Table 4: Percentage of struts with neointimal coverage thicker on the abluminal than on the adluminal side and viceversa. Pooled estimation of the proportions and pooled paired comparison.

		n	Pooled %			Paired comparison			
			Estimate	95% CI		OR	95% CI		p-val
				Low	Up		Low	Up	
Whole sample 114 struts 16 stents	ABL thicker	70	60.7	50.6	70.0	3.35	2.22	5.07	<0.0001
	ADL thicker	20	18.5	11.6	28.1				
ISA 85 struts 12 stents	ABL thicker	55	64.8	52.9	75.2	4.16	2.53	6.82	<0.0001
	ADL thicker	14	18.3	10.4	30.1				
NASB 29 struts 6 stents	ABL thicker	15	47.2	28.0	67.3	1.92	0.90	4.12	0.094
	ADL thicker	6	20.2	7.8	43.0				

ABL: Abluminal side; ADL: Adluminal side; CI: Confidence interval; ISA: Incomplete Stent Apposition; NASB: Non-apposed Side Branch (struts).

DISCUSSION

The main findings of this study are 1) neointimal coverage is thicker on the ABL than on the ADL side in 61.4% of ISA and NASB struts; 2) at least 60.7% and up to 92.1% ISA and NASB struts are covered on the ABL side after 6 months in the BVS.

To the best of our knowledge, this is the first study comparing in vivo the neointimal thickness on the ADL vs. the ABL surface of an intracoronary device in a cohort of patients. This comparison had not been technically possible hitherto for two reasons. Firstly, only struts remaining detached from the vessel wall at follow-up present both ADL and ABL surfaces in which neointimal thickness can be measured. This limits the study to small ISA or side-branch regions, difficult to detect and to track. Second and more importantly, the intense backscattering of the ultrasound or of the optical beam at the metallic struts has prevented visualization of their ABL side in BMS or DES. The translucency of the poly-L-lactide polymer in the BVS enables for the first time quantification of the ABL neointimal coverage.

The assessment of coverage in the BVS with OCT is challenging. The translucency of the polymer results in a frame-shaped backscattering at the strut boundaries. This signal convolutes with the one generated by neointima and they often become indiscernible. We circumvented this limitation by taking the inner contour of the backscattering frame of the strut. Compared with other methods of measurement, this approach offers the advantage of a clear reproducible criterion (unpublished data in(29)), although it overestimates slightly the neointimal thickness due to the inclusion of the polymer backscattering (aprox. 30 μm) in the measurement. Since our current study is based on the relative thickness on one side vs. the other, rather than in absolute thickness values, we chose the most accurate and reproducible method of measurement. Our results strongly suggest that most ISA and NASB struts are covered on the ABL side in the BVS at 6 months: at least 60.7% considering those struts with

ABL>ADL thickness, or up to 92.1% if we include also those struts with ABL thickness >30 µm, regardless of the ADL/ABL ratio. Previous OCT studies reported that only 27.4-34.6% of ISA struts were covered on the ADL side after 9-13 months in metallic DES.(24;30) Our observations would suggest that the ABL side might be a more favourable scenario than the ADL for a complete coverage, but this finding could be also explained by differential characteristics of the BVS, since the ADL coverage of ISA struts was also higher in this study than in previous reports on metallic DES.(24;30)

The differences in neointimal thickness suggest that the neointimal inhibition is for some reason less efficient on the ABL than on the ADL side. Differences in shear stress (SS) between the ADL and ABL sides might likely play a role to explain this finding. An inverse relation between SS and neointimal hyperplasia has been described in bare-metal stents(31) and DES.(32-34) Computational models studying the effect of catheter placement(35;36) and of stent infraexpansion(37) on wall SS have consistently found lower SS levels when the catheter was placed close to the vessel wall(35;36) or beneath the struts of an undersized stent.(37) Therefore SS could be lower at the ABL side and thus explain the thicker neointima. Our results fit well into this SS theoretical model, although fluid dynamics can vary considerably depending on the geometry of the vessel, so the hydrodynamic forces become regionally unpredictable. Surprisingly, NASB struts show similar ADL/ABL thickness ratio to that of ISA struts, although in a bifurcation both sides can be submitted to high SS forces. Side branches >2mm diameter were an exclusion criterion for this study, thus our NASB struts correspond predominantly to tiny side branches, probably with flow patterns closer to the ISA scenario than to the true bifurcation. Other factors, like more intense wound healing reaction in the vicinity of the vascular tissue could also play a role.

The neointimal healing on the ABL side is relevant to understand the mechanism by which acute stent malapposition might be spontaneously corrected over time. We have learned from OCT studies that the proportion of malapposed struts gets spontaneously reduced from approximately 7.7% immediately after stenting to 1.2% at 6 months follow-up,(25) but the physiological mechanism for this correction is to a great extent unknown and important to understand why it happens in some regions but not in others. The thicker ABL neointima suggests that the integration process of malapposed areas into the vessel wall might be the consequence of neointimal growth from the strut to the vessel or bidirectionally, rather than merely from vessel to strut.

Limitations

Although the term "neointimal thickness" is commonly used in OCT studies,(21;22;38;39), its sensitivity and specificity for neointimal detection are still unknown and <100%. OCT coverage correlates with histological neointima and endothelialization after stenting in animal models,(40-43) but OCT is unable to detect thin layers of endothelium below 14µm axial

resolution, and cannot discern between neointima and other material, like fibrin or thrombus. Optical densitometry analysis might be useful in the future.(42) Additionally, OCT has been validated for the assessment of neointimal coverage taking into account only the ADL coverage. This study has been performed under the assumption that the validation on the ADL side can also apply the ABL side: this hypothesis, although theoretically plausible, has not been empirically demonstrated to date.

The observations in this study apply only to the BVS, a bioresorbable everolimus-eluting vascular scaffold. Extrapolation of the conclusions to other intracoronary devices, like BMS or DES must be cautious, even though considerable analogy has been described in the neointimal healing of these devices.

Conclusions

Most of malapposed and side-branch struts are covered on the abluminal side 6 months after BVS implantation, with thicker neointimal coverage than on the adluminal side. The physiologic correction of acute malapposition involves neointimal growth from the strut to the vessel wall or bidirectional.

FUNDING SOURCES

This study analyzes data from a registry sponsored by ABBOTT Vascular, Santa Clara, CA, USA. The core-lab and CRO responsible for the analysis (Cardialysis BV, Rotterdam) and the participating centres (except[2]) have received grants from the sponsor to run the trial.

DISCLOSURES

De Bruyne B, Thuesen L, Ormiston J, McClean DR, Windecker S, Chevalier B, Dudek D, Whitbourn R and Serruys PW have received speakers' fees from the sponsor.

REFERENCE LIST

1. Liu MW, Roubin GS, King SB, III. Restenosis after coronary angioplasty. Potential biologic determinants and role of intimal hyperplasia. Circulation 1989; 79(6):1374-1387.
2. Essed CE, van den BM, Becker AE. Transluminal coronary angioplasty and early restenosis. Fibrocellular occlusion after wall laceration. Br Heart J 1983; 49(4):393-396.
3. Giraldo AA, Esposo OM, Meis JM. Intimal hyperplasia as a cause of restenosis after percutaneous transluminal coronary angioplasty. Arch Pathol Lab Med 1985; 109(2):173-175.
4. Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF. Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1985; 6(2):369-375.
5. Reidy MA, Standaert D, Schwartz SM. Inhibition of endothelial cell regrowth. Cessation of aortic endothelial cell replication after balloon catheter denudation. Arteriosclerosis 1982; 2(3):216-220.
6. Haudenschild CC, Schwartz SM. Endothelial regeneration. II. Restitution of endothelial continuity. Lab Invest 1979; 41(5):407-418.
7. Reidy MA, Schwartz SM. Endothelial regeneration. III. Time course of intimal changes after small defined injury to rat aortic endothelium. Lab Invest 1981; 44(4):301-308.
8. Bjorkerud S, Bondjers G. Arterial repair and atherosclerosis after mechanical injury. 5. Tissue response after induction of a large superficial transverse injury. Atherosclerosis 1973; 18(2):235-255.
9. Reidy MA, Clowes AW, Schwartz SM. Endothelial regeneration. V. Inhibition of endothelial regrowth in arteries of rat and rabbit. Lab Invest 1983; 49(5):569-575.
10. Clowes AW, Karnowsky MJ. Suppression by heparin of smooth muscle cell proliferation in injured arteries. Nature 1977; 265(5595):625-626.
11. Kong D, Melo LG, Gnecchi M et al. Cytokine-Induced Mobilization of Circulating Endothelial Progenitor Cells Enhances Repair of Injured Arteries. Circulation 2004; 110(14):2039-2046.
12. Werner N, Kosiol S, Schiegl T et al. Circulating Endothelial Progenitor Cells and Cardiovascular Outcomes. New Engl J Med 2005; 353(10):999-1007.
13. Joner M, Finn AV, Farb A et al. Pathology of Drug-Eluting Stents in Humans: Delayed Healing and Late Thrombotic Risk. J Am Coll Cardiol 2006; 48(1):193-202.
14. Finn AV, Joner M, Nakazawa G et al. Pathological Correlates of Late Drug-Eluting Stent Thrombosis: Strut Coverage as a Marker of Endothelialization. Circulation 2007; 115(18):2435-2441.
15. Virmani R, Guagliumi G, Farb A et al. Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent: Should We Be Cautious? Circulation 2004; 109(6):701-705.
16. Farb AM, Burke APM, Kolodgie FDP, Virmani RM. Pathological Mechanisms of Fatal Late Coronary Stent Thrombosis in Humans. Circulation 2003; 108(14):1701-1706.
17. Awata M, Kotani Ji, Uematsu M et al. Serial Angioscopic Evidence of Incomplete Neointimal Coverage After Sirolimus-Eluting Stent Implantation: Comparison With Bare-Metal Stents. Circulation 2007; 116(8):910-916.
18. Awata M, Nanto S, Uematsu M et al. Angioscopic Comparison of Neointimal Coverage Between Zotarolimus- and Sirolimus-Eluting Stents. J Am Coll Cardiol 2008; 52(9):789-790.
19. Takano M, Ohba T, Inami S, Seimiya K, Sakai S, Mizuno K. Angioscopic differences in neointimal coverage and in persistence of thrombus between sirolimus-eluting stents and bare metal stents after a 6-month implantation. Eur Heart J 2006; 27(18):2189-2195.

20. Barlis P, Regar E, Serruys PW et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. Eur Heart J 2010; 31(2):165-176.
21. Guagliumi G, Sirbu V, Musumeci G et al. Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI). Circ Cardiovasc Interv 2010; 3(4):367-375.
22. Guagliumi G, Sirbu V, Bezerra H et al. Strut coverage and vessel wall response to zotarolimus-eluting and bare-metal stents implanted in patients with ST-segment elevation myocardial infarction: the OCTAMI (Optical Coherence Tomography in Acute Myocardial Infarction) Study. JACC Cardiovasc Interv 2010; 3(6):680-687.
23. Guagliumi G, Costa MA, Sirbu V et al. Strut Coverage and Late Malapposition With Paclitaxel-Eluting Stents Compared With Bare Metal Stents in Acute Myocardial Infarction: Optical Coherence Tomography Substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial. Circulation 2011; 123(3):274-281.
24. Ozaki Y, Okumura M, Ismail TF et al. The fate of incomplete stent apposition with drug-eluting stents: an optical coherence tomography-based natural history study. Eur Heart J 2010; 31(12):1470-1476.
25. Gutiérrez-Chico J, van Geuns RJ, Koch K et al. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomized trial balloon-first vs. stent first. EuroIntervention 2011; 7(6):711-722.
26. Gutiérrez-Chico J, Jüni P, García-García HM et al. Long term tissue coverage of a biodegradable polylactide polymer-coated biolimus-eluting stent: comparative sequential assessment with optical coherence tomography until complete resorption of the polymer. Am Heart J 2011; 162(5):922-931.
27. Serruys PW, Ormiston JA, Onuma Y et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009; 373(9667):897-910.
28. Ormiston JA, Serruys PW, Regar E et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008; 371(9616):899-907.
29. Serruys PW, Onuma Y, Ormiston JA et al. Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of de novo coronary artery stenosis: 6-month clinical and imaging outcomes. Circulation 2010; 122(22):2301-2312.
30. Gutiérrez-Chico JL, Regar E, Nüesch E et al. Delayed Coverage in Malapposed and Side-Branch Struts With Respect to Well-Apposed Struts in Drug-Eluting Stents. Circulation 2011; 124(5):612-623.
31. Wentzel JJ, Krams R, Schuurbiers JC et al. Relationship between neointimal thickness and shear stress after Wallstent implantation in human coronary arteries. Circulation 2001; 103(13):1740-1745.
32. Gijsen FJH, Oortman RM, Wentzel JJ et al. Usefulness of shear stress pattern in predicting neointima distribution in sirolimus-eluting stents in coronary arteries. Am J Cardiol 2003; 92(11):1325-1328.
33. Tanabe K, Gijsen FJH, Degertekin M et al. True Three-Dimensional Reconstructed Images Showing Lumen Enlargement After Sirolimus-Eluting Stent Implantation. Circulation 2002; 106(22):e179-e180.

34. Thury A, Wentzel JJ, Vinke RVH et al. Focal In-Stent Restenosis Near Step-Up: Roles of Low and Oscillating Shear Stress? Circulation 2002; 105(23):e185-e187.
35. Wentzel JJ, Krams R, van der Steen AFW et al. Disturbance of 3D velocity profiles induced by an IVUS catheter: evaluation with computational fluid dynamics. Comput Cardiol 1997; 24:597-600.
36. Krams R, Wentzel JJ, Cespedes I et al. Effect of catheter placement on 3-D velocity profiles in curved tubes resembling the human coronary system. Ultrasound Med Biol 25[5], 803-810. 1-6-1999.
37. Chen HY, Hermiller J, Sinha AK, Sturek M, Zhu L, Kassab GS. Effects of stent sizing on endothelial and vessel wall stress: potential mechanisms for in-stent restenosis. J Appl Physiol 2009; 106(5):1686-1691.
38. Miyoshi N, Shite J, Shinke T et al. Comparison by optical coherence tomography of paclitaxel-eluting stents with sirolimus-eluting stents implanted in one coronary artery in one procedure. - 6-month follow-up -. Circ J 2010; 74(5):903-908.
39. Takano M, Yamamoto M, Mizuno M et al. Late vascular responses from 2 to 4 years after implantation of sirolimus-eluting stents: serial observations by intracoronary optical coherence tomography. Circ Cardiovasc Interv 2010; 3(5):476-483.
40. Prati F, Zimarino M, Stabile E et al. Does optical coherence tomography identify arterial healing after stenting? An in vivo comparison with histology, in a rabbit carotid model. Heart 2008; 94(2):217-221.
41. Murata A, Wallace-Bradley D, Tellez A et al. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. JACC Cardiovasc Imaging 2010; 3(1):76-84.
42. Templin C, Meyer M, Muller MF et al. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. Eur Heart J 2010; 31(14):1792-1801.
43. Onuma Y, Serruys PW, Perkins LE et al. Intracoronary Optical Coherence Tomography and Histology at 1 Month and 2, 3, and 4 Years After Implantation of Everolimus-Eluting Bioresorbable Vascular Scaffolds in a Porcine Coronary Artery Model. An Attempt to Decipher the Human Optical Coherence Tomography Images in the ABSORB Trial. Circulation 2010; 122(22):2288-2300.

CHAPTER 13

Overlaps

Tissue coverage and neointimal hyperplasia in overlap vs. non-overlap segments of drug-eluting stents 9-13 months after implantation: in vivo-assessment with optical coherence tomography.

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STRUCTURED ABSTRACT

Background: Histologic experimental studies have reported incomplete neointimal healing in overlapping with respect to non-overlapping segments in DES, but these observations have not been confirmed in human coronary arteries hitherto. On the contrary, angiographic and OCT studies suggest that DES overlap elicits rather an exaggerated than an incomplete neointimal reaction.
Methods: Optical coherence tomography (OCT) studies from 2 randomized trials including sirolimus-eluting (SES), biolimus-eluting (BES), everolimus-eluting (EES) and zotarolimus-eluting stents (ZES) were analyzed at 9-13 months follow-up. Coverage in overlapping segments was compared vs. the corresponding non-overlapping segments of the same stents, using statistical pooled analysis.
Results: 42 overlaps were found in 31 patients: 11 in SES, 3 in BES, 17 in EES and 11 in ZES. The risk-ratio of incomplete coverage was 2.35 (95% CI: 1.86 – 2.98) in overlapping vs. non-overlapping segments. Thickness of coverage in overlaps was only 85% (95% CI: 81 – 90%) of the thickness in non-overlaps. Significant heterogeneity of the effect was observed, especially pronounced in the comparison of thickness of coverage (I^2=90.31).
Conclusions: The effect of overlapping DES on neointimal inhibition is markedly heterogeneous: on average DES overlap is associated with more incomplete and thinner coverage, but in some cases the overlap elicits an exaggerated neointimal reaction, thicker than in the corresponding non-overlapping segments. These results might help to understand why overlapping DES is associated with worse clinical outcomes, both in terms of thrombotic phenomena and restenosis-revascularization.
Key words: Coronary vessels; coronary stenosis; drug-eluting stents; sirolimus; biolimus A9; everolimus; zotarolimus; tomography, optical coherence.

CONDENSED ABSTRACT

Histologic studies have reported incomplete neointimal healing in overlapping with respect to non-overlapping segments in DES, but these observations have not been confirmed in human coronary arteries hitherto. Pooling OCT data from two randomized trials, coverage of overlapping vs. non-overlapping segments of 184 2nd-generation DES (104 patients, 42 overlaps) was compared. Risk-ratio of incomplete coverage was 2.35 (95% CI: 1.86 – 2.98) and thickness of coverage in overlaps was 85% (95% CI: 81 – 90%) of that in non-overlaps, although this effect was significantly heterogeneous (I^2=90.31).

LIST OF ABBREVIATIONS

BES: Biolimus-eluting stent
DES: Drug-eluting stent
EES: Everolimus-eluting stent
ISA: Incomplete stent apposition
NASB: Non-apposed side-branch struts
LVLST: Late and very late stent thrombosis
OCT: Optical coherence tomography
RR: Risk ratio
SES: Sirolimus-eluting stent
ZES: Zotarolimus-eluting stent

INTRODUCTION

The reduction of restenosis rates achieved by drug eluting stents (DES)[1] has been obscured by concerns about late and very late stent thrombosis (LVLST)[2, 3]. Pathology studies have described delayed neointimal healing with incomplete endothelialization of the struts[4] as the common morphologic finding in fatal cases of LVLST.

The effect of DES overlap on the neointimal healing process is still poorly understood. Experimental studies on animal models have reported incomplete neointimal healing in overlap compared to non-overlap segments in first-generation DES, with more incomplete endothelialization, greater fibrin deposition and greater cellular inflammatory infiltrates[5]. Drug overdose, larger amounts of polymer, the double metallic layer often altering the structural geometry of the stent might explain the suboptimal neointimal coverage in overlaps. Nevertheless, these observations have not been confirmed in human coronary arteries hitherto. On the contrary, several angiographic studies have associated DES overlap with greater late loss and binary restenosis[6, 7], most frequently involving the overlap segment[7], thus suggesting that DES overlap elicits rather an exaggerated than an incomplete neointimal reaction. Likewise, a randomized single-center clinical trial addressed specifically the neointimal coverage of overlap vs. non-overlap segments in different types of DES, as estimated by optical coherence tomography (OCT)[8]: the percent of covered struts was not significantly different between overlap and non-overlap segments, the thickness of coverage was either not different or even thicker in overlaps and the percent neointimal volume obstruction was larger. A higher metal-to-artery surface ratio or more severe strut-imposed vessel injury could be advocated to explain a hyperproliferative neointimal reaction in the overlaps[9, 10]. Understanding how overlapping DES affect the neointimal healing process after stenting is relevant, because it is a widespread practice, required in approximately one third of the coronary interventions due to excessive lesion length or suboptimal results[11-13], and is associated with worse long-term clinical outcomes, both in terms of repeated revascularization and of death/myocardial infarction[7].

We hypothesize that the neointimal reaction at overlapping segments might be heterogeneous, hence with marked variations between patients and lesions, thus explaining the inconsistency between different histology, angiography and OCT studies. The aim of this study is comparing the OCT tissue coverage of overlap vs. non-overlap segments in different types of DES, using a method that accounts for a potential heterogeneity of the effect.

METHODS

Study sample

Data at follow-up from OCT substudies of two different randomized trials were analyzed: LEADERS (NCT00389220)[14-16], comparing a biolimus-eluting stent (BES) with bioresorbable polymer in abluminal coating (BioMatrix™ Flex, Biosensors International, Morges, CH) vs. a sirolimus-eluting stent (SES) with durable polymer (Cypher™ SELECT, Cordis, Miami Lakes, FL, USA); and the RESOLUTE-All comers (NCT00617084)[17, 18], comparing a zotarolimus-eluting stent (ZES) with hydrophilic-polymer coating (Resolute, Medtronic Inc, Santa Rosa, CA, USA) vs. an everolimus-eluting stent (EES) with fluoropolymer (Xience V, Abbott Vascular, Santa Clara, CA, USA). The design and results of these trials have been published elsewhere[14-18]. Both trials followed an all-comers design, with minimal exclusion criteria. In LEADERS the OCT follow-up was scheduled at 9 months, whereas in RESOLUTE-III it was at 13 months.

OCT study and analysis

OCT pullbacks were obtained at follow-up with M3 or C7 systems (Lightlab Imaging, Westford, Massachusetts, USA), according to the availability at the participating sites, using occlusive or non-occlusive technique, as appropriate[19]. Table 1 summarizes the technical specifications of each OCT system and optical catheters.

OCT pullbacks were analysed offline in a core-laboratory (Cardialysis BV, Rotterdam, NL) by independent staff blinded to stent-type allocation and to other clinical or procedural

Table 1: Technical specifications of the different OCT systems in the study.

	M3	C7
Technique	Non-occlusive	Non-occlusive
Domain	Time	Fourier
Catheter	ImageWire	Dragonfly
Rotation speed (frames/s)	20	100
Pullback speed (mm/s)	3	10-20
Axial resolution (µm)	10-20	10-20
Lateral resolution (µm)	20-90	20-40
Patients / overlaps with SES	9 / 11	0 / 0
Patients / overlaps with BES	3 / 3	0 / 0
Patients / overlaps with EES	3 / 5	8 / 12
Patients / overlaps with ZES	3 / 3	5 / 8
Total nr of patients / overlaps	18 / 22	13 / 20

All systems and catheters from Lightlab Imaging, Westford, Massachusetts, USA.

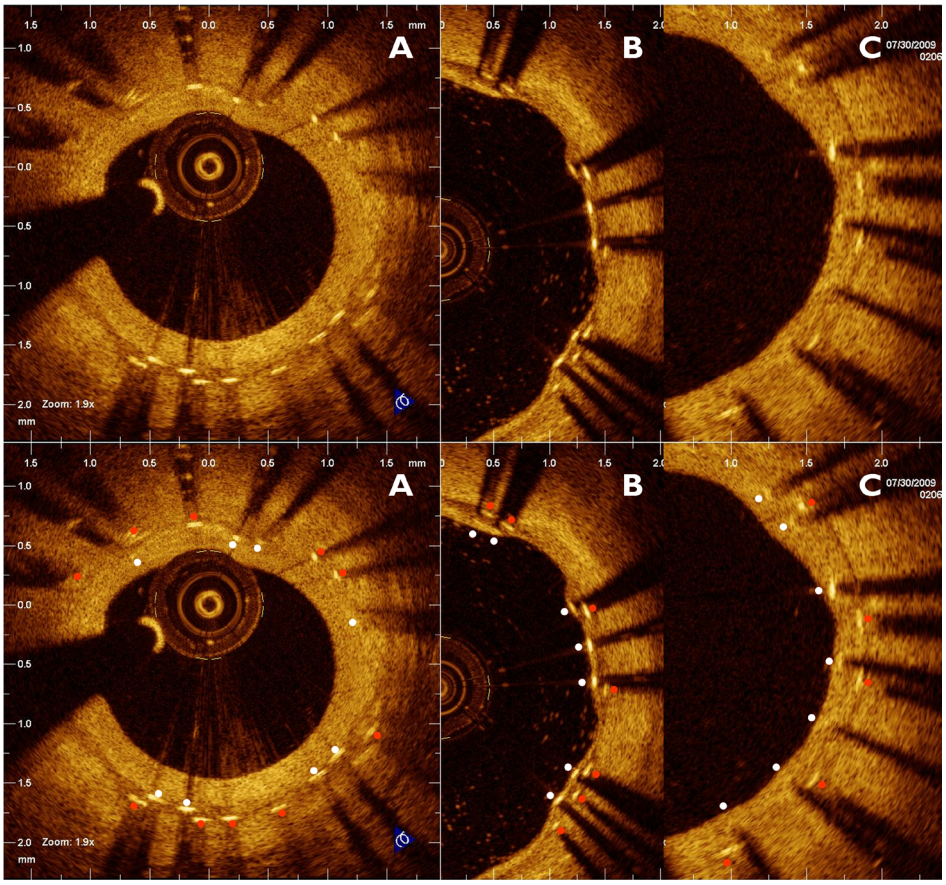


Figure 1: Examples of cross-sections in overlapping segments in which a double struts layer can be clearly identified.
Struts in the outer layer (red dots) are covered more completely (B) and by thicker neointimal (C) than struts in the inner or indeterminate layer (white dots).

variables, using proprietary software (Lightlab Imaging). Cross-sections at 1mm longitudinal intervals within the stented segment were analyzed. Overlapping segments were delimited by their most distal and most proximal cross-sections. Lumen and stent areas were drawn in each cross-section, and neointimal hyperplasia (NIH) area was derived. Stent and NIH volumes were calculated for each segment by multiplying the mean corresponding area by the segment length. In-stent percent neointimal volume obstruction was calculated as: (NIH volume / Stent volume) * 100.

A metallic strut typically appears as a bright signal-intense structure with dorsal shadowing. In the overlapping segments in which a double strut layer could be clearly identified, those struts clearly pertaining to the outer layer were labelled as such (figure 1). Apposition was assessed by measuring the distance between each strut marker and the lumen contour, placing the marker at the adluminal leading edge, in the mid-point of the strut long-axis. Dis-

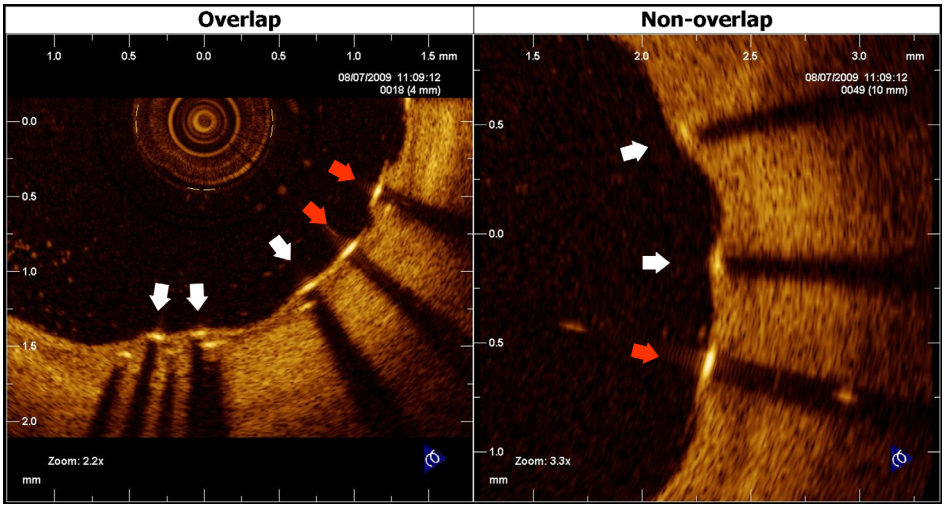


Figure 2: Examples of covered (white arrows) and uncovered struts (red arrows) in overlapping (left) and non-overlapping regions (right) at follow-up.

tance was measured following a straight line connecting this marker with the centre of gravity of the vessel[20]. Struts were classified as incomplete stent apposition (ISA) if the distance between the strut marker and the lumen contour was bigger than the specific strut thickness plus the axial resolution of OCT (14μm)[16, 21, 22]. This resulted in ISA thresholds of >168μm for SES, >131μm for BES, >99μm for EES and 111μm for ZES. Struts located at the ostium of side branches, with no vessel wall behind, were labelled as non-apposed side-branch (NASB) struts and considered an independent category of apposition[16, 18, 21-23].

Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen, or covered if a layer of tissue was visible over all the reflecting surfaces. In covered struts, thickness of coverage was measured from the strut marker to the adluminal edge of the tissue coverage, following a straight line connecting the strut marker with the centre of gravity of the vessel (Figure 2)[8, 15, 16, 18, 20-22, 24].

Statistical analysis

Reproducibility of the total strut count and the outer-layer strut count was tested with non-parametric correlation in all overlapping cross-sections (Kendall's tau-b). For each overlap, the risk ratio (RR) for uncoverage in the overlapping segment vs. the corresponding proximal and distal non-overlapping segments was calculated. Individual RR were pooled using an inverse variance random effects model, taking into account between-clusters and within-the-cluster variability[22, 23, 25]. Stents with no overlap (no exposition) or zero uncovered struts (no events) were not informative to evaluate the RR for uncoverage and discarded from the analysis[22, 23, 25].

A proportional continuity correction was applied to stents with zero uncovered struts (zero events) in only one of the compared segments (either overlap or non-overlap segments)[26].

Given the extremely skewed non-normal distribution of the thickness of coverage in the struts, comparison of this variable was performed using the log transformation of the thickness of coverage[21], calculating the standardized difference of means for each overlap through the Hedges' g method[27]. Individual differences of means were pooled using an inverse variance random effects model.

Analysis of heterogeneity of the effect was reported as I^2 (proportion of the effect attributable to heterogeneity) and the p-value of the Q test, considering statistically significant a p-value ≤0.1. In case of significant heterogeneity of the effect, the influence of the type of stent would be explored by random-effects metaregression and by stratified analysis. Calculations were done with PASW 17.0 (Chicago, IL, USA) and CMA version 2 (Biostat Inc., Englewood, NJ, USA) software packages.

This study has been sponsored by Medtronic Cardio Vascular, Santa Rosa, CA, USA and Biosensors International, Morges, CH. The core-lab and CRO responsible for the analysis (Cardialysis BV, Rotterdam) and the participating centres have received grants to run the trials. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

42 overlaps were found in 31 out of 104 patients screened in the study population (suppl. Figure 1): 11 SES, 3 BES, 17 EES and 11 ZES (16928 struts).

Baseline clinical and procedural characteristics of the patients with overlaps are shown in table 2. Angiographic characteristics of the lesions are available as supplementary material (suppl. table 1). Table 3 summarizes OCT-derived areas and volumes of the overlapping segments compared with the control non-overlapping segments of the same stents. No significant difference in percent neointimal volume obstruction was found, although tended to be slightly lower in overlaps. Areas and volumetric analysis stratified by type of stent can be found in the supplementary material section (suppl. table 2). Total struts count and outer-layer struts count showed optimal interobserverse reproducibility (Kendall's Tau-b 0.864 and 0.951, respectively), with no significant bias in any of the analysts.

Descriptives of coverage in the global sample

Table 4 shows the total count of struts in overlapping and non-overlapping segments, and the raw proportions of coverage stratified by apposition category. 5.1% of all visible struts in overlaps appeared uncovered at follow-up, raising to 6.2% if the struts of the outer layers

Table 2: Patients' and procedural baseline characteristics in the subgroup with overlapping stents, grouped by type of stent.

	SES (n=9)	BES (n=3)	EES (n=11)	ZES (n=8)	p-val
Age (years)	58.2 (8.7)	59.3 (7.0)	60.5 (6.9)	57.4 (12.4)	0.887
Males	6 (66.7%)	3 (100.0%)	8 (72.7%)	7 (87.5%)	0.557
Cardiovascular risk factors					
Hypertension	7 (77.8%)	2 (66.7%)	4 (36.4%)	6 (75.0%)	0.205
DM	2 (22.2%)	1 (33.3%)	2 (18.2%)	3 (37.5%)	0.788
Insulin-requiring	0 (0.0%)	1 (33.3%)	1 (9.1%)	0 (0.0%)	0.180
Hypercholesterolemia	7 (77.8%)	3 (100.0%)	8 (72.7%)	6 (75.0%)	0.791
Smoking	4 (44.4%)	0 (0.0%)	6 (54.5%)	3 (37.5%)	0.396
Current smoker (<30d)	4 (44.4%)	0 (0.0%)	5 (45.5%)	2 (25.0%)	0.419
Family history of CHD	8 (88.9%)	2 (66.7%)	4 (50.0%)	3 (75.0%)	0.368
Antecedents					
Previous MI	3 (33.3%)	3 (100.0%)	4 (36.4%)	2 (25.0%)	0.138
Previous PCI	2 (22.2%)	1 (33.3%)	1 (9.1%)	4 (50.0%)	0.241
Previous CABG	0 (0.0%)	1 (33.3%)	2 (18.2%)	0 (0.0%)	0.199
Clinical presentation					0.374
Stable angina	6 (66.7%)	3 (100.0%)	4 (36.4%)	5 (62.5%)	0.201
Unstable angina	2 (22.2%)	0 (0.0%)	2 (18.2%)	1 (12.5%)	0.817
Myocardial infarction	1 (11.1%)	0 (0.0%)	5 (45.5%)	1 (12.5%)	0.150
STEMI	0 (0.0%)	0 (0.0%)	3 (27.3%)	1 (12.5%)	0.284
Silent ischemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0.396
Procedural characteristics					
Nr vessels treated	1.11 (0.33)	1.33 (0.58)	1.27 (0.47)	1.63 (0.74)	0.272
Nr of lesions treated	2.22 (1.09)	1.67 (1.15)	1.55 (0.82)	1.63 (0.74)	0.398
Nr of stents implanted	2.3 (0.73)	2.00 (1.00)	3.09 (1.22)	3.00 (2.56)	0.144
Total stented length (mm)	48.9 (22.2)	54.7 (24.1)	64.1 (25.5)	60.4 (61.1)	0.829
Small vessel (<2.5mm diam)	4 (44.4%)	2 (66.7%)	6 (75.0%)	2 (25.0%)	0.217

Continuous variables are reported as mean(SD) and categorical variables as n(%); stent groups are compared with one-way ANOVA and Pearson's chi-square, respectively.

BES: Biolimus-eluting stent; BMS: Bare Metal Stent; CABG: Coronary Artery By-pass Graft; CHD: Coronary Heart Disease; DES: Drug-eluting stent; DM: Diabetes Mellitus; EES: Everolimus-eluting stent; LAD: Left anterior descending; LCX: Left Circumflex; LM: Left Main Stem; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; RCA: Right coronary artery; SES: Sirolimus-eluting stent; STEMI: ST elevation myocardial infarction; ZES: Zotarolimus-eluting stent.

were excluded. Only 2.3% of the struts in non-overlapping segments of the corresponding stents were uncovered. The thickness of coverage had a mean of 109µm (median 80µm, interquartile range 40 - 150µm) in the overlaps and of 150µm (median 120µm, interquartile range 60 - 210 µm) in non-overlaps.

Table 3: Areas and volumetric analysis of overlap segments compared with non-overlap segments of the same stents.

All DES 31 patients 33 lesions 42 overlaps	Overlap	Non-overlap			p-value
		Distal	Proximal	Combined	
Stent length (mm)	3.8 (4.8)	16.2 (7.3)	16.2 (7.9)	32.0 (12.5)	**<0.0001***
MLA (mm^2)	6.22 (2.43)	4.58 (2.58)	5.72 (2.47)	4.34 (2.45)	**<0.0001***
Mean lumen Area (mm^2)	6.70 (2.57)	5.86 (2.63)	7.19 (2.56)	7.00 (2.42)	**0.045***
Lumen volume (mm^3)	27.9 (42.2)	91.64 (58.98)	114.3 (67.8)	203.2 (110.0)	**<0.0001***
Min stent area (mm^2)	7.03 (2.44)	5.68 (2.52)	6.81 (2.45)	5.43 (2.31)	**<0.0001***
Mean stent area (mm^2)	7.60 (2.50)	6.87 (2.53)	8.11 (2.42)	7.45 (2.35)	0.315
Stent volume (mm^3)	30.6 (44.0)	107.7 (61.8)	129.3 (71.5)	233.9 (114.4)	**<0.0001**
% frames with ISA	2.68 (9.62)	1.16 (3.46)	3.50 (10.34)	2.29 (5.24)	0.822
Max ISA area (mm^2)	0.02 (0.08)	0.16 (0.53)	0.33 (1.18)	0.48 (1.24)	**0.023***
ISA volume (mm^3)	0.02 (0.06)	0.28 (1.03)	1.12 (5.28)	1.38 (5.26)	0.102
Corrected by stent volume (%)	0.13 (0.50)	0.17 (0.63)	0.78 (3.93)	0.56 (2.38)	0.268
Max NIH area (mm^2)	1.28 (0.86)	1.84 (0.87)	1.87 (0.88)	2.19 (0.88)	**<0.0001***
NIH volume (mm^3)	2.8 (2.9)	16.4 (11.1)	16.1 (12.0)	32.1 (19.5)	**<0.0001***
In-stent NIH vol obstruction (%)	13.3 (10.9)	17.1 (11.2)	13.4 (9.3)	15.0 (9.6)	0.065

* $p \leq 0,05$

DES: Drug-eluting stent; ISA: Incomplete stent apposition; MLA: Minimal lumen area; NIH : Neointimal hyperplasia.

Table 4: Cross-tab showing the raw counts (%) of covered and uncovered struts in the overlapping and non-overlapping segments within the stents, stratified by apposition category (WA: well-apposed; ISA: incomplete stent apposition; NASB: Non-apposed side-branch struts), without clustering by patient or lesion. The overlapping segments are presented according to the two different analysis performed: excluding or including the struts of the outer layer.

		Coverage		Total
		Covered	Uncovered	
Overlaps (excluding outer layer)		**2177 (93.8%)**	**143 (6.2%)**	**2320**
	WA	2168 (94.1%)	135 (5.9%)	2303
	ISA	2 (27.4%)	7 (77.8%)	9
	NASB	7 (87.5%)	1 (12.5%)	8
Overlaps (all struts)		**2674 (94.9%)**	**145 (5.1%)**	**2819**
	WA	2664 (95.1%)	137 (4.9%)	2801
	ISA	2 (22.2%)	7 (77.8%)	9
	NASB	8 (88.9%)	1 (11.1%)	9
Non-overlaps		**13788 (97.7%)**	**321 (2.3%)**	**14109**
	WA	13672 (98.2%)	256 (1.8%)	13928
	ISA	42 (47.2%)	47 (52.8 %)	89
	NASB	74 (80.4%)	18 (19.6%)	92
Total nr of struts (excluding outer layer)		15965 (97.2%)	464 (2.8%)	16429
Total nr of struts (all struts)		16462 (97.2%)	466 (2.8%)	16928

ISA: Incomplete stent apposition; NASB: Non-apposed side-branch (struts); WA: Well-apposed (struts).

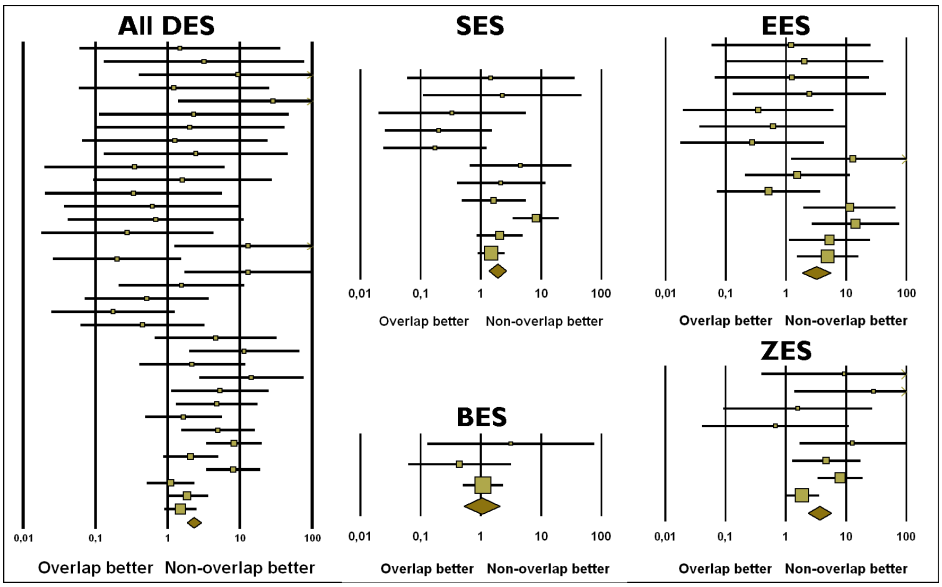


Figure 3 (panel A): Risk ratio of incomplete coverage, excluding the outer layer.

Forest plot showing the risk ratio of incomplete coverage in overlapping vs. non-overlapping segments at 9-13 month in the whole sample and stratified by type of stent. Lines represent the 95% confidence interval for the risk ratio in each overlap, with the pooled risk ratio at the bottom. BES: Biolimus-eluting stent; DES: Drug-eluting stent; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

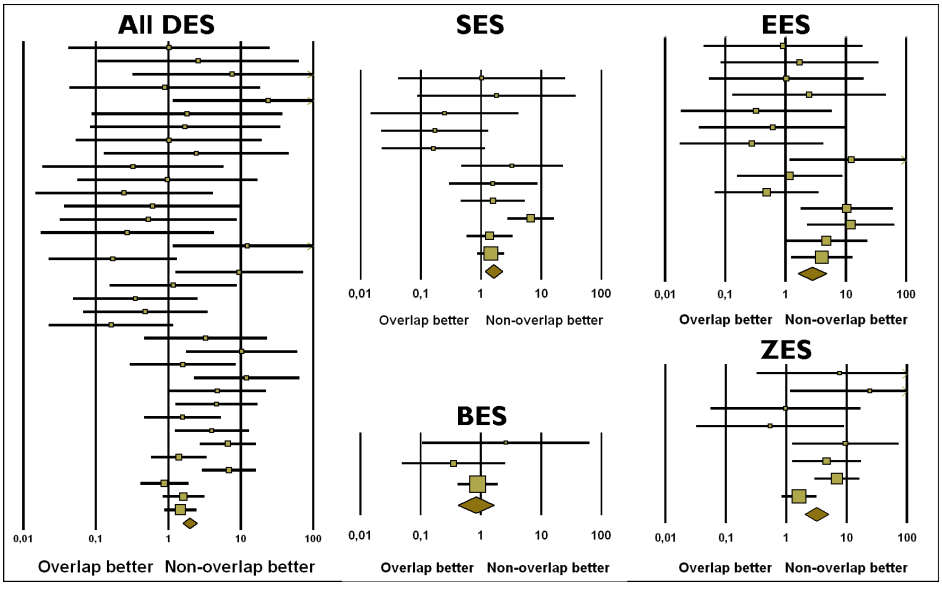


Figure 3 (panel B): Risk ratio of incomplete coverage, all visible struts analyzed.

Forest plot showing the risk ratio of incomplete coverage in overlapping vs. non-overlapping segments at 9-13 month in the whole sample and stratified by type of stent. Lines represent the 95% confidence interval for the risk ratio in each overlap, with the pooled risk ratio at the bottom. BES: Biolimus-eluting stent; DES: Drug-eluting stent; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

Table 5: Pooled analysis of the risk ratio of incomplete coverage in overlap vs. non-overlap segments, stratified by type of stent. The overlapping segments are presented according to the two different analysis performed: excluding or including the struts of the outer layer.

		n	Magnitude of effect			Heterogeneity of the effect	
			RR	95% CI		I^2	p val
				Lower	Upper		
Excl outer layer	DES	36	2.39	1.57	3.63	48.58	0.001
	SES	11	1.59	0.78	3.21	59.60	0.006
	BES	3	0.97	0.48	1.96	0.00	0.689
	EES	14	3.51	1.63	7.57	21.98	0.215
	ZES	8	4.63	2.12	10.13	39.45	0.116
All struts	DES	36	2.00	1.32	3.02	47.78	0.001
	SES	11	1.33	0.68	2.60	55.71	0.012
	BES	3	0.78	0.39	1.58	0.00	0.686
	EES	14	2.98	1.38	6.41	22.25	0.212
	ZES	8	3.96	1.81	8.63	39.65	0.115

BES: Biolimus-eluting stent; DES: Drug-eluting stents; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

RR>1: Higher risk of uncoverage in overlaps; RR<1: Higher risk of uncoverage in non-overlaps.

Risk ratio for non-coverage in overlapping vs. non-overlapping segments

6 overlapping DES were totally covered and hence not suitable for risk ratio estimation. Excluding the struts in the outer layers, the pooled risk ratio of incomplete coverage in overlaps vs. non-overlaps was 2.35 (95% CI: 1.86 – 2.98) for the whole DES sample (table 5, figure 3a). There was moderate heterogeneity of the effect (I^2=48.58), that was not explained by the type of stent (metaregression adjusted r^2=0.029, p=0.234) The magnitude of the effect was only minimally softened if all visible struts in the overlapping segments were considered in the analysis (table 5, figure 3b), with no influence of the type of stent (adjusted r^2=0.035, p=0.212).

Difference in thickness of coverage between overlapping vs. non-overlapping segments

The distribution of the thickness of coverage was normalised by logarithmic transform (figure 4). Excluding the struts in the outer layers, the pooled ratio (thickness in overlap / thickness in non-overlap) was 0.85 (0.81 – 0.89) for the whole DES sample (table 6, figure 5a). There was extreme heterogeneity of the effect (I^2>89.00) , not attributable to the type of stent (metaregression adjusted r^2=-0.010, p=0.441). The magnitude of the effect changed dramatically if all visible struts in the overlapping segments were considered in the analysis (table 6, figure 5b), being close to reach statistical significance in the opposite direction to the one obtained in the analysis of just the inner layer, irrespective of the type of stent (adjusted r^2=-0.019, p=0.640).

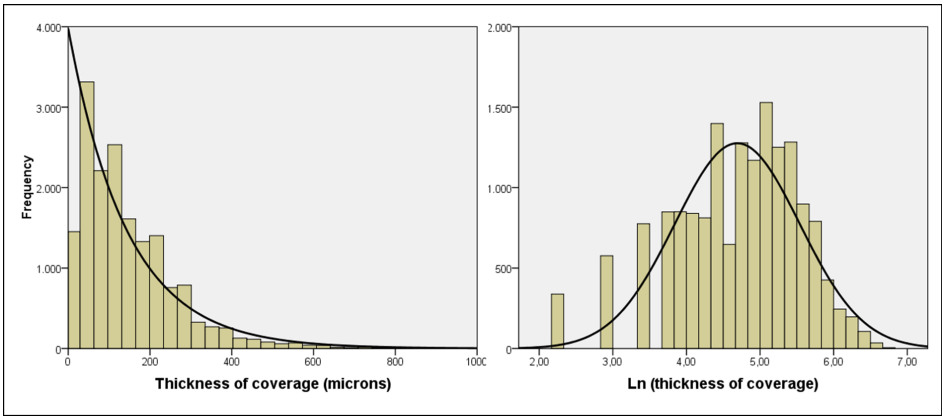


Figure 4: Distribution of the variable thickness of coverage.
The variable follows an extremely skewed distribution, fitting within an exponential curve (left panel). After logarithmic transformation the variable approximates a normal distribution (right panel).

Table 6: Pooled analysis of the thickness of coverage in overlap vs. non-overlap segments, stratified by type of stent. Results presented as ratio "thickness in overlap / thickness in non-overlap", derived from the comparison of standardised differences of means (Hedges' g) after log-transformation. Overlapping segments are presented according to the two different analysis performed: excluding or including the struts of the outer layer.

				Magnitude of effect			Heterogeneity of the effect	
			n	Overlap/non-overlap ratio	95% CI		I^2	p val
					Lower	Upper		
Excl outer layer	DES		42	0.85	0.81	0.89	90.31	<0.0001
		SES	11	0.71	0.64	0.77	92.69	<0.0001
		BES	3	0.93	0.80	1.10	56.19	0.102
		EES	17	0.97	0.89	1.05	89.95	<0.0001
		ZES	11	0.85	0.78	0.93	89.34	<0.0001
All struts	DES		42	1.03	0.99	1.08	90.70	<0.0001
		SES	11	0.92	0.85	1.00	93.91	<0.0001
		BES	3	1.16	1.00	1.35	64.68	0.059
		EES	17	1.10	1.02	1.19	89.56	<0.0001
		ZES	11	1.05	0.97	1.14	90.50	<0.0001

BES: Biolimus-eluting stent; DES: Drug-eluting stents; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

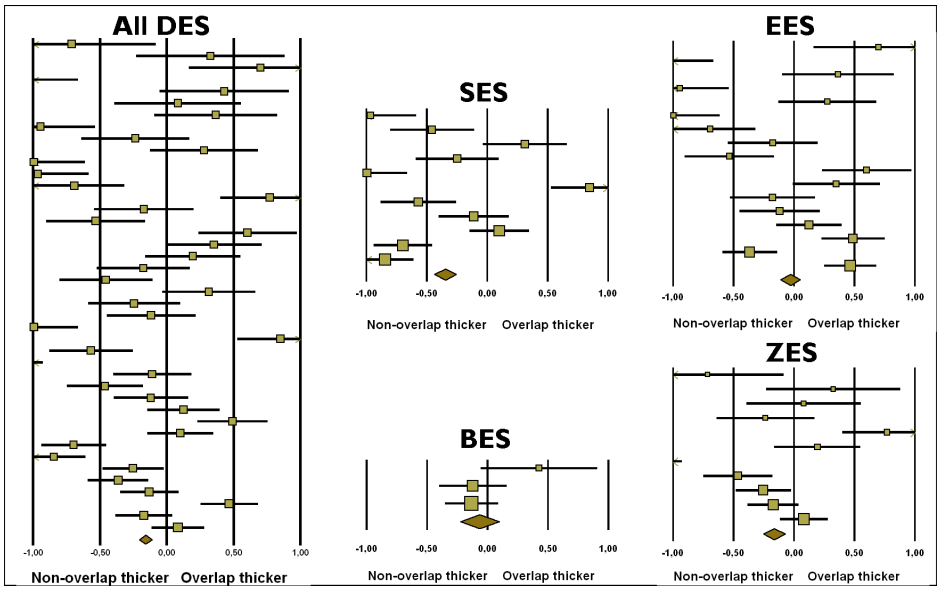


Figure 5 (panel A): Thickness of coverage, excluding the outer layer.

Forest plot showing standardized difference of means (Hedges' g) of the log-transformed thickness of coverage in overlapping vs. non-overlapping segments in the whole sample and stratified by type of stent. Lines represent the 95% confidence interval in each overlap, with the pooled difference of means at the bottom.

BES: Biolimus-eluting stent; DES: Drug-eluting stent; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

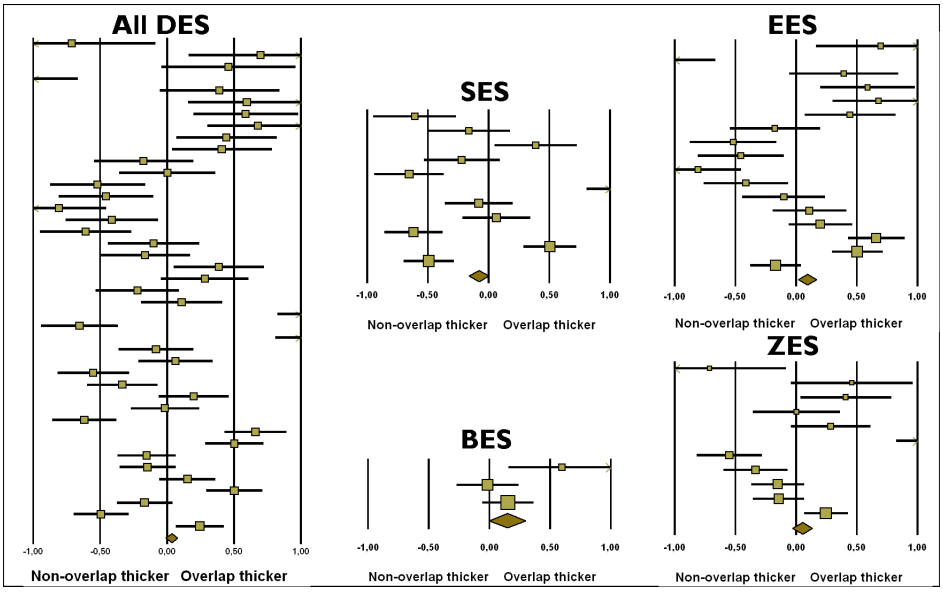


Figure 5 (panel B): Thickness of coverage, all visible struts analyzed.

Forest plot showing standardized difference of means (Hedges' g) of the log-transformed thickness of coverage in overlapping vs. non-overlapping segments in the whole sample and stratified by type of stent. Lines represent the 95% confidence interval in each overlap, with the pooled difference of means at the bottom.

BES: Biolimus-eluting stent; DES: Drug-eluting stent; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

DISCUSSION

The main findings of this analysis are: 1) The neointimal inhibition in DES overlapping segments is markedly heterogeneous: in some cases the overlap shows signs of delayed healing as compared to the corresponding non-overlapping segments, but in other cases the overlap elicits a more exaggerated and thicker neointimal reaction; 2) on average DES overlaps tend to be at higher risk of delayed coverage than non-overlapping segments; 3) the neointimal layer covering the struts in DES overlaps tends to be on average thinner than in non-overlapping segments; 4) this extremely heterogeneous effect of overlaps on the neointimal reaction does not depend on the type of DES.

These results may be interpreted as suggestive of incomplete neointimal healing in DES overlapping regions, with respect to non-overlapping segments in human coronary arteries. This observation in-vivo is consistent with the results of experimental histological studies on rabbit iliac arteries, that had reported more incomplete endothelialisation, greater fibrin deposition and greater cellular inflammatory infiltrates in first-generation DES overlapping regions[5]. Although these studies do not report any formal comparison of the neointimal thickness between overlapping vs. non-overlapping regions, indirect qualitative assessment seems to suggest that the neointimal layer might be thinner in the overlaps[5].

The coverage of overlaps has been specifically analysed by previous OCT studies. The ODES-SA trial randomized 77 patients to an intervention with overlapping BMS, first-generation SES, first-generation paclitaxel-eluting stents or a phosphorylcholine polymer-coated ZES[8]. However the percent of covered struts was similar in overlap and non-overlap segments, the thickness of coverage was either similar or even thicker in the overlaps and the percent neointimal volume obstruction was consistently larger. No single parameter suggested incomplete neointimal healing in overlaps, as reported in preclinical studies, or even seemed to point to the opposite direction: a neointimal reaction rather exaggerated than tamed. Our results might explain this apparent discrepancy on the basis of methodological considerations. One of them is the "layer effect": it could be postulated that the outer layer of struts is covered more completely and by a thicker neointimal layer than the inner layer. If the outer struts are excluded from the analysis, the coverage of the remaining (inner and indeterminate) struts is less complete and thinner in overlaps than in non-overlaps, as hereby demonstrated. Mixing together outer and inner struts increases artificially the thickness of coverage and reduces the proportion of uncovered struts, resulting in an unpredictable average. This is especially relevant for the neointimal thickness, whose results can be utterly reversed depending on the choice for one method or the other. Neither histology nor invasive imaging has taken into account the layer effect so far. This could partially explain some inconsistency within histological studies: although signs of incomplete coverage are generally reported in overlaps[5, 28, 29], some studies did not find impaired endothelialization[29] and sometimes the thickness of coverage was found similar[28] or even thicker than in non-overlaps[28, 29]. Interestingly,

the studies reporting thicker coverage in the overlaps performed the measurement from the outer layer of struts[29]. Likewise, our results for the all-struts analysis are similar to the ones reported by OCT in the ODESSA trial[8]. Nonetheless, factors other than the "layer effect", like differences in overlap length or in the stent-to-artery ratio between experimental and clinical procedures, could also contribute to the discrepancy between histology and OCT studies.

Another important methodological detail is the skewed distribution of the thickness of coverage. Summarizing this variable by a mean can be totally misleading, as previously demonstrated[21]. Normalization of the variable is mandatory if the statistical method requires normal distribution.

Although the average results show significantly greater neointimal inhibition in overlapping regions, it is to notice that the neointimal reaction is subjected to large variability between the different individual cases analysed. This hypothesis led to a pre-specified analysis taking into account an eventually heterogeneous effect. The results confirm the hypothesis, demonstrating and quantifying this heterogeneity. Heterogeneity might explain the discrepancy between histology and some angiographic studies: overlaps are subjected to more intense neointimal inhibition, as suggested by histology and indirectly by some angiographic studies[30], but this effect is not homogeneous and in some cases the neointimal proliferation is rather exaggerated. Angiographic studies usually reflect these hyperproliferative cases, because they lack the resolution to detect subtle changes in the neointimal layer. This would explain the greater angiographic late loss and binary restenosis in overlaps found in most angiographic studies[6, 7], in spite of an average more intense neointimal inhibition, and why clinical studies show worse outcomes both in terms of repeated revascularization and of death/myocardial infarction[7]. The characteristics of the underlying lesion/vessel at the site of overlap could explain partly this heterogeneous response[31].

To our knowledge this is the first OCT study assessing the coverage of overlaps in 2nd generation DES. A similar trend was observed in all types of DES analysed, with no significant deviation in metaregression. The lack of significance in the BES subgroup is likely attributable to the small number of overlaps in this subgroup (n=3) rather than to a true biological effect. These results will deserve further clarification in the future.

Limitations

This is a post-hoc analysis of data prospectively collected in randomised trials[15, 18]; the level of evidence generated by this kind of design is weaker than in a properly randomised study[8].

Considering OCT tissue coverage as surrogate for neointimal healing is biologically plausible and intuitively accepted by the scientific community, but still caution is required. OCT tissue coverage correlates with histological neointimal healing and endothelialization after stenting in animal models[32, 33], but its sensitivity and specificity in human atherosclerotic

vessels are still unknown. OCT cannot detect thin endothelial layers below 14µm axial resolution, and cannot discern between neointima and other material, like fibrin or thrombus. The analysis of optical density might help in the future[24].

The lack of pre-stenting and immediately post-stenting OCT pullbacks prevented to explore the role played in the outcome by the underlying plaque characteristics and the post-procedural intervention results, respectively. These factors might partially explain the heterogeneity of the effect described. This study was underpowered to explore all possible sources of heterogeneity, comprising patient-, vessel-, procedure- and device-related factors. Only the influence of the type of stent was explored by mean of a stratified analysis. This kind of subgroup analysis must be considered exploratory and hypothesis-generating; it cannot be interpreted as a comparison between the different types of stents.

This analysis included OCT studies performed with different OCT systems, at different follow-up periods and using the highest pullback speed available, in order to improve the acquisition with the non-occlusive technique. Although these are potential limitations, the axial resolution in all the systems and pullback speeds remains the same[19, 20, 34] and in each case the follow-up was scheduled after healing was estimated to be maximal. Pullback speed may affect the longitudinal resolution and the distortion induced by cardiac motion artefact, but it does not seem to affect the axial resolution of the images, which is the most relevant feature for assessment of coverage[34]. The statistical analysis compared the coverage in overlaps versus non-overlapping segments of the same stents, thus minimizing the impact of the aforementioned limitations in the final results. Although currently there is no compelling evidence about the optimal longitudinal segmentation for strut analysis in OCT studies, analysis at <1mm intervals might have improved the sensitivity to detect small regions of uncoverage or malapposition.

Our results correspond to a routine clinical scenario in which the length of the overlapping segments was much shorter than that of the non-overlapping segments. The conclusion might be different in a scenario in which the length of the overlap were relatively longer, similarly to some experimental studies[28]. Likewise, this analysis corresponds to those patients who required overlapping stents during the intervention, a relatively small subgroup, eventually reflecting a more adverse clinical scenario than the average PCI patient. This might have introduced some bias in the results and explain partially the differences with previous studies.

CONCLUSION

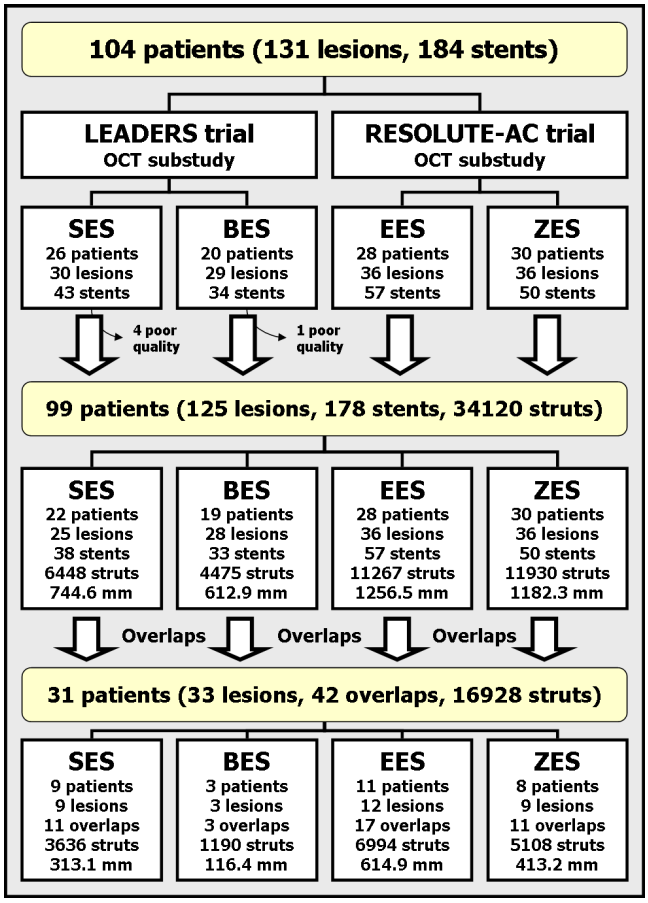
The effect of overlapping DES on neointimal inhibition is markedly heterogeneous: on average DES overlap is associated with more incomplete and thinner coverage, but in some cases the overlap elicits an exaggerated neointimal reaction, thicker than in the corresponding

non-overlapping segments. These results might help to understand why overlapping DES is associated with worse clinical outcomes, both in terms of thrombotic phenomena and restenosis-revascularization.

REFERENCE LIST

1. Garg S, Serruys PW. Coronary Stents: Current Status. *J Am Coll Cardiol* 2010 August 31;56(10, Supplement 1):S1-S42.
2. Iakovou I, Schmidt T, Bonizzoni E et al. Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents. *JAMA* 2005 May 4;293(17):2126-30.
3. Lagerqvist B, James SK, Stenestrand U et al. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. *N Engl J Med* 2007 March 8;356(10):1009-19.
4. Finn AV, Joner M, Nakazawa G et al. Pathological Correlates of Late Drug-Eluting Stent Thrombosis: Strut Coverage as a Marker of Endothelialization. *Circulation* 2007 May 8;115(18):2435-41.
5. Finn AVM, Kolodgie FDP, Harnek JM et al. Differential Response of Delayed Healing and Persistent Inflammation at Sites of Overlapping Sirolimus- or Paclitaxel-Eluting Stents. *Circulation* 2005 July 12;112(2):270-8.
6. Kereiakes DJ, Wang H, Popma JJ et al. Periprocedural and Late Consequences of Overlapping Cypher Sirolimus-Eluting Stents: Pooled Analysis of Five Clinical Trials. *J Am Coll Cardiol* 2006 July 4;48(1):21-31.
7. Räber L, Jüni P, Löffel L et al. Impact of Stent Overlap on Angiographic and Long-Term Clinical Outcome in Patients Undergoing Drug-Eluting Stent Implantation. *J Am Coll Cardiol* 2010 March 23;55(12):1178-88.
8. Guagliumi G, Musumeci G, Sirbu V et al. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. *JACC Cardiovasc Interv* 2010 May;3(5):531-9.
9. Rogers C, Edelman ER. Endovascular Stent Design Dictates Experimental Restenosis and Thrombosis. *Circulation* 1995 June 15;91(12):2995-3001.
10. Garasic JM, Edelman ER, Squire JC, Seifert P, Williams MS, Rogers C. Stent and Artery Geometry Determine Intimal Thickening Independent of Arterial Injury. *Circulation* 2000 February 22;101(7):812-8.
11. Moses JW, Leon MB, Popma JJ et al. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. *N Engl J Med* 2003 October 2;349(14):1315-23.
12. Schofer J, Schluter M, Gershlick AH et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003 October 4;362(9390):1093-9.
13. Holmes DR, Jr., Leon MB, Moses JW et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004 February 10;109(5):634-40.
14. Windecker S, Serruys PW, Wandel S et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008 September 27;372(9644):1163-73.
15. Barlis P, Regar E, Serruys PW et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J* 2010 January;31(2):165-76.
16. Gutiérrez-Chico JL, Jüni P, García-García HM et al. Long term tissue coverage of a biodegradable polylactide polymer-coated biolimus-eluting stent: comparative sequential assessment with optical coherence tomography until complete resorption of the polymer. *Am Heart J* 2011 November 21;162(5):922-31.
17. Serruys PW, Silber S, Garg S et al. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. *New Engl J Med* 2010 June 16;363(2):136-46.

18. Gutierrez-Chico JL, van Geuns RJ, Regar E et al. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J* 2011 June 9;32:2454-63.
19. Gonzalo N, Tearney GJ, Serruys PW et al. Second-generation optical coherence tomography in clinical practice. High-speed data acquisition is highly reproducible in patients undergoing percutaneous coronary intervention. *Rev Esp Cardiol* 2010 August;63(8):893-903.
20. Gonzalo N, Garcia-Garcia HM, Serruys PW et al. Reproducibility of quantitative optical coherence tomography for stent analysis. *EuroIntervention* 2009 June;5(2):224-32.
21. Gutiérrez-Chico JL, van Geuns RJ, Koch K et al. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomized trial balloon-first vs. stent first. *EuroIntervention* 2011 October 30;7(6):711-22.
22. Gutiérrez-Chico JL, Regar E, Nüesch E et al. Delayed Coverage in Malapposed and Side-Branch Struts With Respect to Well-Apposed Struts in Drug-Eluting Stents. *Circulation* 2011 August 2;124(5):612-23.
23. Gutiérrez-Chico JL, Gijsen FJH, Regar E et al. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed and side-branch struts: evidence in vivo about the abluminal healing process. *JACC Cardiovasc Interv* 2012 April 16;5(4):428-35.
24. Templin C, Meyer M, Muller MF et al. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J* 2010 July;31(14):1792-801.
25. Gutiérrez-Chico JL, Wykrzykowska JJ, Nüesch E et al. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. *Circ Cardiovasc Interv* 2012 February 1;5(1):20-9.
26. Sweeting J, Sutton J, Lambert C. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Statist Med* 2004;23(9):1351-75.
27. Hedges LV. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. *J Educ Behav Stat* 1981 June 20;6(2):107-28.
28. John MC, Wessely R, Kastrati A et al. Differential Healing Responses in Polymer- and Nonpolymer-Based Sirolimus-Eluting Stents. *JACC Cardiovasc Interv* 2008 October;1(5):535-44.
29. Wilson GJ, Polovick JE, Huibregtse BA, Poff BC. Overlapping paclitaxel-eluting stents: Long-term effects in a porcine coronary artery model. *Cardiovascular Research* 2007 November 1;76(2):361-72.
30. Dawkins KD, Grube E, Guagliumi G et al. Safety and efficacy of multiple, overlapping polymer-based paclitaxel-eluting stents. *EuroIntervention* 2007 August;3(2):213-21.
31. Tahara S, Bezerra HG, Sirbu V et al. Angiographic, IVUS and OCT evaluation of the long-term impact of coronary disease severity at the site of overlapping drug-eluting and bare metal stents: a substudy of the ODESSA trial. *Heart* 2010 October 1;96(19):1574-8.
32. Prati F, Zimarino M, Stabile E et al. Does optical coherence tomography identify arterial healing after stenting? An in vivo comparison with histology, in a rabbit carotid model. *Heart* 2008 February 1;94(2):217-21.
33. Murata A, Wallace-Bradley D, Tellez A et al. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. *JACC Cardiovasc Imaging* 2010 January;3(1):76-84.
34. Okamura T, Onuma Y, Garcia-Garcia HM, Bruining N, Serruys PW. High-speed intracoronary optical frequency domain imaging: implications for three-dimensional reconstruction and quantitative analysis. *EuroIntervention* 2012 February;7(10):1216-26.



Supplemental figure 1:

Flow chart summarizing the patients and stents included in this study, pooled from two different OCT randomized trials. BES: Biolimus-eluting stent; EES: Everolimus-eluting stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

SUPPLEMENTAL METHODS: DETAILED EXPLANATION OF THE STATISTICAL ANALYSIS

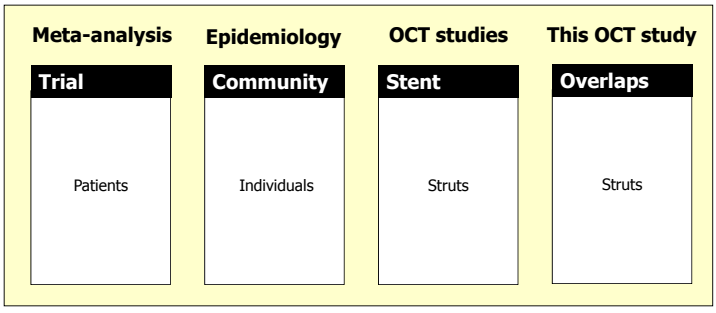
Pooled analysis is particularly suitable for the statistical analysis of an effect by combining data from different groups of subjects, each group submitted to slightly different environmental conditions. In this situation it is not acceptable to merge all the individuals together and apply conventional statistics, because one of the requirements for this approach is not accomplished: the individual measurements are not independent from each other, but strongly interdependent within the groups.

The biomedical community is actually very familiar with the methodology of pooled analysis, because it is used in:

- Meta-analysis[1].
- Epidemiology[2].

In this study we apply a pooled statistical method for the analysis of OCT data, since the clustering of data is an analogous methodological problem to the one faced by meta-analysis or by epidemiologic studies in communities. Pooled analysis has been previously applied to OCT studies[3-5], offering the advantage of presenting the data on a format the biomedical community is more familiar with.

Pooled statistics can be used in meta-analysis (combining different trials or studies), in interventional epidemiology (combining different communities) or in OCT studies (combining the results from different stents, or in this specific case from different overlaps), (suppl. figure 2) A detailed explanation of the principles of pooled analysis applied to OCT studies can be found in Gutiérrez-Chico et al. (Circulation 2011) as supplementary material (supplemental methods)[4].



Supplementary figure 2

Schematic representation of the clustering of measurements in different study designs: meta-analysis, epidemiology and OCT studies. Pooled analysis can be used in all these designs in which individual measurements (patients, individuals or struts) are grouped into different units of clustering (trial, community or stent), respectively.

Number of stents analyzed

The number of stents analyzed depends on the research question, because not all the stents in the sample might be informative for all possible research questions.

In a meta-analysis we search for the trials (or studies) addressing our research question, and then we select those which are truly informative to answer the question.

To be informative a trial must have:

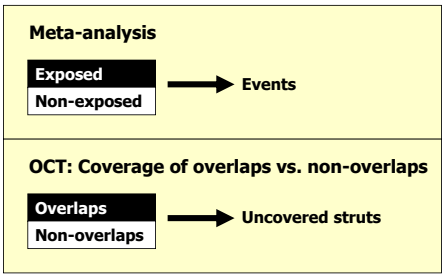
- Exposition to the study factor.
- Events (at least in one of the arms).

In a trial the "exposition" is guaranteed (randomization), but if we performed a meta-analysis of observational studies and we found studies with **no exposition**, they would be discarded (they are not informative for our research question).

Likewise, trials with **no events** (0 events in both arms) should be discarded (they are not informative for our research question).

In our OCT study (suppl. figure 3) these principles are applied as follows:

- Research question: **comparing the coverage of overlapping vs. non-overlapping segments as a binary outcome per strut.**
  - Stents with no exposition (no overlap) are discarded.
  - Stents with no events (complete coverage of overlapping and non-overlapping segments) are discarded.
- Research question: **comparing the thickness of coverage in overlapping vs. non-overlapping segments.**
  - Stents with no exposition (no overlap) are discarded.
  - Stents with no events would be discarded, but in this case every single strut has a thickness of coverage ≥0, so all the overlaps are considered in the comparison.



Supplementary figure 3

Schematic representation of the parallelism between meta-analysis and OCT studies when statistical pooled analysis is applied. If the target variable of our OCT study is coverage, uncovered struts in a stent are equivalent to events in a trial included in a meta-analysis. In this specific OCT we explore the effect of overlapping segments (exposed) as compared to non-overlapping segments (non-exposed) on strut coverage (target variable, events).

REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet* 2003;361:13-20.
2. Haralabidis AS, Dimakopoulou K, Vigna-Taglianti F, Giampaolo M, Borgini A, Dudley ML, Pershagen G, Bluhm G, Houthuijs D, Babisch W, Velonakis M, Katsouyanni K, Jarup L. Acute effects of night-time noise exposure on blood pressure in populations living near airports. *Eur Heart J* 2008;29:658-664.
3. Gutiérrez-Chico J, Wykrzykowska JJ, Nüesch E, van Geuns RJ, Koch K, Koolen JJ, di Mario C, Windecker S, van Es GA, Gobbens P, Jüni P, Regar E, Serruys PW. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. *Circ Cardiovasc Interv* 2012;5:20-29.
4. Gutiérrez-Chico JL, Regar E, Nüesch E, Okamura T, Wykrzykowska J, di Mario C, Windecker S, van Es GA, Gobbens P, Jüni P, Serruys PW. Delayed Coverage in Malapposed and Side-Branch Struts With Respect to Well-Apposed Struts in Drug-Eluting Stents. *Circulation* 2011;124:612-623.
5. Gutiérrez-Chico JL, Gijsen FJH, Regar E, Wentzel JJ, De Bruyne B, Thuesen L, Ormiston JA, McClean D, Windecker S, Chévalier B, Dudek D, Whitbourn R, Brugaletta S, Serruys PW. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed and side-branch struts: evidence in vivo about the abluminal healing process. *JACC Cardiovasc Interv* 2011;(In press).

Suppl. table 1: Angiographic characteristics of the lesions grouped by type of stent.

	SES (n=9)	BES (n=3)	EES (n=12)	ZES (n=9)	p-val
Target vessel					0.182
LM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
LAD	4 (44.4%)	2 (66.7%)	1 (8.3%)	5 (55.6%)	0.073
LCX	0 (0.0%)	0 (0.0%)	3 (25.0%)	1 (11.1%)	0.317
RCA	5 (55.6%)	1 (33.3%)	8 (66.7%)	3 (33.3%)	0.432
TO	1 (11.1%)	1 (33.3%)	2 (16.7%)	1 (11.1%)	0.796
Ostial lesion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	0.432
Bifurcation	0 (0.0%)	0 (0.0%)	4 (33.3%)	3 (33.3%)	0.166
Mod or severe calcific	2 (22.2%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	0.285
QCA characteristics					
Lesion length (mm)	16.7 (10.8)	10.9 (10.0)	18.3 (14.5)	13.6 (11.7)	0.681
Pre-stenting					
RVD (mm)	2.51 (0.60)	3.25 (0.60)	2.37 (0.49)	2.82 (0.41)	0.184
MLD (mm)	0.74 (0.63)	0.78 (1.10)	0.66 (0.48)	0.91 (0.48)	0.794
% diam stenosis	71 (23)	76 (34)	73(18)	68(14)	0.945
Post-stenting					
In-stent					
RVD (mm)	2.85 (0.60)	2.49 (0.78)	2.89 (0.46)	2.89 (0.46)	0.691
MLD (mm)	2.30 (0.49)	2.08 (0.89)	2.39 (0.52)	2.43 (0.38)	0.765
% diam stenosis	19 (6)	17 (14)	18 (8)	16 (8)	0.857
In-segment					
RVD (mm)	2.76 (0.60)	2.37 (0.84)	2.68 (0.52)	2.73 (0.33)	0.721
MLD (mm)	2.02 (0.56)	1.57 (0.56)	1.95 (0.39)	2.14 (0.34)	0.292
% diam stenosis	27 (9)	34 (2)	27 (8)	21 (11)	0.188

Continuous variables are reported as mean(SD) and categorical variables as n(%); stent groups are compared with one-way ANOVA and Pearson's chi-square, respectively.

BES: Biolimus-eluting stent; EES: Everolimus-eluting stent; LAD: Left anterior descending; LCX: Left Circumflex; LM: Left Main Stem; MLD: Minimal Lumen Diameter; QCA: Quantitative Coronary Angiography; RCA: Right coronary artery; RVD: Reference vessel diameter; SES: Sirolimus-eluting stent; TO: Total occlusion; ZES: Zotarolimus-eluting stent.

Suppl. table 2: Areas and volumetric analysis of the overlap segments compared to the proximal and distal non-overlap segments of the same stents, stratified by stent type.

	SES			**BES**			**EES**			**ZES**		
31 patients	9 patients			3 patients			11 patients			8 patients		
33 lesions	9 lesions			3 lesions			12 lesions			9 lesions		
42 overlaps	11 overlaps			3 overlaps			17 overlaps			11 overlaps		
	Overlap	Non-overlap	p-value	Overlap	Non-overlap	p-value	Overlap	Non-overlap	p-value	Overlap	Non-overlap	p-value
Stent length (mm)	4.3 (2.5)	27.1 (11.0)	**0.003***	11.5 (15.8)	32.0 (21.2)	0.285	2.8 (2.6)	33.4 (11.6)	**<0.0001***	2.8 (2.4)	34.7 (13.4)	**0.003***
MLA (mm^2)	6.64 (1.80)	4.35 (2.21)	**0.003***	6.24 (2.80)	3.80 (4.15)	0.285	6.54 (2.92)	4.77 (2.80)	**<0.0001***	5.32 (2.12)	3.83 (1.73)	**0.003***
Mean lumen Area (mm^2)	7.37 (2.28)	7.25 (2.08)	0.722	6.68 (3.03)	6.21 (2.97)	1.000	6.91 (2.94)	7.50 (2.90)	**0.007***	5.68 (2.11)	6.18 (1.76)	**0.041**
Lumen volume (mm^3)	33.1 (22.5)	178.3 (82.1)	**0.003***	92.2 (144.5)	153.7 (48.7)	0.593	20.5 (23.1)	228.6 (129.8)	**<0.0001***	16.4 (15.9)	202.5 (113.5)	**0.003***
Min stent area (mm^2)	7.04 (1.84)	5.25 (1.92)	**0.003***	6.69 (2.66)	4.44 (3.78)	0.285	7.65 (3.07)	6.06 (2.62)	**0.001***	6.13 (1.70)	4.89 (1.74)	**0.004***
Mean stent area (mm^2)	7.83 (2.30)	7.40 (1.91)	0.155	7.19 (2.90)	6.40 (2.93)	1.000	8.19 (2.95)	8.16 (2.81)	0.758	6.56 (1.70)	6.68 (1.69)	0.213
Stent volume (mm^3)	34.7 (22.3)	190.9 (84.2)	**0.003***	96.7 (149.8)	176.5 (77.4)	0.593	24.0 (26.2)	269.3 (126.3)	**<0.0001***	18.7 (16.9)	237.9 (121.0)	**0.003***
% frames with ISA	5.37 (15.05)	4.01 (9.14)	0.917	0.00 (0.00)	0.00 (0.00)	1.000	1.96 (8.08)	2.14 (3.11)	0.236	1.82 (6.03)	1.42 (2.82)	1.000
Max ISA area (mm^2)	0.04 (0.10)	0.99 (2.12)	0.116	0.00 (0.00)	0.00 (0.00)	1.000	0.02 (0.07)	0.47 (0.88)	**0.028***	0.02 (0.08)	0.11 (0.21)	0.109
ISA volume (mm^3)	0.03 (0.09)	3.48 (9.98)	0.116	0.00 (0.00)	0.00 (0.00)	1.000	0.01 (0.05)	1.03 (1.99)	**0.028***	0.01 (0.04)	0.18 (0.41)	0.109
Corrected by stent volume (%)	0.23 (0.65)	1.65 (4.58)	0.345	0.00 (0.00)	0.00 (0.00)	1.000	0.14 (0.59)	0.27 (0.52)	0.237	0.06 (0.19)	0.06 (0.14)	1.000
Max NIH area (mm^2)	0.73 (0.59)	1.70 (0.92)	**0.006***	0.90 (0.39)	1.44 (0.79)	0.285	1.68 (1.01)	2.70 (0.82)	**0.001***	1.31 (0.62)	2.08 (0.49)	**0.003***
NIH volume (mm^3)	1.6 (1.5)	16.2 (12.4)	**0.003***	4.6 (5.4)	22.8 (29.6)	0.285	3.5 (3.5)	41.8 (18.5)	**<0.0001***	2.2 (1.6)	35.6 (14.2)	**0.003***
In-stent NIH vol obstruction (%)	6.2 (6.0)	8.8 (6.4)	0.091	9.0 (7.1)	10.1 (10.0)	1.000	17.3 (12.0)	18.8 (10.8)	0.309	15.5 (10.6)	16.5 (7.1)	0.594

* $p \leq 0,05$

Continuous variables are reported as mean(SD) and categorical variables as n(%); stent groups are compared with one-way ANOVA and Pearson's chi-square, respectively.

BES: Biolimus-eluting stent; DCB: Drug-coated balloon; EES: Everolimus-eluting stent; ISA: Incomplete stent apposition; MLA: Minimal lumen area; NIH : Neointimal hyperplasia; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent.

CHAPTER 14

Bifurcations

Optical coherence tomography in coronary bifurcations.

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Book chapter 12, In: Waksman R, Ormiston JA. Bifurcation stenting. Chichester: Wiley-Blackwell Publishing; 2012.

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INTRODUCTION

Optical Coherence Tomography (OCT) is currently the most accurate intracoronay invasive imaging technology. It provides with the highest axial resolution (10-15 microns), thus enabling a very precise quantitative in-vivo evaluation of relevant parameters after stenting, like apposition or coverage, that influence the quality of the result immediately after the procedure or at follow-up respectively, and have an impact on the clinical outcome (1-6). The interest on OCT has grown exponentially since the advent of drug-eluting stents (DES). In the bare metal stent (BMS) era, the main concern after a percutaneous coronary intervention (PCI) was restenosis (7), that was the result of an excessive neointimal proliferation after the vascular injury induced by PCI (8-15). Restenosis could be reliably quantified with quantitative coronary angiography (QCA) (16-33) or more accurately with intravascular ultrasound (IVUS) (34-37). DES have successfully addressed the problem of restenosis (38-40), however some reports have also suggested higher incidence of stent thrombosis (41-45). Delayed neointimal healing with incomplete endothelialization is the common pathological substrate in most of the cases of late stent thrombosis (4;5). While the axial resolution of conventional IVUS (around 100 μm) yields an accurate assessment of restenosis, the thin neointimal layer covering DES struts is normally below this range, and therefore cannot be reliably measured by IVUS. OCT has risen as the only current alternative for the assessment of struts coverage after stenting. OCT tissue coverage shows an optimal correlation with histological neointimal coverage in animal studies (46-49), with superior performance compared to IVUS (46), and higher reproducibility (50;51). The ability of OCT to implement this hitherto unmet need of evaluating the tissue coverage after stenting has been the main drive for the growing interest toward this technology applied to coronary heart disease.

Nevertheless, the accuracy of OCT is an extraordinary research tool with multiple applications in coronary heart disease, other than tissue coverage and apposition after stenting. Bifurcations are clearly one of the fields where OCT could contribute the most. In spite of some progress achieved in the last years, bifurcations are still a topic resisting to a scientific and quantitative study. Problems like apposition, overlap, NASB struts, scaffolding or the access to the side branch, that are still today a pending issue for the investigators, could be efficiently evaluated and quantified by OCT. However, the intrinsic geometric, anatomical and methodological complexity of bifurcations also represents a challenge that has not been satisfactorily solved yet even by OCT. There is still a lot of work to do and therefore no serious document can make very categorical statements, but on the basis of current ongoing experiences we foresee that OCT will finally shed some "light" on the scope of bifurcations.

METHODOLOGICAL PROBLEMS IN THE STUDY OF BIFURCATIONS

Complex geometry

The first challenge in the study of bifurcations is finding a suitable model for its peculiar geometry. Initially all the quantitative parameters to assess stenosis severity or the result of an intervention have been initially conceived for a cylindrical geometry. In these cylindrical models the proximal and distal reference segments will provide directly with the reference parameters required for the quantitative assessment. Thus, for calculation of % area stenosis in a cylindrical model, the reference area can be reliably estimated from the average of mean area in the proximal and in the distal areas, for example, and the % area stenosis will be hence defined as the quotient between minimal lumen area and the reference area, times 100.

In case of tapering, the above explained approach is no longer valid, because the reference area (or diameter) will vary depending on the location of the minimal lumen area (or diameter), and hence it is not possible to calculate an average reference area valid for any location along the diseased or stented segment. The challenge of tapering is efficiently solved by means of interpolation, using an iterative regression method.

In bifurcations, neither the cylindrical nor the tapering models are valid. Bifurcations follow a model of fractal geometry (52;53) with morphological self-similarity. From a physiologic point of view, this geometry is efficient to preserve the hydrodynamic energy in the vascular system (54). A fractal object is defined by a pattern that is similar at whatever level of observation: this is known as self-similarity or homothetic invariance (55). There have been several attempts to model the pattern of self-similarity in the coronary arteries (56), but the most popular ones among cardiologists are maybe Murray's law (54) and Finet's law (53). Both define the relation in size between the parental vessel or proximal main vessel (PMV) and the two filial ramifications, namely the distal main vessel (DMV) and the side branch (SB), according to their corresponding diameters. In Murray's law the cube of the diameter in the PMV equals the sum of the cubes of the diameters of DMV and SB.

$$\textbf{Murray's law: } D_{PMV}^{\ 3} = D_{DMV}^{\ 3} + D_{SB}^{\ 3}$$

Finet's law is a linearization of Murray's law to simplify eventual calculations.

$$\textbf{Finet's law: } D_{PMV} = 0.678\ (D_{DMV} + D_{SB})$$

According to this geometry, the change in diameter/area between the proximal and the distal segments of a bifurcation is not gradual, like in tapering, but abrupt at the point of bifurcation. This is known as the step-down phenomenon (figure 1), and must be taken into account for defining valid reference values. As a consequence, neither averaging nor interpolation will

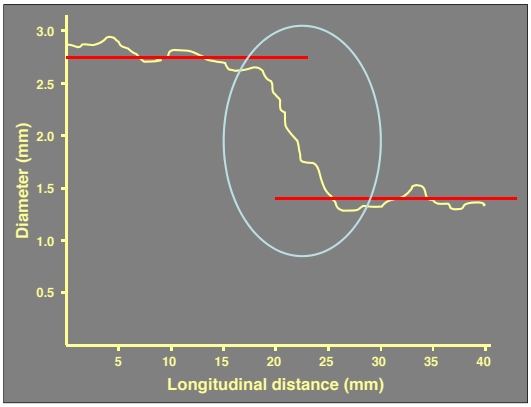


Figure 1:
Step-down phenomenon.
The change in diameter/area between the proximal and the distal segments of a bifurcation is not gradual, like in tapering, but abrupt at the point of bifurcation. This is known as the step-down phenomenon, and is relevant for defining valid reference values for quantitative analysis in bifurcations.
Modified from (75).

calculate valid reference parameters, and the most correct methodological alternative seems to analyze separately each segment of the bifurcation: PMV, DMV and SB.

As an additional turn of the screw, there is a fourth segment whose geometry is totally irregular and cannot be assimilated by any means to a cylindrical model: the segment around the take-off of the side branch. This segment has received diverse denominations by the different bifurcation-dedicated QCA softwares: "polygon of confluence" or "bifurcation core" (57). For invasive imaging "bifurcation core" is preferable, because the definition of the polygon of confluence makes sense only for QCA but is conceptually inappropriate for technologies rendering cross-sectional views.

Summarizing, in order to overcome the intrinsic geometric complexity of coronary bifurcations, we suggest that their study comprises the separate analysis of four different portions:

1) PMV
2) Bifurcation core
3) DMV
4) SB

Complex anatomy

Beyond the geometric complexity there exist multiple anatomic variations diversifying the problem to the limit and sometimes jeopardizing the required homogeneity in definitions for a systematic approach. It is worth that we make some considerations about some of these anatomic issues.

Relevance of the side branch

The relevance of the side branch is important even for the definition itself of bifurcation. The coronary tree is rich in ramifications, but not all of them gather the minimal magnitude required to be considered a bifurcation: only those giving a "relevant" side branch are considered as such. However it is very difficult to define what a "relevant" side branch is. In the past an objective threshold (>2mm diameter) was proposed, but in practice it resulted too rigid and often did not meet other functional considerations. The current consensus is rather flexible, and defines a relevant side branch as a side branch that you do not want to loose. This definition implies that the decision about its relevance is fully left to the operator's discretion.

The designation of the filial vessels deserves also some considerations: which is the DMV and which is the SB? There are two possible approaches: the nosological, that follows the anatomic hierarchy (LAD or LCX will be always the main vessel in relation to the diagonals or the OM, respectively), or the QCA approach, that considers DMV the filial branch with the largest diameter. Thus in a bifurcation LCX-OM like the one showed in figure 2, the OM could be considered either DMV or SB depending on the adherence to one approach or to the other. The QCA criterion seems to fit better to the usual practice in Interventional Cardiology of deploying the stent from the PMV to the vessel of larger calibre, across the vessel of smaller calibre. Nevertheless, a too strict application of this rule could often disregard relevant functional factors. Again, the current consensus leaves the decision of the designation of the filial vessels up to the operator, provided that it is taken upfront, before initiation of the procedure.

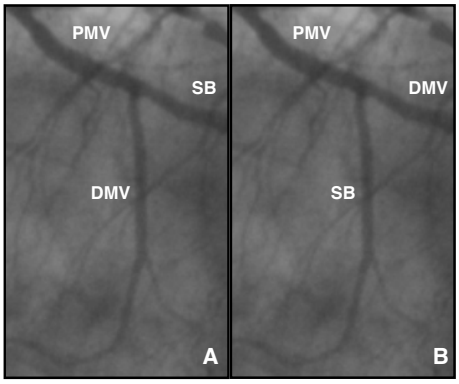


Figure 2:
Designation of the filial vessels.
Bifurcation LCX-OM, illustrating how the designation of the filial vessels can change depending on the adherence to a nosological (A) or a QCA criterion (B). In the nosological approach (A) the anatomical hierarchy is strictly followed, and thus the distal LCX is considered the DMV. In the QCA approach (B), conversely, the OM is considered the DMV, because its diameter is larger than that of the distal LCX.
DMV: Distal main vessel; LCX: Left circumflex; OM: Obtuse marginal; PMV: Proximal main vessel; QCA: Quantitative coronary angiography; SB: Side branch.

In the OCT study we will assume these considerations and these considerations, pursuing terminological and methodological homogeneity with other quantitative techniques.

Angulation

The angulation determined by the take-off of the SB needs three angles to be properly defined: the angle PMV-SB, the angle DMV-SB and the angle PMV-DMV). Each angle is relevant for specific issues that fall out of the scope of this chapter. In bifurcation-dedicated QCA software, the angulation plays a major role, and in some cases it had led to the definition of "T-bifurcations" and "Y-bifurcations". OCT, however, cannot estimate any of the angles of the bifurcations, and it is uncertain if they could affect significantly the measurements or the quality of the image. The angulation could influence the eccentricity of the wire, or the disalignment between the longitudinal axis of the vessel and the optic catheter, but its overall impact on the OCT analysis seems rather moderate. The distinction between T and Y bifurcations does not seem to make sense for OCT, although T-bifurcations will present in-vivo some methodological advantages that we will address properly later, namely they will improve the reproducibility of the delimitation of the bifurcation core.

Varied atherosclerotic affectation

On top of the geometrical and intrinsic anatomical complexity of non-diseased bifurcations, we must add the multiple ways how atherosclerosis can affect its structure, increasing the complexity of the problem even more. After several classification attempts that demanded memoristic efforts, Medina classification (58) has been accepted in consensus (59), with the aim of promoting methodological homogeneity and simplifying the problem as far as possible. Nonetheless, Medina classification is receiving currently a lot of criticism, because its appealing simplicity might eventually not cover a rich spectrum of relevant details, and hence not be predictive of procedural or clinical outcomes.

THE ROLE OF OCT

Minimal methodological requirements

The quantitative analysis of OCT studies is time-consuming, therefore the issue of optimizing the methodological approach is not trivial at all. An efficient method should be as simple and fast as possible, but still should not jeopardize the accuracy of OCT measurements. Unfortunately, bifurcations are too complex and varied, as we have extensively addressed, and to date we cannot rely on any catchy simplification. We propose some generic guidelines

based on our own experience in bench-testing models. Regarding some points the indications might be somewhat vague and imprecise, because the results of these experiments are not conclusive yet. Further efforts in this kind of research are warranted.

We will focus on the post-stenting study. OCT can also bring interesting insights of the lesion prior to the intervention, supplying with interest information to guide the procedure: severity of the stenosis in both branches, involvement of the ostia or the carina, extension of the plaque, calcification, etc… are important issues that can be accurately studied by OCT, whose assessment could have a relevant impact in planning the procedure, and that are often not totally clarified by angiography. The utility of near-infrared spectroscopy for guiding the intervention in bifurcations by determining the amount and extent of lipidic content is being specifically investigated. Maybe in the next future polarization-sensitive OCT will be also able to improve the characterization of plaque components. Nonetheless, this pre-intervention study is usually qualitative and not as methodologically challenging as the quantitative post-stenting analysis.

Two pullbacks

The OCT study of any bifurcation requires the recording of at least **2 different pullbacks**: one starting from the DMV, and another starting from the side branch. Studies recording a single pullback per bifurcation will be limited to the assessment of some specific issues in some specific segments, but cannot provide with a comprehensive analysis. In some interventional techniques for bifurcations it is not possible to record 2 OCT pullbacks: for example, in a provisional stenting-across-SB where final kissing was not necessary, the pullback from the side branch cannot be obtained. This is an important limitation for the comparability of techniques and devices that must be taken into account in the studies involving OCT parameters.

Two landmarks

It is necessary to identify 2 landmarks in each pullback: the **carina** and the **countercarina**. These landmarks will be used to delimit the take-off of the side branch and some regions of particular interest. The carina frame is usually clearly identified in both pullbacks as the most distal frame of the pullback where a tissue structure separates completely both branches of the bifurcation, without any point of connection. Somewhat more problematic results the identification of the countercarina. In a precedent study with IVUS, it was proposed to define the countercarina frame as that one where the main vessel "assumed again a circular shape" (60), that is, the most distal frame where the main vessel assumed again a circular shape, proximal to the bifurcation core. Although the definition is conceptually correct, its reproducibility in in-vivo studies is very poor, because the transition between an oval to a circular lumen shape is usually very gradual, and often influenced by many other factors, as for instance

the performance of a final kissing-balloon. Unfortunately we do not feel confident enough at this point to give clear guidelines regarding the identification of the countercarina frame, but it is our feeling that the ancillary longitudinal images could be helpful in this regard and improve somewhat the reproducibility. In the so called T-bifurcations the identification of the countercarina is significantly easier and more reproducible than in Y-bifurcations, because the transition is usually sharper.

Four segments

Once we have identified the carina and countercarina frames in each pullback, we are in disposition to define the four segments of interest (Figure 3).

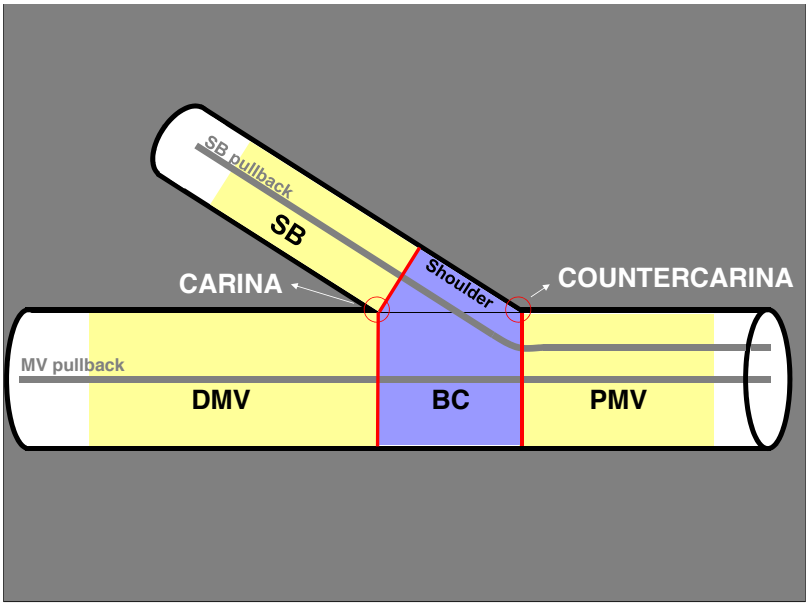


Figure 3:
The four segments in the OCT study of a bifurcation.
1) DMV: distal main vessel; it is imaged only from the main vessel pullback (MV pullback). 2) SB: Side branch; imaged only from the side branch pullback (SB pullback). 3) PMV: Proximal Main Vessel; imaged both from the MV and SB pullbacks, but analyzed only in the MV pullback. 4) BC: Bifurcation core; one part is imaged in the MV pullback, and another part (the shoulder of the bifurcation) is imaged in the SB pullback. BC starts and ends in each pullback in the carina and countercarina frames, respectively.

Distal main vessel (DMV)

It is imaged only in the main vessel pullback, and extends from the most distal frame where struts are identified in a 360º circular shape till the carina frame.

Side branch (SB)

It is imaged only in the side branch pullback. In case the side branch has been stented, it will extend from the most distal frame where struts can be identified in a 360º circular shape till the carina frame. In case the side branch has not beet stented, it will extend from the most distal frame where any strut can be identified till the carina frame.

Proximal main vessel (PMV)

It is imaged both in the main vessel and the side branch pullbacks, and extends from the countercarina frame till the most proximal frame where struts are identified in a 360º circular shape. Until the issues of how much wire eccentricity and vessel-catheter axial disalignment are further clarified, it is our advice to consider only the measurements of the main vessel pullback, where these potential confounding factors are expected to be lower than in the side branch pullback.

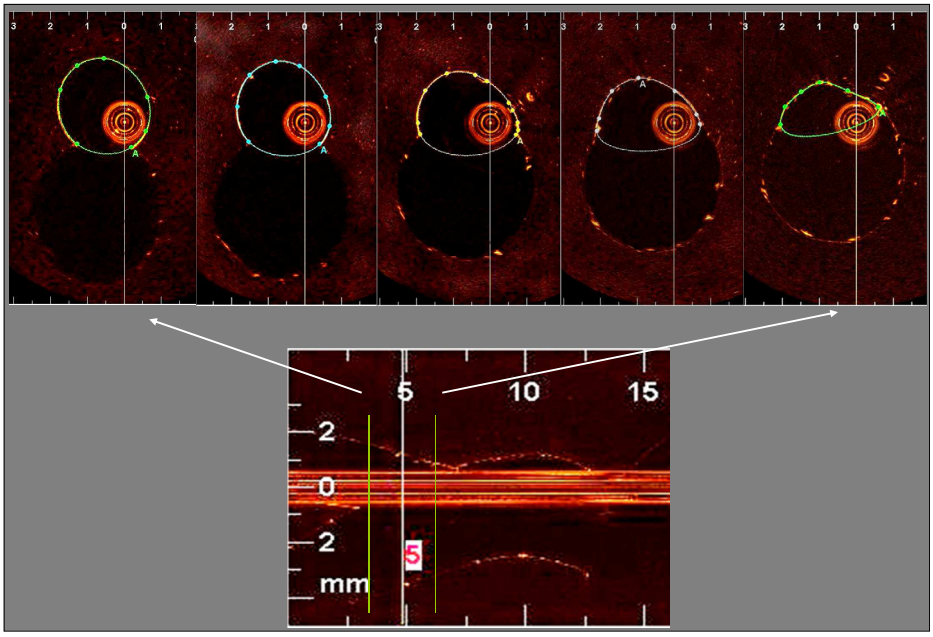


Figure 4:

Interpolation of the lumen contours at the bifurcation core of the main vessel pullback (A) and the side branch pullback (B) in the analysis of a silicon phantom.

The aim of this proposed method is minimizing the duplicity of measurements at the bifurcation core and conferring differential entity to a special region within the bifurcation core: the shoulder of the bifurcation.

Bifurcation core (BC)

It is imaged partially in the main vessel pullback and partially in the side branch pullback. In both pullbacks it extends from the carina frame till the contercarina frame. In order to avoid duplicity of measurements, it is our advice to restrict the analysis to the branch where the optic catheter is placed in each case, disregarding the other branch and interpolating the lumen / stent contours whenever possible (figure 4). Nevertheless, this will not be always possible in every frame, and some minimal duplicity and inaccuracy must be assumed in the bifurcation core. If we follow this method, the BC in the main vessel pullback will represent the portion of MV where the take-off of the SB takes place; whilst the BC in the side branch pullback represents the shoulder of the bifurcation, which is a region of high interest, half way between the main vessel and the side branch, hot spot for malapposition and whose scaffolding or the lack of it is believed to be relevant for the outcome of the intervention (61;62).

Parameters of interest

The cornerstone of the OCT study of a bifurcation is defining the parameters of potential interest that can be assessed. We enumerate a list of them, although their clinical relevance has not been properly tested yet in most of the cases.

- Apposition of the struts.
- Existence of overlap segments or regions with multiple layers of stent.
- Non-apposed side-branch (NASB) struts: struts suspended in the middle of the blood flow, without apparent connection with the rest of the stent structure and with no clear relation to the vessel walls.
- Scaffolding of the carina and the shoulder.
- Access to the side branch.
- Tissue coverage of the struts.

We will analyze deeply into detail each one of these parameters in the following section.

Location

In several of the above mentioned parameters it might be interesting not only its measurement and average reporting, but also giving relevant information about its location. Apposition, overlap and coverage are maybe the parameters where additional topographic specifications would be most interesting. The first obvious step is reporting the results per segment: this gives a first impression of where the problem is mainly located, opening the discussion about eventual explanations for the findings and the possible solutions.

In some cases, however, it would be desirable also to add some information about the cross-sectional distribution of the parameter. Then we must confront the problem of the relative rotation of the catheter. In a conventional OCT pullback we cannot control the random rotation of the catheter respect to the vessel. However this is a minor problem for OCT, given the high pullback speed, hence reducing the relative rotation of the catheter along the imaged segment. This is even more pronounced with Fourier-domain systems, where the pullback speed can reach up to 20 mm/s, therefore the impact of an eventual rotational distortion is minimal. A possible operational correction performed at the level of statistical analysis can be marking the locations of the carina and the countercarina in the corresponding cross-sections, assuming they should coincide in absence of relative rotation of the catheter respect to the vessel. If we find a significant discrepancy, we can assume that it is due to the rotation, and we can correct partially our estimations.

Defining the most efficient longitudinal interval between cross-sections for the analysis

The final consideration is still an open question that has not been properly addressed yet. In a conventional OCT analysis of a stented segment cross-sections are analyzed at 1 mm intervals. In the case of a bifurcation, however, this distance could be too large for the detection of subtle parameters, like the NASB, or the scaffolding. Little protrusions of struts into the lumen or small gaps in the scaffolding will be often of lower magnitude, thus the sensitivity of a method at 1mm intervals is not likely to be high. It seems reasonable to make an analysis at shorter intervals, at least in the bifurcation core, but how shorter? The question is not trivial: if we decide to make the analysis at 0.5mm intervals, we double the time (and eventually the money) required for the analysis; if we go for 0.2mm intervals, then we multiply by five the time and cost of the analysis. What is the most efficient interval for the analysis of the bifurcation core, providing the optimal balance between sensitivity and cost-efficiency? This is still an open question.

Apposition

Incomplete stent apposition (ISA) is associated with worse outcomes after stenting (1;2). Although the mechanism explaining this association is still not clear, ISA struts could represent a handicap per se for a proper neointimal healing (63). Bifurcations are particularly sensitive to malapposition, because stenting techniques using conventional cylindrical stents or bifurcation-dedicated devices cannot always conform to their peculiar geometry and anatomy (figure 5). Moreover, sequential balloon inflations or kissing-balloon techniques may distort the stent structure and induce some degree of malapposition (64).

OCT can assess ISA very accurately. Since the light cannot penetrate the metallic structure of the stent, it is necessary to measure the distance from the leading edge of the strut reflec-

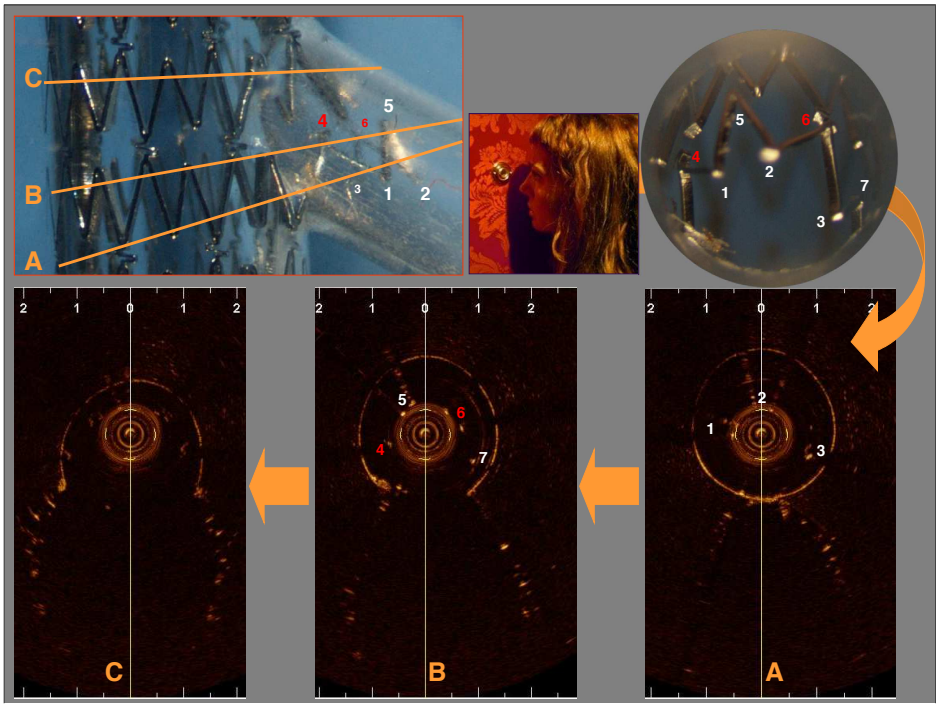


Figure 5:

Malapposition at the soulder of the bifurcation: micro-photography and OCT view in the bench-testing with silicon phantoms.
Preclinical bench-testing of bifurcation-dedicated prototypes of stent. In the case illustrated, the prototype could not conform to the geometry of the bifurcation. To ease the understanding of the correspondence between the different images, the most distal struts in the side branch have been numbered. Struts with a connector appear in red: the connector can be preserved (6) or dislodged (4). The use of OCT during the bench testing permits a precise quantification and detection of subtle degrees of malapposition that are often unadverted by the micro-photography.

tion to the lumen contour. If this distance is higher than the strut thickness, then the strut is malapposed (65). Therefore, precise knowledge of the type of stent implanted and the thickness of its struts is mandatory. The apposition will be quantified as proportion of malapposed struts respect to the total number of analyzed struts, or like ISA areas and volumes. In bifurcations it can be also interesting to report the localization of the ISA struts, because this information might help to improve the techniques or the devices. Some techniques or devices present typical ISA patterns at specific segments (figure 6).

Overlap segments and multilayer segments

There is increasing evidence that overlap is associated to worse clinical and angiographic outcomes (66;67). Most of 2-stents techniques in bifurcations entail some degree of overlap between the different stents implanted, in order to avoid areas of incomplete scaffolding that are believed to be associated to worse outcomes (61;62). In some cases, like the culotte

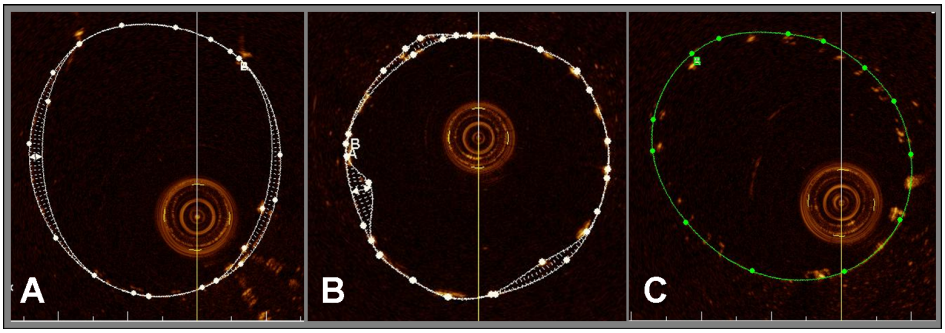


Figure 6:

Typical malapposition patterns in the proximal main vessel (PMV) segment of some bifurcation dedicated stents: bench-testing with silicon phantoms.

Nile-Croco (Minvasys©) (A) is a modular stent whose deployment ends with simultaneous kissing-balloon inflation. Notice the typical oval pattern of the malapposition in the PMV, due to the 8-shaped disposition of the balloons. Tryton (Tryton Medical ©) (B) is a side-branch stent, with a specifically-designed transition zone between the side branch and the main vessel, prolonged into the PMV through a minimal scaffold consisting of 3 legs. Notice how the presence of these 3 legs induces some degree of malapposition in the regions of overlap with the stent in the main vessel. Stentys (Stentys ©) (C) is a self-expandable stent, with minimal malapposition in the main vessel.

or the crush techniques, we will have extensive areas where a double or even triple layer of stent has been implanted (Figure 7). The analysis of overlapped segments with OCT is still problematic: in the usual core-lab analysis of a stented vessel, these regions are excluded from the analysis, to avoid confusion. In most of the frames it is not easy to discern between struts of the outer vs. the inner layer, and therefore it is not clear how most of the variables (nr of struts, apposition, neointimal area, etc…) should be measured in overlap segments.

Nevertheless, in the case of bifurcations analyzing and reporting these overlap / multilayer regions is a must, because they are an intrinsic part of some techniques. The extension of these areas must be reported, and a methodical analysis must be attempted. In the future it is to expect that we get some more experience with the analysis of overlap / multilayer segments.

NASB (Non-apposed side-branch struts)

The struts corresponding to the portion of a stent across a side-branch deserve a separate category. We designate them as Non-apposed side-branch (NASB) struts; but they have been named also "floating" struts. In the OCT cross-sections appear as "suspended" struts in the middle of the flow, with no apparent connection with the rest of the stent structure, and with no vessel wall behind (figure 8). It is common to find that these struts are reported as ISA struts, but it is not correct, because apposition was not pursued by the operator and cannot be assessed, since they have no vessel wall behind. Their clinical implications might be also different than in ISA struts: whilst ISA has been consistently associated with worst outcomes (1;2), the implications of NASB are still a matter of debate. Initial pathological studies pointed

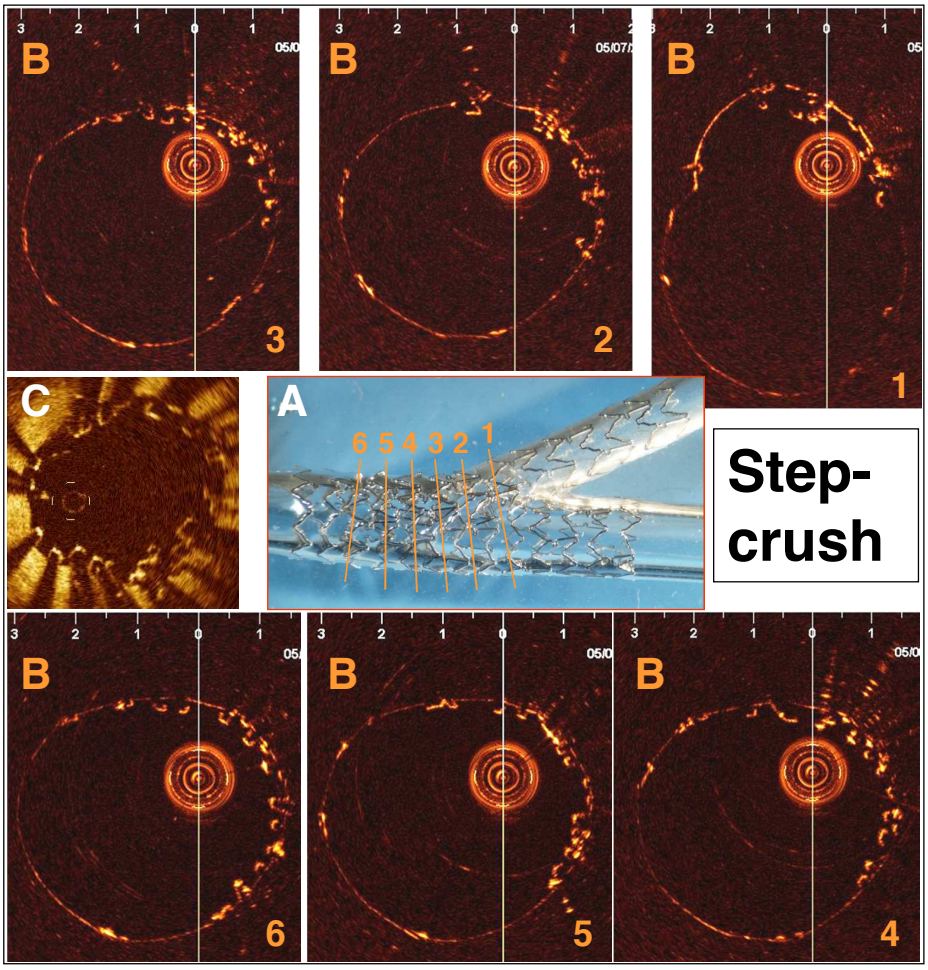


Figure 7:

Overlap and multi-layer regions: area of triple stent layer after a step-crush technique.

View on micro-photography (A) and OCT (B) in a silicon phantom. C illustrates an example of triple stent layer after crush technique in a patient.

at them as posing a higher risk of incomplete neointimal healing and stent thrombosis (5;68); however, recent randomized trial comparing stenting-across vs. other bifurcation techniques or vs. systematic kissing-balloon did not seem to find any clinical disadvantage of the technique producing NASB (69;70). The association of ISA struts to worse outcomes can be hypothetically explained through a triple mechanism: 1) ISA is the consequence of an inflammatory reaction, weakening the vessel wall and triggering thrombosis (71-73); 2) ISA is more frequent at severely-diseased vessel segments, that are more prone to suffer delayed healing and more events; 3) ISA is per se a handicap for proper neointimal healing (63). In the case of NASB, there might be some data supporting that they also represent a handicap for a

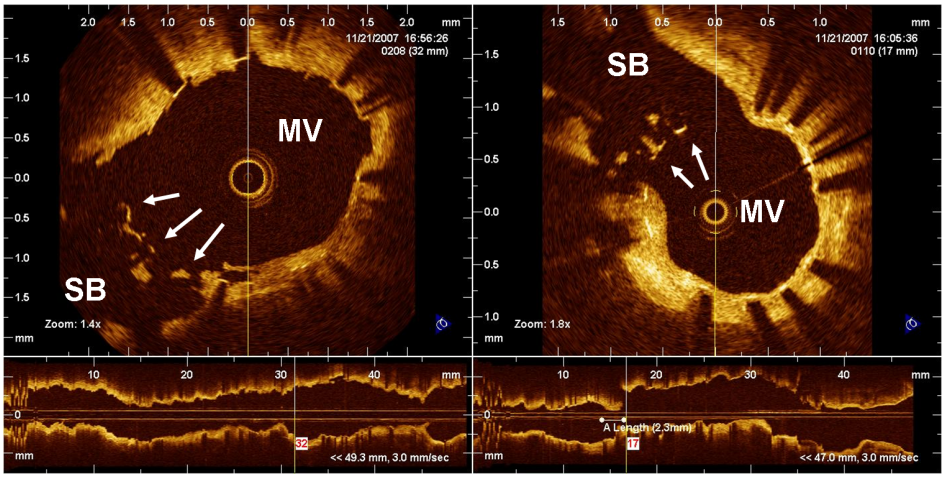


Figure 8:

Non-apposed side-branch (NASB) struts.

Non-apposed side-branch (NASB) struts (arrow): they appear in the OCT cross-sections as "suspended" in the middle of the flow. Apposition cannot be assessed in NASB, because there is no vessel wall behind.

proper neointimal healing (74), but certainly the mechanisms 1 and 2 do not apply to NASB. Therefore, until more evidence about the implications of ISA and NASB struts is available, it seems reasonable to consider them as 2 different categories.

In the stenting techniques that can be studied by OCT it is frequent to find small protrusion of struts at the level of the carina: NASB struts. Usually they will be visualized from both the main vessel and the side branch pullbacks, at the bifurcation core segment. Nonetheless, we recommend to count and to measure them only in the main vessel pullback, where they are best observed, in order to avoid duplication of measurements. A standard analysis at 1mm intervals will have very poor sensitivity to detect NASB struts: we recommend employing shorter intervals in the bifurcation core, with the aim of improving the sensitivity.

As a result of the high spatial resolution of OCT, several NASB struts will be detected in non-bifurcation segments, due to the take-off of tiny side branches. They must be categorized as NASB, despite the fact of not being at a real bifurcation.

Scaffolding of the carina and the shoulder

Incomplete scaffolding has been advocated to explain the worse results of stenting in bifurcations compared to straight vessels (61;62). Although there is no solid evidence supporting the concept (it was just a hypothesis outlined in the discussion of the articles), it has been widely accepted without further inquiries due to its plausibility. Assessing the scaffolding by OCT, despite its apparent simplicity, is resulting in a very slippery target. A systematic approach should include the assessment of scaffolding at 3 different levels:

- **Carina**
  - o Main vessel face: (Main vessel pullback)
  - o Side-branch face. (Side-branch pullback)
- **Shoulder** (Side-branch pullback)

Several parameters are being tested, still with no definitive conclusions to make clear recommendations. According to our preliminary experience on bench-testing models, analyzing the average number of struts per cross-section in the shoulder and in 2mm distal to the carina frame could be a good estimator. By dividing this number by the average number of struts per cross-section in a 2mm reference segment, it would result in a *scaffolding index* for each region (figure 9). The corresponding reference segments for each region must be defined depending on the stenting technique, being in general 2 mm of a monolayer segment outside the bifurcation core (figure 10).

$$\text{Scaffolding index} = \frac{\dfrac{\text{Nr of struts}_{ROI}}{\text{Nr of analyzed cross-sections}_{ROI}}}{\dfrac{\text{Nr of struts}_{RS}}{\text{Nr of analyzed cross-sections}_{RS}}}$$

Figure 9:
Formula for the calculation of the scaffolding indexes at the 3 different regions of interest: shoulder, carina (main vessel) and carina (side branch).
ROI: Region of Interest; RS: Reference segment.

Notice that the scaffolding index of the shoulder is based on the analysis of a narrower sector and therefore will score systematically lower than the carina indexes. Thus, it cannot be used for comparing the scaffolding of the shoulder vs. the one of the carina in a same bifurcation, but it is valid for comparison of the shoulder scaffolding between different patients or different devices.

It is still uncertain if the scaffolding indexes can be substantially modified by analyzing at shorter longitudinal intervals.

Access to the side branch

Although there is no evidence to support this practice, preserving the access to the side branch is actively pursued by many operators in many procedures, particularly if the bifurcation involves vessels of large calibre, like the left main-LAD-LCX. They are many clinical arguments that may be advocated for this preference, that might have sense in particular cases,

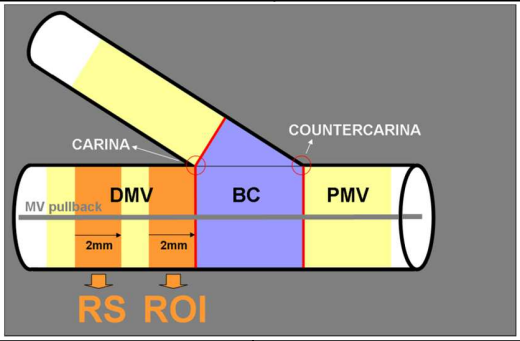
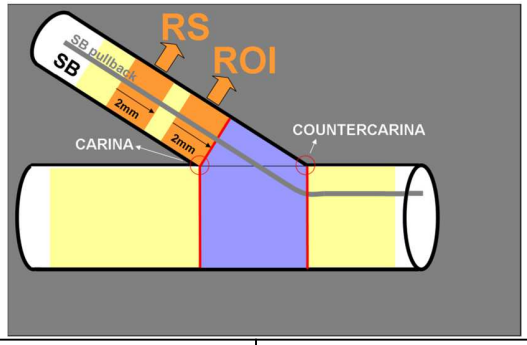
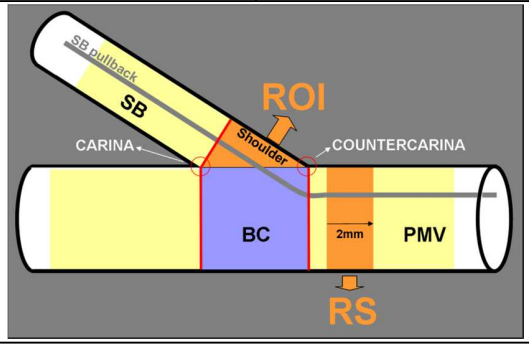
		Pullback	ROI	Reference segment
Carina	MV face	MV	2mm segment distal to the carina frame (inclusive)	Most proximal 2mm segment of a stented monolayer, distal to the ROI
				
	SB face *	SB	2mm segment distal to the carina frame (inclusive)	Most proximal 2mm segment of a stented monolayer, distal to the ROI
				
Shoulder		SB	Segment between the carina frame and the countercarina frame.	Most distal 2mm segment of a stented monolayer, proximal to the ROI
				

Figure 10:

ROIs and corresponding reference segments for the calculation of the scaffolding indexes.

For 1-stent techniques, only the scaffolding of the shoulder and the carina (main vessel) is assessed. In 2-stent techniques stenting the SB, the 3 indexes will be calculated.

*(only in 2 stents techniques where the SB is stented).

BC: Bifurcation core; DMV: Distal main vessel; MV: Main vessel; PMV: Proximal main vessel; ROI: Region of Interest; RS: Reference segment; SB: Side branch.

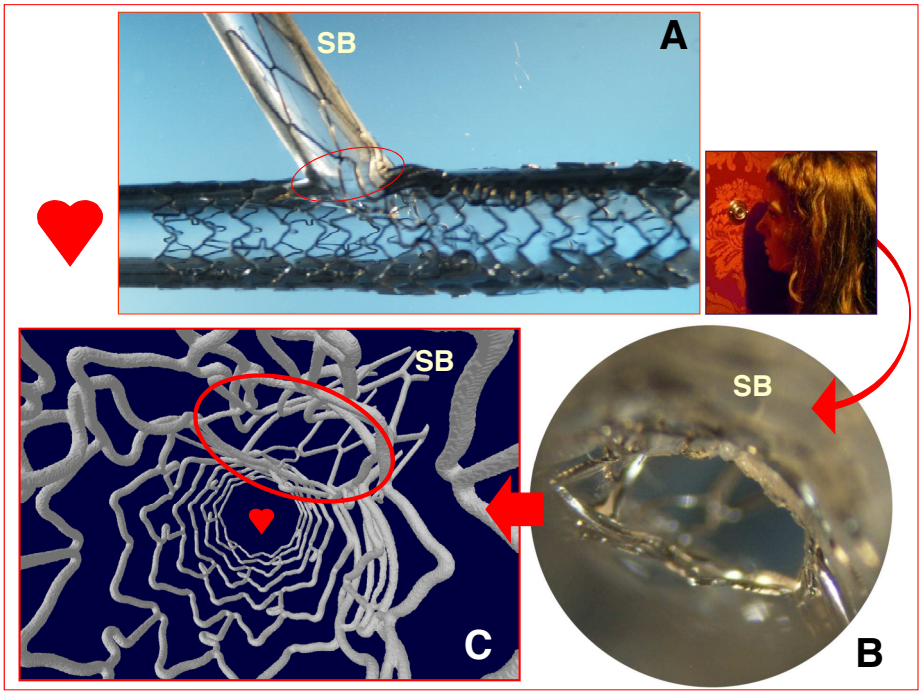


Figure 11:

Concept of SB access area.

The SB access area is the minimal metal-free area that the blood traverses on its way to accede to the side branch. SB access in a silicon phantom of a bifurcation-dedicated stent with a 2-stents technique, as imaged by micro-photography (A, B) and micro-computed tomography (C).

in which generating compelling evidence is not always possible. Many bifurcation-dedicated devices concede importance to keep a good access to the side branch, as well.

Assessing the access to the side branch by OCT, although also apparently simple, is together with the scaffolding the top challenge. Conceptually, we could define the access to the side branch as the smallest metal-free area that the blood traverses on its way to the SB (figure 11). In practice, however, the variations in the take-off angle of the SB, or the different location of this minimal metal-free area depending on the technique and the devices employed (figure 12) make the objective measurement of SB access very complex. Based on preliminary experiences on phantoms, we seem to have found a solid estimator, whose definition will change depending on the moment of assessment (acutely post-implantation vs. follow-up) and on the stenting of the SB with a second stent (figure 13). In all the cases, it will be defined in the side branch pull-back. This way, all the methodological problems due to the take-off angle or to location variants are partially overcome by the own angulation of the SB catheter to accede to the SB. The proposed definitions would not be valid for provisional stenting without final kissing, where the minimal metal-free area would be located in the main vessel

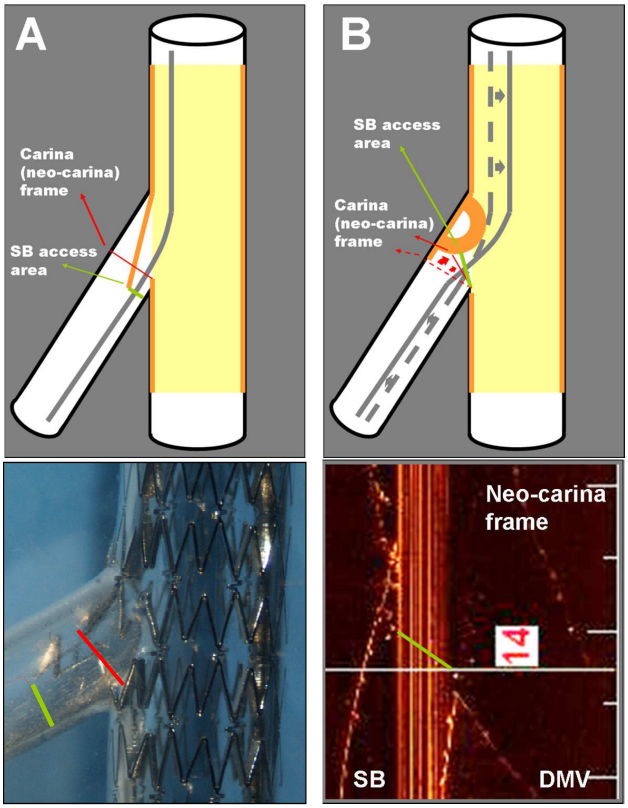


Figure 12:

Variants of the location of the minimal SB access area, depending on the techniques and devices employed.

A) SB access area distal to the carina/neo-carina frame, due to malapposition in the shoulder (A, lower part): in this setting, the carina/neo-carina frame would overestimate the SB access area. To circumvent this bias, the minimal stent area in a segment distal to the carina frame is considered the SB access area.

B) SB access area proximal to the carina/neo-carina frame, due to a technique producing multiple stent layers in the shoulder (step-crush, B lower part): in this setting it is not possible to evaluate accurately the SB access area, because the cross section might not be orthogonal to the longitudinal axis of the catheter. The SB access area would be slightly overestimated in the carina frame, and no plausible solution is currently available. In practice, when the SB access area is small, the catheter itself conforms to the anatomy and modifies its angulation to accede to the SB. This conformation helps to overcome partially the bias, as shown in the figure.

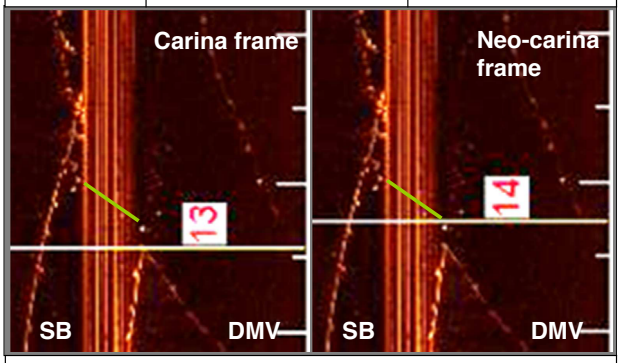
DMV: Distal main vessel; SB: Side branch.

(stent cells), but this technique is currently not suitable for OCT assessment, because the OCT catheter cannot be placed in the SB.

Finally, absolute SB access areas depend on the diameter of the SB and therefore cannot be directly compared. For comparative studies, we recommend to use corrected SB access areas, dividing the absolute SB access area by a reference area, defined as the maximal lumen area in the 5 mm distal to the carina frame (inclusive), in the SB pullback.

Corrected SB access area = Absolute SB access area / reference area

SB access area	No stent in the SB	2nd stent in the SB
Accutely post-implantation	Minimal stent or lumen area (whichever smallest) in the segment between the carina frame and the most distal frame where a strut can be identified.	Minimal stent area in the 2 mm distal to the carina frame (inclusive).
Follow-up	Minimal lumen area in the segment between the carina frame and the most distal frame where a strut can be identified.	Minimal lumen area in the 2 mm distal to the carina frame (inclusive).



In presence of NASB struts prolonging the carina, consider the neo-carina frame, instead of the carina frame for the measurements.

Figure 13:
Different definitions of SB access area, depending of the moment of assessment and the employ of a second stent in the SB.
DMV: Distal main vessel; NASB: Non-apposed Side-branch (struts); SB: Side branch.

In the assessment of the SB access might be also recommendable to measure in shorter longitudinal intervals, but it is unclear hitherto how this could affect the estimations, and no clear guidelines can be stated on a solid basis at this moment.

Coverage

The accuracy of OCT for the assessment of tissue coverage after stenting has been extensively addressed in the introduction of this chapter. OCT is currently the only technology able to assess in vivo the tissue coverage after stenting, due to its high axial resolution (14 µm). The OCT-derived tissue coverage seems to be a good surrogate for histological neointimal healing, according to several animal studies (46-49). This gives OCT a paramount role in the evaluation of intracoronary devices, since delayed neointimal healing has been consistently associated to stent thrombosis in several pathological studies (4;5). Coverage can be assessed by OCT through different parameters, the most commonly used being the proportion of non-covered struts and the mean thickness of the coverage. In the case of the bifurcations, it seems advisable to report the coverage topographically, or at least considering the 4 segments separately, because this can give some valuable clues to understand the problem and to improve the technique or the device. Likewise, the coverage of ISA areas and of NASB struts in the bifurcation core (63;74) deserves especial attention.

BIBLIOGRAPHY

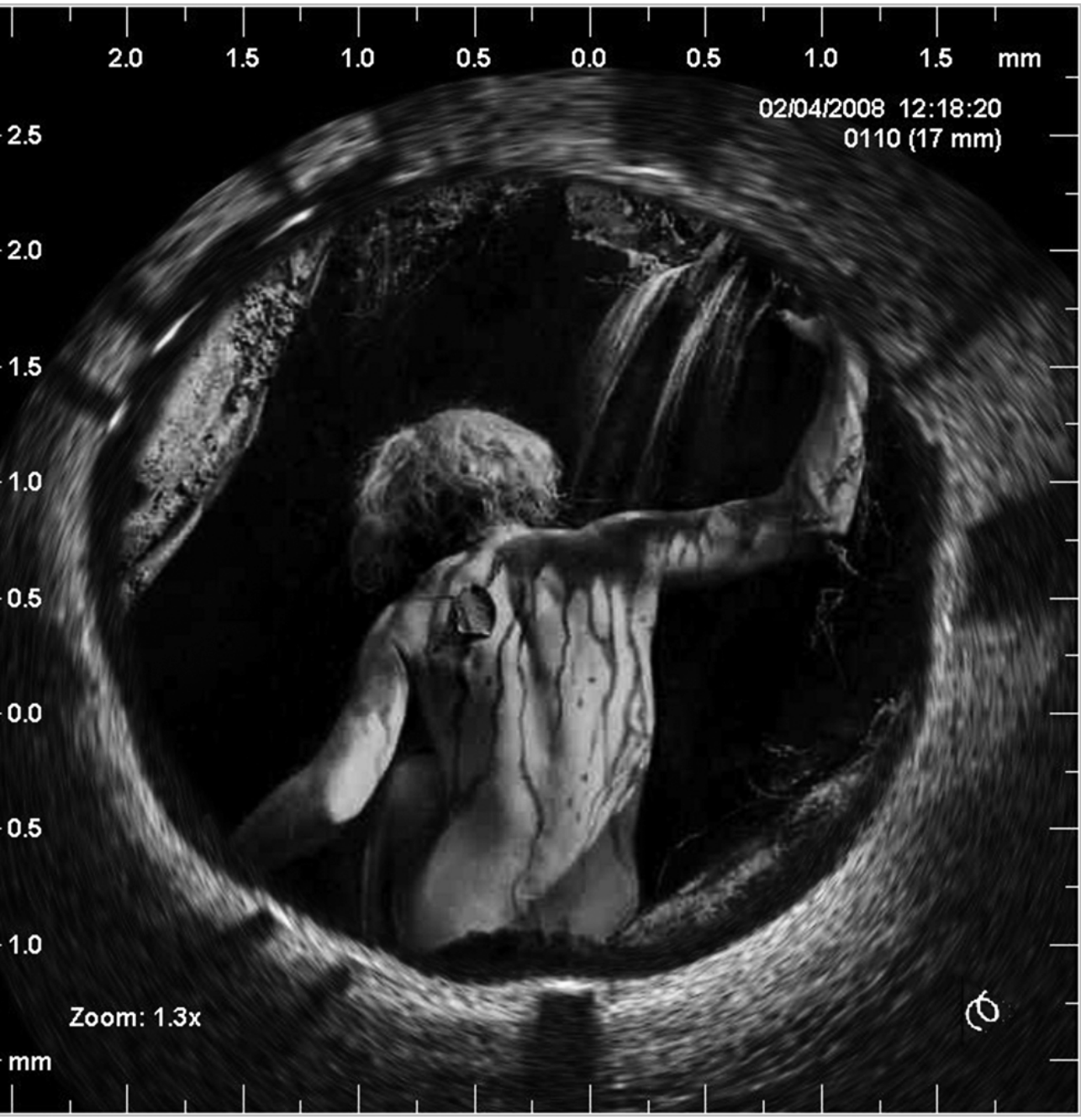
1. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, et al. Incomplete Stent Apposition and Very Late Stent Thrombosis After Drug-Eluting Stent Implantation. Circulation 2007 May 8;115(18):2426-34.
2. Hassan AK, Bergheanu SC, Stijnen T, van der Hoeven BL, Snoep JD, Plevier JW, et al. Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. Eur Heart J 2009 Jan 21.
3. Farb A, Heller PF, Shroff S, Cheng L, Kolodgie FD, Carter AJ, et al. Pathological Analysis of Local Delivery of Paclitaxel Via a Polymer-Coated Stent. Circulation 2001 Jul 24;104(4):473-9.
4. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological Correlates of Late Drug-Eluting Stent Thrombosis: Strut Coverage as a Marker of Endothelialization. Circulation 2007 May 8;115(18):2435-41.
5. Farb AM, Burke APM, Kolodgie FDP, Virmani RM. Pathological Mechanisms of Fatal Late Coronary Stent Thrombosis in Humans. [Article]. Circulation 2003 Oct 7;108(14):1701-6.
6. Farb AM, Sangiorgi GM, Carter AJD, Walley VMM, Edwards WDM, Schwartz RSM, et al. Pathology of Acute and Chronic Coronary Stenting in Humans. [Article]. Circulation 1999 Jan 5;99(1):44-52.
7. Kastrati A, Mehilli J, Dirschinger J, Pache J, Ulm K, Schuhlen H, et al. Restenosis after coronary placement of various stent types. Am J Cardiol 2001 Jan 1;87(1):34-9.
8. Liu MW, Roubin GS, King SB, III. Restenosis after coronary angioplasty. Potential biologic determinants and role of intimal hyperplasia. Circulation 1989 Jun 1;79(6):1374-87.
9. Essed CE, van den BM, Becker AE. Transluminal coronary angioplasty and early restenosis. Fibrocellular occlusion after wall laceration. Br Heart J 1983 Apr;49(4):393-6.
10. Giraldo AA, Esposo OM, Meis JM. Intimal hyperplasia as a cause of restenosis after percutaneous transluminal coronary angioplasty. Arch Pathol Lab Med 1985 Feb;109(2):173-5.
11. Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF. Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1985 Aug;6(2):369-75.
12. Bjorkerud S, Bondjers G. Arterial repair and atherosclerosis after mechanical injury. 5. Tissue response after induction of a large superficial transverse injury. Atherosclerosis 1973 Sep;18(2):235-55.
13. Clowes AW, Clowes MM, Reidy MA. Kinetics of cellular proliferation after arterial injury. III. Endothelial and smooth muscle growth in chronically denuded vessels. Lab Invest 1986 Mar;54(3):295-303.
14. Clowes AW, Schwartz SM. Significance of quiescent smooth muscle migration in the injured rat carotid artery. Circ Res 1985 Jan;56(1):139-45.
15. Clowes AW, Reidy MA, Clowes MM. Mechanisms of stenosis after arterial injury. Lab Invest 1983 Aug;49(2):208-15.
16. Baim DS, Cutlip DE, O'Shaughnessy CD, Hermiller JB, Kereiakes DJ, Giambartolomei A, et al. Final results of a randomized trial comparing the NIR stent to the Palmaz-Schatz stent for narrowings in native coronary arteries. Am J Cardiol 2001 Jan 15;87(2):152-6.
17. Serruys PW, de JP, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994 Aug 25;331(8):489-95.

18. Serruys PW, van HB, Bonnier H, Legrand V, Garcia E, Macaya C, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet 1998 Aug 29;352(9129):673-81.
19. Lansky AJ, Roubin GS, O'Shaughnessy CD, Moore PB, Dean LS, Raizner AE, et al. Randomized comparison of GR-II stent and Palmaz-Schatz stent for elective treatment of coronary stenoses. Circulation 2000 Sep 19;102(12):1364-8.
20. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003 Oct 4;362(9390):1093-9.
21. Kastrati A, Schomig A, Dirschinger J, Mehilli J, Dotzer F, von WN, et al. A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. ISAR-SMART Study Investigators. Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries. Circulation 2000 Nov 21;102(21):2593-8.
22. Park SW, Lee CW, Hong MK, Kim JJ, Cho GY, Nah DY, et al. Randomized comparison of coronary stenting with optimal balloon angioplasty for treatment of lesions in small coronary arteries. Eur Heart J 2000 Nov;21(21):1785-9.
23. Koning R, Eltchaninoff H, Commeau P, Khalife K, Gilard M, Lipiecki J, et al. Stent placement compared with balloon angioplasty for small coronary arteries: in-hospital and 6-month clinical and angiographic results. Circulation 2001 Oct 2;104(14):1604-8.
24. Doucet S, Schalij MJ, Vrolix MC, Hilton D, Chenu P, de BB, et al. Stent placement to prevent restenosis after angioplasty in small coronary arteries. Circulation 2001 Oct 23;104(17):2029-33.
25. Moer R, Myreng Y, Molstad P, Albertsson P, Gunnes P, Lindvall B, et al. Stenting in small coronary arteries (SISCA) trial. A randomized comparison between balloon angioplasty and the heparin-coated beStent. J Am Coll Cardiol 2001 Nov 15;38(6):1598-603.
26. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002 Jun 6;346(23):1773-80.
27. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994 Aug 25;331(8):496-501.
28. Kereiakes DJ, Cox DA, Hermiller JB, Midei MG, Bachinsky WB, Nukta ED, et al. Usefulness of a cobalt chromium coronary stent alloy. Am J Cardiol 2003 Aug 15;92(4):463-6.
29. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001 Jun 12;103(23):2816-21.
30. Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C, et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation 2004 May 11;109(18):2168-71.
31. Gershlick A, De S, I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. Circulation 2004 Feb 3;109(4):487-93.
32. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004 Mar 17;43(6):1110-5.

33. Lansky AJ, Costa RA, Mintz GS, Tsuchiya Y, Midei M, Cox DA, et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. Circulation 2004 Apr 27;109(16):1948-54.
34. Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002 Aug 13;106(7):798-803.
35. Degertekin M, Serruys PW, Foley DP, Tanabe K, Regar E, Vos J, et al. Persistent inhibition of neointimal hyperplasia after sirolimus-eluting stent implantation: long-term (up to 2 years) clinical, angiographic, and intravascular ultrasound follow-up. Circulation 2002 Sep 24;106(13):1610-3.
36. Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med 2003 Apr 17;348(16):1537-45.
37. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. J Am Coll Cardiol 2004 Jun 2;43(11):1959-63.
38. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization. N Engl J Med 2002 Jun 6;346(23):1773-80.
39. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. N Engl J Med 2003 Oct 2;349(14):1315-23.
40. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease. N Engl J Med 2004 Jan 15;350(3):221-31.
41. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents. JAMA 2005 May 4;293(17):2126-30.
42. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005 Jun 21;45(12):2088-92.
43. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006 Dec 19;48(12):2584-91.
44. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J 2006 Dec;27(23):2784-814.
45. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L, et al. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. N Engl J Med 2007 Mar 8;356(10):1009-19.
46. Suzuki Y, Ikeno F, Koizumi T, Tio F, Yeung AC, Yock PG, et al. In vivo comparison between optical coherence tomography and intravascular ultrasound for detecting small degrees of in-stent neointima after stent implantation. JACC Cardiovasc Interv 2008 Apr;1(2):168-73.
47. Deuse T, Erben RG, Ikeno F, Behnisch B, Boeger R, Connolly AJ, et al. Introducing the first polymer-free leflunomide eluting stent. Atherosclerosis 2008 Sep;200(1):126-34.

48. Prati F, Zimarino M, Stabile E, Pizzicannella G, Fouad T, Rabozzi R, et al. Does optical coherence tomography identify arterial healing after stenting? An in vivo comparison with histology, in a rabbit carotid model. Heart 2008 Feb 1;94(2):217-21.
49. Murata A, Wallace-Bradley D, Tellez A, Alviar C, Aboodi M, Sheehy A, et al. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. JACC Cardiovasc Imaging 2010 Jan;3(1):76-84.
50. Gonzalo N, Garcia-Garcia HM, Serruys PW, Commissaris KH, Bezerra H, Gobbens P, et al. Reproducibility of quantitative optical coherence tomography for stent analysis. EuroIntervention 2009 Jun;5(2):224-32.
51. Capodanno D, Prati F, Pawlowsky T, Cera M, La MA, Albertucci M, et al. Comparison of optical coherence tomography and intravascular ultrasound for the assessment of in-stent tissue coverage after stent implantation. EuroIntervention 2009 Nov;5(5):538-43.
52. Zhou Y, Kassab GS, Molloi S. On the design of the coronary arterial tree: a generalization of Murray's law. Phys Med Biol 1999 Dec;44(12):2929-45.
53. Finet G, Gilard M, Perrenot B, Rioufol G, Motreff P, Gavit L, et al. Fractal geometry of arterial coronary bifurcations: a quantitative coronary angiography and intravascular ultrasound analysis. EuroIntervention 2007;3:490-8.
54. Murray CD. The Physiological Principle of Minimum Work: I. The Vascular System and the Cost of Blood Volume. Proc Natl Acad Sci U S A 1926 Mar;12(3):207-14.
55. Bassingthwaighte JB, Van Beek JH, King RB. Fractal branchings: the basis of myocardial flow heterogeneities? Ann N Y Acad Sci 1990;591:392-401.
56. Zamir M, Chee H. Branching characteristics of human coronary arteries. Can J Physiol Pharmacol 1986 Jun;64(6):661-8.
57. Ramcharitar S, Onuma Y, Aben JP, Consten C, Weijers B, Morel MA, et al. A novel dedicated quantitative coronary analysis methodology for bifurcation lesions. EuroIntervention 2008 Mar;3(5):553-7.
58. Medina A, Suarez de LJ, Pan M. A new classification of coronary bifurcation lesions. Rev Esp Cardiol 2006 Feb;59(2):183.
59. Louvard Y, Thomas M, Dzavik V, Hildick-Smith D, Galassi AR, Pan M, et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv 2008 Feb 1;71(2):175-83.
60. van der Waal EC, Mintz GS, Garcia-Garcia HM, Bui AB, Pehlivanova M, Girasis C, et al. Intravascular ultrasound and 3D angle measurements of coronary bifurcations. Catheter Cardiovasc Interv 2009 Jun 1;73(7):910-6.
61. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR, Jr., Spanos V, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation 2004 Mar 16;109(10):1244-9.
62. Pan M, de Lezo JS, Medina A, Romero M, Segura J, Pavlovic D, et al. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. Am Heart J 2004 Nov;148(5):857-64.
63. Gutiérrez-Chico JL, Regar E, Jüni P, Okamura T, García-García HM, van Es GA, et al. Malapposed struts in drug-eluting stents entail higher risk of incomplete tissue coverage at 9- to 13-month follow-up compared to well-apposed struts: in vivo demonstration with optical coherence tomography. Eurointervention (suppl). Communication at EuroPCR, Paris 2010. 28-5-2010.

64. Ormiston JA, Webster MW, El JS, Ruygrok PN, Stewart JT, Scott D, et al. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. Catheter Cardiovasc Interv 2006 Jan;67(1):49-55.
65. Tanigawa J, Barlis P, Di MC. Intravascular optical coherence tomography: optimisation of image acquisition and quantitative assessment of stent strut apposition. EuroIntervention 2007 May;3(1):128-36.
66. Finn AVM, Kolodgie FDP, Harnek JM, Guerrero LJB, Acampado ED, Tefera KB, et al. Differential Response of Delayed Healing and Persistent Inflammation at Sites of Overlapping Sirolimus- or Paclitaxel-Eluting Stents. [Article]. Circulation 2005 Jul 12;112(2):270-8.
67. Räber L, Jüni P, Löffel L, Wandel S, Cook S, Wenaweser P, et al. Impact of Stent Overlap on Angiographic and Long-Term Clinical Outcome in Patients Undergoing Drug-Eluting Stent Implantation. Journal of the American College of Cardiology 2010 Mar 23;55(12):1178-88.
68. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of Drug-Eluting Stents in Humans: Delayed Healing and Late Thrombotic Risk. Journal of the American College of Cardiology 2006 Jul 4;48(1):193-202.
69. Jensen JS, Galloe A, Lassen JF, Erglis A, Kumsars I, Steigen TK, et al. Safety in simple versus complex stenting of coronary artery bifurcation lesions. The nordic bifurcation study 14-month follow-up results. EuroIntervention 2008 Aug;4(2):229-33.
70. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. Circulation 2006 Oct 31;114(18):1955-61.
71. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, et al. Correlation of Intravascular Ultrasound Findings With Histopathological Analysis of Thrombus Aspirates in Patients With Very Late Drug-Eluting Stent Thrombosis. Circulation 2009 Aug 4;120(5):391-9.
72. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent: Should We Be Cautious? Circulation 2004 Feb 17;109(6):701-5.
73. Wilson GJ, Nakazawa G, Schwartz RS, Huibregtse B, Poff B, Herbst TJ, et al. Comparison of Inflammatory Response After Implantation of Sirolimus- and Paclitaxel-Eluting Stents in Porcine Coronary Arteries. Circulation 2009 Jul 14;120(2):141-9.
74. Gutiérrez-Chico J, Regar E, Jüni P, Okamura T, García-García HM, van Es GA, et al. Implications of floating struts at side branches in the tissue coverage of drug-eluting stents at 9- to 13-months follow-up: in vivo assessment with optical coherence tomography. Eurointervention (suppl). Communication at EuroPCR, Paris 2010. 28-5-2010.
75. Lansky A, Tuinenburg J, Costa M, Maeng M, Koning G, Popma J, et al. Quantitative angiographic methods for bifurcation lesions: a consensus statement from the European Bifurcation Group. Catheter Cardiovasc Interv 2009 Feb 1;73(2):258-66.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CHAPTER 15

Primary percutaneous coronary intervention

Residual atherothrombotic material after stenting in acute myocardial infarction – an optical coherence tomographic evaluation.

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ABSTRACT

Background: Thrombus aspiration (TA) in patients with ST segment elevation myocardial infarction (STEMI) results in a better myocardial perfusion. Optical coherence tomography (OCT) after stenting in STEMI, however, often reveals residual atherothrombotic material. We assessed the feasibility of quantification of residual atherothrombotic burden and its relation to indices of myocardial perfusion. The effect of TA on residual in-stent atherothrombotic burden (ATB) is explored.

Methods and Results: Forty patients with STEMI within 12 hours of symptom onset, underwent OCT after stent implantation. No complication related to the invasive imaging was detected and all cases had good image quality. All 40 cases revealed ATB (median, range; 2.85, 0.08 - 8.84) despite an optimal angiographic result. Patients were divided into two groups according to the ATB: ≥4 =ATB_{high} (n=15) and <4 = ATB_{low} (n=25). Patients with ATB_{low} more often obtained a myocardial blush grade (MBG) of 2/3: 24 (96%) vs. 11 (73%), p=0.04 and a ≥ 50% ST segment resolution 24 (96%) vs. 8 (53%) p=0.02. Incomplete stent apposition is more often detected with ATB_{low} : 1.97 (0.62-4.73) vs. 0.33 (0.04-0.92), p= 0.002. TA was performed in 20 (50%) patients. ATB was numerically lower in patients with TA: 2.37(1.70-5.10) vs. 3.40(1.45-4.96), p=0.67). Logistic regression identified ATB as predictor of ST resolution failure (OR: 2.5 (of 2.51 (95% confidence interval : 1.27-4.98), p value =0.008.

Conclusions: OCT can be safely performed in patients presenting for primary PCI and allows quantification of residual atherothrombotic material, the amount of which is associated with worse myocardial perfusion.

Keywords: ST-segment elevation myocardial infarction, Primary percutaneous coronary intervention, Thrombus aspiration, Optical coherence tomography, myocardial perfusion.

INTRODUCTION

A high thrombus load as detected by coronary angiography during primary percutaneous coronary intervention is an important determinant of myocardial reperfusion and major adverse cardiac events.(1-2) Manual thrombus aspiration improves myocardial perfusion and may decrease cardiac death in STEMI patients.(3-4) This effect is at least in part driven by a reduction in thrombus burden which in turn improves distal blood flow, reduces distal embolisation and thereby improves microvascular perfusion.(5) The latter has a direct influence on the final infarct size and together have a significant impact on the short and long term clinical outcome.(6)

Optical Coherence Tomography (OCT) can detect atherothrombotic material in the culprit lesion better than any other imaging modality.(7) Due to its high spatial resolution, OCT can also quantify very small intravascular structures especially those close to the surface of the endothelium. Residual intra-stent material representing atherothrombotic material has been observed with OCT particularly in the setting of acute coronary syndromes.(8) The significance of the amount of residual atherothrombotic material has not been established. Moreover whether primary percutaneous coronary intervention with manual thrombus aspiration effects the in-stent residual atherothrombotic burden is yet unknown. The aims of this prospective exploratory study were firstly to assess the feasibility and reproducibility of measurement of residual atherothrombotic burden after stenting. Secondly, the implications of a high versus a low residual atherothrombotic burden as measured by OCT on indices of microvascular perfusion was explored. Thirdly, we assessed if primary percutaneous coronary intervention (PPCI) with thrombus aspiration (TA) results in a lower atherothrombotic burden as compared to PPCI without TA.

METHODS

Study population

Patients referred to our hospital within twelve hours of an episode of continuous chest pain lasting >30 minutes and having a 12 lead electrocardiogram (ECG) with ST-segment elevation ≥0.1 mV in 2 or more contiguous leads and an angiographically identifiable culprit lesion in a native coronary artery were eligible for enrolment in this study. Patients who were haemodynamically unstable even after corrective measures, as well as patients with a previous stent implantation in the culprit coronary artery were excluded. Also patients in whom successful wiring of the culprit artery and TIMI ≥1 flow allowed angiographic visualisation of a very high thrombus load were excluded. Furthermore patients in whom thrombus aspiration was mandatory according to the treating interventional cardiologist were excluded.

Procedure

Intravenous heparin (100 U/kg), aspirin (300 mg), clopidogrel (600 mg) and oxygen (5 l/min via mask or nasal pronges) were systematically administered immediately on diagnosis at the first point of medical contact which is pre-hospital in the majority of cases. Nitrates and analgesics (diamorphine) were instituted when necessary. Cardiac catheterisation was performed via the femoral or radial approach using a 6-F sheath and appropriate catheters. After contrast injection and angiographic filming of both left and right coronary systems, the culprit artery was identified by angiographic signs including absent or reduced Thrombolysis in Myocardial Infarction (TIMI) flow, evidence of thrombus, and signs of myocardial infarction in the corresponding territory by ECG and/or transthoracic echocardiography. Engagement of the ostium of the artery was followed by intracoronary bolus of nitrate (2mg) and an angiogram. After successful wiring of the vessel with advancement of the wire well beyond the culprit site a second cine angiography was taken. This allowed assessment and reclassification of thrombus grade in patients with TIMI 0 on the first film. At this stage, the interventional cardiologist chose to treat the patient with or without manual thrombus aspiration. In our institution, TA is employed in about 70% of all PPCI's and in about 50% of those with low-intermediate angiographic thrombus grades. By exclusion of high thrombus grades from the study we projected equal distribution of TA and non-TA use in the study cohort.

Manual Thrombus aspiration

A thrombectomy catheter (DIVER, Invatec-Medtronic) was advanced over the wire and the radio-opaque marker was used to position the tip just proximal to the point of occlusion or lesion. A negative pressure was then applied by means of a 30 ml syringe. The catheter tip was slowly advanced across the lesion while maintaining aspiration. Slow retraction of the catheter tip to a site proximal to the culprit lesion allowed re-cross. This manoeuvre was repeated 2-4 times after which a control angiography was performed. In case of residual thrombotic appearance on angiography, further aspiration runs were performed.

Small balloons (<1.5mm diameter) were used where appropriate in patients in the no thrombectomy arm with the aim of improving in TIMI flow and thereby allowing assessment of the culprit lesion in patients presenting with TIMI 0/1. Predilatation with a ballon > 1.5mm was strongly discouraged in favour of direct stenting in both treatment arms.

Optical Coherence Tomography Image acquisition

OCT acquisition was performed with the C7-XR imaging system (St. Jude/LightLab Imaging, Inc, Westford, MA) after angiographically optimal stent implantation and once the treating cardiologist deemed the interventional treatment complete. The image catheter (Dragon-

fly™, St.Jude/LightLab Imaging, Inc, Westford, MA) was advanced and positioned distal to the stented segment. A continuous flush of iso-osmolar contrast through the guiding catheter (Iodixanol 370, Visipaque™, GE Health Care, Ireland) at 3-4ml/s was used for blood clearance while an automated OCT pullback was performed at 20mm/s. Post-dilatation, further thrombus aspiration and any repeat intervention driven primarily by the OCT findings during this pullback were permitted but left to the discretion of the operator and were not included in the main data analysis.

Angiographic analysis

Offline angiographic analysis including quantitative coronary angiographic (QCA) measurements was performed using CAAS 5.5 (Pie Medical, Maastricht, the Netherlands). Thrombus grade (TG) was determined before and after wiring. Thrombus grade of 0 was defined as no angiographic sign of thrombus; 1 – reduced contrast density, haziness, irregular lesion contour suggestive but not diagnostic of thrombus; 2 – definite thrombus with greatest dimensions ≤1/2 the vessel diameter; 3 – definite thrombus with greatest linear dimension >1/2 but <2 vessel diameters; 4 – definite thrombus with the largest dimension ≥2vessel diameter; 5 total occlusion.(9) Reclassification after wiring allowed changes in grading especially for those in which TIMI flow change from 0 to 1 or higher.(2) Thrombolysis In Myocardial (TIMI) flow and myocardial blush were assessed as previously reported.(10) No reflow was defined as reduced antegrade flow to TIMI 0/1 after achievement of TIMI 2/3 flow, in the absence of occlusion at the treatment site or evidence of distal embolization. Slow flow was defined as a decrease in antegrade flow to TIMI 1/2 after stent implantation when compared to optimal TIMI 2/3 flow pre-stent implantation. Distal occlusion was defined as a filling defect distal from the culprit site causing an abrupt cut-off of the distal vessel or branch. Myocardial blush grade (MBG) was measured as previously described.(11)

Acute gain was calculated as change in minimal luminal diameter in the stent area. For all patients including those with TIMI 0 at presentation, the film before balloon/stent inflation was use for pre-procedural minimal luminal diameter (MLD), allowing a more realistic measurement of the actual acute gain. The rest of the QCA parameters were measured as previously described. (12)

ST segment resolution and peak cardiac enzymes

ST segment resolution was defined as a ≥50% decrease in the ST segment elevation between the pre-procedural 12-lead ECG showing the highest elevation and the ST segment elevation on a 12 lead ECG taken 1 hour after the procedure. Blood samples for cardiac enzymes (Creatinine Kinase) were taken regularly every 6 hours. The peak enzyme values were included in the database.

OCT safety and feasibility measures

Safety of OCT on imaging related complications such as vasospasm, dissection, embolisation, arrhythmia, and other major adverse cardiovascular events that were clearly related to the imaging procedure or any other event were recorded.(13) Image quality and appropriateness for planned analysis was also assessed.

OCT analysis

Off-line analysis was performed with the Light Lab software on a dedicated workstation in a core lab setting by an experienced analyst, blinded to treatment assignment, angiographic or clinical outcome. After correction of the Z-Offset, the stented segment including the 5mm proximal and distal peri-stent regions were identified and bookmarked. This allowed systematic analysis in 1mm intervals. The longitudinal view was used to mark and measure the length of the stent (region of interest- ROI) and the thrombotic region of interest- TROI). The latter was defined by the distance between the most distal and the most proximal cross-sectional frame that showed intraluminal material suggestive of thrombus as described by Kubo et al.(14) The lumen area (LA) was obtained by automated edge-detection algorithm and additional manual corrections, when necessary. The stent area (SA) was obtained by a multiple point detection function which linked the points set in the middle of the endoluminal border of stent struts. Intraluminal material which was not clearly attached at any point to the endothelial wall in that frame was measured by multiple point trace function and labelled as free thrombus (FTA). The area between malapposed stent struts and the vessel wall was measured and labelled as incomplete stent apposition area (ISA). The atherothrombotic area (ATA) was calculated by subtracting the LA from the SA and adding FTA while taking into account ISA:

$$ATA = SA - LA + FTA + ISA$$

The atherothrombotic volume (ATV) was calculated by multiplying the mean ATA by the TROI length:

$$ATV = \text{mean ATA} \times TROI$$

The atherothrombotic burden (ATB) was then calculated as a percentage of stent volume (SA multiplied by ROI) and expressed as a percentage:

$$ATB = ATV/SV \times 100$$

The derivation of this parameter is further illustrated in figure 1.

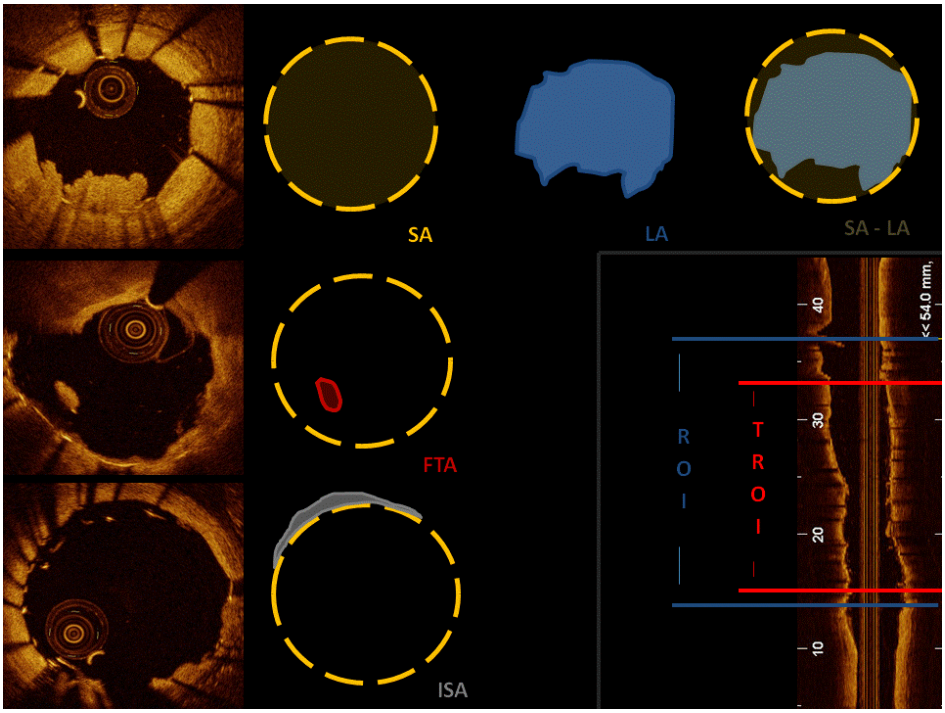


Figure 1.

Measurement of residual in-stent atherothrombotic burden by optical coherence tomography.

Optical coherence tomography (OCT) cross sections taken from patients immediately after stent implantation during primary percutaneous coronary intervention. Intraluminal material extending towards the lumen beyond the defined stent area is considered as thrombus or atherothrombotic material for the purposes of this study. By subtracting the lumen area (LA) from the stent area (SA) this part is obtained. Free thrombus area(FTA) is added to (SA-LA) while areas of incomplete stent apposition (ISA) are added to obtain the mean atherothrombtic area for any given OCT frame. The length over which thrombus is detected in the longitudinal view that is the atherothrombotic region of interest (TROI) is used to calculate a mean atherothrombotic volume. This is then corrected for stent volume (ROI x SA) to obtain the atherothrombotic burden which is expressed as a percentage (see text).

Reproducibility of the OCT measurements

The first 11 pullbacks were analysed by a second experienced observer to determine interobserver variability of atherothrombotic burden measurement. These same pullbacks were analysed by the main observer > 4 weeks apart to obtain intraobserver variability of the measurements.

Clinical Follow-up

Hospitals to which the patients were discharged after the PPCI were contacted for information on relevant clinical events during the hospitalisation following the index event. Patients had clinical visits or were contacted by phone or mail at 6 months and were specifically asked

for symptoms or re-admissions following their index events. Hospital records, general practitioners and peripheral hospitals were contacted for details in case of an event which was then adjudicated by 2 cardiologists with criteria as previously described.(15)

Statistical analysis

Continuous variables are expressed as means (SD) or median and interquartile range. Categorical variables are expressed as percentages. The distribution of ATB in the whole cohort was assessed on a frequency chart. The distribution curve showed a positive skew, with the bulk of the values (and therefore the median) lying to the left of the mean residual ATB value. Since the measurement of interest was ATB, patients were divided into two cohorts; those with ATB below the mean i.e < 4 % or ATB_{low} and those with ATB above the mean i.e. ≥ 4 % or ATB_{high}. Comparisons between these groups were performed with chi-squared test for categorical variables whereas the Student t test or Mann Whitney test was used to compare continuous variables. Multiple logistic regression analysis was performed to assess the independent predictors of failure of ST segment resolution as a measure of myocardial/microvascular perfusion. In a first step, univariate analysis was used to assess predictors of failure of ST resolution. These included age, shock, pain to balloon time multivessel disease, anterior myocardial infarction, left anterior descending, TIMI 0 presenting, and angiographic thrombus grade and ATB. Parameters with value of <0.1 were then entered into a multivariate model to assess their independent association with failure of ST resolution.

For analysis of the effect of thrombus aspiration on atherothrombotic burden, patients were divided into the two groups according to intention to treat. The exploratory nature of the study precluded an up-front formal power calculation of the number of patients needed to include in the study to detect difference in atherothrombotic burden between the two groups. Baseline clinical, procedural and OCT measures including ATB were compared using student t test or chi square test as appropriate.

The interobserver and intraobserver reproducibility of the residual atherothrombotic burden was calculated by estimating the absolute and relative difference between measurements. The relative difference was defined as the absolute difference divided by the average. The data including the limits of agreement (calculated as the mean difference ± 2SD) are depicted in Bland-Altman plots.

RESULTS

OCT pullback was feasible in all patients after stent implantation. There were 6 cases where embolisation of atherothrombotic material was observed however in all cases these were

Table 1. Baseline clinical characteristics, angiographic and procedural characteristics in patients with low and high atherothrombotic burden.

Characteristic	OCT ATB < 4 n = 25	OCT ATB ≥ 4 n = 15	*p* value
Baseline characteristics			
Age, yrs	62 ± 12	65 ± 8	0.34
Male	23 (92)	12 (80)	0.27
Diabetes	3 (12)	2 (13)	0.80
Hypertension	6 (25)	8 (53)	0.06
Hypercholesterolaemia	10 (40)	5 (33)	0.67
Current Smoker	12 (48)	5 (33)	0.36
Family History of CAD	9 (36)	7 (47)	0.51
Clinical Presentation			
Ischaemic time, min	312 ± 133	318 ± 271	0.85
Pulse, bpm	74 ± 16	72 ± 19	0.39
Blood pressure, mmHg			
Systolic	125 ± 25	132 ± 36	0.85
Diastolic	78 ± 11	75 ± 19	0.59
Cardiogenic shock	1 (4)	0 (0)	0.43
Killip Class 1	24 (96)	15 (100)	0.43
Infarct related artery			
LAD	10 (40)	6 (40)	1.0
LCx	3 (12)	2 (13)	0.90
RCA	12 (48)	7 (47)	0.94
TIMI flow grade			
0	13 (52)	6 (40)	0.53
1	2 (8)	0 (0)	0.52
2	3 (12)	2 (13)	0.90
3	7 (28)	7 (47)	0.31
Thrombus grade after wiring			
1	5 (20)	1 (7)	0.26
2	6 (25)	8 (53)	0.06
3	11 (44)	5 (33)	0.51
4	2 (8)	1 (7)	0.88
5	1 (4)	0 (0)	0.43
Multivessel disease	14 (56)	9 (60)	0.81
Procedural characteristics			
Thrombus Aspiration	13 (52)	7 (47)	0.74
Macroscopic thrombus visible on sieve	4 (16)	1 (7)	0.47
Use of small balloon pre-stenting	4 (16)	4 (27)	0.42
Stent implanted			0.33
EES*	19 (36)	9 (60)	
BMS*	4 (16)	5 (33)	
GP IIb/IIIa inhibitors	9 (36)	12 (80)	0.008

Data are expressed as means (standard deviation) and number (percentages). OCT TB= in-stent residual atherothrombotic burden, LAD= left anterior descending coronary artery, LCx= left circumflex coronary artery, RCA= right coronary artery. TIMI=Thrombolysis in myocardial infarction, EES=everolimus eluting stent, BMS bare metal stent, GP glycoprotein.*same multi-link design.

present before insertion of the OCT imaging catheter. There was no major adverse event that could be attributed to the OCT imaging procedure.

All the OCT images were of good quality for analysis. Residual atherothrombotic burden could be measured in all 40 cases (median, range; 2.85%, 0.08 - 8.84) by OCT as opposed to none on angiography. There were no significant differences between patients with an ATB_{high} (n=15) and ATB_{low} (n=25) in the baseline clinical characteristics (table 1). A high ATB was more likely to occur in a vessel with larger reference diameter as measured pre-intervention by quantitative coronary angiography: 3.13 ± 0.65 mm vs. 2.64 ± 0.50 mm, p =0.02. Patients with a ATB_{high} more often developed no reflow: 3 (20%) vs. 0 (0%), p=0.02; embolisation: 5 (33%) vs. 1 (4%), p=0.008 and distal occlusion: 4 (27%) vs. 1 (4%), p=0.03. Those with an ATB_{low} more often obtained a MBG of 3: 24 (96%) vs. 11 (73%), p=0.04 and a ≥ 50% ST segment resolution 24 (96%) vs. 8 (53%) p=0.02. (see figures 2 and 3). Incomplete stent apposition as measured by incomplete stent apposition volume (ISV) was higher in patients with ATB_{low}: 1.97 (0.62-4.73) vs. 0.33 (0.04-0.92), p= 0.002). No association with respect to infarct size as measured by peak creatinine kinase (CK) was found.

Multiple logistic regression was performed to determine the independent predictors of failure to achieve complete ST resolution. In a multivariate model including angiographic

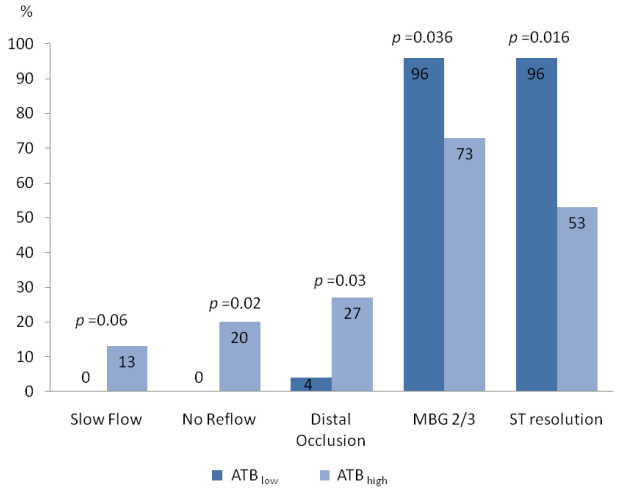


Figure 2.

Microvascular perfusion in patients with high or low residual in-stent atherothrombotic material.

In-stent residual atherothrombotic burden was categorised into low that is <4% (ATB_{low}) and high, that is ≥4% (ATB_{high}) according to frequency distribution. The difference in occurrence of angiographically defined complications of slow-flow, no-reflow and distal occlusion are illustrated as achievement of optimal myocardial blush grade and complete ST resolution (see text for definitions).

thrombus grade, residual atherothrombotic burden, and thrombectomy, the only indepen-

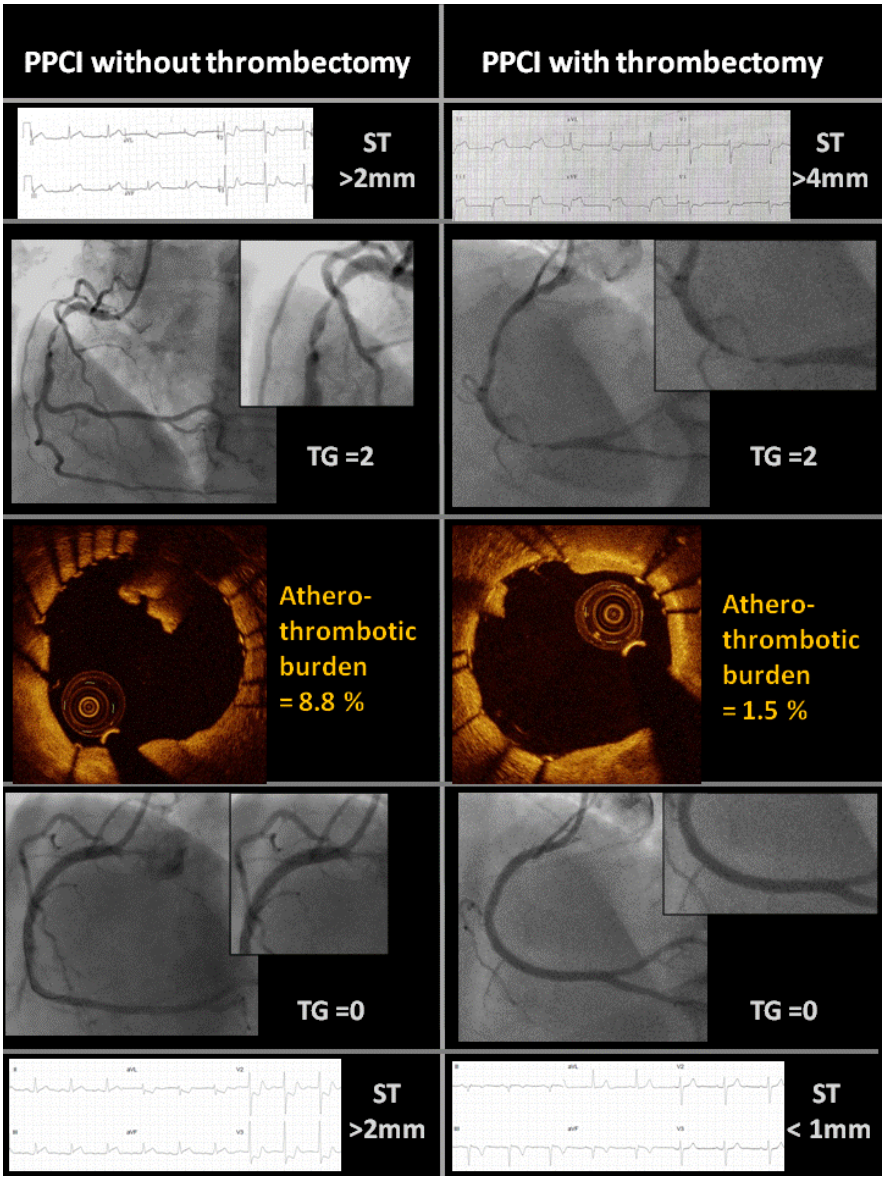


Figure 3.

OCT derived residual in-stent atherothrombotic burden and index of microvascular perfusion.

Two patients presenting with an inferior myocardial infarction and enrolled in the study are shown here. The electrocardiograms (ECG) in the top panels show the degree of ST-segment elevation in the relevant leads. The patient on the left was randomised to treatment without thrombectomy while that on the right to treatment with thrombus aspiration. Angiographic thrombus grade after wiring was similar in both patients. Optical coherence tomography (OCT) after stenting showed a residual atherothrombotic burden of >4% in the patient without thrombectomy and a repeat ECG 1 hour after the procedure showed failure of ST segment resolution (lower panel). The patient on the right had thrombus aspiration and OCT revealed a residual atherothrombotic burden of <4%. ECG at 1 hour shows complete (>50%) ST segment resolution. Note that although both patients had no angiographically detected thrombus on final angiogram (TG=0), OCT in both patients detected residual atherothrombotic material.

dent predictor of failure of ST resolution was residual atherothrombotic burden with odds ratio of 2.51 (95% confidence interval : 1.27-4.98), p value =0.008. Furthermore, addition of other baseline parameters in the multivariate model did not significantly change the odds ratio for ATB.

Thrombus aspiration vs. no aspiration

Baseline clinical characteristics were similar in both treatment groups (Table 2). Manual Thrombus Aspiration (TA) was more often performed in patients with TIMI 3 flow: 11 (55%) vs. 3 (15%) p=0.02, however there was no difference in angiographic thrombus (TG) graded after wiring of the culprit coronary artery TG 1-3, 19 (95%) vs. 18 (90%) p= 1.0). (table 3)

Table 2. Baseline clinical characteristics in patients with and without thrombus aspiration.

Characteristic	Thrombectomy n=20	No Thrombectomy n=20	*p* value
Age (yrs)	61 ± 9	63 ± 12	0.84
Male	18 (90)	17 (85)	0.63
Diabetes			
Type 1	2 (10)	0 (0)	0.15
Type 2	2 (5)	1 (5)	0.55
Hypertension	7 (35)	7 (35)	1
Hypercholesterolaemia	10 (50)	5 (25)	0.10
Smoker			
Current	9 (45)	8 (40)	0.75
Ex	5 (25)	3 (15)	0.43
Family History of CAD	7 (35)	9 (45)	0.52
Previous MI	2 (10)	2 (10)	1
Previous PCI	1 (5)	0 (0)	0.31
Location of MI			
Anterior	10 (50)	5 (25)	0.10
Inferior	10 (50)	15 (75)	0.10
Ischaemic time, min	271 ± 247	326 ± 233	0.71
Pulse, bpm	72 ± 17	78 ± 21	0.48
Blood pressure, mmHg			
Systolic	126 ± 31	132 ± 29	0.54
Diastolic	76 ± 16	77 ± 15	0.96
Cardiogenic shock	1 (5)	0 (0)	0.31
Killip Class 1	19 (95)	20 (100)	0.31

Categorical data are expressed as number (percentage) while continuous data are expressed as mean ± standard deviation. CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention.

Table 3. Baseline angiographic characteristics in patients with and without thrombus aspiration.

Characteristics	Thrombectomy n=20	No Thrombectomy n=20	*p* value
Infarct related artery			
LAD	**10 (50)**	**6 (30)**	**0.20**
LCx	**2 (10)**	**3 (15)**	**0.63**
RCA	**8 (40)**	**11 (55)**	**0.34**
TIMI flow presenting			
0	**13 (65)**	**6 (30)**	**0.027**
1	**1 (5)**	**1 (5)**	**1**
2	**2 (10)**	**3 (15)**	**0.63**
3	**11 (55)**	**3 (15)**	**0.019**
Thrombus grade after wiring			
1	**1 (5)**	**5 (25)**	**0.08**
2	**7 (35)**	**7 (35)**	**1**
3	**9 (45)**	**7 (35)**	**0.52**
4	**2 (10)**	**1 (5)**	**0.55**
5	**1 (5)**	**0 (0)**	**0.31**
Multivessel disease	**11 (55)**	**12 (60)**	**0.75**
MI SYNTAXscore	**16 ± 8**	**11 ± 7**	**0.07**
Lesion length, mm	**19 ± 11**	**16 ± 11**	**0.23**
Minimal Luminal Diameter, mm	**1.11 ± 0.44**	**1.02 ± 0.47**	**0.81**
Reference vessel diameter, mm	**2.83 ± 0.47**	**2.75 ± 0.68**	**0.38**
% Diameter Stenosis	**60 ± 15**	**61 ± 15**	**0.86**
cTFC after wiring	**54 ± 32**	**45 ± 31**	**0.31**

Data is expressed as mean ± standard deviation or number (percentage). LAD= left anterior descending coronary artery; LCx= left circumflex artery; RCA= right coronary artery. TIMI= thrombolysis in myocardial infarction flow grade; cTFC= corrected TIMI count. MI SYNTAXscore= Myocardial infarction SYNTAXscore.

In the TA group, patients had an average of 2 aspiration runs. Macroscopic athero-thrombotic material on the collection sieve was observed in only 25% of those undergoing this adjunctive interventional therapy. Procedure duration was significantly longer (50 min. vs. 39 min., p=0.02) in the thrombus aspiration group. Other procedural characteristics however were not different between the two treatment arms as shown in table 4. Everolimus eluting stents (XIENCE V, Abbott Vascular, Santa Clara, CA) were used in the majority of patients. The bare metal stents implanted had the same stent design as the drug-eluting stents (Multilink Vision, Abbott Vascular, Santa Clara, CA) Stent overlap was deemed appropriate in 23% while postdilatation (non-OCT driven) was performed in 48%. Glycoprotein IIb/IIIa inhibitors were given in 53 % of patients.

OCT parameters measured in both groups are shown in table 5. The stented length (ROI, mm) was longer for patients with TA 26 (20-32), vs. 18 (15-25) p=0.04. OCT measurements of atherothrombotic material were numerically lower in the TA group however none reached sta-

Table 4. Procedural characteristics in patients with or without thrombus aspiration.

Characteristic	Thrombectomy n=20	No Thrombectomy n=20	*p* value
Aspiration runs	2 ± 1	0	< 0.001
Macroscopic thrombus visible on sieve	5 (25)	-	0.57
Use of small balloon pre-stenting	3 (15)	5 (25)	0.43
Stent implanted			
EES	15 (75)	15 (75)	1
BMS	5 (25)	5 (25)	1
Number lesions with > 1 stent	4 (20)	5 (25)	0.71
Total stent length, mm	31 ± 13	28 ± 17	0.14
Stent overlap	4 (20)	5 (25)	0.71
Postdilatation	11 (55)	8 (40)	0.34
GP IIb/IIIa inhibitors	12 (60)	9 (45)	0.34
Heparin units peri-procedural	5275 ± 1642	6000 ± 2051	0.23
Contrast used, mls	241 ± 69	207 ± 61	0.15
Procedure time, min	50 ± 15	39 ± 20	0.02

Data are expressed in mean ± standard deviation and number (percentage). EES= everolimus eluting stent; BMS=bare metal stent; GP = glycoprotein.

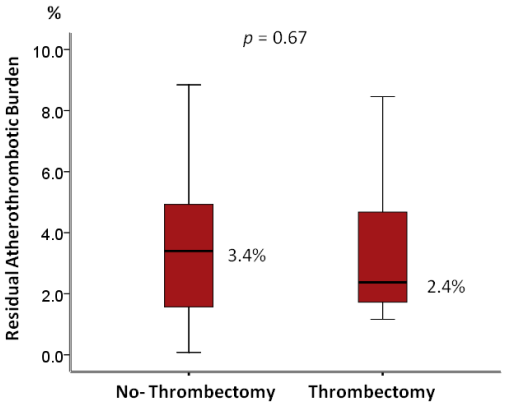


Figure 4.

In-stent atherothrombotic burden in patients treated with and without manual aspiration thrombectomy.

Thrombus aspiration shows a trend towards a reduction in residual in-stent atherothrombotic burden which however did not reach statistical significance. Note that only 5 of the 20 patients in the thrombus aspiration arm had macroscopic thrombus retrieved on the sieve while none of the patients showed angiographic evidence of residual thrombus.

Table 5. Optical coherence tomographic parameters in patients with and without thrombus aspiration.

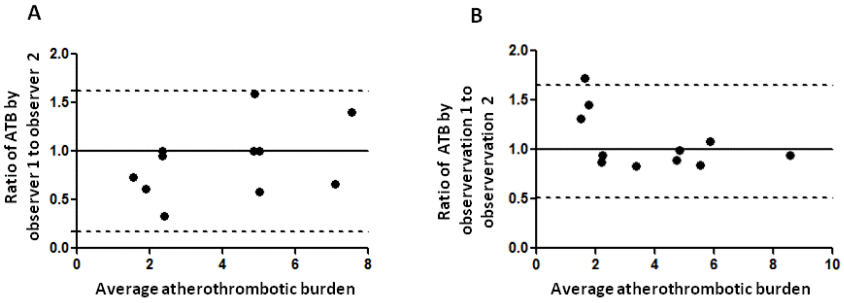
OCT parameter	Thrombectomy n=20	No Thrombectomy n=20	*p* value
Analysable pullbacks	20	20	1
ROI (stent length), mm	26 (20-32)	18 (15-25)	0.04
Mean Lumen area, mm^2	9.29 ± 2.53	9.38 ± 2.78	0.87
Mean Stent Area, mm^2	9.45 ± 2.73	9.64 ± 3.03	0.96
Minimal Luminal Area, mm^2	7.20 ± 2.46	7.47 ± 2.79	0.87
TROI, mm	20 (11-26)	12 (10-25)	0.21
Mean ATA, mm^2	0.24 (0.17-0.42)	0.36 (0.12-0.73)	0.46
Maximal ATA, mm^2	1.20 (0.92-1.91)	0.83(0.53-2.05)	0.31
Free ATA, mm^2	0.00 (0.00-0.01)	0.00 (0.00-0.02)	0.67
Stent Volume, mm^3	259 ± 137	210 ± 127	0.16
Atherothombotic volume, mm^3	6.31(3.20-1.57)	3.32(2.04-15.0)	0.61
Atherothrombotic burden, %	2.37 (1.70-5.10)	3.40 (1.45-4.96)	0.67
ISA area, mm^3	0.046 (0.01-0.10)	0.049(0.01-0.11)	0.88
ISA volume	1.31 (0.30-3.05)	0.92 (0.18-2.58)	0.72
% ISA	0.001	0.001	NS

Data is expressed in mean ± standard deviation and median (interquartile range). ROI= region of interest; TROI= atherothrombotic region of interest; ATA= atherothrombotic area; ISA=incomplete stent apposition.

tistical significance. Thus TROI (mm) that is the length over which atherothrombotic material was measured was: 20 (11-26) vs. 12 (10-25), p=0.21; Residual atherothrombotic burden was also 30% lower in the TA group, however no statistical significance was reached; TB: 2.37(1.70-5.10) vs. 3.40(1.45-4.96), p=0.67; (see figure 4). As consequence the minimal flow area as a ratio of mean stent area was numerically higher for TA patients 0.75 ± 0.10 vs. 0.77 ± 0.15 p=0.64 indicating a possibly lower degree of narrowing in the stented segment. Incomplete stent strut apposition was not different between the two groups. There was no difference in terms of angiographic complications including slow flow, no-reflow, embolisation, or distal occlusion. The same number of patients with and without TA achieved optimal MBG 2/3 (18, 90%) and ST segment resolution 1 hour after the procedure was not different between the two arms (15 vs. 17, p=0.59). The peak CK tended to be higher in patients undergoing TA (2601 ± 276 vs. 1251 ± 905, p=0.06). Acute stent thrombosis occurred in one patient assigned to the no TA group and in-hospital cardiac death in one patient in the TA group. At 6 months follow-up there was no significant differences in outcome between the groups.

Reproducibility of the residual in-stent atherothrombotic burden

Bland Altman plots for intra and interobserver variability are illustrated in figure 5. The variability and limits of agreement are good for this parameter as shown.



Interobserver variability

						Limits of agreement	
	Observer 1	Observer 2	Absolute difference	Relative difference	Reproducibility	Lower	Upper
ATB	4.30 ± 2.13	3.87 ± 2.43	0.43 ± 1.78	1.3	0.90	0.176	1.62

Intraobserver variability

	Observation 1	Observation 2				
ATB	3.80 ± 2.13	3.87 ± 2.43	-0.06 ± 0.58	1.1	1.1	0.51	1.62

Figure 5.
Reproducibility of in-stent atherothrombotic burden.
Bland Altman plots and tables with limits of agreement for interobserver (A) and intraobserver (B) for measurement of residual in-stent atherothrombotic burden (ATB).

DISCUSSION

The main findings of this study are that OCT can (1) be performed safely in patients presenting for primary PCI, (2) OCT allows detection of residual atherothrombotic material after stent implantation treated for STEMI even after use of thrombectomy devices. This is not appreciated by angiography. Moreover, OCT can quantify the amount of residual in-stent atherothrombotic material. (3) Patients with a high ATB as quantified by OCT are more likely to show angiographic complications of impaired flow including no reflow, slow flow, embolisation and distal occlusion than those with low atherothrombotic burden. Also these patients show reduced microvascular reperfusion as seen by a lower attainment of optimal myocardialblush grade and lower ST segment resolution.

From its conception to date, optical coherence tomography technology has undergone remarkable improvements that make its applicability to clinical practice a reality. Procedure safety is of particular importance in patients with unstable coronary artery disease especially patients with acute STEMI. OCT studies in this unstable patient population proved feasible with the first generation time domain imaging, though cumbersome. The development of

fourier domain second generation systems with short monorail OCT catheters that can be easily and quickly manoeuvred into the coronary artery, very fast pullbacks and the change from an occlusive technique to a flush technique that avoids induction of ischemia, has certainly improved the safety of this invasive imaging modality. Although embolisations of intraluminal atherothrombotic material may be perceived as a concern for applying this technique in patients, we did not observe any cases that were clearly induced by the OCT catheter insertion or the contrast injection for blood clearance during pullback. Furthermore, high image quality can be reliably achieved and reproducibility of the measurements is very good as demonstrated in our study.

The sensitivity of thrombus detection by angiography is desirable as it may influence the need for adjunctive antithrombotic treatment. Higher thrombus load may require more aggressive or repeated use of thrombectomy, antiplatelet or thrombolytic therapy. However thrombus load detection and quantification with the imaging modalities employed in daily practice for treatment of acute coronary syndromes have severe limitations.(16) Thrombus especially if mural is less likely to be detected by a luminogram and can be misinterpreted as stenotic plaque. This may lead to an underestimation of the thrombus load and perhaps also importantly overestimate the degree of coronary stenosis. The latter is important in intermediate or low grade stenosis in which stenting may not be necessary. In an earlier study, Kubo et al. have shown that in patients with acute myocardial infarction, intracoronary thrombus was observed in all cases by OCT and by coronary angioscopy, but it was identified in 33% by IVUS (vs. OCT, $p < 0.001$).(14) In their study, OCT was performed before stenting but after thrombectomy. This allowed assessment of the lesion and residual thrombus. Whether performing OCT at this stage prior to stenting poses a risk of embolisation of the residual atherothrombotic material is not yet known. Our positive safety results relate only to OCT pullbacks post-stenting and these results cannot be extrapolated to pre-stenting OCT procedures. From our experience, OCT performed prior to stent implantation in patients with either a high degree stenosis or a high thrombus load most often does not yield good quality images, mainly due to inadequate blood clearance. This would have resulted in exclusion of a significant number of patients, possibly limiting our analysis and conclusions. Also, since especially large thrombus in the lumen results in an optical shadow which restrains our ability to delineate the true endoluminal border behind it, this would compromise accurate and reproducible measurement of thrombus and of the other coronary structures. On the other hand with our methodology we used the ability of the stent to delineate the endoluminal border, leaving less room for measurement variability. The correlation we found with residual in-stent atherothrombotic material and ST segment resolution supports the role thrombus and embolisation/microembolisation has in determining microvascular perfusion and infarct size. Both of the latter are important surrogate markers of mortality in patients treated for STEMI.(6). A reduction in residual atherothrombotic burden by mechanical or pharmacological means seems desirable and likely to improve myocardial perfusion. This novel index may

therefore be used to assess the efficacy of future therapeutic options that target thrombus reduction in STEMI patients.

We found a non-significant trend towards a reduction in thrombus burden with thrombus aspiration. A reason for failure to reach statistical significance could be lack of power, that is low number in both groups. In order to detect a 30% (3.4-2.37) reduction in thrombus load by a thrombectomy device with a sample size of at least 50 subjects is needed. Another reason could be the suboptimal use of the thrombectomy device or the actual suboptimal efficacy of the device. These reasons are plausible explanations of the lack of influence of TA in our study cohort on indices of myocardial perfusion.

The safety of drug eluting stent implantation in myocardial infarction has been questioned by some researchers and although this study was not designed to address this problem it offers some insights into this issue. (17-18) Previous observational studies have reported a higher incidence of malapposed stent struts at follow-up in patients with acute myocardial infarction when compared to patients with stable coronary artery disease.(18) Our study lends support to the hypothesis of the role of atherothrombotic burden. We observed a higher incidence of incomplete stent apposition in patients with a low TB. A large amount of thrombus can obscure our appreciation of whether stent struts are properly apposed to the true endolumen as opposed to apposition with mural thrombus. Resolution of mural thrombus may lead to ISA at follow-up. The relevance of this observation will need to be addressed in OCT studies with baseline and follow-up studies.

Limitations

The study is an exploratory study and although we found a strong relation of residual in-stent atherothrombotic burden and indices of myocardial perfusion, the study was not sufficiently powered to assess its significance on hard clinical endpoints. The method we used to define atherothrombotic material has its limitations for a number of reasons. We use any intraluminal material within the TROI, limited within the stented segment to define atherothrombotic burden. This measure realistically includes both thrombus as well as atheromatous and plaque material. However this is systematically and blindly done for all patients and should not affect the results or conclusions of our analysis. Measurement of thrombus before and after thrombectomy but before stenting by an imaging modality that does not interfere with the thrombus would be the best measure of the efficacy of thrombus aspiration. However in our study, OCT was performed after stenting and therefore the residual atherothrombotic burden may have been influenced by unaccounted interventions other than thrombus aspiration. This may have occurred despite our efforts in the study to minimalise differences between the TA and non-TA group except for thrombus aspiration. A randomised trial would be needed to confirm our findings. Analysis was done on an intention to treat basis which resulted in patients undergoing thrombectomy but without visible thrombus on the sieve.

Although we did not do histolpathological analysis of the aspirate, failure to retrieve macroscopic atherotherothrombotic material does not imply failure of thrombectomy and these patients may still have benefited from the adjunctive treatment.(3)

CONCLUSIONS

OCT can detect and quantify residual atherothrombotic material after stent implantation in patients with acute STEMI. The residual in-stent atherothrombotic burden is associated with angiographic and ECG -derived markers of myocardial and microvascular perfusion. Incomplete stent apposition is less often detected in patients with high residual atherothrombotic material. These findings may be important surrogates of clinical outcome in patients treated with stent implantation for acute STEMI. Thrombus aspiration seems to lead to lower tissue protrusion in stent as quantified by OCT, possibly reflecting a reduction in the thrombus load. An adequately powered study is needed to confirm these findings.

REFERENCES

1. Singh M, Berger PB, Ting HH, Rihal CS, Wilson SH, Lennon RJ, et al. Influence of coronary thrombus on outcome of percutaneous coronary angioplasty in the current era (the Mayo Clinic experience). Am J Cardiol. 2001 Nov 15;88(10):1091-6.
2. Sianos G, Papafaklis MI, Daemen J, Vaina S, van Mieghem CA, van Domburg RT, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol. 2007 Aug 14;50(7):573-83.
3. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet. 2008 Jun 7;371(9628):1915-20.
4. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med. 2008 Feb 7;358(6):557-67.
5. Henriques JP, Zijlstra F, Ottervanger JP, de Boer MJ, van 't Hof AW, Hoorntje JC, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J. 2002 Jul;23(14):1112-7.
6. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol. 2010 May 25;55(21):2383-9.
7. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. Implication of plaque color classification for assessing plaque vulnerability: a coronary angioscopy and optical coherence tomography investigation. JACC Cardiovasc Interv. 2008 Feb;1(1):74-80.
8. Gonzalo N, Serruys PW, Okamura T, Shen ZJ, Onuma Y, Garcia-Garcia HM, et al. Optical coherence tomography assessment of the acute effects of stent implantation on the vessel wall: a systematic quantitative approach. Heart. 2009 Dec;95(23):1913-9.
9. Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. Circulation. 2001 May 29;103(21):2550-4.
10. Gibson CM, Schomig A. Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion. Circulation. 2004 Jun 29;109(25):3096-105.
11. Henriques JP, Zijlstra F, van 't Hof AW, de Boer MJ, Dambrink JH, Gosselink M, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation. 2003 Apr 29;107(16):2115-9.
12. Serruys PW, Foley, D.P., de Feyter, P.P.J. Quantitative Coronary Angiography in Clinical Practice. Springer; 1 edition,. 1993 December 31, .
13. Barlis P, Gonzalo N, Di Mario C, Prati F, Buellesfeld L, Rieber J, et al. A multicentre evaluation of the safety of intracoronary optical coherence tomography. EuroIntervention. 2009 May;5(1):90-5.
14. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol. 2007 Sep 4;50(10):933-9.
15. Magro M, Nauta S, Simsek C, Onuma Y, Garg S, van der Heide E, et al. Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: The MI SYNTAXscore study. Am Heart J. 2011 Apr;161(4):771-81.

16. Rentrop KP. Thrombi in acute coronary syndromes : revisited and revised. Circulation. 2000 Apr 4;101(13):1619-26.
17. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008 Sep 9;118(11):1138-45.
18. Gonzalo N, Barlis P, Serruys PW, Garcia-Garcia HM, Onuma Y, Ligthart J, et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. JACC Cardiovasc Interv. 2009 May;2(5):445-52.

"Life is the art of drawing sufficient conclusions from insufficient premises".

The Note-Books

Samuel Butler

Summary and conclusions

SUMMARY, DISCUSSION AND CONCLUSIONS

Drug-eluting stents (DES) seemed to have addressed the main shortcoming of bare metal stents (BMS), namely restenosis. The stent platform opposed a mechanical radial resistance to avoid elastic recoil and the subsequent constrictive remodelling, considered the main mechanism of restenosis after balloon angioplasty[1-3], but the second mechanism involved in restenosis, i.e. neointimal hyperplasia, remained unaffected or even enhanced after BMS implantation[1-3], thus resulting in restenosis rates of 20.0 – 50.3%[4, 5]. DES released an anti-proliferative agent to prevent neointimal hyperplasia, thus acting specifically against both mechanisms involved in stent restenosis and reducing its incidence to 7.9 - 8.9 %[6-8]. Notwithstanding these excellent results, the initial optimism was soon obscured by concerns about higher rates of late and very late stent thrombosis, eventually resulting in higher mortality rates in the long term[9-15].

This PhD thesis was undertaken in this context of deep concern about the risk of DES thrombosis, with an unprecedented momentum of technological innovation intended to improve the biocompatibility of intracoronary devices through very different approaches, in order to improve their safety profile. It was not a matter of mere chance that the largest progress in the development of intracoronary applications for optical coherence tomography (OCT) coincided in time with this concern about stent thrombosis. As intracoronary imaging tool, OCT met the theoretical and technical conditions to monitor in vivo the neointimal healing process after stenting, even in a clinical scenario, thus emerging as a potential detector of cases with higher likelihood of thrombosis. As a consequence, this thesis has generated evidence about:

1) the performance of some of these technological innovations in intracoronary devices
2) the potential of intracoronary OCT for the assessment of neointimal healing after stenting and for other investigational and clinical applications
3) the neointimal healing process itself.

PERFORMANCE OF NEWLY-DEVELOPED INTRACORONARY DEVICES

Drug-coated balloons

Part 1, chapters 1-3 of this thesis appraises the rationale for use, the current clinical indications and the technical characteristics of drug-coated balloons (DCB), explaining in detail the role played by each of their specific components[16-18]. The DE NOVO pilot study was the first-in-man study of a novel paclitaxel-coated balloon with proprietary (unspecified) carrier (Moxy ®, Lutonix Inc, Maple Grove, MN, USA) and the first randomised trial testing the efficacy of a DCB with an OCT-derived primary endpoint, namely the percentage of neointimal volume

obstruction[18]. Its results provided additional evidence about the biological effect exerted by DCB in the modulation of neointimal hyperplasia, complementary of the already existing clinical and angiographic evidence[19-21]: the overall in-stent neointimal volume obstruction (primary endpoint) and the uncorrected mean thickness of coverage per strut (25.1% and 242 µm, respectively) were comparable to those reported for paclitaxel-eluting stents (22.2 – 25.8 %, 200 – 240 µm)[22, 23], lower than in some DES and far from those in BMS (53.9 %, 530 µm)[22]. Also the proportion of uncovered struts (7%) was in the range reported for paclitaxel-eluting (5 – 7 %) or sirolimus-eluting stents (8 %), and higher than in BMS (1 %)[22, 23]. This study was also the first one to use the combination of a DCB plus a non-premounted BMS for treatment of de novo coronary lesions, proving its feasibility and efficacy. Nonetheless, in-stent lumen late loss (0.49 mm) and in-segment binary restenosis (21.7 %) were substantially higher than previously reported for other DCB (0.09-0.19mm and 5-7%, respectively, in other clinical scenarios[19, 21], therefore casting some doubts about the efficacy of combining BMS plus DCB for this specific clinical indication. This is consistent with previous findings in the PEPCAD-III trial, in which the combination of a BMS premounted on a DCB failed to prove non-inferiority vs. a sirolimus-eluting stent for the treatment of de novo coronary lesions[24, 25].

The study failed to answer convincingly the question about the optimal sequence of application: DCB-first or BMS-first. With the only exception of a significantly better apposition in the sequence BMS-first, no other significant difference was found in any other parameter[18]. The results about percentage of uncovered struts and average thickness of coverage seem to suggest a discrete trend to more efficient neointimal inhibition with the sequence DCB-first, but the numbers are inconclusive[18]. A possible explanation for this finding might be axial mismatching, defined as the inability of the inflated balloon to get in contact with the underlying vessel around the 360° of the vessel cross-section. Anticipating this circumstance, this study was the first one in proposing an exploratory graphic method to assess the axial mismatching, although no clear association with suboptimal neointimal inhibition was detected[18]. A larger sample size could have provided more convincing answers for these insufficiently addressed questions.

Finally, I would like to highlight an important lesson learned from this modest study, utmost relevant from a methodological point of view and however insufficiently recognised hitherto. Most OCT studies (including some studies in this thesis) had previously reported and compared "mean" thickness of coverage per strut[22, 23, 26, 27]. However this is an invalid approach, because the variable thickness of coverage follows an extremely skewed distribution. The comparison or mean thickness of coverage can be totally misleading, as nicely illustrated in the DE NOVO pilot trial: this study was the first one to pay attention to this detail, and to propose the normalization (log transformation) of the variable thickness of coverage. After normalization, the comparison of thickness between both groups was completely reversed with respect to the uncorrected thickness[18]. Posterior publications have developed this concept further[28].

Second generation drug-eluting stents

Reservoirs

Part 4, chapter 6 of this thesis presents the results of the EUROSTAR-II trial. They prove the efficacy of reservoirs technology for inhibition of neointimal hyperplasia and for clinically relevant prevention of restenosis, in direct comparison with an identical BMS platform[29]. The efficacy of reservoirs technology had been questioned after the COSTAR-II trial failed to prove non-inferiority of the same reservoirs-platform used in EUROSTAR-II vs. a first-generation conformal-coating paclitaxel-eluting stent (Taxus Express, Boston Scientific, Maple Grove, MN, USA)[30]. Furthermore, in the COSTAR-II study, the performance of the CoStar reservoirs DES seemed non-significantly different from the "imputed" (i.e. theoretically constructed) virtual BMS[30]. EUROSTAR-II solves definitely this dilemma, providing a higher level of evidence about the efficacy of reservoirs than indirect hypothetical placebo imputations. These results are consistent with preceding evidence about reservoirs DES[31-33] and with the ulterior results of another reservoir DES, tested in the NEVO trial[34]. Although the sample size of the EUROSTAR-II trial was underpowered to draw a solid conclusion about the incidence of stent thrombosis, it is important to notice the absence of thrombotic events in the reservoirs DES group, what is compatible with the hypothesis that a bioresorbable polymer might avoid delayed hypersensitivity reactions that trigger very late thrombosis[29].

Biocompatible polymers

Part 5, chapter 7 of this thesis compares the coverage of two DES with biocompatible polymers, as assessed by OCT. The RESOLUTE zotarolimus-eluting stent (Medtronic Inc, Santa Rosa, CA, USA) is coated by a BioLinx polymer, an amphiphilic molecule, with topographic orientation of its hydrophilic components towards the outer surface in contact with the cells or the blood[35, 36]. These characteristics confer the stent an improved biocompatibility profile, since hydrophilic polymers elicit a lesser inflammatory reaction[37, 38], thus easing a fast, homogeneous and uncomplicated neointimal healing process[39]. Conversely, the XIENCE everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) is coated by a hydrophobic fluoropolymer, namely poly(vinylidene fluoride-co-hexafluoropropylene). Hydrophobic polymers are less biocompatible but more haemocompatible than hydrophilic polymers. That means hydrophobic polymers are more pro-inflammatory but less pro-trhombotic than hydrophilic polymers. Additionally, the fluoropolymer surface elicits a biological response known as "fluoropassivation" which consists of minimizing the fibrin deposition and thrombogenicity, reducing the inflammatory reaction and enhancing a faster neointimal healing[40, 41]. Whether the abovementioned characteristics of these two biocompatible polymers

translated into any advantage in the vascular healing process for any of the devices was unknown.

The RESOLUTE-OCT substudy did not find significant differences in coverage between the RESOLUTE zotarolimus-eluting stent and the XIENCE everolimus-eluting stent at the 13th month after implantation[27]. If we accept the coverage assessed by OCT as a valid estimator of the degree of neointimal healing, as consistently validated in several experimental studies using histology as gold-standard[42-46], the results of our study could be interpreted as lack of significant differences in the degree of neointimal healing between both stents at the 13th month after implantation.

Biodegradable polymer in abluminal coating

The LEADERS (Limus Eluted from A Durable vs. ERodable Stent coating) trial was the first randomised trial to include an OCT substudy for the evaluation of coverage in two different types of DES[47, 48]. It compared a new-generation biolimus-eluting stent (BES) with a biodegradable polylactic acid (PLA) polymer in abluminal coating vs. a 1st generation sirolimus-eluting stent (SES) with durable polymer in conformal coating. At 9 months BES was associated with a significant reduction in the percentage of uncovered struts as compared with SES (weighted estimate 0.6 vs. 2.1%, p=0.04)[48]. Part 6, chapter 8 of this thesis analyses the coverage at the 24th month after implantation, thus becoming also the first OCT sequential study comparing two different stent designs[49]. Unexpectedly, the initial advantage of BES over SES in terms of strut coverage at 9 months[48] was followed by improvement of the SES coverage between 9-24 months, resulting in similar coverage in both types of stents at the 24th month. Both stent types converged at a maximum plateau around 98% strut coverage. Taken together, these results suggest that BES indeed is associated with faster healing than SES, achieving a percentage of coverage close to the maximum plateau (97%) at 9 months, while SES is catching up subsequently.

To our knowledge, this was the first clinical in-vivo study with sequential OCT suggesting that different stent designs can promote different healing rates. This might be relevant for tailoring the duration of dual antiplatelet therapy after stenting. Moreover, the improvement in coverage observed in SES between 9-24 months challenges the currently accepted model for neointimal healing after stenting. Experimental studies suggested that the re-endothelialization process ensuing a vessel injury, e.g. stenting, was limited in time[50-52]. However our results suggest a more dynamic process, still evolving between 9 and 24 months.

Bioresorbable vascular scaffold

Part 7, chapters 9-11 analyse different aspects of the Abbott Bioresorbable Vascular Scaffold (BVS). The BVS (Abbott Vascular, Santa Clara, CA, USA) consists of a semi-crystalline poly-L-lactide (PLLA) backbone, coated by a thin amorphous layer of poly-D,L-lactide (PDLLA) containing the antiproliferative agent everolimus. Both poly-lactide polymers are progressively degraded by hydrolysis so the device is fully resorbed 2 years after implantation[53]. Sustained elution of everolimus is coupled with the PDLLA degradation. The BVS has unique imaging characteristics requiring a dedicated methodology of analysis: it is translucent to optical radiation and totally radiolucent to gamma radiation, with the only exception of the radiopaque platinum markers at the edges.

The translucency to optical radiation is however altered at some points after implantation in vivo, as observed in a series of intriguing images, named "scattering centers" by the investigators, and consisting of focal hyperintense signals in the strut core without apparent contact with either the axial or transversal strut edges. Chapter 9 analyses the spatial distribution of these scattering centres immediately post-implantation and at the 6th month, by means of spread-out vessel charts, a tool for spatial representation of OCT data originally developed for several studies in this PhD thesis. This analysis reveals that the scattering centres only appear at hinge points of the scaffold structure and that they were stable over time. These findings strongly suggest that the scattering centres are due to crazes in the polymer during the processes of crimping and deployment[54].

Chapter 10 compares different imaging modalities (quantitative coronary angiography by edge detection and video densitometry, intravascular ultrasound [IVUS] and OCT) in the BVS immediately after implantation and at 6 months. This time point represents the transition between the restoration phase (loss of structural integrity, restoration of vascular reactivity) and the resorption phase (loss of mass) of the device[55]. The agreement between techniques for measurement of stent length and minimal lumen area (MLA) was explored in a methodologically challenging scenario, because all the analysed scaffolds had exactly the same nominal size (3x18mm), what precluded the application of conventional statistical tests for the analysis of agreement, initially conceived to test a linear relationship between two different methods along a range of different values. Nonetheless an original approach, creating novel tools for this specific analysis ("target chart" , "chess tables", etc…) permitted to compare the agreement between these imaging modalities in strict statistical orthodoxy[56]. OCT was the most accurate method to measure BVS length, whilst QCA incurred systematic underestimation and solid state IVUS incurred random error. It is important to notice, however, that the IVUS used in this study was non-sheath based solid-state IVUS. The accuracy of IVUS for length measurement would have likely improved, if a sheath-based IVUS system had been employed in the study. There was very poor agreement between QCA, IVUS and OCT for the estimation of in-stent MLA, and no linear relation between any of the methods could

be demonstrated[56]. Important to notice, however, is that in-stent MLA measured by OCT was larger than by IVUS immediately post-stenting. This is at variance with other comparative publications in non-stented vessels where IVUS areas were systematically larger than those measured by OCT, either with occlusive or non-occlusive technique[57-59]. This paradoxical finding can be explained by current methodology used to measure MLA immediately after BVS implant, which includes the area corresponding to the inter-struts spaces[56]. Finally, the agreement between edge-detection and video densitometry methods for MLA measurement can be considered an indirect sign of the preservation of regular luminal geometry, and therefore of structural integrity of the scaffold at the 6th month.

The BVS produces a highly reflective signal outlining struts in OCT. This signal interferes with the measurement of strut thickness, as the boundaries cannot be accurately identified, and with the assessment of coverage, because the neointimal backscattering convolutes that of the polymer, frequently making them indistinguishable from one another. Chapter 11 of this PhD thesis describes how fitting the raw OCT backscattering signal to a Gaussian line spread function facilitates the identification of the interfaces between BVS polymer and lumen or tissue. Such analysis enables more precise measurement of the strut thickness and an objective assessment of coverage[60].

INVESTIGATIONAL AND CLINICAL APPLICATIONS OF OCT

Assessment of coverage as surrogate for completeness of the neointimal healing process

The validation of OCT for the assessment of neointimal coverage had been already performed by previous studies: coverage assessed by means of OCT correlates with histological neointimal healing and endothelialisation after stenting in animal models[42-46]. This evidence is solid and consistent enough to consider the OCT-derived coverage as a valid estimator of the completeness of neointimal coverage in an intracoronary device, although its sensitivity and specificity are below 100% at the single-strut level. OCT cannot detect thin layers of neointima below its axial resolution (10-20 μm, limited sensitivity), and cannot discern between neointima and other material like fibrin or thrombus (limited specificity). This is a limitation shared by most of the diagnostic tools used by clinicians in their daily practice, so it should not be an excuse to neglect the precious contribution of OCT to the knowledge about the neointimal healing process after stent implantation. In fact, the assessment of neointimal coverage after stenting is the most important current application of OCT and the primary endpoint in most OCT trials and studies hitherto[22, 23, 26, 27, 48, 49, 61, 62], under the assumption that the completeness of neointimal coverage might be protective against stent thrombosis. Actually, the extraordinary development of OCT for intracoronary applications is intimately

coupled with the concern about DES thrombosis, and the immediate challenge for OCT experts will be keeping the momentum now, when stent thrombosis is not an issue any more.

This PhD thesis was developed in this specific context, accepting OCT-derived coverage as a valid estimator of neointimal coverage, and focusing the research in generating clinically relevant evidence from this OCT application. The DE NOVO pilot trial assessed the coverage of a paclitaxel-coated balloon used in combination with a BMS, comparing the sequence of application (DCB-first vs. BMS-first), and concluding that the percentage of uncovered struts was similar to those reported in OCT studies for paclitaxel-eluting stents[18]. The RESOLUTE-OCT substudy compared the coverage of two different 2nd-generation DES, the first one coated by a hydrophilic polymer (i.e. biocompatible polymer, favouring optimal healing) vs. another DES coated by a hydrophobic polymer (i.e. haemocompatible polymer, preventing thrombotic events) that could also induce fluoropassivation. No significant difference in coverage was found between both devices, suggesting a comparable safety profile[27]. The LEADERS trial compared the coverage of a 2nd-generation biolimus-eluting stent (BES) with biodegradable polymer in abluminal coating vs. a 1st-generation sirolimus-eluting stent (SES) with durable polymer in conformal coating, sequentially at 9 and 24 months[48, 49]. At the 9th month the BES was significantly better covered than the SES[48], but SES coverage improved subsequently, so at the 24th month there was no significant difference between both devices, that converged at a maximum plateau of 98% covered struts[49]. These results suggest that BES is associated with faster healing than SES. The SECRITT study analysed the coverage of a self-expandable nitinol stent with low chronic outward force, specifically engineered for treatment of thin-cap fibroatheromas[63]. As mentioned above, all these original studies have been pioneer in this kind of research, have generated relevant evidence to orient the clinical applications of these devices and have made key methodological contributions for future studies on this topic.

The assessment of neointimal coverage in the BVS is more challenging than in metallic stents, because the optical impedance of the neointima and the poly-lactide polymer are very similar, and often no clear interface can be identified by the unaided eye using logarithmic signal. Chapter 11 describes an objective method to assess the coverage in the BVS through analysis of the light intensity on raw linear OCT signal[60]. The same methodology, if applied to metallic stents, could improve OCT sensitivity for the detection of coverage[60], similarly to the method described by Templin et al. also using light intensity analysis of raw linear OCT signal to improve OCT specificity[46].

OCT-derived coverage as indicator of the propensity to stent thrombosis?

This OCT-oriented PhD thesis wants to avoid any overoptimistic triumphal message about the capabilities of this technology. Indeed at this very moment the credibility of OCT for the

assessment of coverage might be jeopardised by contradictory results. A recent OCT study has described high proportion of uncovered struts in some cases of very late stent thrombosis[64], but this scenario does not demonstrate that a certain proportion of uncovered struts can predict stent thrombosis prospectively in the mid or the long term. Indeed results from large prospective sufficiently powered studies correlating coverage with stent thrombosis are missing to date. Furthermore, the OCT substudies conducted within large clinical trials have yielded discouraging results: those trials without significant differences in thrombosis found differences in coverage[48, 62], whereas those trials with significant differences in thrombosis did not find any difference in coverage rates[27]. Methodological considerations play for sure a capital role to explain this paradox: at this moment there is no consensus about the methodology of analysis for assessment of coverage, so every core-lab, every research group or every individual investigator follows a different protocol. We must understand that OCT provides a huge amount of information, and it is therefore extremely sensitive to apparently minor methodological details, in the core-lab measurements as well as in the statistical analysis. As far as we do not reach a consensus, the results from different groups cannot be compared or pooled together, so the validity of each study will be limited to its local particular environment, which is at variance with the universal vocation of Science. Long-term results should be also taken into consideration, because the studies with a very long-term assessment of coverage seem to correlate better with clinical thrombotic events[49, 65]. Finally, we should keep in mind the pathophysiology of the events we intend to predict or to prevent. Currently we seem to agree that late stent thrombosis is mainly due to delayed neointimal healing, whereas very late stent thrombosis is mainly due to hypersensitivity reactions or to the development of neoatherosclerosis. According to this pathophysiology, it seems reasonable to accept that the coverage assessed by OCT could predict just the cases of LATE stent thrombosis. Actually, if we consider the lessons learned from all these studies, OCT-derived coverage appears better correlated with the incidence of thrombotic events. The results from LEADERS, revisited under this prism, illustrate very nicely the potential of OCT in relation with the pathophysiology of stent thrombosis: no significant difference in late stent thrombosis rates was found between BES and SES at the 9th month (2.6% vs. 2.2%, p=0.66)[47], although OCT reported then significantly less uncovered struts in BES than in SES (0.6% vs.2.1%, p=0.04); nonetheless this difference in coverage had disappeared at the 24th month (the assessment might have been performed too early). Late coverage is then perfectly correlated with LATE stent thrombosis. In the very long term follow-up, BES polymer has been completely resorbed and therefore cannot trigger hypersensitivity reactions any more, whereas the durable polymer in SES is permanently present and able to act as an allergen. Consistent with this mechanism, the incidence of very late stent thrombosis is higher in SES than in BES at 4 years follow-up[66]. In summary, OCT is a tool potentially able to predict the risk of thrombotic events, but it requires a careful scientific guidance from a deep pathophysiologic knowledge, and this potentiality is still far from having been demonstrated. Oversimplistic approaches and the

lack of universal standards might be discrediting this technology in front of the scientific community.

Bench testing applications and detection of structural anomalies in the device

Chapter 14 makes a review of OCT for bench testing studies on a methodologically challenging topic: bifurcation stenting. OCT can provide accurate and detailed information about many different parameters in bench testing and experimental studies[67]. In close relation with these applications of OCT, we have described above how this technology can identify structural defects in intracoronary devices[54].

THE HEALING PROCESS

Although OCT has limitations for the assessment of neointimal healing after stenting, as previously described, it has also some advantages with respect to histology, the current gold standard. Most importantly, OCT can obtain information in vivo under physiological conditions, which is not possible in histology, in which the specimens must undergo a complex preparation process, potentially altering their characteristics at some extent. OCT can be repeated as many times as required, enabling sequential studies on the very same subjects, and provides a systematic, detailed and thorough information of the whole stented segment, in contrast with histologic studies, that make a single time-point analysis, limited to a few cross-sections. Making the most of these advantages, OCT has provided us with a different insight into the healing process after stenting.

Very late healing phenomenon

The improvement in coverage observed in SES between 9-24 months challenges the currently accepted model for neointimal healing after stenting[49]. Experimental studies suggested that the re-endothelialization process ensuing a vessel injury, e.g. stenting, was limited in time[50-52]. Endothelial denudation of carotid arteries was followed by re-endothelialization that stopped after 2 weeks (in the rabbit) or after 6 weeks (in the rat), even though the endothelial continuity had not been restored[68, 69]. This experimental evidence seemed consistent with the results of sequential angioscopic studies in SES, showing no improvement in the minimum coverage between 6 and 24 months, with increase in the maximum[70], and only slight improvement in the predominant score between 4-11-21 months[71], eventually suggesting an arrested healing process undergoing phenomena of intima maturation or plaque progression. Nevertheless, long-term OCT results questioned this static time-limited model of neointimal healing, suggesting a more dynamic process, still evolving between 9 and 24 months. Previous non-

comparative studies using OCT suggested also this possibility: improvement of SES coverage had been reported between 3-24-48[72-74] months or between 6-12 months[75]. Owed to its high resolution (10-20μm) and ability for detailed analysis, OCT could detect subtle changes in neointimal coverage, unnoticed by angioscopy or other imaging techniques.

Acute malapposition and side-branch struts

Part 8, chapter 12 is dedicated to the coverage of incomplete stent apposition (ISA) and non-apposed side-branch (NASB) struts. Previous descriptive OCT studies had suggested that the neointimal healing of ISA struts might be suboptimal[76]. Original studies in this thesis demonstrate that the coverage of ISA and NASB struts is delayed with respect to well-apposed struts in DES[77, 78]. Interestingly, coverage of ISA struts is delayed with respect to NASB struts in DES[77]. These findings suggest that the detachment of struts from the vessel wall poses higher risk of delayed coverage as compared with correct apposition in DES, but this risk is higher if the detachment is due to malapposition (ISA) than to the presence of a side-branch (NASB). A possible explanation for this differential biologic behaviour might be the fact that ISA were the consequence of a more severely diseased vessel segment, with impaired healing capabilities, more distorted stent geometry and more irregular drug release, as compared with the scenario in NASB struts[77].

These studies demonstrate for the first time that coverage is delayed in acute ISA, irrespective the type of stent (DES or BMS), consistently through different analytical approaches[77, 78]. Furthermore, they describe that the risk for an ISA strut to persist malapposed at follow-up and to be grossly uncovered depends on the ISA size, either estimated as ISA volume or as maximal ISA distance[78]. Indeed 71.5% of the ISA regions are spontaneous- and completely integrated into the vessel wall at follow-up[78]. These results could be interpreted as a rationale for the OCT-guided optimization of acute ISA: most minor ISA regions will be spontaneously corrected without need of any additional intervention, therefore only regions with a maximal ISA distance >280-400 μm might be worth to optimise[78].

Finally, the association between maximal ISA distance and risk of ISA persistence and of strut uncoverage suggests that biomechanical forces, namely shear stress, might be involved in the deficient coverage of ISA struts[78]. Shear stress could be also advocated to explain the differences in neointimal thickening between the adluminal and abluminal sides of ISA struts observed in the BVS[79]. The translucency of the BVS has enabled the description of the healing process in the abluminal side of the strut in vivo for the first time[79].

Overlapping stents

The effect of DES overlap on the neointimal healing process is still poorly understood. Experimental studies on animal models have reported delayed neointimal healing in overlapping

as compared to non-overlapping segments[80], potentially explained by drug overdose or larger amounts of polymer. Conversely, several clinical and angiographic studies have associated DES overlap with greater late loss and binary restenosis[81, 82], most frequently involving the overlap segment[82], thus suggesting that DES overlap elicits rather an exaggerated than an incomplete neointimal reaction. A higher metal-to-artery surface ratio or more severe strut-imposed vessel injury could be advocated to explain a hyperproliferative neointimal reaction in the overlaps[83, 84]. In part 8, chapter 13, the neointimal healing reaction in DES overlapping segments is compared with the corresponding non-overlapping segments of the very same DES, following a careful methodology. On average, overlapping segments are at higher risk of incomplete coverage and are covered by a thinner neointimal layer than the corresponding non-overlapping distal and proximal segments in DES. However the effect observed in overlaps is extremely heterogeneous, what means that in some cases the overlapping segment presents incomplete coverage, whereas in other cases presents a hyperproliferative reaction[28]. These findings permit to understand the apparent discrepancy between histologic, angiographic and clinical studies.

METHODOLOGICAL AND STATISTICAL CHALLENGES

Many of the studies compiled in this thesis have been pioneer on their field, so they have been compelled to build their own methodological approach. This has been a tough but stimulating challenge, finally translated into several original methodological contributions, many of them having become a reference for posterior studies. We have already mentioned the chess tables for friendly intuitive presentation of multimodality comparisons[56], the target-chart, for graphic representation of test-retest agreement[56], the exploratory method for assessment of axial mismatching in DCB studies[18], or the solution proposed for the analysis of extremely skewed clustered variables, like the thickness of coverage[18, 28]. All of them have been original methodological contributions, specifically designed for the corresponding studies.

The problem of clustering

The quantitative analysis of OCT must face a cumbersome methodological problem: the level of measurement (struts) is different from the level of analysis (normally the patient, occasionally the lesion or the stent), or using the statistical language, the units of measurement (struts) are not independent from each other, but strongly interdependent, because they are clustered, what precludes the use of conventional statistical at the strut level. The problem of clustering had been already pointed out in angiographic studies including patients with >1 lesions treated. However, the effect of clustering in these studies (in which one patient could have maximum 2-4 lesions treated) was minimal, and therefore the correction for cluster-

ing was deemed not mandatory[85, 86]. In OCT, however, each stent contributes with 250-500 measurements to the study, so the clustering becomes an issue. The first method proposed to solve statistically the problem of clustering was a Bayesian hierarchical model[48, 49]. Studies in this thesis propose as well multilevel regression[18, 27] or are the first ones to apply statistical pooled analysis in OCT studies[28, 77-79], which is a method the Cardiology community is certainly more familiar with. The statistical accuracy in the analysis of OCT data is not just a baroque ornamental detail: this thesis contains examples of how misleading a wrong analysis can be[18, 28].

Graphic representation of spatial distribution

The graphic representation of the spatial distribution of OCT data can depict the problem of clustering and help to understand it intuitively at first glance (in right-hemispheric cognitive style), without need of abstract statistical reasoning (typical left-hemispheric cognitive style). Previous studies had already presented the spatial distribution of OCT outcomes at the frame level[48]. Studies in this thesis created a more advanced graphic representation of the spatial distribution: the "spread-out vessel chart"[27]. The chart represents the distance from the distal edge of the stent to the strut in the X-axis and the angle where the strut is located in the circular cross section with respect to the centre of gravity of the vessel in the Y-axis, taking as reference 0º the position at three o'clock. The result is a graphic representing the spatial distribution of the OCT outcome (e.g. uncovered struts) along the stent, as if it had been cut along the reference angle (0º) and spread out on a flat surface[27]. The "spread-out vessel charts" and the "spread-out vessel summaries" summarise in one-shot extremely complex analysis and depict the spatial distribution on a simple but detailed fashion. For analytical purposes, the spread-out vessel charts might be preferable to current 3D-rendering techniques, that are appealing tools but with limited analytical capabilities. The spread-out vessel charts have been exploited in several studies in this thesis[18, 27, 49, 54], and they have inspired further developments for graphic representations to other investigators[87].

REFERENCE LIST

1. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty. A study in the normal rabbit and the hypercholesterolemic Yucatan micropig. *Circulation* 1994 June;89(6):2816-21.
2. Mintz GS, Popma JJ, Pichard AD et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996 July 1;94(1):35-43.
3. Mintz GS, Popma JJ, Hong MK et al. Intravascular ultrasound to discern device-specific effects and mechanisms of restenosis. *Am J Cardiol* 1996 August 14;78(3A):18-22.
4. Kastrati A, Mehilli J, Dirschinger J et al. Restenosis after coronary placement of various stent types. *Am J Cardiol* 2001 January 1;87(1):34-9.
5. Garg S, Serruys PW. Coronary Stents: Current Status. *J Am Coll Cardiol* 2010 August 31;56(10, Supplement 1):S1-S42.
6. Morice MC, Serruys PW, Sousa JE et al. A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization. *N Engl J Med* 2002 June 6;346(23):1773-80.
7. Moses JW, Leon MB, Popma JJ et al. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. *N Engl J Med* 2003 October 2;349(14):1315-23.
8. Stone GW, Ellis SG, Cox DA et al. A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease. *N Engl J Med* 2004 January 15;350(3):221-31.
9. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005 June 21;45(12):2088-92.
10. Pfisterer M, Brunner-La Rocca HP, Buser PT et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006 December 19;48(12):2584-91.
11. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006 December;27(23):2784-814.
12. Lagerqvist B, James SK, Stenestrand U et al. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. *N Engl J Med* 2007 March 8;356(10):1009-19.
13. Daemen J, Wenaweser P, Tsuchida K et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *The Lancet* 2007 February 24;369(9562):667-78.
14. Wenaweser P, Daemen J, Zwahlen M et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol* 2008 September 30;52(14):1134-40.
15. Serruys PW, Onuma Y, Garg S et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 2010 March 16;55(11):1093-101.
16. Gutiérrez-Chico JL, Serruys PW. Drug-coated balloons. *Controversies and Consensus in Imaging and Intervention* 2011 August 9;Available at: URL: http://mail.c2i2.org/web11-01/drug-coated-balloons.asp.
17. Gutiérrez-Chico JL, Regar E, van Geuns RJ et al. Moxy(R) drug-coated balloon: a novel device for the treatment of coronary and peripheral vascular disease. *EuroIntervention* 2011 June;7(2):274-7.

18. Gutiérrez-Chico JL, van Geuns RJ, Koch K et al. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomized trial balloon-first vs. stent first. *EuroIntervention* 2011 October 30;7(6):711-22.
19. Scheller B, Hehrlein C, Bocksch W et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006 November 16;355(20):2113-24.
20. Scheller B, Hehrlein C, Bocksch W et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol* 2008 October;97(10):773-81.
21. Unverdorben M, Vallbracht C, Cremers B et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* 2009 June 16;119(23):2986-94.
22. Guagliumi G, Musumeci G, Sirbu V et al. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. *JACC Cardiovasc Interv* 2010 May;3(5):531-9.
23. Guagliumi G, Sirbu V, Musumeci G et al. Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI). *Circ Cardiovasc Interv* 2010 August;3(4):367-75.
24. Hamm CW. Paclitaxel-eluting PTCA-balloon in combination with the Cloroflex Blue stent vs. the sirolimus coated Cypher stent in the treatment of advanced coronary artery disease. Presented at American Heart Association Scientific Sessions 2009; Orlando, FL. 14-11-0009.

    Ref Type: Abstract
25. Fischer D, Scheller B, Schafer A et al. Paclitaxcel-coated balloon plus bare metal stent vs. sirolimus-eluting stent in de novo lesions: an IVUS study. *EuroIntervention* 2012 August;8(4):450-5.
26. Guagliumi G, Sirbu V, Bezerra H et al. Strut coverage and vessel wall response to zotarolimus-eluting and bare-metal stents implanted in patients with ST-segment elevation myocardial infarction: the OCTAMI (Optical Coherence Tomography in Acute Myocardial Infarction) Study. *JACC Cardiovasc Interv* 2010 June;3(6):680-7.
27. Gutierrez-Chico JL, van Geuns RJ, Regar E et al. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J* 2011 June 9;32:2454-63.
28. Gutiérrez-Chico JL, Räber L, Regar E et al. Tissue coverage and neointimal hyperplasia in overlap vs. non-overlap segments of drug-eluting stents 9-13 months after implantation: in vivo-assessment with optical coherence tomography. *Am Heart J* 2011;(e-pub ahead of print).
29. Silber S, Gutiérrez-Chico JL, Behrens S et al. Effect of paclitaxel elution from reservoirs with bioabsorbable polymer compared to a bare metal stent for the elective percutaneous treatment of de novo coronary stenosis: the EUROSTAR-II randomised clinical trial. *EuroIntervention* 2011 May;7(1):64-73.
30. Krucoff MW, Kereiakes DJ, Petersen JL et al. A novel bioresorbable polymer paclitaxel-eluting stent for the treatment of single and multivessel coronary disease: primary results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study. *J Am Coll Cardiol* 2008 April 22;51(16):1543-52.
31. Finkelstein A, McClean D, Kar S et al. Local drug delivery via a coronary stent with programmable release pharmacokinetics. *Circulation* 2003 February 11;107(5):777-84.

32. Serruys PW, Sianos G, Abizaid A et al. The Effect of Variable Dose and Release Kinetics on Neointimal Hyperplasia Using a Novel Paclitaxel-Eluting Stent Platform: The Paclitaxel In-Stent Controlled Elution Study (PISCES). *J Am Coll Cardiol* 2005 July 19;46(2):253-60.
33. Dawkins KD, Verheye S, Schuhlen H et al. The European cobalt STent with Antiproliferative for Restenosis trial (EuroSTAR): 12 month results. *EuroIntervention* 2007 May;3(1):82-8.
34. Ormiston JA, Abizaid A, Spertus J et al. Six-Month Results of the NEVO RES-ELUTION I (NEVO RES-I) Trial: A Randomized, Multicenter Comparison of the NEVO Sirolimus-Eluting Coronary Stent With the TAXUS Liberte Paclitaxel-Eluting Stent in De Novo Native Coronary Artery Lesions. *Circ Cardiovasc Interv* 2010 November 9.
35. Udipi K, Melder RJ, Chen M et al. The next generation Endeavor Resolute Stent: role of the BioLinx Polymer System. *EuroIntervention* 2007 May;3(1):137-9.
36. Udipi K, Chen M, Cheng P et al. Development of a novel biocompatible polymer system for extended drug release in a next-generation drug-eluting stent. *J Biomed Mater Res A* 2008 June 15;85(4):1064-71.
37. Hezi-Yamit A, Sullivan C, Wong J et al. Impact of polymer hydrophilicity on biocompatibility: implication for DES polymer design. *J Biomed Mater Res A* 2009 July;90(1):133-41.
38. Rogers C, Welt FG, Karnovsky MJ, Edelman ER. Monocyte recruitment and neointimal hyperplasia in rabbits. Coupled inhibitory effects of heparin. *Arterioscler Thromb Vasc Biol* 1996 October;16(10):1312-8.
39. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol* 1998 January;31(1):224-30.
40. Guidoin R, Marois Y, Zhang Z et al. The benefits of fluoropassivation of polyester arterial prostheses as observed in a canine model. *ASAIO J* 1994 July;40(3):M870-M879.
41. Xie X, Guidoin R, Nutley M, Zhang Z. Fluoropassivation and gelatin sealing of polyester arterial prostheses to skip preclotting and constrain the chronic inflammatory response. *J Biomed Mater Res B Appl Biomater* 2010 May;93(2):497-509.
42. Suzuki Y, Ikeno F, Koizumi T et al. In vivo comparison between optical coherence tomography and intravascular ultrasound for detecting small degrees of in-stent neointima after stent implantation. *JACC Cardiovasc Interv* 2008 April;1(2):168-73.
43. Deuse T, Erben RG, Ikeno F et al. Introducing the first polymer-free leflunomide eluting stent. *Atherosclerosis* 2008 September;200(1):126-34.
44. Prati F, Zimarino M, Stabile E et al. Does optical coherence tomography identify arterial healing after stenting? An in vivo comparison with histology, in a rabbit carotid model. *Heart* 2008 February 1;94(2):217-21.
45. Murata A, Wallace-Bradley D, Tellez A et al. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. *JACC Cardiovasc Imaging* 2010 January;3(1):76-84.
46. Templin C, Meyer M, Muller MF et al. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J* 2010 July;31(14):1792-801.
47. Windecker S, Serruys PW, Wandel S et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008 September 27;372(9644):1163-73.

48. Barlis P, Regar E, Serruys PW et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J* 2010 January;31(2):165-76.
49. Gutiérrez-Chico JL, Jüni P, García-García HM et al. Long term tissue coverage of a biodegradable polylactide polymer-coated biolimus-eluting stent: comparative sequential assessment with optical coherence tomography until complete resorption of the polymer. *Am Heart J* 2011 November 21;162(5):922-31.
50. Haudenschild CC, Schwartz SM. Endothelial regeneration. II. Restitution of endothelial continuity. *Lab Invest* 1979 November;41(5):407-18.
51. Reidy MA, Schwartz SM. Endothelial regeneration. III. Time course of intimal changes after small defined injury to rat aortic endothelium. *Lab Invest* 1981 April;44(4):301-8.
52. Bjorkerud S, Bondjers G. Arterial repair and atherosclerosis after mechanical injury. 5. Tissue response after induction of a large superficial transverse injury. *Atherosclerosis* 1973 September;18(2):235-55.
53. Serruys PW, Ormiston JA, Onuma Y et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 2009 March 14;373(9667):897-910.
54. Gutierrez-Chico JL, Radu MD, Diletti R et al. Spatial distribution and temporal evolution of scattering centers by optical coherence tomography in the poly(L-lactide) backbone of a bioresorbable vascular scaffold. *Circ J* 2012;76(2):342-50.
55. Oberhauser JP, Hossainy S, Rapoza RJ. Design principles and performance of bioresorbable polymeric vascular scaffolds. *EuroIntervention Supplement* 2009 December;5(Supplement F):F15-F22.
56. Gutierrez-Chico JL, Serruys PW, Girasis C et al. Quantitative multi-modality imaging analysis of a fully bioresorbable stent: a head-to-head comparison between QCA, IVUS and OCT. *Int J Cardiovasc Imaging* 2011 February 26.
57. Gonzalo N, Serruys PW, Garcia-Garcia HM et al. Quantitative ex vivo and in vivo comparison of lumen dimensions measured by optical coherence tomography and intravascular ultrasound in human coronary arteries. *Rev Esp Cardiol* 2009 June;62(6):615-24.
58. Kawase Y, Hoshino K, Yoneyama R et al. In vivo volumetric analysis of coronary stent using optical coherence tomography with a novel balloon occlusion-flushing catheter: a comparison with intravascular ultrasound. *Ultrasound Med Biol* 2005 October;31(10):1343-9.
59. Okamura T, Gonzalo N, Gutierrez-Chico JL et al. Reproducibility of coronary Fourier domain optical coherence tomography: quantitative analysis of in vivo stented coronary arteries using three different software packages. *EuroIntervention* 2010 August;6(3):371-9.
60. Sheehy A, Gutiérrez-Chico J, Oberhauser JP et al. In-vivo characterization of the strut borders in a bioresorbable vascular scaffold at baseline and after neointimal coverage using analysis of the optical coherence tomography intensity spread function. *EuroIntervention* 2011;(under review).
61. Moore P, Barlis P, Spiro J et al. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. *JACC Cardiovasc Interv* 2009 May;2(5):437-44.
62. Guagliumi G, Costa MA, Sirbu V et al. Strut Coverage and Late Malapposition With Paclitaxel-Eluting Stents Compared With Bare Metal Stents in Acute Myocardial Infarction: Optical Coherence Tomography Substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial. *Circulation* 2011 January 25;123(3):274-81.
63. Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL et al. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS

and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). *EuroIntervention* 2012 June 6.

64. Guagliumi G, Sirbu V, Musumeci G et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv* 2012 January;5(1):12-20.
65. Raber L, Baumgartner S, Garcia HM et al. Long-term vascular healing in response to sirolimus- and paclitaxel-eluting stents: an optical coherence tomography study. *JACC Cardiovasc Interv* 2012 September;5(9):946-57.
66. Stefanini GG, Kalesan B, Serruys PW et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011 December 3;378(9807):1940-8.
67. Gutiérrez-Chico JL, van Geuns RJ, Serruys PW, Regar E. Optical coherence tomography in coronary bifurcations. In: Waksman R, Ormiston JA, editors. *Bifurcation stenting*.Chichester: Wiley-Blackwell; 2012. p. 103-20.
68. Reidy MA, Standaert D, Schwartz SM. Inhibition of endothelial cell regrowth. Cessation of aortic endothelial cell replication after balloon catheter denudation. *Arteriosclerosis* 1982 May;2(3):216-20.
69. Reidy MA, Clowes AW, Schwartz SM. Endothelial regeneration. V. Inhibition of endothelial regrowth in arteries of rat and rabbit. *Lab Invest* 1983 November;49(5):569-75.
70. Takano M, Yamamoto M, Xie Y et al. Serial long-term evaluation of neointimal stent coverage and thrombus after sirolimus-eluting stent implantation by use of coronary angioscopy. *Heart* 2007 December;93(12):1533-6.
71. Awata M, Kotani Ji, Uematsu M et al. Serial Angioscopic Evidence of Incomplete Neointimal Coverage After Sirolimus-Eluting Stent Implantation: Comparison With Bare-Metal Stents. *Circulation* 2007 August 21;116(8):910-6.
72. Takano M, Inami S, Jang IK et al. Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. *Am J Cardiol* 2007 April 15;99(8):1033-8.
73. Takano M, Yamamoto M, Inami S et al. Long-Term Follow-Up Evaluation After Sirolimus-Eluting Stent Implantation by Optical Coherence Tomography: Do Uncovered Struts Persist? *Journal of the American College of Cardiology* 2008 March 4;51(9):968-9.
74. Takano M, Yamamoto M, Mizuno M et al. Late vascular responses from 2 to 4 years after implantation of sirolimus-eluting stents: serial observations by intracoronary optical coherence tomography. *Circ Cardiovasc Interv* 2010 October;3(5):476-83.
75. Katoh H, Shite J, Shinke T et al. Delayed neointimalization on sirolimus-eluting stents: 6-month and 12-month follow up by optical coherence tomography. *Circ J* 2009 June;73(6):1033-7.
76. Ozaki Y, Okumura M, Ismail TF et al. The fate of incomplete stent apposition with drug-eluting stents: an optical coherence tomography-based natural history study. *Eur Heart J* 2010 June 1;31(12):1470-6.
77. Gutiérrez-Chico JL, Regar E, Nüesch E et al. Delayed Coverage in Malapposed and Side-Branch Struts With Respect to Well-Apposed Struts in Drug-Eluting Stents. *Circulation* 2011 August 2;124(5):612-23.

78. Gutiérrez-Chico JL, Wykrzykowska JJ, Nüesch E et al. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. *Circ Cardiovasc Interv* 2012 February 1;5(1):20-9.
79. Gutiérrez-Chico JL, Gijsen FJH, Regar E et al. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed and side-branch struts: evidence in vivo about the abluminal healing process. *JACC Cardiovasc Interv* 2012 April 16;5(4):428-35.
80. Finn AVM, Kolodgie FDP, Harnek JM et al. Differential Response of Delayed Healing and Persistent Inflammation at Sites of Overlapping Sirolimus- or Paclitaxel-Eluting Stents. *Circulation* 2005 July 12;112(2):270-8.
81. Kereiakes DJ, Wang H, Popma JJ et al. Periprocedural and Late Consequences of Overlapping Cypher Sirolimus-Eluting Stents: Pooled Analysis of Five Clinical Trials. *J Am Coll Cardiol* 2006 July 4;48(1):21-31.
82. Räber L, Jüni P, Löffel L et al. Impact of Stent Overlap on Angiographic and Long-Term Clinical Outcome in Patients Undergoing Drug-Eluting Stent Implantation. *J Am Coll Cardiol* 2010 March 23;55(12):1178-88.
83. Rogers C, Edelman ER. Endovascular Stent Design Dictates Experimental Restenosis and Thrombosis. *Circulation* 1995 June 15;91(12):2995-3001.
84. Garasic JM, Edelman ER, Squire JC, Seifert P, Williams MS, Rogers C. Stent and Artery Geometry Determine Intimal Thickening Independent of Arterial Injury. *Circulation* 2000 February 22;101(7):812-8.
85. Gibson CM, Kuntz RE, Nobuyoshi M, Rosner B, Baim DS. Lesion-to-lesion independence of restenosis after treatment by conventional angioplasty, stenting, or directional atherectomy. Validation of lesion-based restenosis analysis. *Circulation* 1993 April 1;87(4):1123-9.
86. Kastrati A, Schömig A, Elezi S, Schühlen H, Wilhelm M, Dirschinger J. Interlesion Dependence of the Risk for Restenosis in Patients With Coronary Stent Placement in Multiple Lesions. *Circulation* 1998 June 23;97(24):2396-401.
87. Ha J, Kim BK, Kim JS et al. Assessing Neointimal Coverage After DES Implantation by 3D OCT. *JACC Cardiovasc Imaging* 2012 August;5(8):852-3.

SAMENVATTING, DISCUSSIE EN CONCLUSIES

De medicijn – eluerende stent (DES) leek de belangrijkste tekortkoming van de metalen stent (BMS), namelijk restenose te hebben aangepakt . De stent gedraagt zich als een mechanische weerstand tegen radiale elastische terugslag en de daaropvolgende constrictieve remodelering als het voornaamste mechanisme van restenose na ballon angioplastie[1-3]. Echter, het tweede mechanisme betrokken bij restenose, dwz neointimale hyperplasie, bleef onaangetast of verergerde na BMS implantatie[1-3], resulterende in restenose percentages van 20.0 – 50.3%[4, 5]. DES geven antiproliferatieve medicijnen af om neointimale hyperplasie voorkomen en verminderen de restenose tot 7.9 - 8.9 %[6-8]. Ondanks deze uitstekende resultaten, werd de aanvankelijke optimisme al snel overschaduwd door zorgen over hogere tarieven van de late en zeer late stent trombose, uiteindelijk resulterend in hogere sterftecijfers op de lange termijn[9-15].

Dit proefschrift werd ondernomen in de context van diepe bezorgdheid over het risico van DES trombose, met een ongekende dynamiek van technologische innovatie bedoeld om de biocompatibiliteit van intracoronaire stents te verbeteren door zeer verschillende benaderingen, om hun veiligheidsprofiel te verbeteren. Het was geen kwestie van louter toeval dat de grootste vooruitgang in de ontwikkeling van intracoronaire toepassingen voor optische coherentie tomografie (OCT) samen vielen in de tijd met deze bezorgdheid over stent trombose. Als intracoronaire imaging tool, bracht OCT de theoretische en technische voorwaarden tesamen die het in vivo bestuderen van het neointimale genezingsproces na stenting mogelijk maakte, zelfs in een klinische scenario. Daarmee was het in opkomst als potentiële identificator of voorspeller van gevallen met een hogere kans op trombose. Als gevolg hiervan heeft dit proefschrift bewijs gegenereerd over:

1) de prestaties van technologische innovaties in intravasculaire therapie
2) het potentieel van intracoronaire OCT voor de beoordeling van neointima genezing na stenting en andere onderzoeks- of klinische toepassingen
3) de neointimale genezingsproces zelf.

PRESTATIES VAN DE NIEUW ONTWIKKELDE INTRACORONAIRE THERAPIEËN

Drug-coated balloons

Deel 1, hoofdstukken 1-3 van dit proefschrift beoordeelt de beweegredenen voor het gebruik, de huidige klinische indicaties en de technische kenmerken van medicijn-gecoate ballonnen (DCB), met in detail de rol die elk van hun specifieke componenten speelt [16-18]. De DE NOVO pilot-studie was de eerste-in-de-mens studie van een nieuwe paclitaxel beklede ballon met eigen (niet gespecificeerd) drager (Moxy ®, Lutonix Inc, Maple Grove, MN, USA) en

de eerste gerandomiseerde studie die die werkzaamheid van een DCB met een OCT-afgeleide primaire eindpunt onderzocht, namelijk het percentage neointimale volume obstructie[18]. De resultaten verstrekten aanvullend bewijs voor het biologische effect uitgeoefend door DCB in de modulatie van neointimale hyperplasie. Complementair aan het reeds bestaande klinische en angiografische bewijs[19-21]: de totale in-stent neointima volume obstructie (primair eindpunt) en de gecorrigeerde gemiddelde dikte van dekking per stut (25.1% en 242 µm, respectievelijk) waren vergelijkbaar met die gemeld voor paclitaxel-eluting stents (22,2-25,8%, 200-240µm)[22, 23], en lager dan in sommige DES en ver van die van BMS (53,9%, 530 µm)[22]. Ook het aantal onbedekte stent draden (7%) was gelijk aan het aantal zoals beschreven voor paclitaxel-eluting (5-7%) of sirolimus-eluting stents (8%), en hoger dan BMS (1 %)[22, 23]. Deze studie was de eerste die de combinatie van een DCB plus een niet-voorgemonteerde BMS gebruikte voor de behandeling van de novo coronaire laesies, waaruit haalbaar en werkzaamheid bleek. Niettemin, laat in-stent lumen verlies (0,49 mm) en in-segment restenose (21,7%) waren aanzienlijk hoger dan eerder gerapporteerd voor andere DCB (0.09-0.19mm en 5-7%, respectievelijk), in andere klinische scenarios[19, 21], daarom waren er wat twijfels over de effectiviteit van het combineren van BMS plus DCB voor deze specifieke klinische indicatie. Dit was in overeenstemming met eerdere bevindingen in de PEPCAD-III-studie, waarbij de combinatie van een BMS voorgemonteerd op een DCB niet het non-inferioriteit versus bewijs kon leveren in vergelijking met een sirolimus-eluerende stent voor de behandeling van de novo coronaire lesies[24, 25].

De studie kon niet overtuigend de vraag over de optimale volgorde van de toepassing beantwoorden: DCB-eerst of BMS-eerst. Met uitzondering van een significant betere stent appositie in de sequentie BMS-eerst, werd geen ander significant verschil gevonden in andere parameters[18]. De resultaten over het percentage bloot liggende stent draden en de gemiddelde dikte van de dekking lijken een discrete trend te laten zien in een efficiëntere neointimale remming met de volgorde DCB-eerst, maar de cijfers zijn niet eenduidig[18]. Een mogelijke verklaring voor deze bevinding zou axiale mismatching kunnen zijn, gedefinieerd als het onvermogen van de opgeblazen ballon om in contact te komen met de onderliggende vat rond de 360° van de bloedvat doorsnede. Vooruitlopend op deze omstandigheid, was deze studie de eerste die een verkennend grafische methode gebruikte om de axiale mismatching beoordelen, hoewel er geen duidelijk verband met suboptimale neointimal remming werd gedetecteerd[18]. Een grotere steekproef zou meer overtuigende antwoorden op deze onvoldoende aangepakt vragen hebben verstrekt.

Tot slot wil ik een belangrijke les die we geleerd hebben van deze bescheiden studie aangeven, uiterste relevant vanuit methodologisch oogpunt en echter onvoldoende tot nog toe erkend. De meeste OCT studies (waaronder een aantal studies in dit proefschrift) had eerder de "gemiddelde" dikte van de dekking per strut gemeld en vergeleken [22, 23, 26, 27]. Dit is echter een ongeldig aanpak, omdat de variabele dikte van de dekking een zeer scheve verdeling volgt. De vergelijking of gemiddelde dikte van de dekking kan zijn totaal misleidend, zo mooi

geïllustreerd in het DE NOVO pilot studie: deze studie was de eerste die aandacht heeft besteed aan dit detail, en normalisatie (log transformatie) van de variabele dikte van de dekking voorstelde. Na normalisatie werd de vergelijking van dikte tussen beide groepen volledig omgekeerd ten opzichte van de gecorrigeerde dikte[18]. Navolgende publicaties hebben dit concept verder ontwikkeld[28].

Tweede generatie drug-eluting stents

Reservoirs

Deel 4, hoofdstuk 6 van dit proefschrift beschrijven de resultaten van de Eurostar-II trial. Ze tonen de werkzaamheid van reservoir technologie voor remming van neointima hyperplasie en klinisch relevante preventie van restenose, in directe vergelijking met een identiek BMS platform[29]. Aan de werkzaamheid van reservoir technologie werd getwijfeld nadat de COSTAR-II-studie faalde in het aantonen van non-inferioriteit van hetzelfde reservoir-platform zoals gebruikt in de Eurostar-II versus een eerste-generatie conformal-coating paclitaxel-eluting stent (Taxus Express, Boston Scientific, Maple Grove, MN, USA)[30]. Verder leken in de COSTAR-II studie de prestaties van de CoStar reservoir-DES niet significant verschillend van de "fictieve" (dwz theoretisch opgebouwde) virtuele BMS[30]. EUROSTAR-II lost zeker dit dilemma op, op een hoger niveau van bewijs over de werkzaamheid van reservoirs dan indirecte hypothetische placebo verdachtmakingen. Deze resultaten zijn consistent met voorgaande aanwijzingen over reservoirs DES[31-33] en de latere resultaten van een reservoir DES, getest in de NEVO trial[34]. Hoewel de monstergrootte van de Eurostar-II studie niet groot genoeg was om een harde conclusie over de incidentie van stent trombose te trekken, is het belangrijk om het ontbreken van trombotische gebeurtenissen in de reservoirs DES groep op te merken, wat binnen de hypothese valt dat een bioresorbeerbaar polymeer misschien vertraagde overgevoeligheidsreacties vermijd die zeer laat trombose veroorzaken[29].

Biocompatibele polymeren

Deel 5, hoofdstuk 7 van dit proefschrift vergelijkt de weefsel dekking van twee DES met biocompatibele polymeren, zoals beoordeeld door OCT. De RESOLUTE zotarolimus-eluting stent (Medtronic Inc, Santa Rosa, CA, USA) wordt bedekt door een BioLinx polymeer, een amfifiel molecuul met een topografische oriëntatie van de hydrofiele bestanddelen naar het buitenoppervlak in contact met de weefsels of het bloed[35, 36]. Deze kenmerken verlenen de stent een verbeterd biocompatibiliteits profiel, omdat hydrofiele polymeren minder ontstekingsreacties opwekken[37, 38], en daarmee een snelle, homogene en ongecompliceerde neointimale genezingsproces versoepelen[39]. Omgekeerd is het XIENCE everolimus-eluting

stent (Abbott Vascular, Santa Clara, CA, USA) bekleed met een hydrofobe fluoropolymeer, namelijk poly(vinylidene fluoride-co-hexafluoropropylene). Hydrofobe polymeren zijn minder biocompatibel maar haemocompatibel dan hydrofiele polymeren. Dat betekent dat hydrofobe polymeren meer pro-inflammatoir maar minder pro-thrombogeen zijn dan hydrofiele polymeren. Bovendien, het fluorpolymeer oppervlak lokt een biologische reactie uit, bekend als "fluoropassificatie", die bestaat uit het minimaliseren van de fibrine depositie en trombogeniciteit, waardoor de ontstekingsreactie verminderd en een snellere neointimal genezing versterkt[40, 41]. Of de hierboven genoemde kenmerken van deze twee biocompatibele polymeren omgezet werden in een voordeel in het vasculaire genezingsproces van deze toepassingen was onbekend.

De RESOLUTE-OCT substudy leverde geen significante verschillen in weefsel bedekking op tussen de RESOLUTE zotarolimus-eluting stent en de XIENCE everolimus-eluting stent op de 13e maand na implantatie[27]. Als we de weefseldekking beoordeeld door OCT als geldige schatter accepteren van de mate van neointima heling, zoals vaste gevalideerd in verschillende experimentele studies met histologie zoals gouden-standaard[42-46], kunnen we de resultaten van onze studie interpreteren als gebrek aan bewijs voor significante verschillen in neointima heling tussen beide stents op de 13e maand na implantatie.

Biodegradeerbare polymeer in abluminale coating

De LEADERS (Limus Eluted from A Durable vs. ERodable Stent coating) trial was de eerste gerandomiseerde trial die een OCT deelstudie includeerde voor de evaluatie van de weefsel bedekking in twee verschillende types van DES[47, 48]. Het vergeleek een nieuwe generatie biolimus-eluting stent (BES) met een biologisch afbreekbaar polymelkzuur (PLA) abluminale polymere coating versus een 1e generatie sirolimus-eluerende stent (SES) met een duurzam polymeer in conforme coating. Op 9 maanden werd BES geassocieerd met een significante verlaging van het gehalte van ongedekte stent draden vergeleken met SES (gewogen schatting 0.6 vs. 2.1%, p=0.04)[48]. Deel 6, hoofdstuk 8 van dit proefschrift analyseert de weefsel bedekking op de 24e maand na de implantatie, waardoor zij ook de eerste OCT sequentiële studie is die twee verschillende stentontwerpen vergelijkt[49]. Onverwacht, werd het aanvankelijke voordeel van BES in vergelijking met SES qua weefsel bedekking op 9 maanden[48] gevolgd door verbetering van de dekking SES tussen 9-24 maanden, resulterend in gelijkwaardige bedekking in beide typen stents op de 24e maand. Beide typen stents convergeerden op een maximaal plateau rond de 98% stent draad bedekking. Tezamen bieden deze resultaten de suggestie dat BES inderdaad geassocieerd zijn met een snellere genezing dan SES, het bereiken van een percentage van de dekking in de buurt van de maximale plateau (97%) op 9 maanden, terwijl SES vervolgens een inhaalslag doen.

Voor zover wij weten, was dit de eerste klinische in-vivo studie met sequentieel OCT vervolg die suggereerde dat verschillende stentontwerpen verschillende snelheden in vasculaire

wondgenezing kunnen bevorderen. Dit kan van belang zijn voor het afstemmen van de duur van dubbele anti-bloedplaatjes therapie na stenting. Bovendien betwetwist de verbetering in de weefsel bedekking zoals waargenomen voor de SES tussen 9-24 maanden het momenteel aanvaarde model voor neointima genezing na stenting. Experimentele studies suggereren dat het re-endothelialisatie proces volgend op bloedvat letsesl, bijv. stenting, beperkt was in de tijd[50-52]. Maar onze resultaten suggereren een meer dynamisch proces, dat nog steeds in ontwikkeling is tussen de 9 en 24 maanden na stent plaatsing.

Bioresorbeerbare vasculaire stut

Deel 7, hoofdstukken 9-11 analyseren verschillende aspecten van de Abbott Bioresorbeerbare Vasculaire Stut (BVS). De BVS (Abbott Vascular, Santa Clara, CA, USA) bestaat uit een semi-kristallijne poly-L-lactide (PLLA) basis, bekleed met een dunne amorfe laag van poly-D, L-lactide (PDLLA) met het antiproliferatieve middel everolimus. Beide poly-lactidepolymeren worden geleidelijk afgebroken door hydrolyse, zodat de stut 2 jaar na implantatie volledig is geresorbeerd[53]. Aanhoudende elutie van everolimus is gekoppeld met het PDLLA degradatie. De BVS heeft unieke imaging kenmerken die een specifieke analysemethode mogelijk maakt: het is doorschijnend voor optische straling en totaal radiolucent voor gammastraling, met als enige uitzondering de straling ondoorlatende platina markers aan de randen.

De lichtdoorlatende eigenschappen voor optische straling veranderen echter op enkele punten na implantatie in vivo, zoals waargenomen in een reeks intrigerende beelden die door de onderzoekers "verstrooiingscentra" zijn genoemd. Deze bestaan uit focale hyperintense signalen in de kern van de stut, zonder duidelijk contact met de axiale of transversale strut randen. Hoofdstuk 9 analyseert de ruimtelijke verdeling van deze verstrooiing centra onmiddellijk na de implantatie en bij de 6e maand, door middel van spreid-uit vat grafieken, een instrument voor ruimtelijke weergave van OCT gegevens die ontwikkeld is voor verschillende studies in dit proefschrift. Uit deze analyse blijkt dat de verstrooiing centra alleen verschijnen bij scharnierpunten in de stut structuur en dat ze waren stabiel in de tijd. Deze bevindingen suggereren sterk dat de verstrooiings centra te wijten zijn aan veranderingen in het polymeer tijdens de processen van het aanbrengen van de stut op de ballon en gedurende het ontplooien van de stut in het bloedvat[54].

Hoofdstuk 10 vergelijkt verschillende beeldvormende modaliteiten (kwantitatieve coronaire angiografie met rand-detectie en video densitometrie, intravasculair ultrageluid [IVUS] en OCT) in de BVS onmiddellijk na implantatie en na 6 maanden. Dit tijdstip is de overgang tussen de herstel fase (verlies van structurele integriteit, herstel van vasculaire reactiviteit) en de resorbtiefase (massaverlies) van de strut[55]. De overeenkomst tussen de technieken voor het meting van de stent lengte en minimale lumengebied (MLA) werd onderzocht in een methodologisch uitdagend scenario, omdat alle geanalyseerde stutten precies dezelfde nominale grootte hadden (3x18mm), wat zich verzet tegen de toepassing van conventionele

statistische tests voor de analyse voorwaarden, oorspronkelijk ontworpen om een lineair verband tussen twee verschillende methoden naast een aantal verschillende waarden te testen. Desondanks liet een originele aanpak, het creëren van nieuwe instrumenten voor deze specifieke analyse toe ("doel-kaarten", "schaak tabellen", etc …), om de overeenkomst tussen deze beeldvormende modaliteiten te vergelijken in strikte orthodoxe statistische methodologie[56]. OCT was de meest nauwkeurige methode om BVS lengte te meten, terwijl QCA een systematische onderschatting gaf en solid state IVUS een opgelopen toevallige fout. Het is belangrijk te noteren dat de IVUS in deze studie niet een mantel-gebaseerd solid-state IVUS was. De nauwkeurigheid van IVUS voor lengtemeting zou waarschijnlijk verbeterd zijn geweest, wanneer wel een mantel-gebaseerd IVUS systeem was gebruikt in de studie. Er was een slechte overeenkomst tussen QCA, IVUS en OCT voor de schatting van in-stent MLA, en er kon geen lineair verband tussen een van de methoden worden aangetoond[56]. Belangrijk om op te merken is echter dat de in-stent MLA gemeten met OCT groter was dan met IVUS onmiddellijk na het stutten. Dit is in tegenspraak met andere vergelijkbare publicaties in niet-gestente vaten waar IVUS gebieden systematisch groter waren geschat dan wanneer gemeten met OCT, hetzij met occlusieve of niet-occlusieve techniek[57-59]. Deze paradoxale bevinding kan verklaard worden door de huidige methode die gebruikt wordt om de MLA na BVS implantatie te meten en die het gebied includeert dat correspondeert met de interstrut ruimte[56]. Ten slotte kan de overeenkomst tussen rand-detectie-en video densitometrie methoden voor het MLA meting worden beschouwd als een indirect teken van het behoud van de reguliere luminale geometrie, en dus van de structurele integriteit van de stut in de 6e maand.

De BVS produceert een sterk reflecterende signaal die stut draden definieert in OCT. Dit signaal interfereert met de meting van de stut draad dikte, aangezien de grens niet nauwkeurig kan worden geïdentificeerd, en met de beoordeling van de weefsel bedekking, omdat de intima terugverstrooiing convolueert met die van het polymeer, waardoor ze vaak niet te onderscheiden zijn van elkaar. Hoofdstuk 11 van dit proefschrift beschrijft hoe montage van het ruwe OCT backscattering signaal in een Gaussische lijn spreid functie de identificatie van de de contactlaag tussen de BVS polymeer en lumen of weefsel vergemakkelijkt. Een dergelijke analyse maakt meer nauwkeurige meting van de strut dikte en een objectieve beoordeling van de dekking mogelijk[60].

ONDERZOEK EN KLINISCHE TOEPASSINGEN VAN OCT

Evaluatie van de weefsel bedekking als surrogaat voor de volledigheid van het neointimale genezingsproces

De validatie van OCT voor de beoordeling van neointimale dekking werd al uitgevoerd door eerdere studies: de dekking beoordeeld door middel van OCT correleert met histologische neointimale genezing en endothelialisatie na stenting in diermodellen[42-46]. Dit bewijs is helder en krachtig genoeg om de OCT afgeleide weefsel bedekking als geldige schatter te gebruiken voor de volledigheid van neointima bedekking van een intracoronaire stent of stut, hoewel de gevoeligheid en specificiteit beneden de 100 % ligt op afzonderlijk stent draad niveau. OCT kan dunne lagen van neointima onder de axiale resolutie (10-20µm, beperkte gevoeligheid) niet detecteren, en kan geen onderscheid maken tussen neointima en ander materiaal zoals fibrine of trombus (beperkte specificiteit) . Dit is een beperking die gedeeld wordt door de meeste diagnostische instrumenten gebruikt door artsen in hun dagelijkse praktijk. Derhalve mag het geen excuus zijn om de kostbare bijdrage van OCT aan de kennis over het neointimale genezingsproces na stent implantatie te verwaarlozen. Feitelijk is de beoordeling van nieuwe intima bedekking na stent plaatsing de belangrijkste huidige toepassing van OCT en het primaire eindpunt in de meeste OCT trials en studies tot nu toe[22, 23, 26, 27, 48, 49, 61, 62], in de veronderstelling dat de volledigheid van neointimale dekking beschermend zou zijn tegen stent trombose. Eigenlijk is de buitengewone ontwikkeling van OCT voor intracoronaire toepassingen nauw gekoppeld aan de bezorgdheid over DES trombose, en de directe uitdaging voor OCT experts zal het behouden zijn van het momentum, nu stent trombose geen issue meer is.

Dit proefschrift is ontwikkeld in deze specifieke context, het aanvaarden OCT-afgeleide weefsel bedekking als een geldige schatter van neointimal bedekking, en de nadruk van het onderzoek bij het genereren van klinisch relevante aanwijzingen uit deze OCT toepassing. De DE NOVO pilot trial beoordeelde de weefsel bedekking van een paclitaxel-coated balloon in combinatie met een BMS, het vergelijken van de sequentie van toepassing (DCB-eerst versus BMS-eerst) en concluderen dat het percentage onbedekte stent draden was vergelijkbaar met die in OCT studies voor paclitaxel-eluting stents[18]. De RESOLUTE-OCT substudy vergeleek de weefsel bedekking van twee 2e generatie DES, de eerste bekleed met een hydrofiel polymeer (dwz biocompatibel polymeer ter begunstiging van optimale genezing) tegen een DES bekleed met een hydrofoob polymeer (bv. haemocompatible polymeer ter voorkomen van trombose) die kunnen ook fluoropassivatie induceerde. Er werd geen significant verschil in de weefsel bedekking gevonden tussen beide apparaten wat een vergelijkbaar veiligheidsprofiel suggereert [27]. De LEADERS studie vergeleek de weefseldekking van een 2-generatie biolimus-eluting stent (BES) met biologisch afbreekbaar polymeer in abluminale coating tegen een 1-e generatie sirolimus-eluerende stent (SES) met een duurzame polymeer

in een conforme coating, achtereenvolgens op 9 en 24 maanden[48, 49]. Op de 9e maand was de BES significant beter bedekt dan de SES[48], maar de dekking verbeterde vervolgens in de SES, zodat er na 24 maanden geen significant verschil meer was tussen beide ontwerpen en die convergeerden naar het hoogste plateau van 98% bedekte struts[49]. Deze resultaten suggereren dat BES is gekoppeld snellere genezing dan SES. De SECRITT studie analyseerde de dekking van een zelfexpanderende nitinol stent met lage chronische buitenwaartse kracht, speciaal ontwikkeld voor de behandeling van thin-cap fibroatheromas[63]. Zoals hierboven vermeld, zijn al deze originele studies pioniers geweest in dit soort onderzoek. Ze hebben relevant bewijsmateriaal gegenereerd ter oriëntatie van de klinische toepassingen van deze stents en stutten, en een belangrijke methodologische bijdrage geleverd voor toekomstige studies over dit onderwerp.

De beoordeling van neointima dekking in de BVS is moeilijker dan in metalen stents, omdat de optische impedantie van de neointima en de poly-lactide polymeer zeer vergelijkbaar zijn, en vaak geen duidelijke grenslaag kan worden geïdentificeerd door het blote oog met behulp van logaritmische signaal. Hoofdstuk 11 beschrijft een objectieve methode om de weefsel bedekking te beoordelen in de BVS door analyse van de lichtintensiteit op het niveau van ruwe lineaire OCT signaal[60]. Dezelfde methode, indien toegepast op metalen stents, kan ook hier de OCT gevoeligheid voor de detectie van de weefsel bedekking vergroten[60], vergelijkbaar met de werkwijze beschreven door Templin et al., die ook lichtintensiteit analyse van OCT ruwe lineaire signaal gebruiken om OCT specificiteit verbeteren[46].

OCT-afgeleide dekking als indicator van de neiging tot stent trombose?

Dit OCT-georiënteerde proefschrift wil een al te optimistische triomfantelijke boodschap over de mogelijkheden van deze technologie voorkomen. Inderdaad op dit moment kan de geloofwaardigheid van OCT voor de beoordeling van de weefsel bedekking in gevaar kan komen door tegenstrijdige resultaten. Een recente OCT studie beschreef een hoog aandeel van onbedekte stent draden en stutten in sommige gevallen van zeer late stent trombose[64], maar dit scenario kan niet aantonen dat een bepaald deel van ongedekte stutten stent trombose prospectief zou kunnen voorspellen op de middel-lange of lange termijn. Resultaten uit grote prospectieve studies die weefsel bedekking met stent trombose correleren, ontbreken tot op heden. Bovendien hebben de OCT deelonderzoeken uitgevoerd binnen grote klinische studies ontmoedigende resultaten opgeleverd: trials zonder significante verschillen in trombose vonden wel verschillen in dekking[48, 62], terwijl studies met significante verschillen in trombose geen verschil in weefsel bedekkingsgraad vonden[27]. Methodologische overwegingen spelen zeker een kapitale rol om deze paradox te verklaren: op dit moment is er geen consensus over de methodiek van analyse voor de beoordeling van de dekking, zodat ieder core-lab, elke onderzoeksgroep of elke individuele onderzoeker een ander protocol volgt.

We moeten begrijpen dat OCT een enorme hoeveelheid informatie biedt, en het is daarom uiterst gevoelig voor ogenschijnlijk mindere methodiek, zowel in de core-laboratorium metingen als in de statistische analyse. Zolang wij hierin geen consensus bereiken, kunnen de resultaten van verschillende groepen niet worden vergeleken of samengevoegd, zodat de geldigheid van elk onderzoek zal worden beperkt tot de lokale bijzondere omgeving, die in strijd is met de universele roeping van Wetenschap. Met lange termijn resultaten moet ook rekening worden gehouden, omdat de studies met een zeer lange termijn beoordeling van de weefsel bedekking beter lijken te correleren met klinische trombose.[49, 65]. Tot slot moeten we rekening houden met de pathofysiologie van de evenementen die we van plan zijn om te voorspellen of te voorkomen. Momenteel lijken we het erover eens dat late stent trombose is voornamelijk te wijten is aan een vertraagde neointimale genezing, terwijl zeer late stent trombose is voornamelijk het gevolg van overgevoeligheidsreacties of aan de ontwikkeling van neo-atherosclerose. Volgens deze pathofysiologie, lijkt het redelijk aan te nemen dat de weefsel bedekking beoordeeld door OCT alleen de gevallen van late stent trombose kon voorspellen. Eigenlijk, als we rekening houden met de lessen die uit al deze studies, lijkt OCT-afgeleide weefsel bedekking beter gecorreleerd met de incidentie van trombotische gebeurtenissen. De resultaten van LEADERS, herzien op grond van dit prisma, illustreren zeer mooi het potentieel van OCT in verband met de pathofysiologie van stent trombose: er werd geen significant verschil in de incidentie van late stent trombose gevonden tussen BES en SES op de 9e maand (2.6% vs. 2.2%, p=0.66)[47] ondanks aanmerkelijk minder onbedekte struts in BES dan in SES (0.6% vs.2.1%, p=0.04); desalniettemin was het verschil in weefsel bedekking na 24 maanden verdwenen. Wellicht was het onderzoek (9 maanden) te vroeg uitgevoerd en was 24 maanden een beter tijdstip geweest). Late dekking wordt dan perfect gecorreleerd met LATE stent trombose. In de zeer lange termijn follow-up, is BES polymeer volledig geresorbeerd en kan daarom geen overgevoeligheidsreacties meer teweegbrengen, terwijl het duurzame polymeer in SES permanent aanwezig is en wel kan optreden als een allergeen. Consistent met dit mechanisme was de incidentie van zeer late stent trombose hoger in SES dan in BES op 4 jaar follow-up[66]. Samengevat, OCT is een gereedschap waarmee men mogelijk het risico van trombotische gebeurtenissen kan voorspellen, maar het verlangt een zorgvuldige wetenschappelijke begeleiding en inzicht in de pathofysiologie, en dit potentieel is nog lang niet bewezen. Te simplistische benaderingen en het ontbreken van een universele standaard kan deze technologie in diskrediet brengen voor de wetenschappelijke gemeenschap.

Werkbank toepassingen en de opsporing van structurele afwijkingen in endovasculaire prothesen

Hoofdstuk 14 geeft een overzicht van OCT voor werkbank studies in een methodologisch uitdagend onderwerp: bifurcatie stenting. OCT kan accurate en gedetailleerde informatie

geven over vele verschillende parameters in werkbank testen en experimentele studies[67]. In nauwe relatie met deze toepassingen van OCT, hebben we hierboven beschreven hoe deze technologie structurele defecten in intra-coronaire prothesen kunnen identificeren[54].

HET HELINGSPROCES

Hoewel OCT beperkingen heeft voor de beoordeling van neointimale heling na stenting, zoals eerder beschreven, heeft het ook een aantal voordelen ten opzichte van histologie, de huidige gouden-standaard. Belangrijker nog, kan OCT informatie in vivo vinden onder fysiologische omstandigheden, wat niet mogelijk is in histologie waar het weefsel soms een complexe bereidingswerkwijze moet ondergaan, dat weefsel en prothese eigenschappen in enige mate kan veranderen. OCT kan zo vaak als nodig herhaald worden wat sequentiele studies op hetzelfde onderwerp mogelijk maakt, en daarmee systematische, grondige en gedetailleerde informatie van de gehele stent segment kan geven. Dit in tegenstelling tot histologische studies, dat door een tijdpunt analyse beperkte informatie geeft, meestal van een paar cross-secties. Door gebruik te maken van deze voordelen, heeft OCT ons een ander inzicht gegeven in het helingsproces na stentplaatsing.

Het hele late helings fenomeen

De verbetering van de dekking waargenomen in SES tussen 9-24 maanden daagt het huidige geaccepteerde model voor neointimal heling na stentplaatsing uit[49]. Experimentele studies suggereren dat het re-endothelialisatie proces van bloedvaten na bijv. stenting, beperkt was in de tijd[50-52]. Endotheliale denudatie van halsslagaders gevolgd door her-endothelializatie die leek te stoppen na 2 weken (bij konijnen) of na 6 weken (in de rat), hoewel de endotheliale continuïteit niet was hersteld[68, 69]. Deze experimentele gegevens bleken overeen te komen met de resultaten van sequentiële angioscopie studies in SES, die geen verbetering gaven in het minimum bereik tussen 6 en 24 maanden, met verhoging van de maximum[70], en slechts geringe verbetering van de overheersende score tussen 4-11-21 maanden[71], en suggereren een aangehouden helingsproces met verschijnselen van intima rijping of plaque progressie. De lange termijn OCT resultaten plaatst dit statische tijd-beperkte model van neointimale heling in discussie en duidt op een meer dynamisch proces dat nog steeds in ontwikkeling is tussen de 9 en 24 maanden. Eerdere niet-gepaarde studies met behulp van OCT stelde ook deze mogelijkheid: verbetering van de SES dekking was gemeld tussen 3-24-48 maanden[72-74] of tussen 6-12 maanden[75]. Met dank aan zijn hoge resolutie (10-20µm) en de mogelijkheid voor een gedetailleerde analyse, kon OCT subtiele veranderingen in neointimale weefsel bedekking detecteren, onopgemerkt door angioscopie of andere beeldvormende technieken.

Acute malappositie en zijtak stutten

Deel 8, hoofdstuk 12 is gewijd aan de weefsel bedekking van incomplete stent appositie (ISA) en niet-aanliggende zijtak (NASB) stutten. Vorige beschrijvende OCT studies hadden gesuggereerd dat de neointimale heling van ISA stutten suboptimaal kunnen zijn[76]. Originele studies in dit proefschrift laten zien dat de weefsel bedekking van de ISA en NASB stutten wordt vertraagd met betrekking tot goed-aanliggende stutten in DES[77, 78]. Interessant is dat de dekking van ISA stutten sterker vertraagd is dan in NASB stutten in DES[77]. Deze bevindingen suggereren dat losliggende draden een hoger risico op vertraagde weefsel bedekking geven ten opzichte van juist aanliggende DES, en dat dit risico groter bij malapposition (ISA) dan bij de aanwezigheid van een zijtak (NASB). Een mogelijke verklaring voor dit verschil in biologisch gedrag kan zijn dat ISA het gevolg is van een ernstiger ziek bloedvat segment met meer vertraagde heling, meer vervormd stent geometrie en een onregelmatigere geneesmiddelen afgifte ten opzichte van het scenario bij NASB stutten[77].

Deze onderzoeken demonstreren voor de eerste keer dat weefsel bedekking wordt vertraagd in acute ISA, ongeacht het type stent (DES of BMS), en consistent bij verschillende analytische benaderingen[77, 78]. Bovendien beschrijven zij het risico voor blijvende ISA bij vervolg studies afhangt van de grootte van ISA, ofwel geschat als ISA volume ofwel als maximale ISA afstand[78]. Inderdaad 71.5% van de ISA gebieden zijn spontaan en volledig geïntegreerd in de vaatwand bij vervolg[78]. Deze resultaten kunnen worden geïnterpreteerd als een reden voor de OCT-geleide optimalisatie van acute ISA: de meeste kleine ISA gebieden zullen spontaan worden gecorrigeerd zonder de noodzaak van extra ingrijpen, dus alleen gebieden met een maximale ISA afstand >280-400 μm zijn misschien de moeite waard om te optimaliseren[78].

Tenslotte, de associatie tussen maximale afstand ISA en risico van ISA persistentie en onbedekte struts stelt dat biomechanische krachten, namelijk schuifspanning een rol zou kunnen spelen bij de deficiënte weefsel bedekking van ISA stutten[78]. Afschuifspanning kan ook worden ingeroepen om de verschillen in neointimale verdikking tussen de adluminale en abluminale zijde van ISA stutten zoals waargenomen in de BVS te verklaren[79]. De transparantie van de BVS heeft de beschrijving van het genezingsproces mogelijk gemaakt aan de abluminale zijde van de strut in vivo, voor de eerste keer[79].

Overlappende stents

Het effect van DES overlapping op het neointimale helingsproces is vrij onduidelijk. Experimentele studies in diermodellen vermelden vertraagde neointima genezing in overlappende ten opzichte van niet-overlappende segmenten[80], dat mogelijk verklaard wordt door een overdosis medicijn of grotere hoeveelheden polymeer. Omgekeerd hebben verschillende klinische en angiografische studies DES overlap geassocieerd met een grotere *late loss* en binaire restenose[81, 82], meestal betrekking hebbend op het segment met overlap[82], wat

erop wijst dat DES overlap eerder een overdreven dan een onvolledige neointima reactie opwekt. Een hogere metaal-slagader oppervlakteverhouding of ernstiger vaatletsel kan een hyperproliferatieve neointimale reactie in de overlappende gebieden verklaren[83, 84]. In deel 8, hoofdstuk 13, werd de neointimale helingsreactie van overlappende DES segmenten vergeleken met de overeenkomstige niet-overlappende segmenten van dezelfde DES met een zorgvuldige methode. Gemiddeld overlappende segmenten vertonen een hoger risico opn onvolledige weefsel bedekking en worden bedekt door een dunnere neointimale laag dan de overeenkomstige niet-overlappende distale en proximale segmenten in DES. Het effect in de overlappende gebieden is echter zeer heterogeen, wat betekent dat in sommige gevallen de overlappende segmenten onvolledige bedekt zijn, terwijl in andere gevallen een hyperproliferatieve reactie wordt gezien[28]. Deze bevindingen vergemakkelijken het de schijnbare discrepantie tussen histologische, angiografische en klinische studies te begrijpen.

METHODOLOGISCHE EN STATISTISCHE UITDAGINGEN

Veel van de studies gebundeld in dit proefschrift zijn pionier op hun vakgebied, zodat ze werden gedwongen hun eigen methodologische aanpak te bouwen. Dit is een moeilijke, maar stimulerende uitdaging, uiteindelijk vertaald in verschillende originele methodologische bijdragen, en velen van hen zijn een voorbeeld geworden voor volgende studies. We hebben de schaak tabellen voor de intuïtieve voorstelling van multimodaliteit vergelijkingen[56], het doel-grafieken, voor grafische weergave van test-her-test overeenkomsten[56], de verkennende methode voor de beoordeling van de axiale mismatching in DCB studies[18], of de oplossing voor de analyse van de extreem-scheef geclusterd variabelen, zoals de dikte van de weefsel bedekking[18, 28]. Ieder van hen zijn originele methodologische bijdragen, speciaal ontworpen voor de overeenkomstige studies.

Het probleem van clustering

De kwantitatieve analyse van OCT moet omslachtige methodologische problemen confronteren: het niveau van de meting (stutten) verschilt van het niveau van analyse (gewoonlijk de patiënt, soms de laesie of de stent), of, in statistische taal, de meeteenheden (stutten) zijn niet onafhankelijk van elkaar, maar sterk afhankelijk, omdat ze geclusterd zijn, welke het gebruik van conventionele statistische methoden op stut niveau uitsluiten. Het probleem van clustering was reeds aangeduid in angiografische studies waarin patiënten met > 1 laesies behandeld werden. Het effect van clustering in deze studies (waarin een patiënt een maximum 2-4 behandelde lesies kan hebben) was minimaal en dus werd de correctie voor clustering niet verplicht geacht[85, 86]. In OCT, echter, draagt elke stent 250-500 metingen bij aan het onderzoek, zodat de clustering een probleem wordt. De eerste methode steld voor

om statistisch het probleem van clustering op te lossen met een Bayesiaanse hiërarchisch model[48, 49]. Studies in dit proefschrift stellen eveneens meerlagige regressie voor[18, 27] of zijn de eersten die statistische gepoolde analyse in OCT studies toepassen[28, 77-79], methodes waarmee de Cardiologie gemeenschap meer vertrouwd is. De statistische nauwkeurigheid in de analyse van OCT data is niet alleen een barok sier detail: dit proefschrift bevat voorbeelden van hoe misleidend een verkeerde analyse kan zijn[18, 28].

Grafische weergave van de ruimtelijke verdeling

De grafische weergave van de ruimtelijke verdeling van OCT gegevens kan het probleem van clustering zichtbaar maken en helpt om het intuïtief te begrijpen op het eerste gezicht (typische rechter-hersenhelft cognitieve stijl), zonder de noodzaak van abstracte statistische redeneringen (typische linker-hersenhelft cognitieve stijl). Eerdere studies hadden al de ruimtelijke verdeling van de OCT uitkomst gepresenteerd op het frame-niveau[48]. Studies in dit proefschrift creëerden een meer geavanceerde grafische weergave van de ruimtelijke verdeling: de "uitgespreide bloedvat kaarten"[27]. De grafiek geeft de afstand tussen de distale rand van de stent en de stent draad in de X-as en de hoek waar de stent draad zich bevind in de cirkelvormige dwarsdoorsnede ten opzichte van het zwaartepunt van het bloedvat in de Y-as, waarbij als referentie 0 º de positie om drie uur is genomen. Het resultaat is een grafische weergave van de ruimtelijke verdeling van de OCT uitkomst (bijv. onbedekt stutten) langs de stent, alsof het was gesneden langs de referentie-hoek (0 º) en uitgespreid op een vlakke ondergrond[27]. De "uitgespreide bloedvat kaarten" en de "uitgespreide bloedvat samenvattingen " vatten een uiterst complexe analyse samen en verbeelden de ruimtelijke verdeling op een eenvoudige maar gedetailleerde wijze. Voor analytische doeleinden, zijn de "uitgespreide bloedvat kaarten" te verkiezen boven de huidige 3D-weergave technieken, die aantrekkelijke instrumenten zijn, maar met beperkte analytische mogelijkheden. De "uitgespreide bloedvat kaarten" zijn in verschillende studies in dit proefschrift uitgebuit[18, 27, 49, 54], en hebben andere onderzoekers geïnspireerd voor de verdere ontwikkelingen van grafische voorstellingen [87].

REFERENCE LIST

1. Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty. A study in the normal rabbit and the hypercholesterolemic Yucatan micropig. *Circulation* 1994 June;89(6):2816-21.
2. Mintz GS, Popma JJ, Pichard AD et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996 July 1;94(1):35-43.
3. Mintz GS, Popma JJ, Hong MK et al. Intravascular ultrasound to discern device-specific effects and mechanisms of restenosis. *Am J Cardiol* 1996 August 14;78(3A):18-22.
4. Kastrati A, Mehilli J, Dirschinger J et al. Restenosis after coronary placement of various stent types. *Am J Cardiol* 2001 January 1;87(1):34-9.
5. Garg S, Serruys PW. Coronary Stents: Current Status. *J Am Coll Cardiol* 2010 August 31;56(10, Supplement 1):S1-S42.
6. Morice MC, Serruys PW, Sousa JE et al. A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization. *N Engl J Med* 2002 June 6;346(23):1773-80.
7. Moses JW, Leon MB, Popma JJ et al. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. *N Engl J Med* 2003 October 2;349(14):1315-23.
8. Stone GW, Ellis SG, Cox DA et al. A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease. *N Engl J Med* 2004 January 15;350(3):221-31.
9. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005 June 21;45(12):2088-92.
10. Pfisterer M, Brunner-La Rocca HP, Buser PT et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006 December 19;48(12):2584-91.
11. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006 December;27(23):2784-814.
12. Lagerqvist B, James SK, Stenestrand U et al. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. *N Engl J Med* 2007 March 8;356(10):1009-19.
13. Daemen J, Wenaweser P, Tsuchida K et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *The Lancet* 2007 February 24;369(9562):667-78.
14. Wenaweser P, Daemen J, Zwahlen M et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol* 2008 September 30;52(14):1134-40.
15. Serruys PW, Onuma Y, Garg S et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 2010 March 16;55(11):1093-101.
16. Gutiérrez-Chico JL, Serruys PW. Drug-coated balloons. *Controversies and Consensus in Imaging and Intervention* 2011 August 9;Available at: URL: http://mail.c2i2.org/web11-01/drug-coated-balloons.asp.
17. Gutiérrez-Chico JL, Regar E, van Geuns RJ et al. Moxy(R) drug-coated balloon: a novel device for the treatment of coronary and peripheral vascular disease. *EuroIntervention* 2011 June;7(2):274-7.

18. Gutiérrez-Chico JL, van Geuns RJ, Koch K et al. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomized trial balloon-first vs. stent first. *EuroIntervention* 2011 October 30;7(6):711-22.
19. Scheller B, Hehrlein C, Bocksch W et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006 November 16;355(20):2113-24.
20. Scheller B, Hehrlein C, Bocksch W et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol* 2008 October;97(10):773-81.
21. Unverdorben M, Vallbracht C, Cremers B et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* 2009 June 16;119(23):2986-94.
22. Guagliumi G, Musumeci G, Sirbu V et al. Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. *JACC Cardiovasc Interv* 2010 May;3(5):531-9.
23. Guagliumi G, Sirbu V, Musumeci G et al. Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI). *Circ Cardiovasc Interv* 2010 August;3(4):367-75.
24. Hamm CW. Paclitaxel-eluting PTCA-balloon in combination with the Cloroflex Blue stent vs. the sirolimus coated Cypher stent in the treatment of advanced coronary artery disease. Presented at American Heart Association Scientific Sessions 2009; Orlando, FL. 14-11-0009.

    Ref Type: Abstract
25. Fischer D, Scheller B, Schafer A et al. Paclitaxcel-coated balloon plus bare metal stent vs. sirolimus-eluting stent in de novo lesions: an IVUS study. *EuroIntervention* 2012 August;8(4):450-5.
26. Guagliumi G, Sirbu V, Bezerra H et al. Strut coverage and vessel wall response to zotarolimus-eluting and bare-metal stents implanted in patients with ST-segment elevation myocardial infarction: the OCTAMI (Optical Coherence Tomography in Acute Myocardial Infarction) Study. *JACC Cardiovasc Interv* 2010 June;3(6):680-7.
27. Gutierrez-Chico JL, van Geuns RJ, Regar E et al. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J* 2011 June 9;32:2454-63.
28. Gutiérrez-Chico JL, Räber L, Regar E et al. Tissue coverage and neointimal hyperplasia in overlap vs. non-overlap segments of drug-eluting stents 9-13 months after implantation: in vivo-assessment with optical coherence tomography. *Am Heart J* 2011;(e-pub ahead of print).
29. Silber S, Gutiérrez-Chico JL, Behrens S et al. Effect of paclitaxel elution from reservoirs with bioabsorbable polymer compared to a bare metal stent for the elective percutaneous treatment of de novo coronary stenosis: the EUROSTAR-II randomised clinical trial. *EuroIntervention* 2011 May;7(1):64-73.
30. Krucoff MW, Kereiakes DJ, Petersen JL et al. A novel bioresorbable polymer paclitaxel-eluting stent for the treatment of single and multivessel coronary disease: primary results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study. *J Am Coll Cardiol* 2008 April 22;51(16):1543-52.
31. Finkelstein A, McClean D, Kar S et al. Local drug delivery via a coronary stent with programmable release pharmacokinetics. *Circulation* 2003 February 11;107(5):777-84.

32. Serruys PW, Sianos G, Abizaid A et al. The Effect of Variable Dose and Release Kinetics on Neointimal Hyperplasia Using a Novel Paclitaxel-Eluting Stent Platform: The Paclitaxel In-Stent Controlled Elution Study (PISCES). *J Am Coll Cardiol* 2005 July 19;46(2):253-60.
33. Dawkins KD, Verheye S, Schuhlen H et al. The European cobalt STent with Antiproliferative for Restenosis trial (EuroSTAR): 12 month results. *EuroIntervention* 2007 May;3(1):82-8.
34. Ormiston JA, Abizaid A, Spertus J et al. Six-Month Results of the NEVO RES-ELUTION I (NEVO RES-I) Trial: A Randomized, Multicenter Comparison of the NEVO Sirolimus-Eluting Coronary Stent With the TAXUS Liberte Paclitaxel-Eluting Stent in De Novo Native Coronary Artery Lesions. *Circ Cardiovasc Interv* 2010 November 9.
35. Udipi K, Melder RJ, Chen M et al. The next generation Endeavor Resolute Stent: role of the BioLinx Polymer System. *EuroIntervention* 2007 May;3(1):137-9.
36. Udipi K, Chen M, Cheng P et al. Development of a novel biocompatible polymer system for extended drug release in a next-generation drug-eluting stent. *J Biomed Mater Res A* 2008 June 15;85(4):1064-71.
37. Hezi-Yamit A, Sullivan C, Wong J et al. Impact of polymer hydrophilicity on biocompatibility: implication for DES polymer design. *J Biomed Mater Res A* 2009 July;90(1):133-41.
38. Rogers C, Welt FG, Karnovsky MJ, Edelman ER. Monocyte recruitment and neointimal hyperplasia in rabbits. Coupled inhibitory effects of heparin. *Arterioscler Thromb Vasc Biol* 1996 October;16(10):1312-8.
39. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol* 1998 January;31(1):224-30.
40. Guidoin R, Marois Y, Zhang Z et al. The benefits of fluoropassivation of polyester arterial prostheses as observed in a canine model. *ASAIO J* 1994 July;40(3):M870-M879.
41. Xie X, Guidoin R, Nutley M, Zhang Z. Fluoropassivation and gelatin sealing of polyester arterial prostheses to skip preclotting and constrain the chronic inflammatory response. *J Biomed Mater Res B Appl Biomater* 2010 May;93(2):497-509.
42. Suzuki Y, Ikeno F, Koizumi T et al. In vivo comparison between optical coherence tomography and intravascular ultrasound for detecting small degrees of in-stent neointima after stent implantation. *JACC Cardiovasc Interv* 2008 April;1(2):168-73.
43. Deuse T, Erben RG, Ikeno F et al. Introducing the first polymer-free leflunomide eluting stent. *Atherosclerosis* 2008 September;200(1):126-34.
44. Prati F, Zimarino M, Stabile E et al. Does optical coherence tomography identify arterial healing after stenting? An in vivo comparison with histology, in a rabbit carotid model. *Heart* 2008 February 1;94(2):217-21.
45. Murata A, Wallace-Bradley D, Tellez A et al. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. *JACC Cardiovasc Imaging* 2010 January;3(1):76-84.
46. Templin C, Meyer M, Muller MF et al. Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J* 2010 July;31(14):1792-801.
47. Windecker S, Serruys PW, Wandel S et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008 September 27;372(9644):1163-73.

48. Barlis P, Regar E, Serruys PW et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J* 2010 January;31(2):165-76.
49. Gutiérrez-Chico JL, Jüni P, García-García HM et al. Long term tissue coverage of a biodegradable polylactide polymer-coated biolimus-eluting stent: comparative sequential assessment with optical coherence tomography until complete resorption of the polymer. *Am Heart J* 2011 November 21;162(5):922-31.
50. Haudenschild CC, Schwartz SM. Endothelial regeneration. II. Restitution of endothelial continuity. *Lab Invest* 1979 November;41(5):407-18.
51. Reidy MA, Schwartz SM. Endothelial regeneration. III. Time course of intimal changes after small defined injury to rat aortic endothelium. *Lab Invest* 1981 April;44(4):301-8.
52. Bjorkerud S, Bondjers G. Arterial repair and atherosclerosis after mechanical injury. 5. Tissue response after induction of a large superficial transverse injury. *Atherosclerosis* 1973 September;18(2):235-55.
53. Serruys PW, Ormiston JA, Onuma Y et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 2009 March 14;373(9667):897-910.
54. Gutierrez-Chico JL, Radu MD, Diletti R et al. Spatial distribution and temporal evolution of scattering centers by optical coherence tomography in the poly(L-lactide) backbone of a bioresorbable vascular scaffold. *Circ J* 2012;76(2):342-50.
55. Oberhauser JP, Hossainy S, Rapoza RJ. Design principles and performance of bioresorbable polymeric vascular scaffolds. *EuroIntervention Supplement* 2009 December;5(Supplement F):F15-F22.
56. Gutierrez-Chico JL, Serruys PW, Girasis C et al. Quantitative multi-modality imaging analysis of a fully bioresorbable stent: a head-to-head comparison between QCA, IVUS and OCT. *Int J Cardiovasc Imaging* 2011 February 26.
57. Gonzalo N, Serruys PW, Garcia-Garcia HM et al. Quantitative ex vivo and in vivo comparison of lumen dimensions measured by optical coherence tomography and intravascular ultrasound in human coronary arteries. *Rev Esp Cardiol* 2009 June;62(6):615-24.
58. Kawase Y, Hoshino K, Yoneyama R et al. In vivo volumetric analysis of coronary stent using optical coherence tomography with a novel balloon occlusion-flushing catheter: a comparison with intravascular ultrasound. *Ultrasound Med Biol* 2005 October;31(10):1343-9.
59. Okamura T, Gonzalo N, Gutierrez-Chico JL et al. Reproducibility of coronary Fourier domain optical coherence tomography: quantitative analysis of in vivo stented coronary arteries using three different software packages. *EuroIntervention* 2010 August;6(3):371-9.
60. Sheehy A, Gutiérrez-Chico J, Oberhauser JP et al. In-vivo characterization of the strut borders in a bioresorbable vascular scaffold at baseline and after neointimal coverage using analysis of the optical coherence tomography intensity spread function. *EuroIntervention* 2011;(under review).
61. Moore P, Barlis P, Spiro J et al. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. *JACC Cardiovasc Interv* 2009 May;2(5):437-44.
62. Guagliumi G, Costa MA, Sirbu V et al. Strut Coverage and Late Malapposition With Paclitaxel-Eluting Stents Compared With Bare Metal Stents in Acute Myocardial Infarction: Optical Coherence Tomography Substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial. *Circulation* 2011 January 25;123(3):274-81.
63. Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL et al. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS

and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). *EuroIntervention* 2012 June 6.

64. Guagliumi G, Sirbu V, Musumeci G et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv* 2012 January;5(1):12-20.
65. Raber L, Baumgartner S, Garcia HM et al. Long-term vascular healing in response to sirolimus- and paclitaxel-eluting stents: an optical coherence tomography study. *JACC Cardiovasc Interv* 2012 September;5(9):946-57.
66. Stefanini GG, Kalesan B, Serruys PW et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011 December 3;378(9807):1940-8.
67. Gutiérrez-Chico JL, van Geuns RJ, Serruys PW, Regar E. Optical coherence tomography in coronary bifurcations. In: Waksman R, Ormiston JA, editors. *Bifurcation stenting*.Chichester: Wiley-Blackwell; 2012. p. 103-20.
68. Reidy MA, Standaert D, Schwartz SM. Inhibition of endothelial cell regrowth. Cessation of aortic endothelial cell replication after balloon catheter denudation. *Arteriosclerosis* 1982 May;2(3):216-20.
69. Reidy MA, Clowes AW, Schwartz SM. Endothelial regeneration. V. Inhibition of endothelial regrowth in arteries of rat and rabbit. *Lab Invest* 1983 November;49(5):569-75.
70. Takano M, Yamamoto M, Xie Y et al. Serial long-term evaluation of neointimal stent coverage and thrombus after sirolimus-eluting stent implantation by use of coronary angioscopy. *Heart* 2007 December;93(12):1533-6.
71. Awata M, Kotani Ji, Uematsu M et al. Serial Angioscopic Evidence of Incomplete Neointimal Coverage After Sirolimus-Eluting Stent Implantation: Comparison With Bare-Metal Stents. *Circulation* 2007 August 21;116(8):910-6.
72. Takano M, Inami S, Jang IK et al. Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. *Am J Cardiol* 2007 April 15;99(8):1033-8.
73. Takano M, Yamamoto M, Inami S et al. Long-Term Follow-Up Evaluation After Sirolimus-Eluting Stent Implantation by Optical Coherence Tomography: Do Uncovered Struts Persist? *Journal of the American College of Cardiology* 2008 March 4;51(9):968-9.
74. Takano M, Yamamoto M, Mizuno M et al. Late vascular responses from 2 to 4 years after implantation of sirolimus-eluting stents: serial observations by intracoronary optical coherence tomography. *Circ Cardiovasc Interv* 2010 October;3(5):476-83.
75. Katoh H, Shite J, Shinke T et al. Delayed neointimalization on sirolimus-eluting stents: 6-month and 12-month follow up by optical coherence tomography. *Circ J* 2009 June;73(6):1033-7.
76. Ozaki Y, Okumura M, Ismail TF et al. The fate of incomplete stent apposition with drug-eluting stents: an optical coherence tomography-based natural history study. *Eur Heart J* 2010 June 1;31(12):1470-6.
77. Gutiérrez-Chico JL, Regar E, Nüesch E et al. Delayed Coverage in Malapposed and Side-Branch Struts With Respect to Well-Apposed Struts in Drug-Eluting Stents. *Circulation* 2011 August 2;124(5):612-23.

78. Gutiérrez-Chico JL, Wykrzykowska JJ, Nüesch E et al. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. *Circ Cardiovasc Interv* 2012 February 1;5(1):20-9.
79. Gutiérrez-Chico JL, Gijsen FJH, Regar E et al. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed and side-branch struts: evidence in vivo about the abluminal healing process. *JACC Cardiovasc Interv* 2012 April 16;5(4):428-35.
80. Finn AVM, Kolodgie FDP, Harnek JM et al. Differential Response of Delayed Healing and Persistent Inflammation at Sites of Overlapping Sirolimus- or Paclitaxel-Eluting Stents. *Circulation* 2005 July 12;112(2):270-8.
81. Kereiakes DJ, Wang H, Popma JJ et al. Periprocedural and Late Consequences of Overlapping Cypher Sirolimus-Eluting Stents: Pooled Analysis of Five Clinical Trials. *J Am Coll Cardiol* 2006 July 4;48(1):21-31.
82. Räber L, Jüni P, Löffel L et al. Impact of Stent Overlap on Angiographic and Long-Term Clinical Outcome in Patients Undergoing Drug-Eluting Stent Implantation. *J Am Coll Cardiol* 2010 March 23;55(12):1178-88.
83. Rogers C, Edelman ER. Endovascular Stent Design Dictates Experimental Restenosis and Thrombosis. *Circulation* 1995 June 15;91(12):2995-3001.
84. Garasic JM, Edelman ER, Squire JC, Seifert P, Williams MS, Rogers C. Stent and Artery Geometry Determine Intimal Thickening Independent of Arterial Injury. *Circulation* 2000 February 22;101(7):812-8.
85. Gibson CM, Kuntz RE, Nobuyoshi M, Rosner B, Baim DS. Lesion-to-lesion independence of restenosis after treatment by conventional angioplasty, stenting, or directional atherectomy. Validation of lesion-based restenosis analysis. *Circulation* 1993 April 1;87(4):1123-9.
86. Kastrati A, Schömig A, Elezi S, Schühlen H, Wilhelm M, Dirschinger J. Interlesion Dependence of the Risk for Restenosis in Patients With Coronary Stent Placement in Multiple Lesions. *Circulation* 1998 June 23;97(24):2396-401.
87. Ha J, Kim BK, Kim JS et al. Assessing Neointimal Coverage After DES Implantation by 3D OCT. *JACC Cardiovasc Imaging* 2012 August;5(8):852-3.

"The most dangerous bites are the slanderer's among wild beasts, and the flatterer's among tame ones".

Diogenes of Sinope

Ackowledgements

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To **Chrysafios Girasis**, the master of Quantitative Coronary Angiography. You were the first person in Erasmus Medisch Centrum to accompany me to the room in which I would have my desk for the following years. Thank you for your master lessons in QCA, for your systematic approach to the analysis of bifurcations and for being helpful whenever I needed. I wish you best of luck in the future.

To **Elina Papadopoulou**, expert in non-invasive imaging applied to interventional Cardiology and remarkably good person. I was happy to meet you and your joyful group of friends from the Radiology Department (among them **Alessia Rossi**, important to highlight!) at any occasion. You made my day every time we had lunch or dinner together. Thank you for creating a pleasant corner of human warmth.

To **Vasim Farooq** and to **Bill Gogas**, some of the latest friends I had opportunity to make in Rotterdam before my departure. Let me group you together, since you used to be always working, making breaks and having fun together, on a pretty well coordinated fashion. Our time of overlap in Rotterdam was indeed quite short, but still I think we managed to make a

nice cooperation. I know Vas became a worldwide renowned expert in 3D optical coherence tomography, culminating a project that my good friend Taka started months before, and Bill made relevant achievements in Experimental Cardiology. I am happy for you, because I know your beginning was not easy at all. It is pleasant to meet you in scientific symposia and international congresses. I wish you best of luck in your future.

To **Lorenz Räber**, future international key opinion leader in Interventional Cardiology and amazing master chef of the haut-cuisine. It is not surprising that we connected so much, even though our overlap period in Rotterdam was relatively short. We shared areas of expertise, like optical coherence tomography, stent design and clinical evaluation of intracoronary devices. Moreover, we had incredibly similar intellectual approaches to every problem. It was funny to realise how our peer review evaluations for manuscripts in EuroIntervention or in European Heart Journal were conceptually and structurally so coincident. Actually, notwithstanding the peer review was an anonymous process, we had no problem in recognising each other: "You have reviewed this manuscript, haven't you?"; "Yes, I have. You were also reviewer 2, weren't you?" "Yes, I was". A funny dialog we have repeated many times. Perhaps my rotation in Inselspital Bern has influenced me much more than I thought. Anyway I keep fantastic memories of my time in Bern, so I feel sympathy for anybody coming from there. Lorenz, you have a privileged brain, you are methodical, disciplined, ambitious, goal-oriented, inexhaustible hard worker and you have the best possible mentor in one of the best cardiovascular centres in Europe. I would wish you good luck, but you are already lucky and it is obvious you are making the most of that opportunity. (I am quite jealous, actually!). Thank you for your respect, your Swiss neutrality, your cooperation, your smile, your good mood and your friendship. I will always remember the absolutely gorgeous dinner at your flat, in which you stunned me with a flavour tasting menu that might fit into the most refined restaurant in Paris. Please, keep on surprising me in the future.

To my best friends in Rotterdam, **Apostolos Tzikas, Katerina Paximadis** and **Giovanna Sarno**. Thank you for being my family abroad and for bringing balance, support, cosiness and joy to my life. Apostolos, you have played a key role during my research fellowship in Rotterdam. I started helping you with a small project, but your gratitude gave me much more in return. You have the emotional intelligence I lack and you were my master in diplomatic skills. I owe you my friendship with Peter and a considerable proportion of my international visibility. Thank you for creating me a good reputation wherever you go and for mediating in so many crisis. Katerinula (sorry, but I am the only one allowed to call you so), thank you for lighting the fire at your home so often in our meetings and for keeping the fire of our friendship alive. Thank you for being sometimes the only reasonable person who forced all of us to pay attention to the truly relevant things in life, like our friends, irrespective of our burden of work or our level of pressure. Thank you for your pleasant conversation, for your deep psychological insights and for your emotional support. Very few persons felt so confident with me as to reprove me as you did (you are allowed to, as offset for my Katerinula license).

Last but not least, Giovanna, my closest neighbour in Rotterdam (just across Heemraadssingel!), the nicest fellow ever in Rotterdam, lovely and charming person. It was very frustrating for me to realise how your many talents did not have the chance to shine in Rotterdam, perhaps because aggressive ambition did not like talented ambition. I celebrate you have finally found a place where you got your deserved professional acknowledgement and your personal happiness. We gathered thousands of funny stories together, like when we were having dinner while you were on call and then your beeper announced an acute myocardial infarction. You had only a few minutes to reach the hospital, so I volunteered to accompany you by subway. However only one of our cards was working and we were too short of time as to buy a new one (it was not a straightforward process!), so we passed together through the automatic door, using a single card. The alarm rang then and the security guards in the station saw us, but luckily they ignored the fault. We could go ahead for ages. Congratulations for your success. Please, go on demonstrating that ambition is the motor of progress, but it does not necessarily mean predation. Dear friends, we created a nice group to relax, to discuss, to debate, to enjoy and to have fun. We were probably the proudest "pigs" in the whole European Union, able to find a reasonable solution for each problem coming to discussion in our symposia (because we drank together). We combined perfectly the Mediterranean spirit with the Nordic attitude, finding a charming balance. Please, do not give up: I do not take care of my friends as they deserve, so I use to keep just those friends who never give up. Please, survive this crisis and our rulers without paying them too much attention. Remember they came to discuss whether Greece should be in or out of Europe: they probably ignored that Europe without Greece should rather change its name for something like "Expanded Carolingian Empire", or something definitely less appealing.

To **Cihan Simsek**, brilliant PhD student. Although you were not properly a research fellow then, we worked together shoulder-close-to-shoulder as if you were. Thank you for your kindness, exquisite education and generous smile. I remember when you volunteered to bring back my last poster in Erasmus MC for me to keep it as a souvenir. I track your scientific production and I am glad to say that you are doing quite well. You have a promising near future.

To **Cardialysis BV**, for the chance to access such a huge collection of high quality data. That chance has certainly played a relevant role in allowing me the publication of so many high quality studies in so high impact journals and in so short period of time. My involvement into the core-lab, the statistical department, the clinical trials, the grant applications and so many strategy meetings has provided me with a valuable background that is already paying off. I will carefully stop my public gratitude at this point in order to avoid disclosing too much information entering in conflict with any confidentiality agreement I signed. I would like however to dedicate a more personal message to some remarkable friends:

To **Marie-Angèle Morel**, amazing person, impossible to summarise in a few lines. You are the factotum in the company, indeed. Thank you for the enthusiasm in your eyes, resembling often a child, for your good heart, for your continuous irradiation of positive energy. Thank you for keeping the neutrality your heart dictated you, for mediating in the conflicts, for looking for solutions instead of victories. You used to work so much that we had scarce free time to share, but when we did it, it was a pleasure. I remember the (frustrated) summer cinema, the evenings in Boudewijn, the concerts in De Doelen, the birthdays, the farewells, etc…. You are so good person, that sometimes I feel tempted to advise you not to be so good, but I will not do it: you would lose part of your charm if you changed.

To my friends **Jolanda de Groot**, **Ton de Vries**, **Linda Roest**, **Eliane Lopes dos Santos**, **Jessica Kandt** and many other nice people who joined at some point the so called "Banda del Concierto", using a funny translation into Spanish for "the gang of the concert", in which Google translator might have had something to do. We started meeting every Wednesday for the 30 minutes "Middag concert" in De Doelen, thereby the name. Finally we became very good friends and shared very good moments. Thank you for being absolutely great. I miss you a lot.

To **Pierre Gobbens**, fabulous statistician and great person. Thank you for your patience and for you company while we crossed the hell together.

To **Tessa Rademaker, Eric van Remortel, Marco Bressers** and so many other people in the statistical department. Thank you for your patience and your help. I learned a lot working with you and it was a wonderful experience.

To **Bianca Backx**, one of the two best project managers I have ever known, charming woman and excellent person. Thank you, Bianca, for being warm and for being fair. When the world turned down, you stole time to your family to talk to me, to encourage me to keep on fighting, to bring the smile back to my lips. I appreciate it a lot. The world would be definitely better with more people like you.

To **Monique Schuijers**, the other one of the two best project managers I have ever known. Thank you for your smile, your patience and your help.

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To **Johannes Schaar**, privileged brain and great guy. Thank you for your help when I needed it. Thank you for your particular sense of humour and intelligent irony. I hope to enjoy it in more occasions in the future.

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To the many persons in Cardialysis who helped me and made my work there more pleasant: **Teun Smits, Ana Guimarães, Yvonne van der Lint** (who speaks lovely Spanish!), **Omar,** etc…. You were so many ones that I could not list you all: thank you for smiling in the good and in the bad times, thank you for your humour, your jokes, for making me feel at home.

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To **Richard Rapoza, Jim Oberhauser, Joel Harrington, Mary Beth Kossuth, Thierry Glauser, Alexander Sheehy** and all the team in the Research Department of Abbott Vascular, for the privilege of working together in one of the most fascinating projects for an interventional cardiologist to date: bioresorbable scaffolds, a true breakthrough. The days working with your team in Santa Clara, California, were truly stimulating. Thanks, Jim, for your thoughtful reviews and enlightening insights. Let me dedicate a special mention to Alec, because we made a successful team approach to solve a real problem. Alec, you made the most relevant intellectual contribution to this project, still you were so humble as to let me decide the list of authors we were going to propose. It was a pleasure to cooperate with you and I hope to have more occasions to do it in the future.

To **Frank van Leeuwen, Manuela Negoita** and all the persons from Medtronic Inc. involved in the Resolute-all comers trial. Thank you for helping me to accomplish my tasks in this huge project, cornerstone of the highest impact publications within this thesis.

To **Susanne Meis**, the soul of Biosensors, amazing person and great friend. It was a pleasure to collaborate with you in the LEADERS trial. Thank you for your unusual common sense, for your enthusiasm, for your kindness, for the great time together in Munich and Paris. I hope to accept your invitation to go skiing when our holiday schedules are more convenient. You have become slightly dangerous, since you have proven an extraordinary ability to obtain risky confidences from me, but I do not mind because you are definitely someone I can trust.

To **Dennis Wahr, Jim Pavliska, Scott Naisbitt, Maggie Peterson** and all those persons in Lutonix Inc. involved into the De Novo pilot trial. Thank you for your help and for doing your best to make my life easier. I would be delighted to collaborate with you again, so please, do not hesitate to contact me if you anticipate an occasion to do it, or just to catch up a bit.

To **Jean de Schepper**, true Belgian gentleman, paradigm of politeness and refinement. Thank you for your kind help in the SECRITT trial and in my projects involving nitinol self-expandable stents. It was a pleasure I hope to repeat in future occasions.

To **Gonzague Issenmann** and **René Spaargaren**, the active brains and executive arms in STENTYS. Your visits to Cardialysis were always stimulating, because one had to be truly awaken to follow your rhythm. You are brilliant, energetic, passionate and a perfect paradigm of how the small fish must fight to survive, to find its place and to grow. Thank you for your continuous friendly feedback.

To **Dr Sigmund Silber,** key opinion leader in German and European Cardiology. Thank you for giving me the opportunity to get involved in the EUROSTAR-II trial. Our cooperation agreement was mutually satisfactory and allowed the final publication of relevant results for the technology of drug-eluting stents with reservoirs. Let it be a good beginning for a long story of future collaborations.

To **Dr Carlo di Mario** and **Dr Stefan Windecker**, two of the most relevant names for the Interventional Cariology in Europe. It has been a true privilege working shoulder-to-shoulder with you in so many clinical trials and feeling you interest and your continuous support.

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To the many persons I have unintentionally forgotten in this list. Please, accept my apologies and do not feel disappointed. At some point I had to close the enrolment phase of these acknowledgements even though I am hundred per cent sure many people who deserved a mention remained out. Thank you for leaving your trace in my life, for being nice to me in that period of "just landed" in the Netherlands, when I felt so vulnerable.

To the many persons I have intentionally forgotten in this list. Thank you for being a permanent stimulus to move forward. Comfort, resignation and the eager to enjoy an uncomplicated happiness are the main hindrances for many people to fully develop their capabilities and to reach the level of competence in which they can be more proficient and happier. I must admit that suffering iniquity has been one of the most powerful incentives for me to keep on permanently investing in my future. For the sake of pragmatism let me remind you about Newton's third law, also known as action-reaction: the more you pull me down, the higher I will fly.

Finally, I want to dedicate my last acknowledgement to a very special person whose participation was crucial for the consecution of the main projects in this PhD thesis: **Dick Goedhart**. Indeed without Dick's help this PhD thesis would have been totally thwarted. We had reached a critical point, in which no progress seemed possible, due to one of those entangled bureaucratic nightmares that I would rather not to explain. The pressure on me was increasing, my time was running out and most of the projects I had started were at jeopardy. In such a competitive environment as Interventional Cardiology is, I could expect no mercy from my colleagues if I ended up in Rotterdam with just minor scientific publications, so resignation was not an option: if my projects failed, I would have to consider seriously resuming my musical career. It was time to take an audacious decision, so I asked you, Dick, for your help. You volunteered to make a break in your happy retirement and to work with me for a whole day until we found the way to analyse clustered OCT data in trials. The Resolute-all

comers was the first OCT trial in which we applied our method (your method actually). After that, we did it in De Novo and in many others. We succeeded to do it with the handicap of not breaking the confidentiality agreements (no question!), what compelled us to follow funny working protocols. We still worked together a couple of times, but then I learned to do it on my own: my production was unblocked and speeding up. Thank you, Dick, for saving my thesis, my projects, my grant and my professional future. You will not find your name among my co-authors, although you fully deserved it. I only could offer you a mention in the acknowledgements. Let this last acknowledgement amend that grievance by highlighting your true merit and expressing you my most sincere and indebted gratitude.

Juan Luis Gutiérrez-Chico.

Munich, 17th of February 2013

"Egotist is a person of low taste: more interested in himself than in me".

The Devil's Dictionary

Ambrose G. Bierce

Curriculum vitae

CURRICULUM VITAE

Personal details

Name:	Juan Luis Gutiérrez-Chico
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Academic degrees:

- MD, Graduated in Medicine and Surgery.
  - Valladolid University, ES 1996.
- ECFMG certificate.
  - Educational Comission for Foreign Medical Graduates, USA 1998
- Specialist in Cardiology.
  - Fundación Jiménez Díaz, Madrid ES 2003
- Accreditation in Interventional Cardiology.
  - Spanish Society of Cardiology, Madrid ES 2007
- PhD-degree
  - Complutense University, Madrid ES 2008.
  - Directors: José Luis Zamorano, Carlos Macaya
  - Thesis: Usefulness of real-time three-dimensional transthoracic echocardiography in the segmental analysis of mitral prolapse.
  - Qualification: Excellent "cum laude", unanimity.
- Statistics and Research Methodology
  - Diploma; Autonomous University of Barcelona, ES 2007
  - Master; Autonomous University of Barcelona, ES 2009
- International and Research Fellowships:
  - Universitäts-Klinikum Friedrich-Alexander, Erlangen, D 1994
    - Clerkship grant
  - Benjamin-Franklin Krankenhaus (Klinikum Steglitz), Berlin, D 1995
    - Elective grant
  - Schweizer Herz- und Gefäßzentrum, Kardiovaskuläre Prävention und Rehabilitation, Inselspital, Bern, CH 2002-2003

    - Rotation (Gastarzt)
  - Hospital Clínico San Carlos, Cardiovascular Imaging Department, Madrid ES 2003-2005
    - Research Fellowship
  - Erasmus Medisch Centrum – Thoraxcentrum, Interventional Cardiology Dpt., Rotterdam, NL 2009-2011
    - Research Fellowship
- Awards:
  - "Fundación San Nicolás" award, Spanish Royal Academy of Medicine, Madrid 1999.
  - 3rd award to the Best Scientific Communication, ("*Szabo technique versus conventional angiographic placement in bifurcations 010-001 and aorto-ostial lesions: safety and procedural results".* **Gutiérrez-Chico JL**, Villanueva-Benito I, Vázquez-Fernández S, Kleinecke C, Gielen S, Íñiguez-Romo A). EuroPCR, Barcelona, May 2009.

Current position

Interventional Cardiologist and Senior Researcher in Interventional Cardiology Department, Hospital of the Friedrich-Schiller University, Jena (Thüringen), DE, since December 2013.

Previous appointments

- Burgos Military Hospital, Burgos ES, 1997-1998.
  - Military Doctor of the Spanish Army.
- Fundación Jiménez Díaz, Madrid ES, 1998-2003.
  - Resident in Cardiology
- Hospital Clínico San Carlos, Madrid ES, 2003- 2004.
  - Research Fellow, Cardiovascular Imaging Department
- Hospital de la Princesa, Madrid ES, 2004 – 2005.
  - Consultant in Acute Cardiac Care Unit and Echocardiography
- Fuenlabrada Hospital, Madrid ES 2005.
  - Consultant in Cardiology
- Vigo University Hospital 2005-2013.
  - Interventional Cardiologist
- Hospital of the Ludwig-Maximilian University, Munich, DE, 2013
  - Interventional Cardiologist and senior researcher.

Academic experience

- Nursing School, Autonomous University of Madrid ES, 2001-2005.

- Research Methodology (Assistant lecturer)
- Human Physiology (College lecturer)

- Complutense University, Madrid ES.
  - PhD course: "Advanced Cardiac Imaging"; Cardiology Department, Prof. José Luis Zamorano, 2004
    - Teacher.
- International Master or Cardiac Imaging, Prof. José Luis Zamorano, Since 2011.
    - Associated professor, invasive cardiac imaging.

Membership of Scientific societies:

- Member of the Spanish Society of Cardiology
- Fellow of the European Society of Cardiology (2005).
- Member of the European Association for Percutaneous Coronary Interventions (EAPCI)
- Member of the Working group in e-Cardiology.
- Fellow of the American College of Cardiology (2011).
- Complimentary membership in the American Society of Echocardiography (2012)

Editorial activity

- Member of the International Editorial Board EuroIntervention Journal (2011)
- Peer expert reviewer:
  - Nature Medicine
  - Circulation
  - J Am Coll Cardiol
  - Am Heart J
  - Am J Cardiol
  - Eur Heart J
  - Int J Cardiol
  - Int J Cardiovasc Imaging
  - Eurointervention
  - J Am Soc Echocardiography
  - Material Science and Engineering

Granted Research Projects as Principal Investigator:

- Study of pacemaker-induced mitral regurgitation with 3D echocardiography. Grant from the Spanish Society of Cardiology, October 2003.

- Program for consolidation of the Southern Galician Cardiovascular Research Network. (INCITE08ENA9105078ES). Galician Regional Government, Office for Research and Industry, Spain, 2008-2011.
- Combination of Fourier-domain optical coherence tomography and intracoronary biomechanics for the detection of the vulnerable plaque (BA09/90044), Carlos III Health Institute, Spain, 2008-2011.
- Heating of a novel intracoronary stent by electromagnetic induction for restenosis modulation (TRA2009_0007), Spanish Office for Science and Research, 2009-2010.

Languages:

- Spanish: Mother language
- English: Fluent and correct.
- German: Fluent and correct.
- Italian: Fluent and correct.
- French: Fluent and correct.
- Galician: Fluent.
- Dutch: Fluent comprehension, basic expression.

"I libri non sono fatti per crederci, ma per essere sottoposti a indagine. Di fronte a un libro non dobbiamo chiederci cosa dica ma cosa vuole dire".

(Books are not intended to be believed, but to be submitted to investigation. In front of a book, we must not wonder about what it says, but rather about what it wanted to say)

Il nome della rosa

Umberto Eco

List of publications

LIST OF SCIENTIFIC PUBLICATIONS

PhD-thesis:

- **Gutiérrez Chico JL,** Zamorano JL, Macaya C. *"Utilidad de la ecocardiografía tridimensional en tiempo real transtorácica para el análisis segmentario en el prolapso mitral"*, Universidad Complutense de Madrid, Madrid 2008. ISBN: 978-84-692-1074-1

Book chapters:

- **Gutiérrez Chico JL.** El eco en el paciente con arritmias. In: García Fernández MA, Zamorano Gómez JL, García Robles JA. Manual de Ecocardiografía. Madrid; 2005. ISBN:84-688-9698-5
- **Gutiérrez-Chico JL**, Marcos-Alberca P, Zamorano JL. Echocardiography of mitral regurgitation. In: Haase J, Schäfers HJ, Sievert H, Waksman R. Cardiovascular Interventions in Clinical Practice. 2010; Blackwell Publishing Ltd, Chichester, UK. ISBN 9781405182775.
- **Gutiérrez-Chico JL**. Methodology of search. Booklet: Costa M, Regar E, Serruys P. In: Clinical Research Compendium: A summary of Cardiovascular Optical Coherence Tomography Literature. Westford, MA: Lightlab Imaging Inc, 2009.
- **Gutiérrez-Chico JL**, van Geuns RJ, Serruys PW, Regar E. Optical coherence tomography in coronary bifurcations, book chapter 12. In: Waksman R, Ormiston JA. Bifurcation stenting. Chichester UK: Wiley-Blackwell Publishing; 2012. ISBN 9781444334623.

Original peer-reviewed articles:

1. Polo SJ, **Gutiérrez-Chico JL**, Sabillón O, Diaz Curiel M. Cardiac tamponade as initial manifestation of late onset systemic lupus erythematosus. *An Med Interna* 2003;20:329-330.
2. **Gutiérrez-Chico JL**, Zamorano JL, Perez d, I, Orejas M, Almería C, Rodrigo JL, Ferreiros J, Serra V, Macaya C. Comparison of left ventricular volumes and ejection fractions measured by three-dimensional echocardiography versus by two-dimensional echocardiography and cardiac magnetic resonance in patients with various cardiomyopathies. *Am J Cardiol* 2005;95:809-813.
3. Caiani EG, Corsi C, Zamorano J, Sugeng L, MacEneaney P, Weinert L, Battani R, **Gutiérrez-Chico JL**, Koch R, Pérez de Isla L, Mor-Avi V, Lang RM. Improved semiautomated quantification of left ventricular volumes and ejection fraction using 3-dimensional echocardiography with a full matrix-array transducer: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr* 2005;18:779-788.
4. **Gutiérrez-Chico JL**, Zamorano JL, Prieto-Moriche E, Hernández-Antolín RA, Bravo-Amaro M, Pérez de Isla L, Sanmartín-Fernández M, Baz-Alonso JA, Íñiguez-Romo A. Real-time

three-dimensional echocardiography in aortic stenosis: a novel, simple, and reliable method to improve accuracy in area calculation. *Eur Heart J* 2008;29:1296-1306.

5. **Gutiérrez-Chico JL**, Zamorano Gómez JL, Rodrigo-López JL, Mataix L, Pérez de Isla L, Almería-Valera C, Aubele A, Macaya-Miguel C. Accuracy of real-time 3-dimensional echocardiography in the assessment of mitral prolapse. Is transesophageal echocardiography still mandatory? *Am Heart J* 2008;155:694-698.
6. Zamorano J, Rodríguez PL, Cosín J, Hernandiz A, **Gutiérrez-Chico JL**, Pérez de Isla L, Aristegui R, Masramón X. Amlodipine reduces predicted risk of coronary heart disease in high-risk patients with hypertension in Spain (The CORONARIA Study). *J Int Med Res* 2008;36:1399-1417.
7. Tzikas A, Piazza N, van Dalen BM, Schultz C, Geleijnse ML, van Geuns RJ, Galema TW, Nuis RJ, Otten A, **Gutiérrez-Chico JL**, Serruys PW, de Jaegere PP. Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010;75:43-49.
8. **Gutiérrez-Chico JL**, Villanueva-Benito I, Villanueva-Montoto L, Vázquez-Fernández S, Kleinecke C, Gielen S, Íñiguez-Romo A. Szabo technique versus conventional angiographic placement in bifurcations 010-001 of Medina and in aorto-ostial stenting: angiographic and procedural results. *EuroIntervention* 2010;5:801-808.
9. Wykrzykowska JJ, **Gutiérrez-Chico JL**, van Geuns RJ. "Over-and-under" pericardial covered stent with paclitaxel balloon in a saphenous vein graft. *Catheter Cardiovasc Interv* 2010;75:964-966.
10. Okamura T, Garg S, **Gutiérrez-Chico JL**, Shin ES, Onuma Y, García-García HM, Rapoza RJ, Sudhir K, Regar E, Serruys PW. In vivo evaluation of stent strut distribution patterns in the bioabsorbable everolimus-eluting device: an OCT ad hoc analysis of the revision 1.0 and revision 1.1 stent design in the ABSORB clinical trial. *EuroIntervention* 2010;5:932-938.
11. Okamura T, Gonzalo N, **Gutiérrez-Chico JL**, Serruys PW, Bruining N, de WS, Dijkstra J, Commissaris KH, van Geuns RJ, van SG, Ligthart J, Regar E. Reproducibility of coronary Fourier domain optical coherence tomography: quantitative analysis of in vivo stented coronary arteries using three different software packages. *EuroIntervention* 2010;6:371-379.
12. Sarno G, Garg S, Onuma Y, **Gutiérrez-Chico JL**, van den Brand MJ, Rensing BJ, Morel MA, Serruys PW. Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). *Am J Cardiol* 2010;106:1369-1375.
13. Tzikas A, van Dalen BM, Van Mieghem NM, **Gutiérrez-Chico JL**, Nuis RJ, Kauer F, Schultz C, Serruys PW, de Jaegere PP, Geleijnse ML. Frequency of conduction abnormalities after transcatheter aortic valve implantation with the Medtronic-CoreValve and the effect on left ventricular ejection fraction. *Am J Cardiol* 2011;107:285-289.

14. Kirschbaum SW, Springeling T, Rossi A, Duckers E, **Gutiérrez-Chico JL**, Regar E, de Feyter PJ, van Geuns RJ. Comparison of adenosine magnetic resonance perfusion imaging with invasive coronary flow reserve and fractional flow reserve in patients with suspected coronary artery disease. *Int J Cardiol* 2011;147:184-186.
15. **Gutiérrez-Chico JL**, Serruys PW, Girasis C, Garg S, Onuma Y, Brugaletta S, García-García HM, van Es GA, Regar E. Quantitative multi-modality imaging analysis of a fully bioresorbable stent: a head-to-head comparison between QCA, IVUS and OCT. *Int J Cardiovasc Imaging* 2012; 28:467-78.
16. Garg S, Sarno G, **Gutiérrez-Chico JL**, García-García HM, Gómez-Lara J, Serruys PW. Five-year outcomes of percutaneous coronary intervention compared to bypass surgery in patients with multivessel disease involving the proximal left anterior descending artery: an ARTS-II sub-study. *EuroIntervention* 2011;6:1060-1067.
17. Silber S, **Gutiérrez-Chico JL**, Behrens S, Witzenbichler B, Wiemer M, Hoffmann S, Slagboom T, Harald D, Suryapranata H, Nienaber C, Chevalier B, Serruys PW. Effect of paclitaxel elution from reservoirs with bioabsorbable polymer compared to a bare metal stent for the elective percutaneous treatment of de novo coronary stenosis: the EUROSTAR-II randomised clinical trial. *EuroIntervention* 2011;7:64-73.
18. **Gutiérrez-Chico JL**, Regar E, van Geuns RJ, Garg S, Schultz C, van Mieghem N, Duckers H, Serruys PW. Moxy® drug-coated balloon: a novel device for the treatment of coronary and peripheral vascular disease. *EuroIntervention* 2011;7:274-277.
19. **Gutiérrez-Chico JL**, van Geuns RJ, Regar E, van der Giessen WJ, Kelbæk H, Saunamäki K, Escaned J, Gonzalo N, di MC, Borgia F, Nuesch E, García-García HM, Silber S, Windecker S, Serruys PW. Tissue coverage of a hydrophilic polymer-coated zotarolimus-eluting stent vs. a fluoropolymer-coated everolimus-eluting stent at 13-month follow-up: an optical coherence tomography substudy from the RESOLUTE All Comers trial. *Eur Heart J* 2011;32:2454-2463.
20. **Gutiérrez-Chico JL**, Regar E, Nüesch E, Okamura T, Wykrzykowska J, di Mario C, Windecker S, van Es GA, Gobbens P, Jüni P, Serruys PW. Delayed coverage in malapposed and side-branch struts with respect to well-apposed struts in drug-eluting stents: in vivo assessment with optical coherence tomography. *Circulation* 2011;124:612-623.
21. **Gutiérrez-Chico JL**, García-García HM, Ligthart J, Bol-Raap G, Garg S, Bekkers JA, Serruys PW. How should I treat impaired systolic function and clinical deterioration after surgery of type A aortic dissection? *EuroIntervention* 2011;7:638-646.
22. **Gutiérrez-Chico JL**, van Geuns RJ, Koch KT, Koolen JJ, Duckers H, Regar E, Serruys PW. Paclitaxel-coated balloon in combination with bare metal stent for treatment of de novo coronary lesions: an optical coherence tomography first-in-human randomised trial, balloon first vs. stent first. *EuroIntervention* 2011;7:711-722.
23. **Gutiérrez-Chico JL**, Jüni P, García-García HM, Regar E, Nüesch E, Borgia F, van der Giessen WJ, Davies S, van Geuns RJ, Secco GG, Meis S, Windecker S, Serruys PW, di Mario C. Long-

term tissue coverage of a biodegradable polylactide polymer-coated biolimus-eluting stent: comparative sequential assessment with optical coherence tomography until complete resorption of the polymer. *Am Heart J* 2011;162:922-931.

24. **Gutiérrez-Chico JL**, Radu MD, Diletti R, Sheehy A, Kossuth MB, Oberhauser JP, Glauser T, Harrington J, Rapoza RJ, Onuma Y, Serruys PW. Spatial distribution and temporal evolution of scattering centers by optical coherence tomography in the poly(L-lactide) backbone of a bioresorbable vascular scaffold. *Circ J* 2012;76:342-350.
25. Sheehy A, **Gutiérrez-Chico JL**, Diletti R, Oberhauser JP, Glauser T, Harrington J, Kossuth MB, Rapoza RJ, Onuma Y, Serruys PW. In vivo characterisation of bioresorbable vascular scaffold strut interfaces using optical coherence tomography with Gaussian line spread function analysis. *EuroIntervention* 2012;7:1227-1235.
26. **Gutiérrez-Chico JL**, Wykrzykowska J, Nüesch E, van Geuns RJ, Koch KT, Koolen JJ, di Mario C, Windecker S, van Es GA, Gobbens P, Jüni P, Regar E, Serruys PW. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. *Circ Cardiovasc Interv* 2012;5:20-28.
27. **Gutiérrez-Chico JL**, Alegría-Barrero E, Teijeiro-Mestre R, Chan PH, Tsujioka H, de Silva R, Viceconte N, Lindsay A, Patterson T, Foin N, Akasaka T, di Mario C. Optical coherence tomography: from research to practice. *Eur Heart J Cardiovasc Imaging* 2012;13:370-84.
28. Magro M, Regar E, **Gutiérrez-Chico JL**, García-García HM, Simsek C, Schultz C, Zijlstra F, Serruys PW, van Geuns RJ. Residual atherothrombotic material after stenting in acute myocardial infarction - An optical coherence tomographic evaluation. *Int J Cardiol* 2013;*167:656-63*.
29. **Gutiérrez-Chico JL**, Gijsen F, Regar E, Wentzel J, Thuesen L, McClean D, Windecker S, Dudek D, Whitbourn R, Brugaletta S, Ormiston J, Serruys PW. Differences in neointimal thickness between the adluminal and the abluminal sides of malapposed struts in a bioresorbable vascular scaffold at 6 months follow-up: evidence about the abluminal healing process. *JACC Cardiovasc Interv* 2012;5:428-35.
30. **Gutiérrez-Chico JL**, Räber L, Regar E, Okamura T, Wykrzykowska J, di Mario C, Windecker S, van Es GA, Gobbens P, Serruys PW. Tissue coverage and neointimal hyperplasia of overlap vs. non-overlap segments in drug-eluting stents 9-13 months after implantation: in vivo-assessment with optical coherence tomography. *Am Heart J* 2013*;166:83-94*.
31. Wykrzykowska JJ, Diletti R, **Gutiérrez-Chico** JL, van Geuns RJ, van der Giessen WJ, Ramcharitar S, Duckers HE, Schultz C, de Feyter P, van der Ent M, Regar E, de Jaegere P, Garcia-Garcia HM, Pawar R, Gonzalo N, Ligthart J, de Schepper J, van den Berg N, Milewski K, Granada JF, Serruys PW. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). *EuroIntervention* 2012;8:945-54.

32. **Gutiérrez-Chico** JL, Jochheim D, Mehilli J. Biodegradable-polymer-based drug-eluting stent for left main coronary artery disease. *Minerva Cardioangiol* 2013;61:563-574.
33. **Gutiérrez-Chico** JL, Mehilli J. Gender differences in cardiovascular therapy: Focus on antithrombotic therapy and percutaneous coronary intervention. *Drugs* 2013; (e-pub ahead of print).

Non peer-reviewed / non-indexed articles:

- Alonso Martín JJ, Serrano Antolín JM, **Gutiérrez Chico JL**, Melgares Delgado L, Talavera Calle P, Curcio Ruigómez A. Estrategia invasiva contemporánea en los pacientes con síndrome coronario agudo sin elevación del segmento ST. Rev Esp Cardiol 2005;5 (Supl C):26-39.
- **Gutiérrez Chico JL**, Íñiguez Romo A, Baz Alonso JA, Sanmartín M, Hervert F, Claro R, González González J. Situación actual del Intervencionismo coronario percutáneo en el síndrome coronario agudo. MONOCARDIO. Revista de la Sociedad Castellana de Cardiología (2006).
- **Gutiérrez-Chico JL,** Serruys PW. Drug-coated balloons. Controversies and Consensus in Imaging and Interventions 2011, e-journal: http://mail.c2i2.org/web11-01/drug-coated-balloons.asp