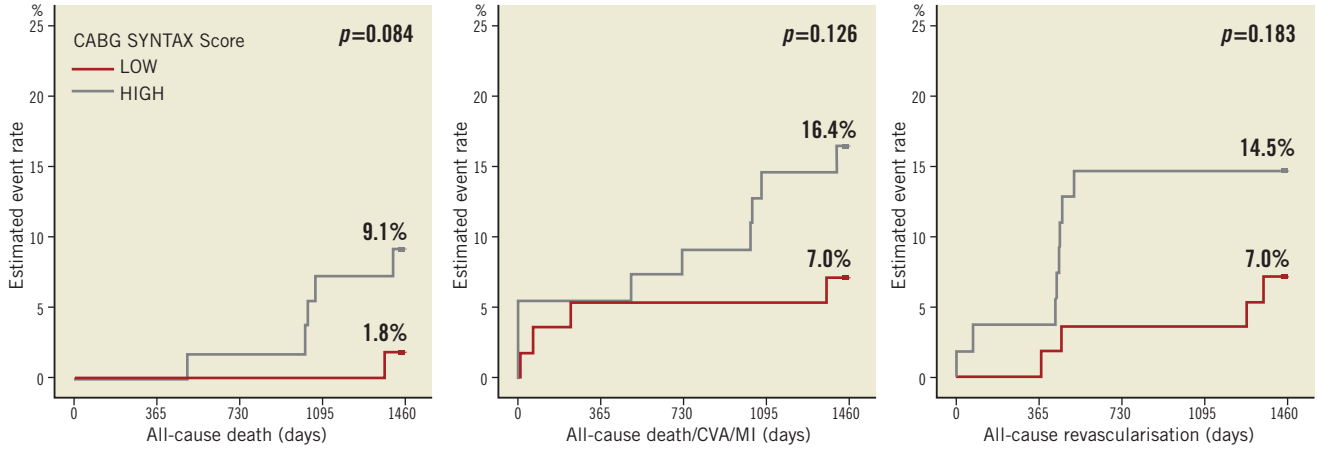

Figure 9. *Clinical outcomes separated by the median of the CABG SYNTAX Score into low (0-21) (n=58) and high (≥22) (n=55) score groups. A non-significant trend towards higher mortality (left image) and all-cause death/CVA/MI (middle image) were evident in the high CABG SYNTAX Score group at four years.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

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

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

ASSOCIATION OF THE CABG SYNTAX SCORE WITH CLINICAL OUTCOMES

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

PREVIOUS STUDIES

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

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

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

IMPLICATIONS OF THE CABG SYNTAX SCORE FOR CLINICAL PRACTICE

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

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

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

POTENTIAL CLINICAL AND RESEARCH APPLICATIONS OF THE CABG SYNTAX SCORE

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

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

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

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

STUDY LIMITATIONS

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

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

FUTURE DIRECTIONS

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

Conclusion

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

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Conflict of interest statement

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

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

Online data supplement

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

Online data supplement

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Chapter 17

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

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

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

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

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

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

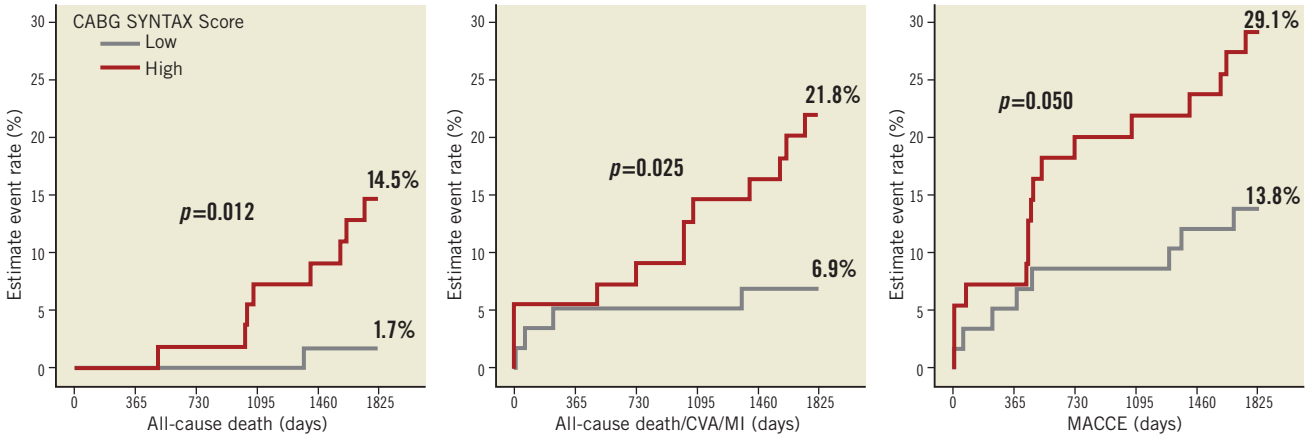

Figure 1. *Outcomes (Kaplan-Meier curves) separated by the median of the CABG SYNTAX Score into low (0-21) (n=58) and high (≥22) (n=55) score groups. At 5 years, significantly greater all-cause mortality (left image), significantly greater all-cause death/CVA/MI (middle image) and MACCE (right image)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

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Conflict of interest statement

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

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PART V

Summary and conclusions
Samenvatting en conclusies
PhD Portfolio
List of publications
Acknowledgements
About the author

Summary and conclusions

Bifurcation QCA: development and validation

Since its inception in 1958, invasive coronary angiography has been considered essential in the diagnostic evaluation of coronary artery disease and the guidance of percutaneous coronary intervention (PCI). Quantitative coronary angiography (QCA) has already been proven an objective and reproducible way to quantify the extent of coronary stenoses located in single-vessel segments. However, in the analysis of bifurcation lesions, the validity of single-vessel QCA has been brought into dispute, as it fails to predict the functional significance of ostial side-branch (SB) stenosis. Dedicated bifurcation software algorithms have been developed in order to make up for the shortcomings of single-vessel QCA. However definitions of angiographic measures, such as the reference vessel diameter (RVD), are at variance, thus resulting in different measures for the percent diameter stenosis (DS). Therefore, the European Bifurcation Club has advocated the reconciliation of diverse methodologies and the creation of a standard QCA approach for the evaluation of bifurcation lesions.

However, before embarking on the validation of these algorithms we had to come up with a suitable gold standard. After a thorough review of the relevant literature, we designed and precision manufactured six plexiglas phantoms **(Chapter 2),** each phantom mimicking a coronary vessel with three successive bifurcations lesions with variable anatomy and Medina class.

Using the aforementioned bifurcation phantoms, we first validated two models for bifurcation two-dimensional (2-D) QCA analysis **(Chapter 3)** each of them reporting minimal lumen diameter (MLD), RVD and DS over a varying number of segments. The former, a simplified 6-segment model, reflects the proximal main vessel (PMV), the distal main vessel (DMV) and the SB allowing a quick overview of results during a procedure. The latter, a more detailed 11-segment model, provides additional sets of results for ostial DMV and SB positions and the bifurcation region itself aiming at accurate localization of MLD, RVD and DS pre-, post-PCI and at follow-up angiography. Both models provided highly repeatable results in terms of diameter derived parameters and in excellent agreement with each other and with the true phantom dimensions. However, this study had two limitations; firstly, accuracy and precision was somewhat diminished for small phantom MLD values (≤0.70 mm) and secondly, only local reference (user-defined) obstruction analysis was employed.

An advanced lumen detection algorithm integrated into the following version of the same software improved MLD quantification for true MLD <0.7 mm and thereby resulted in highly accurate and precise diameter measurements over the entire range of diameter values anticipated in clinical practice **(Chapter 4)**. Furthermore, an optimized algorithm for automatic reference (interpolated) obstruction analysis, resulted in significantly higher reproducibility for RVD and DS values compared with local reference analysis. Naturally these effects are pronounced in real coronary cases. Operators may choose different landmarks dependent on individual perception of what constitutes a true bifurcation. Thus analyzed segments may become exceedingly long and tapered, which is the case where automatic reference analysis is preferred. Local reference analysis can still be beneficial in ectatic or diffusely diseased vessels, where interpolation could be severely mistaken, based on either too large or too small diameter values, respectively.

Next to diameter-derived measurements, 2-D bifurcation angle (BA) was calculated with a dedicated algorithm following the definitions adopted by the European Bifurcation Club; angle calculations were model independent and highly reproducible. Bearing in mind that the phantom BA values were determined in a 3-D space, the 2-D BA calculated values showed remarkable accuracy and precision not varying significantly between software versions. The widest opening of a given bifurcation and the best view of the SB ostium usually coexist in one single good 2-D image, the antero-posterior view in the phantoms' design. Declining accuracy and precision for 2-D BA calculations in rotated views reflect this phenomenon **(Chapter 3 and 4)**.

In order to overcome potential limitations associated with 2-D QCA of bifurcation lesions, we developed a novel and dedicated 3-D bifurcation QCA software **(Chapter 5)**. We described the methodology, whereby combining two 2-D image data sets, the new software is able to correct for the geometric distortion of the angiography gantry, perform a spatially accurate 3-D reconstruction and true quantitative 3-D bifurcation analysis determining lesion characteristics including BA values. The novelty but also the accuracy of the reconstruction and the derived measurements heavily relies upon the definition of the central bifurcation area, described as the polygon of confluence.

Since 3-D reconstruction combines two 2-D projections, the issue of overlapping vessels in tortuous bifurcation lesions may still be a problem; a reconstruction utilizing more than two projections may yield optimal 3-D images, at the expense of increasing

complexity of analytical software. Following this reasoning, we revised our 3-D reconstruction methodology in order to allow reconstructions of more than two 2-D projections **(Chapter 6)**. Furthermore, we adopted the methodology described for 2-D bifurcation automatic reference obstruction analysis applying it to the 3-D reconstructed model. Concepts introduced in **Chapter 4** are projected to the current 3-D methodology, resulting in a comprehensive 3-D bifurcation QCA analysis. Measurements for MLD, RVD, DS and BA derived from the QCA 3-D bifurcation software were validated against our precision manufactured phantom bifurcations **(Chapter 6)** showing high accuracy, precision and reproducibility.

In vitro validation has the obvious limitation of being based on static objects, acquired under ideal angiographic conditions. In our phantom bifurcations, lesions were circular-shaped in cross-sectional view for design simplicity and due to manufacturing constraints. On the contrary, more than 50% of coronary lesions are asymmetric, where 2-D analysis is known to be inaccurate. Furthermore, as opposed to straight phantom vessel segments, coronary vessels usually have curved trajectories, which augment the effect of foreshortening in 2-D projection images. Therefore, we have to assume that the incremental value of 3-D bifurcation QCA as compared to 2-D analysis may have been underestimated.

Visual assessment has been the intuitive way to interpret the coronary angiogram; nevertheless, “eyeballing” has been proven to be rather inaccurate and highly variable. This effect is even more pronounced in bifurcation lesions compared with single-vessel segments. The intuitive way, in which even experienced operators interpret stenosis severity at or close to the ostia of distal bifurcation branches, is by referring to the PMV segment, thus resulting in overestimated DS values. Conversely, lesions in the PMV may be underestimated. Indeed, these phenomena were replicated when conducting our survey among experts in the field of bifurcation PCI **(Chapter 7)**; visual estimates of DS in phantom bifurcation lesions were highly variable compared to current bifurcation QCA standards. The recorded large variability of visual estimates in equivocal stenoses and the low inter-observer agreement in derived Medina classification may justify the inclusion of online bifurcation QCA in the decision making process.

Bifurcation QCA in clinical studies

Following the development and validation of dedicated bifurcation QCA software, the application in real-life clinical settings was the next step. We reported long-term outcome data on the V stenting technique in *de novo* bifurcation lesions using drug-eluting stents in patients from the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and the T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registries (**Chapter 8).** We concluded that in this real-world cohort, late clinical events stand in accord with studies on competitive techniques. Early outcome was less encouraging, probably due to the baseline risks, but on closer scrutiny could appear circumstantial and endpoint-dependent. Angiographic parameters, both diameter-derived ones as well as BA values, were determined with dedicated bifurcation QCA algorithms according to a multiple segment model in all patients where films could be retrieved, thereby confirming feasibility of analysis in this relatively small study.

Furthermore, we investigated the long-term clinical outcomes and independent predictors of major cardiac events in unprotected left main coronary artery disease patients treated by PCI with drug-eluting stents in patients from the RESEARCH and T-SEARCH registries (**Chapter 9)**. We reported a late increase in adverse events up to 4 years, which warrants careful follow-up of the patients receiving drug-eluting stents in the left main stem. Among other variables BA was evaluated as a possible parameter for risk stratification. Although 3-D QCA was available, it was feasible in only half the patients due to the unavailability of 2 separate angiographic views of more than 30° apart; in the remaining patients 2-D QCA was performed. Pre-PCI distal BA, that is the angle between the left anterior descending and left circumflex arteries following the European Bifurcation Club definition, was determined both in the diastolic and systolic phase. Systolic BA values exhibited a weak statistical association with the 4-year patient-oriented composite endpoint in the univariate analysis, wherein patients with higher pre-PCI BA values showed a trend for worse outcome. However, BA did not remain as a significant predictor of adverse clinical outcomes in the multivariate analysis; this could be attributed to heterogeneous QCA analysis and a relatively small number of patients.

Motivated by these mixed signals, a promise for predictive ability of the BA parameters in an underpowered study with relatively low rates of 3-D analysis, we decided to further investigate the 3-D BA parameters of the left main coronary artery, the effect of

PCI on this angulation, and the impact of 3-D BA on 1-year clinical outcomes in a larger cohort, namely the patients randomized to left main PCI within the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial **(Chapter 10)**. Complete 3-D BA analysis, before and after PCI, was feasible in 75% of cases; one could expect that prospective collection of appropriate cineangiograms with the view to perform this kind of analysis could further limit the number of non-analyzable cases to <10%. This study was the largest one to-date to describe the 3-D left main angulation; BA parameters were shown to vary considerably. Furthermore, we showed that cardiac motion exerts a reciprocal effect on proximal and distal BA, the former being increased and the latter decreased during systole. In addition, PCI primarily modifies the distal BA; overall, angles were decreased, whereas the narrowest pre-PCI angles were actually increased after the procedure. However, our analysis did not show enough evidence to support 3-D BA as a potential predictor of outcome; there was a weak trend indicating higher adverse event rates in patients with wider distal left main angles when 2 stents were implanted in the left main bifurcation.

As soon as the 5-year clinical outcomes of the SYNTAX trial were made available, the impact of 3-D BA parameters was further investigated **(Chapter 11)**. Similar to our 1-year findings, stratification across pre-PCI diastolic distal BA tertiles failed to show any difference in adverse event rates either in the entire study population or in the patients who had actually undergone bifurcation PCI. On the other hand, bifurcation PCI patients with a restricted post-PCI systolic-diastolic distal BA range, meaning a diminished "freedom of movement" of the left main bifurcation, showed significantly higher adverse event rates. Even when adjusted for various clinical, angiographic and procedural variables, it still proved an independent predictor of 5-year adverse clinical events. It is possible that this study provides us with new insights into the biomechanics of stent failure in bifurcation lesions, the left main bifurcation being the most important of all in the human coronary tree.

Finally, we reported the acute procedural and 6-month clinical outcomes after left main PCI with a dedicated bifurcation stent in patients included in the TRYTON left main multicentre registry (**Chapter 12).** The use of the dedicated bifurcation stent studied for treatment of left main bifurcation lesions was associated with a high rate of device and procedural success without complications in such a high-risk patient and lesion cohort.

Angiographic analysis was performed per protocol with the dedicated 2-D bifurcation QCA algorithm presented and validated in **Chapter 4** of this thesis following a standardized operator procedure. Diameter-derived measures from both 11- and 6-segment models were of apparent use when adjudicating the post-procedural angiographic results; effect of PCI on BA parameters was also studied. Interestingly, the mean DS values established by QCA analysis in this cohort were lower than 50% in PMV, DMV and SB. This implies that angiographic measurements were not the sole criterion used to determine whether the left main bifurcation should be treated or not. Equally to our surprise, 3-D QCA analysis was feasible in only ~30% of the cases. Notwithstanding the per protocol angiographic analysis, the high level of expertise among operators involved and the challenging anatomy, one would have to conclude that proper prospective acquisition of angiograms both pre- and post-procedure, as well as incremental value of 3-D QCA are lessons that still need to be learned.

The SYNTAX score and other derivative scores

The SYNTAX score is an important tool to grade angiographic complexity; it has been integrated in both the European and U.S. revascularization guidelines for the risk stratification of patients with complex coronary artery disease, facilitating the choice of the most appropriate revascularization modality. In the randomized SYNTAX trial, it proved effective in predicting clinical outcomes after elective PCI procedures in patients with three-vessel and/or left main coronary artery disease. We assessed the SYNTAX score's predictive ability for a number of clinical outcomes in "all-comers" populations with a varying extent of coronary artery disease undergoing both elective and emergent PCI procedures.

Initially, we reviewed the reproducibility of the SYNTAX score **(Chapter 13).** Despite its important role in risk stratification, the calculation of the SYNTAX score relies on the visual assessment of coronary lesions, and therefore is subject to intra-and inter-observer variability. In our study, the SYNTAX score was calculated on two occasions 8 weeks apart in 100 patients randomly selected from the SYNTAX trial by a team made up of three interventional cardiologists. Our analysis demonstrated that the SYNTAX score has moderate intra-observer reproducibility, which is consistent with a prior evaluation performed by core lab analysts. The scoring of bifurcation lesions remains the main

source of inconsistency, which may be improved by the use of additional imaging modalities together with a review of its definition.

Furthermore, we assessed the predictive value of the SYNTAX score for major adverse cardiac events both in the already described cohort of unprotected left main PCI patients from the RESEARCH and T-SEARCH registries as well as in the all-comers population of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial**.** In the former study, SYNTAX score emerged as an independent predictor for both all-cause mortality and the patient-oriented composite endpoint up to 4 years, wherein patients in the high score tertile demonstrated significantly higher event rates (**Chapter 9)**. Similarly, in LEADERS a significantly higher number of patients showed major adverse events in the highest tertile of SYNTAX score at 1-year follow-up. However, it is important to mention that overall this patient population had much lower SYNTAX scores than the SYNTAX trial population and/or the left main registries; nevertheless, the SYNTAX score still appeared to have good discriminatory power for risk assessment. Thereby, we demonstrated that the prognostic value of the SYNTAX score is valid for all patients with *de novo* coronary artery disease undergoing percutaneous revascularization **(Chapter 14)**.

In **Chapter 15** we investigated the ability of SYNTAX score and Clinical SYNTAX score to predict very long-term outcomes in an all-comers population enrolled in the SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent for coronary revascularization (SIRTAX) trial. In this trial SYNTAX score mean and tertile values were even lower than the respective ones in the LEADERS reflecting the earlier time periods of enrolment and the lower prevalence of comorbidities in SIRTAX. Therefore, clinical variables would be expected to compensate for this possible decrease in sensitivity of the SYNTAX score. Our results showed that both SYNTAX score and Clinical SYNTAX score were independent predictors of 5-year major adverse cardiac events. In addition, Clinical SYNTAX score was an independent predictor for 5-year mortality; its superior discriminatory power and calibration compared with SYNTAX score resulted in a significant improvement in risk stratification for respective mortality endpoints. An additional potential role of the Clinical SYNTAX score regarding the risk stratification in stent selection was also identified, wherein significantly increased adverse event rates

with paclitaxel-eluting stents were observed within the subgroup of patients with the highest Clinical SYNTAX score.

A limitation of the SYNTAX score is the inability to differentiate outcomes in patients who have undergone coronary artery bypass graft (CABG) surgery. We discussed the rationale, development and feasibility of the newly developed CABG SYNTAX score **(Chapter 16)**, and we concluded that the calculation of this score appeared feasible, reproducible and may have a long-term prognostic role in patients with complex coronary disease undergoing surgical revascularization. Furthermore, we reported the 5-year outcomes from the CABG arm of the SYNTAX-LE MANS left main angiographic substudy stratified across the mean CABG SYNTAX score (**Chapter 17)**. According to our analysis significantly greater rates of 5-year all-cause mortality and other adverse composite endpoints were evident in the high CABG SYNTAX score group compared to the low score group. The CABG SYNTAX score and its PCI equivalent, the residual SYNTAX score, both provide objective measures of the complexity of the residual disease and level of revascularization. These scores may aid in determining a level of "reasonable revascularization", and may have a long-term prognostic role in identifying high-risk patients undergoing CABG or PCI.

Samenvatting en conclusies

Kwantitatieve coronair angiografie van bifurcaties: de ontwikkeling en validatie

Sinds de start van invasieve coronair angiografie in 1958 is het gebruik hiervan niet meer weg te denken uit de dagelijkse praktijk van het katheterisatie laboratorium en wordt deze afbeeldings techniek beschouwd als een essentieel onderdeel in de diagnostische evaluatie van coronaire hartziekte en de begeleiding van percutaan coronaire interventie (PCI). Kwantitatieve coronaire angiografie (QCA) kan gebruikt worden om de omvang van de stenosis graad in coronair segmenten te bepalen, en de objectiviteit en reproduceerbaarheid van deze methode zijn al aangetoond. Echter, het gebruik van QCA in een segment die een bifurcatie bevat staat ter discussie, omdat met de huidige methode niet afdoende de significante stenoses gedetecteerd worden. Met software, die speciaal ontwikkeld is om de stenosis graad in een bifurcatie segment te bepalen, zijn een aantal beperkingen van de huidige QCA opgelost. Echter het bepalen van een referentie diameter (RVD) in het gebied rond een bifurcatie is niet vanzelfsprekend, en kan bij het kwantificeren van de stenose graad als nog tot grote variaties in diameter stenose (DS) leiden. Daarom pleit de Europese Bifurcatie Club voor een standaard methodologie voor het bepalen van de stenose graad in een bifurcatie segment.

Voor het valideren van de nieuwe bifurcatie-QCA software is een relevante gouden standaard vereist. Omdat zo'n gouden standaard niet beschikbaar was hebben we na een grondig review van de relevante literatuur, 6 plexiglas bifurcatie fantomen ontwikkelt met behulp van precisie technologie **(Hoofdstuk 2)**. Elk fantoom bevat drie opeenvolgde bifurcaties met variërende anatomie, stenose graad en Medina klasse.

Met behulp van de fantomen konden we 2 type 2-D bifurcatie-QCA software (6-segmenten model, 11- segmenten model) valideren en de minimale lumen diameter (MLD), de RVD en de DS bepalen **(Hoofdstuk 3).** Met het 6-segmenten model worden data gerapporteerd van zowel het proximale hoofd vat (PMV), het distale hoofd vat (DMV) en de zijtak (SB) en hiermee kan eenvoudig een overzicht verkregen worden van de bifurcatie dimensies tijdens een procedure. Het 11-segmenten model geeft gedetailleerdere informatie over de bifurcatie en vooral over de dimensies van het ostial gedeelte van de distale branches en de zijtak posities. Dit model is vooral geschikt om de

locatie van de MLD, RVD en DS voor en na een bifurcatie behandeling en bij follow-up te vergelijken. Beide software methodes waren goed reproduceerbaar wat betreft de verkregen diameter gebaseerde parameters en in goede overeenstemming met elkaar en met de dimensies van het fantoom. Echter, deze studie toonde ook aan dat deze methodes a) niet goed presteren voor lumen diameters <0.7mm en b) dat alleen de zgn. lokalereferentie diameter analyse ('user-gedefinieerd') wordt bepaald.

Een geavanceerd lumendetectiealgoritme geïntegreerd in de volgende versie van de dezelfde software, verbeterde de MLD-kwantificering voor MLD <0.7mm en resulteerde daardoor in zeer nauwkeurige diameter metingen over het gehele diameter bereik die in de klinische praktijk kan worden verwacht **(Hoofdstuk 4).** Verder resulteerde een geoptimaliseerd algoritme voor automatische referentie (geïnterpoleerde) bepaling in aanzienlijk hogere reproduceerbaarheid voor RVD- en DS-waarden in vergelijking met lokale referentieanalyses. Vanzelfsprekend is de verbetering het meest uitgesproken in daadwerkelijke klinische coronaire vaataandoeningen.Technici kunnen op basis van oriëntatiepunten en individuele perceptie bepalen wat een echte bifurcatie is. Aldus kunnen geanalyseerde segmenten buitengewoon lang worden en taps toelopend, in die gevallen heeft automatische referentie-analyse de voorkeur. Het lokaal bepalen van de referentie diameter kan nog steeds nuttig zijn in ectatische of diffuus zieke vaten, waar interpolatie tot te grote of te kleine diameters kan leiden.

Naast de parameters, die zijn afgeleid van de lokale metingen, worden ook de 2-D bifurcatiehoeken berekend met een toegewijd algoritme welke werkt volgens de definities van de Europese Bifurcatie Club. Onze resultaten toonden aan dat de berekende hoeken onafhankelijk waren van het gebruikte model en zeer reproduceerbaar. Ondanks dat de fantoom bifurcatie hoeken in 3-D zijn gedefinieerd, bleken de hoeken die met de 2-D software waren bepaald, opmerkelijk nauwkeurig en precies en was er niet veel variatie in uitkomst tussen de softwareversies. De grootste hoek van een bifurcatie en de beste afbeeldingsprojectie van het ostium van de zijtak bestaan meestal naast elkaar in een enkele goede 2-D afbeelding, d.w.z. de antero-posterieure richting voor het fantoom. De nauwkeurigheid en precisie namen dan ook af als de fantoom bifurcatie werd afgebeeld vanuit een andere, geroteerde, hoek **(Hoofdstuk 3 en 4).**

Om mogelijke beperkingen in verband met de 2-D QCA kwantificatie van de bifurcatie te minimaliseren, hebben we een nieuwe 3-D bifurcatie QCA-software ontwikkeld **(Hoofdstuk 5)**. We beschreven de methodologie, waarbij twee 2-D angiografie beelden werden gecombineerd tot een 3-D reconstructieve van de bifurcatie. Deze nieuwe software kan corrigeren voor de geometrische vervorming van de 2-D angiogrammen en een kwantitatieve analyse uitvoeren van de 3-D gereconstrueerde bifurcatie. De nauwkeurigheid van de 3-D reconstructie en de afgeleide metingen zijn sterk afhankelijk van de definitie van het centrale splitsingsgebied, beschreven als de 'polygoon of confluence' (POC).

Omdat de 3-D reconstructie is gebaseerd op twee 2-D projecties, kunnen overlappende, kronkelige zijtakken een probleem vormen bij het correct reconstrueren van het bifurcatie gebied; een 3-D reconstructie die gebaseerd is op meer dan twee 2-D projecties kan een beter resultaat opleveren. Dit betekent wel dat de analyse software hiermee veel complexer wordt. Naar aanleiding van deze redenering hebben we onze 3-D software herzien en het gebruik van meer dan twee 2-D projecties mogelijk gemaakt **(Hoofdstuk 6)**. Verder hebben we de methodologie die is beschreven voor de 2-D bifurcatie automatische referentieobstructie-analyse toegepast op de 3-D gereconstrueerde bifurcaties. Concepten geïntroduceerd in Hoofdstuk 4 worden geprojecteerd op de huidige 3-D methodologie, resulterend in een uitgebreide 3-D bifurcatie-QCA-analyse. Metingen voor MLD, RVD, DS en Bifurcatie-hoek (BA) afgeleid van de QCA 3-D bifurcatiesoftware werden gevalideerd tegen onze met precisie gefabriceerde fantomen **(Hoofdstuk 6)** en toonden een hoge nauwkeurigheid, precisie en reproduceerbaarheid.

In vitro validatie heeft de voor de hand liggende beperking dat deze is gebaseerd op statische objecten en dat de beelden zijn verkregen onder ideale angiografische omstandigheden. De vernauwingen in onze fantomen waren concentrisch als gevolg van productie beperkingen. Echter, meer dan 50% van coronaire plaques zijn asymmetrisch, en juist deze asymmetrie geeft vaak aanleiding tot onnauwkeurigheden. Bovendien zijn de bifurcaties in het fantoom gelegen in een plat vlak. Echter, de bifurcaties in humane coronair vaten hebben meestal gebogen trajecten uit het 2-D vlak en vormen daarmee ware 3-D geometrieën. Als deze ware 3-D geometrieën worden afgebeeld met 2-D projecties worden ze soms verkort weergegeven. Daarom moeten we aannemen dat de

incrementele waarde van 3-D bifurcatie QCA in vergelijking met 2-D analyse is onderschat met het gebruik van het huidige fantoom.

Visuele beoordeling was de intuïtieve manier om het coronaire angiogram te interpreteren; desalniettemin is het bewezen dat "Eye balling" nogal onnauwkeurige en zeer variabele uitkomsten geeft. Deze onnauwkeurigheden vinden we vaker bij vernauwingen in bifurcaties, dan bij vernauwing in een gewoon segment. De intuïtieve manier waarop zelfs ervaren operatoren de stenose ernst in het distale hoofd vat en de zijtak interpreteren is gebaseerd op de diameter van het proximale hoofd vat en resulteert daarmee vaak in een overschatting van DS-waarden. Omgekeerd kunnen vernauwingen in de PMV worden onderschat. Inderdaad, deze observaties werden bevestigd tijdens het uitvoeren van ons onderzoek onder experts op het gebied van bifurcatie behandeling **(Hoofdstuk 7)**; visuele schattingen van DS in de fantoom bifurcaties waren zeer variabel in vergelijking met de huidige bifurcatie QCA-normen. De geregistreerde grote variabiliteit van visuele schattingen in twijfelachtige stenosen en de lage inter-observer overeenkomst in de Medina classificatie kan de rechtvaardiging vormen voor de opname van online bifurcatie-QCA in het besluitvormingsproces.

Kwantitatieve coronair angiografie van bifurcaties in klinische onderzoeken

Na de ontwikkeling en validatie van specifieke bifurcatie-QCA-software was de toepassing in de klinische praktijk in real-time de volgende stap. We rapporteerden lange-termijn uitkomstgegevens van de V-stentingtechniek in de-novo bifurcaties behandeld met medicijn afgevende stents (DES) bij patiënten van de RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) en de T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) studies **(Hoofdstuk 8).** We concludeerden dat in deze real-world cohorten, late klinische gebeurtenissen overeenkomen met studies over competitieve technieken. De eerste uitkomsten waren minder bemoedigend, waarschijnlijk vanwege de risicofactoren op baseline, maar bij nadere beschouwing leken deze anekdotisch en eindpuntafhankelijk. Angiografische parameters, zowel diameter-afgeleide als BA-waarden, werden bepaald met toegewijde bifurcatie QCA-algoritmen volgens het meerdere-segmenten model in alle patiënten

waarvan cinefilms konden worden teruggevonden. Hierdoor werd de uitvoerbaarheid van analyse in dit relatief kleine onderzoek bevestigd.

Verder hebben we de lange-termijn klinische uitkomsten en onafhankelijke voorspellers van belangrijke cardiale gebeurtenissen onderzocht bij patiënten met aandoening van de linkerhoofdkransslagader behandeld met DES in de RESEARCH- en T-SEARCH studies **(Hoofdstuk 9).** We rapporteerden een toename van late bijwerkingen tot 4 jaar, welke een zorgvuldige follow-up vereiste van deze patiënten behandelt met DES in de linker hoofdstam. Naast andere variabelen werd de BA beoordeeld als een mogelijke parameter voor risicostratificatie. Hoewel 3-D QCA beschikbaar was, was het bij slechts de helft van de patiënten uitvoerbaar vanwege het niet beschikbaar zijn van 2 afzonderlijke angiografische projecties met meer dan 30° verschil; bij de overige patiënten werd 2-D QCA uitgevoerd. Pre-PCI distale BA, d.w.z. de hoek (volgens de definitie van de European Bifurcation Club) tussen linker anterieure dalende bloedvat (LAD) en linker circumflex (LCX), werd zowel in de diastolische als de systolische fase bepaald. Systolische BA-waarden vertoonden een zwakke statistische associatie met patiënt-georiënteerde samengestelde eindpunten (PoCE) in de univariate analyse op 4-jaar follow-up, waarbij patiënten met hogere pre-PCI BA-waarden een trend toonden voor slechtere uitkomsten. BA bleek echter niet een significante voorspeller van ongunstige klinische resultaten in de multivariate analyse; dit kan worden toegeschreven aan de heterogene QCA-analyse en een relatief klein aantal patiënten.

Gestimuleerd door deze gemengde signalen en de belofte van het voorspellend vermogen van de BA-parameters in deze underpowered studie met relatief weinig 3-D analyses, hebben we besloten om de 3-D BA-parameters van de linkerhoofdkransslagader verder te onderzoeken, het effect van PCI op deze BA, en de impact van 3-D BA op de 1-jaars klinische uitkomsten in een groter cohort, namelijk de patiënten gerandomiseerd naar hoofdstam PCI binnen de SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial **(Hoofdstuk 10).** Complete 3-D BA-analyse, voor en na PCI was haalbaar in 75% van de gevallen; men zou kunnen verwachten dat prospectieve verzameling van geschikte cine-angiogrammen het aantal niet-analyseerbare gevallen verder zou kunnen terugdringen tot <10%. Deze studie was de grootste tot nu toe om de 3-D hoofdstam BA te beschrijven; BA-parameters bleken aanzienlijk te variëren. Verder toonden we aan dat

hartbeweging een onderling effect uitoefent op proximale en distale BA, waarbij de eerste werd verhoogd en de laatste afnam tijdens de systole. Bovendien modificeert een PCI ingreep vooral de distale BA; in het algemeen waren de hoeken afgenomen terwijl de smalste pre-PCI-hoeken na de procedure juist waren toegenomen. Onze analyse toonde echter niet genoeg bewijs om 3-D BA te ondersteunen als een potentiële voorspeller van de klinische uitkomst; er was een trend die wijst op hogere bijwerkingen bij patiënten met een wijdere BA wanneer 2 stents waren geïmplanteerd in de linker hoofdstam bifurcatie.

Zodra de 5-jaars klinische resultaten van de SYNTAX-trial beschikbaar waren, werd de impact van 3-D BA-parameters verder onderzocht **(Hoofdstuk 11).** Net als bij onze 1-jarige bevindingen, leek de stratificatie van pre-PCI diastolische distale BA-tertielen geen enkel verschil te vertonen in de mate van bijwerkingen in de gehele studiepopulatie versus patiënten die bifurcatie-PCI hadden ondergaan. Aan de andere kant toonden bifurcatie-patiënten met een beperkt post-PCI systolisch-diastolisch distaal BA-bereik (d.w.z. een verminderde "bewegingsvrijheid" van de linker hoofdvertakking), significant hogere ongunstige bijwerkingen. Zelfs na correctie voor verschillende klinische, angiografische en procedurele variabelen bewees het nog steeds een onafhankelijke voorspeller te zijn van nadelige klinische gebeurtenissen op 5-jaar. Het is mogelijk dat deze studie ons nieuwe inzichten verschaft in de biomechanica van het falen van de stent in bifurcatieletsels, waarbij de linker hoofdstam bifurcatie de belangrijkste kransslagader is.

Ten slotte, rapporteerden we de acute procedurele en klinische resultaten 6 maanden na PCI van de hoofdstam met een speciale bifurcatie-stent in de multicenter TRYTON studie **(Hoofdstuk 12).** Het gebruik van deze specifieke bifurcatiestent die werd bestudeerd voor de behandeling van hoofdstam bifurcatie laesies was geassocieerd met een hoog percentage stent-device en procedure succes zonder complicaties in deze hoog risico laesies/patiënten. Angiografische analyse werd uitgevoerd met het speciale 2-D bifurcatie QCA-algoritme gepresenteerd en gevalideerd in Hoofdstuk 4 van dit proefschrift volgens een gestandaardiseerde procedure. Diameter-afgeleide metingen van zowel 11- als 6-segmentmodellen waren doelmatig bij het beoordelen van de post-procedurele angiografische resultaten; effect van PCI op BA-parameters werd ook bestudeerd. Interessant is dat de gemiddelde DS-waarden vastgesteld met behulp van

QCA-analyse in dit cohort minder dan 50% waren in PMV, DMV en SB. Dit impliceert dat angiografische metingen niet het enige criterium was dat werd gebruikt om te bepalen of de hoofdstam bifurcatie al dan niet behandeld moest worden. Ook waren we verbaasd dat 3-D QCA-analyse slechts in ~30% van de gevallen mogelijk was. Ondanks de angiografische per-protocol analyse, het hoge niveau van deskundigheid van de betrokken operators en de uitdagende anatomie, moeten we concluderen dat een goede prospectieve acquisitie van angiogrammen zowel vóór als na de procedure en de incrementele waarde van 3-D QCA lessen zijn die nog geleerd moeten worden.

De SYNTAX-score en andere afgeleide scores

De SYNTAX-score is een belangrijk hulpmiddel om de angiografische complexiteit te beoordelen; het is geïntegreerd in zowel de Europese als Amerikaanse revascularisatie-richtlijnen voor de risicostratificatie van patiënten met complexe coronaire hartziekte zodat de keuze van de meest geschikte revascularisatiemodaliteit wordt vergemakkelijkt. In de gerandomiseerde SYNTAX-studie bleek het effectief bij het voorspellen van klinische uitkomsten na electieve PCI bij patiënten met drie-vat en/of linker hoofdstamlijden. We hebben de voorspellende waarde van de SYNTAX-score beoordeeld voor een aantal klinische uitkomsten in "all-comers" populaties met een verschillende mate van coronaire hartziekte in zowel electieve als urgente PCI-procedures.

In eerste instantie hebben we de reproduceerbaarheid van de SYNTAX-score beoordeeld **(Hoofdstuk 13).** Ondanks de belangrijke rol in risicostratificatie, is de berekening van de SYNTAX-score afhankelijk van visuele beoordeling van coronaire laesies en is daarom onderhevig aan intra- en inter-observer variabiliteit. In onze studie werd de SYNTAX-score twee maal berekend met een interval van 8 weken in 100 patiënten willekeurig geselecteerd uit de SYNTAX-studie door een team bestaande uit drie interventionele cardiologen. Onze analyse toonde aan dat de SYNTAX-score een gematigde intra-observer reproduceerbaarheid heeft, wat consistent is met een eerdere evaluatie uitgevoerd door corelaboratory analisten. Het scoren van bifurcatie-laesies blijft de belangrijkste bron van inconsistentie, die kan worden verbeterd door het gebruik van aanvullende beeldvormingmodaliteiten samen met een herziening van de definitie.

Verder hebben we de voorspellende waarde van de SYNTAX-score voor belangrijke cardiale gebeurtenissen beoordeeld, zowel in het al beschreven cohort van de hoofdstam PCI-patiënten uit de RESEARCH- en T-SEARCH-registers als ook in de populatie van de 'all-comers' LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) studie. In de vorige studie kwam de SYNTAX-score naar voren als een onafhankelijke voorspeller voor zowel mortaliteit als ook voor patiëntgeoriënteerde samengestelde eindpunten (PoCE) tot 4 jaar, waarbij patiënten in het tertiel met hoge SYNTAX-score significant hogere incidentiepercentages vertoonden **(Hoofdstuk 9).** In de LEADERS studie zagen we een significant hoger aantal patiënten met ernstige bijwerkingen in het hoogste tertiel van de SYNTAX-score na 1 jaar follow-up. Het is echter belangrijk om te vermelden dat deze patiëntenpopulatie over het algemeen een veel lagere SYNTAX-score had dan de SYNTAX-studie populatie en/of de PCI hoofdstam populatie; desalniettemin leek de SYNTAX-score nog steeds een goede discriminerende waarde te hebben voor risicobeoordeling. Daarbij hebben we aangetoond dat de SYNTAX-score een prognostische waarde heeft voor alle patiënten die een PCI ondergaan voor de-novo coronaire hartziekte **(Hoofdstuk 14)**.

In **Hoofdstuk 15** hebben we de potentie van de SYNTAX-score en de Clinical SYNTAX-score onderzocht op het voorspellen van de resultaten op zeer lange termijn in een 'all-comers' populatie van de SIRTAX studie (SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent for coronary revascularization). In deze studie waren de gemiddelde SYNTAX-score en de tertielwaarden zelfs lager dan die in de LEADERS studie, dit reflecteert een vroegere tijdsperiode van inclusie en de lagere prevalentie van comorbiditeiten in de SIRTAX. Daarom werd verwacht dat de klinische variabelen deze mogelijke afname in sensitiviteit van de SYNTAX-score compenseren. Onze resultaten lieten zien dat zowel de SYNTAX-score als de Clinical SYNTAX-score onafhankelijke voorspellers waren van 5-jaars cardiale gebeurtenissen. Bovendien was de Clinical SYNTAX-score een onafhankelijke voorspeller voor mortaliteit gedurende 5 jaar; het superieure onderscheidend vermogen en kalibratie in vergelijking met de SYNTAX-score resulteerde in een significante verbetering van de risicostratificatie voor de respectievelijke mortaliteit eindpunten. Een extra potentiële rol van de Clinical SYNTAX-score met betrekking tot de risicostratificatie en stentselectie werd ook geïdentificeerd, waarbij significant verhoogde ongunstige bijwerkingen met de paclitaxel-eluerende

stents werden waargenomen binnen de subgroep van patiënten met de hoogste Clinical SYNTAX-score.

Een beperking van de SYNTAX-score is het onvermogen om uitkomsten te differentiëren bij patiënten die een coronaire bypass operatie (CABG) hebben ondergaan. We bespraken de rationale, ontwikkeling en haalbaarheid van de nieuw ontwikkelde CABG SYNTAX-score **(Hoofdstuk 16)** en we concludeerden dat de berekening van deze score haalbaar en reproduceerbaar leek en mogelijk een lange termijn-prognostische rol speelt bij patiënten met complexe coronaire aandoeningen die chirurgisch worden behandeld. Verder rapporteerden we de 5-jaarsresultaten van de CABG-arm van de SYNTAX-LE-MANS(hoofdstam)substudie, gestratificeerd voor gemiddelde CABG SYNTAX-score **(Hoofdstuk 17)**. Volgens onze analyse waren significant hogere percentages van 5-jaars mortaliteit en andere ongunstige eindpunten zichtbaar in de hoge CABG SYNTAX-score groep in vergelijking met de groep met de laagste score. De CABG SYNTAX-score en PCI-equivalent (de residuele SYNTAX-score), bieden beide objectieve metingen van de complexiteit van de residuele coronaire ziekte en mate van revascularisatie. Deze scores kunnen helpen bij het bepalen van het niveau van "redelijke revascularisatie" en kunnen mogelijk op lange termijneen prognostische rol spelen bij het identificeren van hoog risicopatiënten die CABG of PCI ondergaan.

PhD Portfolio

Portfolio of awarded ECTS points

Name PhD student: Chrysafios Girasis

Erasmus MC department: Cardiology

Research school: COEUR, Erasmus MC

PhD period: 2008 – 2014

Promotor: Prof. Dr. P.W.J.C. Serruys

Erasmus MC courses	**Date**	**ECTS**
CC02-Classical Methods for Data-analysis	22/9-17/10 2008	5.7
EP03-Modern Statistical methods (exam passed)	24/11–5/12 2008	4.3

COEUR Research seminars:	**Date**	**ECTS**
Surgical and percutaneous aortic valve implantation; indications, techniques and follow-up	January 2009	0.4
New developments in percutaneous revascularisation	April 2009	0.4

Lectures/conference presentations:	**Date**	**ECTS**
Physical Activity is Effective in Prevention and Treatment of Coronary Artery Disease: Role of Endothelial Phenotype	25/8/2008	0.1

Symposia and congresses (0.3 ECTS points/day):	**Date, location and number of days:**	**ECTS**
3rd international symposium on Biomechanics in Vascular Biology and Cardiovascular Disease	24-25/4 2008, Rotterdam, NL (2)	0.6
EuroPCR 2008	13-16/5 2008, Barcelona, Spain (4)	1.2
ESC congress 2008	30/8 -3/9 2008, Munich, Germany (5)	1.5
TCT 2008	12-16/10 2008, Washington DC, USA (5)	1.5
29th Panhellenic Cardiological Congress	30/10-1/11 2008, Athens, Greece (3)	0.9

EuroECHO 2008	10-13/12 2008, Lyon, France (4)	1.2
ACC/i2 Summit 2009	28-31/3 2009, Orlando, FL, USA (4)	1.2
Cardiology and Vascular Medicine – ESC Update and Perspective	11-13/5 2009, Rotterdam, NL (3)	0.9
EuroPCR 2009	19-22/5 2009, Barcelona, Spain (4)	1.2
7th International Vulnerable Plaque Meeting 2009	21-23/6 2009, Athens, Greece (3)	0.9
5th European Bifurcation Club meeting 2009	16-17/10 2009, Berlin, Germany (2)	0.6
Cardiovascular Research Technologies (CRT) 2010	21-23/2 2010, Washington DC, USA (3)	0.9
5th international symposium on Biomechanics in Vascular Biology and Cardiovascular Disease	15-16/4 2010, Rotterdam, NL (2)	0.6
ACC/i2 Summit 2010	13-16/3 2010, Atlanta, GE, USA, (4)	1.2
EuroPCR 2010	25-28/5 2010, Paris, France (4)	1.2
6th European Bifurcation Club meeting 2010	22-23/10 2010, Budapest, Hungary (2)	0.6
Optics in Cardiology Symposium	01-02/12 2011, Rotterdam, NL (2)	0.6
Patrick Serruys Symposium	19th May 2012, Rotterdam, NL (1)	0.3
Optics in Cardiology Symposium	21-22/3 2013, Rotterdam, NL (2)	0.6
EuroPCR 2013	21-24/5 2013, Paris, France (4)	1.2
PORTICO Transcatheter Aortic Valve Implantation system training seminar	12/9/2013, Paris, France (1)	0.3

9th European Bifurcation Club meeting 2013	18-19/10 2013, London, UK (2)	0.6
Joint Interventional Meeting (JIM)	13-15/2 2014, Rome, Italy (3)	0.9
EuroPCR 2014	20-23/5 2014, Paris, France (4)	1.2
Complex PCI training course	9-10/6 2016, Brno, Czech Republic (2)	0.6
14th European Bifurcation Club meeting 2018	12-13/10 2018, Brussels, Belgium (2)	0.6
11th congress of Innovations in Interventional Cardiology & Electrophysiology (IICE)	13-15/9 2018, Thessaloniki, Greece (3)	0.9
Interventional Cardiovascular Education (ICE) 2018	30/11–01/12 2018, Heraklion, Greece (2)	0.6

Oral presentations	**Date and location**	**ECTS**
Three-Dimensional Bifurcation Angle Analysis in Patients with Left Main Disease Treated with PCI	TCT 2008, 12-16/10 2008, Washington DC	0.5
Syntax Score in Patients with Left Main Disease: Prediction of Long-Term Clinical Outcome Following PCI	ACC 2009, 28-31/3, 2009, Orlando, FL, USA	0.5
Three-Dimensional Bifurcation Angle in Patients With Left Main Disease: Impact on Long-Term Clinical Outcome Following PCI	ACC 2009, 28-31/3, 2009, Orlando, FL, USA	0.5
Three-Dimensional Bifurcation Angle Analysis in Patients With Left Main Disease: a Substudy of the SYNTAX Trial	ACC 2009, 28-31/3, 2009, Orlando, FL, USA	0.5
Clinical relevance of 3D-QCA angulation measurements in left main bifurcation disease	EuroPCR 2009, 19-22/5 2009, Barcelona, Spain	0.5
Evaluation of Stent Expansion and Need for Post Deployment Optimization with an Angiography Based Software Tool (Stent Optimizer)	Innovations in Cardiovascular Interventions, 6-8/12, 2009, Tel-Aviv, Israel	0.5

Bifurcation angle of the LM: anatomy/geometry revisited	7th International Vulnerable Plaque Meeting, 21-23/6, 2009, Athens, Greece	0.5
Is Left Main angulation really a predictor of mortality?	5th EBC meeting, 16-17/10, 2009, Berlin, Germany	0.5
QCA: Evolution of a "simple" tool	1st A.T.I.CA meeting 6/2, 2010, Athens, GR	0.5
Dedicated Software for Bifurcation QCA: Pie Medical (CAAS 5.9) and MEDIS (QAngio XA 7.2.). Validation on phantom analysis	6th EBC meeting, 22-23/10, 2010, Budapest, Hungary	0.5
The bifurcation dilemmas: Current consensus	14th International Symposium on Atherosclerosis and Related Risk Factors 19-20/10, 2010, Athens, Greece	0.5
Optical Coherence Tomography and Intracoronary echocardiography	IICE 2018, 13-15/9, 2018, Thessaloniki, Greece	0.5
Antiplatelet treatment during the first 12 months post-PCI	ICE 2018, 30/11-1/12, 2018, Heraklion, Greece	0.5

Total		**41.40**

List of publications

Articles in peer-reviewed journals

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6. Mantziari A, Vassilikos VP, Giannakoulas G, Karamitsos TD, Dakos G, **Girasis C**, Papadopoulou KN, Ditsios K, Karvounis H, Styliadis IH, Parcharidis G. Left ventricular function in elite rowers in relation to training-induced structural myocardial adaptation. Scand J Med Sci Sports; 20(3):428-433.

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8. Garg S, **Girasis C**, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, van Es GA, Serruys PW. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv; 75(6):946-952.

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11. **Girasis C**, Schuurbiers JC, Onuma Y, Serruys PW, Wentzel JJ. Novel bifurcation phantoms for validation of quantitative coronary angiography algorithms. Catheter Cardiovasc Interv; 77(6):790-797.

12. Onuma Y, **Girasis C**, Piazza N, Garcia-Garcia HM, Kukreja N, Garg S, Eindhoven J, Cheng JM, Valgimigli M, van Domburg R, Serruys PW. Long-term clinical results following stenting of the left main stem: insights from RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. JACC Cardiovasc Interv; 3(6):584-594.

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27. Serruys PW, **Girasis C**, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. EuroIntervention; 8(4):511-519.

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Acknowledgements

This section has traditionally been the one that every past fellow, staff member, collaborator and certainly my promotor checks out; it is the most difficult and at the same time the most enjoyable one. Alas, it has been quite a long time now and memory is starting to fade, however, there are that many people that I have come across during my days in Rotterdam (15/2/2008-31/3/2012) who earned their right to be mentioned, that I trust it will all eventually come back, if I take the story from the beginning.

As early as May 2006, at a time that I had just returned to Greece from the United States after a two-month fellowship at Henry Ford Hospital in Detroit, and already having made up my mind that I wanted to pursue a career as an Interventional Cardiologist, I was torn between two perspectives. On one hand to take the USMLE exams, which would claim my undivided attention for at least a year, and then try to get an interventional fellowship in the States, possibly starting with Detroit, or on the other hand to try a European center. The answer came from my mentor Professor Stavros Hadjimiltiades, with whom I had been working closely together in my early steps in Interventional Cardiology during my cardiology fellowship at AHEPA hospital in Thessaloniki. And it was an unexpected and at the same time career defining answer; Dr Hadjimiltiades, despite being one of the first Greek cardiologists fully trained in Interventional Cardiology in the States, suggested I should rather opt for Europe. When I asked why so, he argued it would save me time, and when I in turn asked “where to”, he cryptically replied “we will see to that”. It turned out that my dearest Stavros would call in a favor from Akis Arampatzis, a former fellow of Thoraxcenter, asking him to write a letter to the world-known Professor Patrick Serruys and vouch for me. Admittedly, Akis was more than eager to do it and helped me liaise with an institution I then thought to be beyond my reach; moreover, he gave me a very accurate account of what I was to expect and how I should make the most out of a potential fellowship. This turned out to be really useful when I had a series of interviews arranged with Prof Serruys and all the other staff members of the Interventional Department in March 2007. This first visit to Erasmus MC gave me two full days to wander around the premises, check out the people, the place, the city, and reflect on the possibility of a long-time investment there. A couple of weeks later an offer came for a combined research and clinical two-year fellowship in Interventional Cardiology! It turned out to be a four-year adventure…

Erasmus Medical Center

Fellows

Having finished in the meantime my cardiology fellowship in Thessaloniki, and trying to tie up all loose ends regarding my Greek PhD, I embarked on this adventure in early 2008 together with my then partner, now wife, *Elina*, who had just graduated from medical school. We arrived in Rotterdam on a sunny February afternoon and after settling down I

appeared a few days later at Prof Serruys' office, to be informed that I should find my working place in an office in the 14th floor of the main building. And there I found myself in the company of three brilliant individuals, Yoshi Onuma, Nicolo Piazza and Neville Kukreja.

Yoshi-san had already arrived in Rotterdam mid 2007; being in close daily collaboration with Prof, he was the one person suited to answer any queries I might have or lend a helping hand. This included fine-tuning powerpoint presentations, retrieving patient files and CDs, and getting started with statistical analyses. Above all, he was a good and patient listener; the word "no" was never an option. I suppose I will never know for sure what part of all this has to be ascribed to his Japanese culture and what part to Yoshi himself. In the end it was no surprise that he turned out to be my closest collaborator and most frequent co-author next to Prof. It seems now like a whole era has passed between the time he was living on the other side of our street, having his occasional but ever changing haircut at the Kappersakademie, frequently riding his bike all the way from Mariniersweg to Prof's house at Nachtegaallaan and back (many times in rain), to the moment I will present this thesis, Yoshi being a deserved member of the plenary committee.

Nicolo "the pseudo-Italian", is an entirely different story. He had arrived from Montreal literally days before me and had already shown his huge interest to be involved in the TAVI literature, first task being the anatomic relationship between the left bundle branch and the aortic valve, and the clinical sequelae thereof. I can still recall the incident when after having an impacted tooth extracted he had returned to the office, because he wanted to make some calls and have internet access, trying to contact Professor Anderson in the UK. Having had nothing to eat, and still feverish and exhausted, it occurred to him that sleeping on the office floor would save him some time. Naturally that did not work out as planned, still it was quite evident that the guy meant business. Nicolo travelling to Leipzig having to learn German from scratch in record time was just one more of many examples that bolstered this impression.

Neville was the guy, whom other fellows would turn to for a language review by a native English speaker, if so required. Being the eldest of the four, he was often out of office, allegedly being better concentrated on his writing when at home (I totally empathize with him on that part), whereas he was also involved in an endless solicitation to ensure the best possible job back home in the UK. Since I did not have a dire need for an English review, did I only later realize, usually during gatherings in the Shabu Shabu establishment just two floors under Cardialysis, his other qualities that appealed to me; his heretic mind whereby he could always give you a new perspective, his generosity, and his love of life (and malt whisky). I have been frequently meeting him in congresses after his departure from Rotterdam, and am always glad to see him do well both in his business as well as his private life.

Biomedical Engineering Group

Jolanda Wentzel, Hans Schuurbiers and *Frank Gijsen* were without a doubt pivotal in the creation of this thesis. This is actually quite easy to tell, if one reviews the first chapters, which form to a certain extent the intellectual foundations of this thesis. The series of bifurcation phantoms that we devised, built and imaged was a fruit of exemplary cooperation between the clinicians and the engineers; couple of brainstorming meetings at first, and then serial meetings in their hospitable office helped us refine our plan, figure out details and arrive at practical solutions. Moreover, when writing the series of relevant manuscripts, I knew I could count on poignant and well-meant remarks. We can all be proud that these phantoms have served as the gold standard for many more manuscripts extending our original work.

On a personal note, Jolanda shared the same enthusiasm with me on the project and was such a cool and down to earth person, that a fruitful cooperation was visible from the start; hence, we found out that there was room for collaboration on a few other projects as well. Therefore, her becoming my co-promotor next to Prof was only natural; her contribution to the very defense of this thesis was equally substantial, even including the Dutch translation of the first part of Summary and Conclusions!

Thoraxcenter

Senior staff

Professor Pim de Feyter: A perfect gentleman in and outside of the Cathlab; a cardiologist and a researcher of huge caliber. Unfortunately I did not have the opportunity to do many cases with him, since I was still in my early steps in my clinical assignment, when he stepped out of the CathLab. However, in any given opportunity, especially during the EuroPCR and the EuroIntervention editorial meetings, I could only respect his huge academic background, appreciating his openness to new ideas, whereas at the same time he would make kind but poignant suggestions, where he felt there was room for improvement. Last but not least, I will forever be grateful to him for acknowledging and embracing Elina's research potential and mentoring her towards her PhD.

The late *Professor Wim van der Giessen* was an imposing figure, not only for his skill and vast knowledge on the field of Interventional Cardiology, but also for his overall education and approach to medicine, music, philosophy and life. Always maintaining his cool, he was keen to let me work our cases in the CathLab as a first operator, always prepared to help, but equally patient to let me finish a given case, no matter how difficult, and give me the credit afterwards. Naturally this required respecting his overall philosophy towards

patients and, not before long, adopting his mentality reflected in lines such as “why do you want to do this? Are you gonna make the patient better?”, “no” you had to reply, “so, don’t do it”; or the famous moto “take the money and run” as soon as you were done tackling an elderly patient’s culprit lesion. I was really sad and shocked to hear the news about his untimely demise; his presence and guidance would have been invaluable, and he will sorely be missed.

Peter de Jaegere: When I arrived at Thoraxcenter and for the next few years, Peter was almost entirely dedicated to the TAVI program, a field then almost impenetrable to a rookie from an operator’s perspective, hence we did not work so frequently in the Cathlab; nevertheless, similar to Wim, he was always welcoming young fellows taking on responsibilities under his supervision.

Robert-Jan van Geuns: A motivated and clearly talented interventional cardiologist, probably one of the seniors with whom I have worked most frequently in the Cathlab. Working on that many cases together, it was not always possible to avoid occasional friction between a rising star such as him and an often impatient, “pushy” Greek fellow such as myself. Fortunately, we managed to come to terms acknowledging our mutual dedication to the task, do challenging procedures together, especially on the field of bifurcation PCI, and even collaborate on some manuscripts, to the extent that his place in my thesis’ plenary committee is entirely expectable.

Evelyn Regar and *Eric Duckers*: Devoted scientists, each of them on her/his own field, striving for perfection regarding acquisition and adherence to the protocol. I will always remember Evelyn being the most adamant of all when it came to speaking 100% Dutch in the Cathlab, or Eric always maintaining his cool, always speaking in a (very) low voice “in order to have everybody paying attention”, and with a genuine interest in anyone’s current and future research projects.

Martin van der Ent: I remember Martin as a fast and effective operator, especially in emergencies (always going to “twintig” when direct stenting culprit lesions in MIs), always fond of difficult procedures, especially CTOs. I guess it served him well to leave for Zuider Ziekenhuis, in order to enjoy more allocated time for this kind of procedures.

Arie de Vries and *Attila Dirkali:* Both of them being on the on-call rooster in Thoraxcenter in the time where the PCI service had not started yet in Dordrecht, I enjoyed their good company and co-working spirit, especially in my early steps as a first operator. As a matter of fact, Arie was my senior in the vast majority of my early on-calls; his patience and willingness to help me gain confidence in my first primary PCIs is naturally very much appreciated.

My compatriot *George Sianos* definitely put in a good word for me during my first series of interviews, which I am grateful for. However, we just overlapped for a mere 12 days,

before he left for Greece; this is how I missed out on the challenge of working with George in the Cathlab!

Last but not least, *Professor Felix Zijlstra*: I definitely enjoyed working with him in the Cathlab, taking the opportunity of doing case after case as a first operator under his very discrete supervision. Unfortunately, due to inconvenient timing, I missed the opportunity of extending my stay in Thoraxcenter, despite his initially more than welcoming approach to the matter.

Clinical Fellows

Carl Schultz, *Joanna W*… (let's not pretend I could ever spell or pronounce her last name correctly) and *Nicholas van Mieghem* shared for a shorter or longer time the interventional fellows room with me. If a single word comes to mind for all three of them, this would be "dedicated". Carl was sure to rent an apartment just opposite the Thoraxcenter; he could not afford to waste time, neither as a fellow nor as a young senior. Joanna sure made good use of her US background and her American upbringing always looking out for practical solutions. I have to admit that to the best of my knowledge she was probably the one with the highest percentage of enrolled patients; despite her at first moderate Dutch, she would strive and to a large part also succeed to find a perfect match between a given study protocol, be it for SECRITT or any of the stent and/or imaging trials, and her patients of the day. And Nicholas, what can you mention first about Nicholas, eh? His competitive nature I guess, as reflected in his screensaver capture of him swimming butterfly-style, in his quick American ways going back to his NY days, his purely aggressive approach in the Cathlab, and finally our inside "15 minute" joke; this was allegedly the setup and acquisition time needed for a near infrared spectroscopy scan of a culprit MI lesion, at least in the beginning, evidently an eternity for Nicholas, before he could be allowed to attack the lesion. Considering all this, their respective accomplishments and professional success, be it in Australia for Carl, Amsterdam for Joanna, or the Thoraxcenter for Nicholas, are entirely deserved.

Anne-Louise Gaster and *Steve Ramcharitar* belonged to the prior generation of clinical fellows, hence I did not have the opportunity to work with them. However, I had time enough to appreciate Anne-Louise's kind heart and warm hospitality in her house on the outskirts of Rotterdam, and we even made it together with Elina and Anne-Louise's boyfriend to the blooming Keukenhof gardens, which was one of our most enjoyable excursions in the Netherlands. On the other hand, Steve's published research overlapped to a certain extent with my bifurcation related projects; I therefore partially followed his work and could appreciate his enthusiasm and his zeal to succeed. *Michael Magro*, on the opposite hand, was a clinical fellow from Malta who was equally interested in bifurcation PCI but was also involved in an array of research topics. Michael was one of the kindest,

most humble and self-sacrificing fellows I have ever come across; in the end, these qualities helped him succeed in a place of fierce competition. Naturally, I would also like to mention my compatriot *Apostolos Tzikas,* whom I also shared the fellows' room with. Apostolos focused on the TAVI procedures and succeeded to conclude a concise thesis in a relatively short time thanks to the mentorship of Peter de Jaegere, as he was eager to embark on some clinical work as well, following the Structural Heart program in Montreal.

Finally, I would like to thank all the *Dutch fellows* we shared the room with (and there have been so many of them), for being friendly, cooperative, and eager to show me the ropes around the lab, the ward, the clinics, and, at least in the start, occasionally check my Dutch, either in my angio/PCI reports or when asking patients for consent.

Cathlab staff

I would naturally like to acknowledge the work and professionalism of the entire Cathlab staff, with whom I had to work long and hard, quite often in the wee hours, but also enjoyed their company between procedures. *Marjo de Ronde* definitely stands out as the head nurse anyone would like to have in any Cathlab; steadfast, decisive, protective of her staff, but ever so friendly and pleasant to anybody willing to work hard. *Tieneke, Marianne, Elsa, Linda, Mercedes, Houda, Rixt, Dick, Bas, Nico, John de Heide*, you were all willing to help out, at first assisting with simple but important aspects of the job, such as the table set-up, and later on during the procedures as my back-up.

On the other hand, my utter respect goes out to all Cathlab technicians *Anne-Marie, Karen, Angelique, John de Vries, Elco, Sander, Rob, Patrick and Paul*, small geniuses to a certain degree, who knew their way around virtually every piece of equipment, helping out with the acquisition, the interpretation and the measurements during cases. A special thank you from my side should go out to John, Elco and Sander, for offering their help with the retrieval and copy of literally hundreds of angio CDs for my first QCA studies. And then it is *Jürgen Ligthart*; as a matter of fact, Jürgen never needed a last name or further introduction. To every fellow having ever worked a single day in that Cathlab he was always a smiling face welcoming you to the Thoraxcenter at the same time being a tireless teacher and a brilliant scientist, who had indulged in all imaging and acquisition technologies, especially in IVUS, to a level even today unparalleled by a large part of seasoned interventional cardiologists.

Cardialysis

Research Fellows

There have been so many fellows in Cardialysis throughout this time-period, I am afraid I am going to overlook somebody; if so, certainly not intentionally, but probably due to the fact that I spent half the working week in Thoraxcenter.

Hector: Obviously, I could not start with anybody else but my first and only Mexican friend so far. From my point of view, Hector does not belong to this group, since he had already arrived in Rotterdam three and a half years before myself; the word coordinator rather comes to mind. Already mastering IVUS with a global view of every other intravascular imaging technology, he was next to Prof the one trying to match every new-comer with an evolving project, obviously also depending on one's preferences. More than that, he would be the one trying to reconcile differences between fellows consistently trying to bring everybody together during our lunch breaks or dinners. I am quite sure that to a certain extent this controlled, reconciling behavior had to do with the fact that he enjoyed the company of his lovely wife and family. This was the major factor that would keep him going through a seemingly endless effort to get a European license in order to practice medicine, especially Interventional Cardiology, on Dutch soil. I was surprised to hear that he had left for Washington, US, since he had become such an integral part of Cardialysis, however I trust that he followed an opportunity he could not refuse.

Nieves was also already there upon my arrival, on her way to become the OCT expert she is. Beyond her diligence on the seemingly endless analysis of OCT runs, she was such a sweet and pleasant individual, that everybody was happy seeing her not only finish her PhD, but much more importantly, finding her companion in life in Koen. *Taka Okamura* definitely filled her shoes regarding OCT related projects, naturally also becoming an expert on the field, to be succeeded by the other *Taka* (*Muramatsu*), an equally devoted, slightly more extrovert young Japanese fellow.

Naturally, when one talks of fellows with a taste for OCT, one definitely has to mention *Lorenz Räber* and *Maria Radu,* and their scientific "child", the OCT Atlas. Lorenz came in from Bern at the suggestion of Professor Stephan Windecker to run a relatively short, but immensely productive fellowship. However, I am proud to say that even before coming to Rotterdam, we had already paved the way for his Cardialysis days with our joint project on the SIRTAX study. It was clear from the start that he was very committed, and I am quite sure that a great career in Interventional Cardiology is in the making. Maria on the other hand had different things on her plate to begin with, thus we did not interact to the same degree; however, she was very sociable and pleasant, eager to bring people together organizing dinners especially at Christmas time.

Scot Garg: A brilliant mind, a charismatic writer who could absorb information in record time and then dissect a given topic in more ways than one could imagine; at the same time a very down to earth and easy to work with guy. Mentioning Scot, I instantly think about *Giovanna Sarno* as well, since the three of us had a very fruitful collaboration in relatively short time, co-authoring a number of manuscripts. Giovanna being a very bright and talented Italian girl and having already defended her PhD was nevertheless constantly on the lookout for bigger and better opportunities; having moved for a number of years now to Sweden, I hope she finally found what she was looking for.

Salvatore Brugaletta and *Roberto Diletti* arrived in Rotterdam at pretty much the same time; I can still recall seeing them for the first time at the thesis defense of Scot and Apostolos. Both of them enjoyed a great deal of success, Roberto taking on a clinical assignment and in the end becoming a senior at Thoraxcenter, and Salvatore defending his thesis and then moving back to his beloved Barcelona to carry on with clinical work. Nonetheless, it was never all work for them, as we used to enjoy every now and then a dinner together with Elina and her best Italian friend Alexia. Speaking of Barcelona, *Josep Gomez-Lara* comes to mind; a really extrovert Catalan fellow, with a tangible passion for his home city, soccer and naturally Barcelona FC! *Juan-Luis* on the other hand was an elegant, talented fellow from Spain, with a huge array of interests. He has developed a taste for OCT related research, which must have served him well in his ongoing endeavors around Europe for the last years; I sincerely hope he finds the perfect working environment without having to compromise too much.

Vasim Farooq: A very enthusiastic fellow from the UK, all too eager to convince other fellows of his point of view, including myself. I do feel I still have to apologize to other fellows on his behalf as well for occasionally creating too much noise throughout Cardialysis during our common projects on the CABG SYNTAX score; it was not that we were arguing, we were just adjudicating the angiograms very vividly! And a last thing in order to restore the historical truth; Vas, according to his thesis acknowledgements, is still in possession of a certain recording of myself allegedly admitting I was wrong. My dear Vas, you can be even prouder; that statement actually read “Yes Vas, you are right!!”

Christos (Chris) Bourantas: A talented Greek fellow, a prolific author, so concentrated on his projects that he would occasionally face certain difficulties (!) with trains, buses, and automobiles, especially when abroad; the stories are endless thanks to his very vivid descriptions! Elina and I were privileged to attend his wedding with his wife *Thekla*, but also happy to meet with their growing family whenever the opportunity was given.

Technicians, personnel, industry and more…

I had a very fruitful cooperation with all the technicians involved in QCA analysis, especially *Wietze*, learning a lot from each other. Being to a rather small part involved in

IVUS and OCT related projects I naturally had to resort for help to relevant technicians as well. I am afraid I am at a loss for names, however *Ravindra* definitely stands out, thanks to his vivid personality but also because he was the one most eager to accompany us during lunch time. I would like to thank *Koen* and *Glenda* for their technical assistance, our statisticians, *Gerrit-Anne van Es*, *Ana Guimaraes*, and naturally *Bianca Backx* and *Monique Schuijer*, from the time of my involvement with Tryton IDE and ABSORB, not only for their professionalism but also because they were so much fun to be with!

Paul Cummins was the managing editor of EuroIntervention during my time in Rotterdam; more than that, he was the one to consult with during my first days in Rotterdam regarding simple logistics, accommodation, or the nearest bar/restaurant for any given occasion. He was also the one giving me hints regarding the first papers I would review for the journal. *Sylvie* was his tireless assistant always trying to help fellows either with their own manuscripts or with their review assignments.

It would really be unforgivable, if I did not bring up the people from industry, with whom I worked very close together. From Pie Medical in particular, I would like to thank *Folkert Tijdens*, an ever smiling gentleman and resourceful engineer, *Jean-Paul Aben*, the brains behind the development of their software and an invaluable co-author in my validation papers, *René Guillaume* and *Boudewijn Verstraelen* for trusting me with the validation of their products at the same time fully respecting my validation plan and above all my scientific integrity and independence. I would also like to acknowledge Professor *Hans Reiber* and *Gerhard Koning* for their co-operation in my validation of Medis bifurcation QCA software in a spirit of professionalism and collaboration, and the people from Paieon, the company which provided us with the 3-D QCA software I used during my SYNTAX bifurcation angle studies, a tiring, often frustrating, but in the end quite rewarding project.

Hanny Boutkan: On a first, simple level, Hanny has been Prof's secretary since late 2010; naturally even dissecting this simple fact, one has to be reminded whose secretary she really is. On a personal level, Hanny is by far one of the kindest persons I have ever come across; more than that utterly professional, proactive and hard working. In particular, I must give her the credits for constantly but gently pushing me towards my thesis defense continuously sending out reminders for regulations and deadlines, even when my enthusiasm had dissipated. Finally, when the goal was in plain sight, she facilitated the process to the best of her abilities following up on seemingly endless correspondence, many times in out-of-office hours. And what's priceless; every e-mail invariably started with her heartfelt salutations in Greek!

Marie-angèle: In a nutshell, the heart and soul of the entire organization; in more detail, a tireless administrator, the hardest working analyst, a welcoming face to every fellow coming to Cardialysis and when needed a buffer zone between him/her and Prof. Especially regarding my QCA projects Marie-angèle was the person to show me the

workstations and the software, help me liaise with Cardialysis personnel and industry, and, what's more important, provide the assurance that she would always be around somewhere in the building, mostly in her office on the second floor, to lend a helping hand if necessary. And all of this integrated with a charming, cheerful and ever so enjoyable personality, with a warm laughing voice equally loud with my own; the ruckus the two of us could create just having an occasional drink was unprecedented to the point that Prof could track us from a distance even in a crowded airport such as JFK "just following the noise"! Hence, almost from day one, there was never a shred of doubt in my mind that she would be one of my paranymphs!

Professor

One cannot be appreciative enough either of Prof's achievements on the field of Interventional Cardiology or, not less importantly, of his decisive contribution to the career of any fellow who had the privilege of serving under him, as a research or as a clinical fellow; in my case it was both, hence twice the honor and the responsibility. The thought occurred at first to try and cite the numbers of published peer-reviewed manuscripts, theses, fellows, awards etc; I almost immediately discarded it. Any attempt to write up-to-date numbers would be futile; I would have to run to the publisher every other day and correct the numbers, such a prolific writer and overwhelming personality that Prof is.

Even during my cardiology fellowship I had the opportunity of attending a number of lectures he had given in Greek congresses; it was the early DES era and his appearance was larger than life. However, my first ever face to face meeting was March 22, 2007 for my scheduled interview. It had been set rather late in the afternoon, and he had just finished with a number of challenging TAVI cases. Still in his scrubs Prof was going through a large pile of printed material on his desk searching for my CV; when he found it and read my first name, Greek first names being notoriously difficult to pronounce, I can remember him lifting his head asking kindly but yet decisively "and what should we call you?" I felt it was time to be practical and replied "I suppose we could cut it down to Chris", hence I was stuck with that ever since.

The start of my fellowship was initially unimpressive. However, several weeks into this awkward "marinating" phase, my office phone rang on a Monday morning; it was Anja, Prof's former secretary, telling me on his behalf that I would have to take care of an outstanding bifurcation QCA analysis for the V-stenting registry, a project started by a former fellow. When I called her back after an initial surprise to ask for details, she just replied "he wants it by Friday". With that the famous Patrick Serruys universal fellow routine started consisting in but not limited to early morning and/or late night phone calls praising other fellows' work and asking about the progress of your own projects, early

Sunday morning visits to his attic, endless meetings, you name it. Only later would you realize how this routine consistently brought the best out of you, speaking volumes for Prof's unsurpassed people management skill. Having worked with a vast array of ambitious young people from all over the globe he had the wisdom of adapting his ways to one's personality, if he saw promise. In my case and during my early days at least, diplomacy was admittedly not among my strong points; Prof was wise to let this slide and valued my straight talking, even if at times it was a little bit bolder than expected. Later on, when he had become sure I had found my way, he was generous in accolades of my work actively helping with grant submissions, scholarships and professional solicitation.

Regarding my clinical training, when seeing CG/PWS written on the Cathlab schedule board next to the cases of the next day, I just knew I would have to be prepared for everything! One can easily imagine that when you have Prof almost literally breathing down your neck, scrutinizing your way with the wires equally with your line of thinking and intellectual justification of your actions, no matter your level of self-confidence, you would simply have to deliver, almost invariably having a much faster heart rate than the patient. Naturally after that kind of exposure there would be hardly ever any clinical setting that would stress me more, which I soon realized that I would have to be eternally grateful for to Prof.

Treasuring all of this experience I realized that defending my thesis even at this later time would certainly be worthwhile, this way also acknowledging Prof's contribution to my career. After all, one of the highlights of my Rotterdam times has been the opportunity to attend the Patrick Serruys symposium in May 2012 honoring Prof's legacy and see him enjoy the deserved admiration, friendship and love surrounded by his co-workers, friends and family; this is certainly a large but distinguished company everybody would like to be a member of.

Friends and family

I would like to start by mentioning our dear Greek friends *Natasa*, *Roula* and *Dimitris*, whom Elina and myself were fortunate to meet with early on during our Rotterdam days; enjoying their company regularly during weekends we kind of kept our home country a little bit closer, even when away. All of them have been for a long time now accomplished professionals deeply rooted in the Netherlands, and it is always a privilege and a motivation to meet with them every time we return to Rotterdam.

My dear parents have always been there for me and my brother, consistently and almost selflessly trying to provide us with the best possible education. It was no surprise that when the opportunity arose for me for a fellowship in Rotterdam, they facilitated my early steps without any hesitation, even with a sense of consolation since Rotterdam would be

at least on this side of the Atlantic as opposed to a US alternative. Regrettably they could not make it to Rotterdam even for a short visit, however I think they would have loved it; by some strange coincidence my father had already spent some 2 ½ years in the greater Belgium, Netherlands and Luxemburg area almost forty years before!

Last but not least, *Elina*, my soul-mate, best friend and companion in life and since 2013 my wife. Our relationship has been intricately connected with Rotterdam; it was not even three months after we had started dating, that I had come to Rotterdam for my interviews. Elina was back then finishing with her medical diploma; the perspective of me departing for Rotterdam alone gave her ample motivation to graduate just in time to accompany me on this great adventure. I understand that it must have been frustrating for her during the first months having no concrete plans, or when later on she repeatedly came so close to starting a PhD in the Netherlands, but yet could not nail it. It turned out to be for the best, since thanks to Pim de Feyter she was integrated in MSCT related projects with a shared appointment in Cardiology and Radiology Departments in Erasmus MC which led to her thesis, but more importantly to a time well and productively spent. During these early times it was probably her love for me but also for travel and adventure that kept her going, which was after all the thing that originally brought us together. I cannot stress enough the level of her contribution to any success I might have had in my fellowship, either by her sheer presence and emotional support, but to a certain part even due to her phenomenal computer skills, Elina being to the date an avid provider of whatever computer application I would need to facilitate my writing and my presentations. Finally, I would probably not have come around to defending my thesis, if it were not for Elina insisting otherwise in her own uniquely quiet but ever so consistent and powerful ways. After all, this would only be the most fitting closure of the first but ever so challenging and worthwhile chapter of many more to come in our common life!

About the author

Curriculum Vitae

PERSONAL DATA:

Name: Chrysafios Girasis

Date of birth: 07.07.1972

Place of birth: Thessaloniki, Greece

Nationality: Greek

EDUCATION AND ACADEMIC QUALIFICATIONS

1990 High school diploma, German School of Thessaloniki, Greece

1990 - 1996 Medical School, Aristotle University of Thessaloniki, Greece
Summa cum Laude Graduate (8.59/10)

2013 PhD graduate, Summa cum Laude, Aristotle University of Thessaloniki, School of Medicine. Supervisor: Prof. V. Vassilikos
Thesis Subject: *Atrial Fibrillation in patients with Hypertrophic Cardiomyopathy. Risk Stratification by non–invasive techniques*

POSTGRADUATE CLINICAL TRAINING

1996 - 1998 Military service, medical officer

1998 - 1999 Clinical Internship, National Health System Regional Community Clinic, Sidirokastro, Serres, Greece

2000 - 2002 Internal Medicine Residency, Veria General Hospital, Greece

2002 - 2003 Postgraduate Programme on Pre-hospital Emergency Medicine
National Health System, Emergency Medical Service

2003 - 2007 Cardiology Fellowship (4 years), 1st Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece

2006 Two-month observership in the Heart and Vascular Institute at the Henry Ford Hospital, Detroit, MI, USA

2008 - 2012 Research & clinical fellowship in Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands, under the direct supervision of Professor Patrick W. Serruys

CURRENT POSITION

2015 to date Senior Interventional cardiologist, Private sector, Thessaloniki, Greece

SENIOR PROFESSIONAL EXPERIENCE

2012 - 2014 Senior staff member, 1st Cardiology Division, Interventional Cardiology, Onassis Cardiac Surgery Center, Athens, Greece

HONORS/AWARDS/GRANTS:

1984-1990 Awards of excellence in academic performance from the Greek Ministry of Education for every year of Secondary Education

1990 Federal Republic of Germany High School Graduation Diploma (Abitur)

1990 German Academic Exchange Committee (DAAD) Scholarship Merit

1993 National Scholarship Foundation of Greece Award for Academic Excellence

2009 Scholarship awarded by the Cardiology Society of Northern Greece (KEBE), linked to the fellowship in Interventional Cardiology at Erasmus MC

2009 Scholarship/ postgraduate educational grant awarded by the A.G. Leventis Foundation, linked to the fellowship in Interventional Cardiology at Erasmus MC

2010 Scholarship awarded by the Hellenic Cardiologic Society, linked to the fellowship in Interventional Cardiology at Erasmus MC

2010 Scholarship awarded by the Hellenic Foundation of Cardiology (ELIKAR) linked to the fellowship in Interventional Cardiology at Erasmus MC

LANGUAGES:

English	Level: excellent
German	Level: excellent
Dutch	Level: good
Greek	Level: native speaker