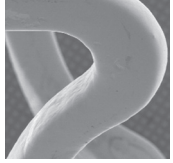
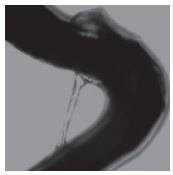
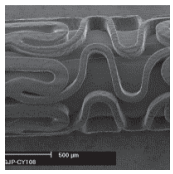
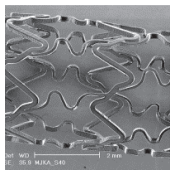
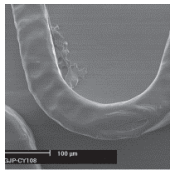
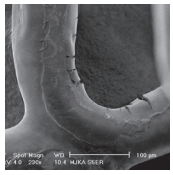
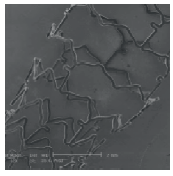
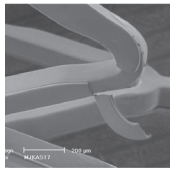
Drug-eluting Stents: From Bench-top to Clinical Research

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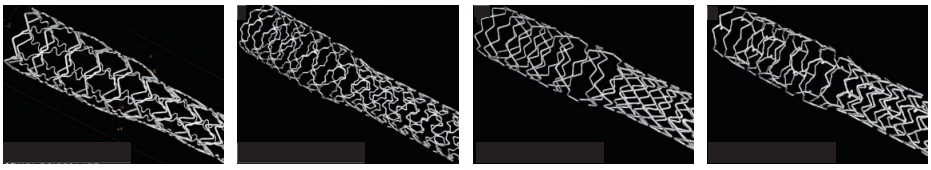

TWENTE

DRUG-ELUTING STENTS: FROM BENCH-TOP TO CLINICAL RESEARCH

MOUNIR BASALUS

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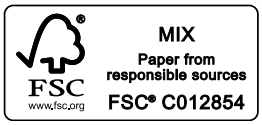

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dedicated to Foekje and Damian

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CONTENTS

CHAPTER 1

INTRODUCTION

Cardiovascular diseases are the most common cause of mortality and morbidity in western countries. Coronary atherosclerosis has a progressive nature, develops over several decades, and may ultimately lead to hemodynamically significant coronary obstructions and symptomatic coronary artery disease (CAD), which is associated with high morbidity and mortality [1,2] In 1964, Charles T. Dotter and Melvin P. Judkins described angioplasty as a non-surgical, percutaneous treatment of flow-limiting atherosclerotic obstructions [3], and in 1977, Andreas Grüntzig performed the first coronary balloon angioplasty to dilate a severely narrowed proximal coronary artery.[4] Since then, the technique of percutaneous coronary interventions (PCI) has been refined and extended by developing various diagnostic tools and therapeutic devices other than balloon catheters. As a result, PCI is nowadays the most frequently performed therapeutic procedure in cardiology.[5]

Coronary stents

In the early days, balloon angioplasty procedures were hampered by the risk of abrupt vessel closure due to large, occlusive dissections of the vessel wall, which motivated the development of fine metallic mesh tubes, so-called stents, that could be implanted as bailout device to maintain vessel patency.[6] As a result, procedural safety and efficacy of PCI was improved because stents counteracted the elastic recoil of the vessel wall, which in angioplasty procedures was responsible for significant lumen loss after deflation of the balloon catheter.[7] Elastic recoil, late unfavorable remodeling of the vessel wall, and neointimal proliferation at the site of balloon injury were mechanisms that could result in recurrence of lumen obstruction, the so-called restenosis, causing recurrence of symptoms and the need for repeat revascularization in 30-50% of the patients.[8,9] Randomized clinical trials demonstrated in the 1990's that routine implantation of stents resulted in superior long-term clinical success with less angiographic late lumen loss and lower restenosis risk as compared to balloon angioplasty only.[10,11] However, even after stenting, a substantial risk of restenosis remained, necessitating reinterventions in up to one third of stented patients.[12] The placement of the stent causes vessel injury, which induces an inflammatory reaction around the stent struts that triggers a cascade of events that lead to proliferation of smooth muscle cells and deposition of extracellular matrix. This neointimal hyperplasia and proliferation has been demonstrated to be the underlying mechanism of restenosis. Another concern that was raised by the introduction of stents was the acute thrombotic vessel closure, known as stent thrombosis. Stent thrombosis has been a feared complication of intracoronary stents from the beginning, and is associated with a high mortality. The initial use of Wallstents in the late 1980s was overshadowed by 24% stent thrombosis rates. The peri-procedural antithrombotic regimen at that time consisted of aspirin, in conjunction with oral anticoagulants. The shift to dual antiplatelet therapy resulted in a significant drop in stent thrombosis rates < 2%. Earlier antiplatelet loading and use of glycoprotein IIb/IIIa receptor blockers further reduced stent thrombosis rates.

Drug-eluting stents

Several methods for local or systemic application of therapies to prevent in-stent restenosis failed to achieve this goal before drug-eluting stent (DES) were developed.[13] These devices were coated with a polymer layer that carried and delivered an antiproliferative drug directly at the site of treatment. Use of DES reduced restenosis and the need for reintervention in patients undergoing PCI.[13,14] However, the antiproliferative drug on DES prolonged the process of stent endothelialization in DES compared to standard bare metal stents, which led to the need for longer dual antiplatelet therapy. In addition, there were unsettled discussions with regard to long-term outcome after DES implantation, because long-term follow-up data of first-generation DES showed that these devices did not improve mortality and were associated with a significant risk of late and very late stent thrombosis.[15-18]

Several factors and mechanisms have been suggested as potential explanations.[19] Widely discussed was the limited biocompatibility of the first-generation DES coatings, of which some were shown to be associated with hypersensitivity and inflammation that can promote the formation of stent thrombosis.[20] In addition, deliverability and side branch access of first-generation DES was limited [21]; and in complex patients with advanced disease, as seen in routine clinical practice, the reduction in need for reinterventions did not completely match that of the initial randomized DES trials, which had been performed in more selected patient populations.[22]

These discussions about long-term safety of DES within the medical community together with the widespread use of DES in clinical practice entailed extensive clinical research with the result that DES are one of the best-examined medical devices in terms of clinical research.[23] On the contrary, published independent bench top and pre-clinical research on DES is scarce.[24] However, bench top data of different types of DES may be of interest as they could help to clarify some aspects of clinical DES performance. For that reason, we studied different DES of different generations, both at bench top and in clinical settings.

Surface of drug-eluting stents

Antiproliferative drugs do not adequately adhere to the smooth surface of metallic stent platforms. Therefore, polymer coatings were applied on the metal (either on the entire stent or on the abluminal stent surface only), which bind and carry the drugs and have appropriate release kinetics to elute the drug at the treatment site. As a result, the surface of most DES is partly or entirely covered by a polymer-based coating. The texture of these coatings may differ between DES types and is exposed to blood flow for a relatively long period of time. The latter is due to the slower endothelialization in DES as compared to bare metal stents.

The coating material of DES can be classified into durable polymer-based (also termed nonerodible, permanent or biostable) and biodegradable polymer-based coatings. Durable polymer-based coatings with complete coverage of the metallic DES platform were the first

successful vehicles for drug-loading and release. The abluminal biodegradable polymer-based coatings were developed later. These coatings are hydrolyzed slowly into monomers that can be further metabolized in vivo.

The development of DES strives for devices with optimal biocompatibility (i.e. low thrombogenicity and limited stimulation of inflammation in adjacent tissues)[25,26], and very favorable long-term mechanical properties of the coating to cope with the repetitive cyclic movement of the vessel wall as a result of cardiac motion.[27] In addition, the integrity of DES coatings should endure the mechanical stress applied during stent implantation and stent post-dilation. The latter is performed quite frequently, using high inflation pressures and occasionally oversizing the stent, in order to adapt stent geometry to the vessel anatomy and correct stent malapposition.

Coating irregularities on the surface of drug-eluting stents

Early bench top research suggested that first-generation DES partially meet the aforementioned demands upon polymeric DES coatings. However, it also suggested that some unfavorable clinical aspects of DES could be related to the polymer coating, which might occasionally trigger stent thrombosis and embolization of coating fragments.[28-32] Various mechanisms might be involved: first, decreased thickness or absence of the coating may locally decrease the anti-restenotic effect of a DES; secondly, displacement of coating with or without embolization of fragments (of a relevant size) may lead to (micro)vascular obstruction and peri-procedural myocardial necrosis; and thirdly, an increased roughness of the DES surface may increase thrombogenicity which might promote stent thrombosis.[33] On the other hand, we realize that some mild coating irregularities might have favorable effects, by enhancing the rate of endothelialization.[34]

Bench top imaging of drug-eluting stents

A wide variety of imaging techniques could be used for bench top assessment of DES. The following paragraph describes the most widely applied techniques that were also used in this thesis. Light microscopy can be used to examine DES surface irregularities (Figure 1). However, its two-dimensional nature and light artifacts reflected from the stents, limit the examination of many DES coating irregularities. This makes this technique less suitable for quantitative assessment. These limitations are overcome by imaging with scanning electron microscopy (SEM; Figure 2), which has a three-dimensional character and the ability to acquire highly magnified images at a high resolution.[35] A scanning electron microscope creates pictures by scanning the sample with a beam of electrons. The electron beam interacts with electrons of the sample, resulting in various signals that can be detected, and provides highly detailed information on the surface topography (and the composition) of the sample. The beam generally scans in a raster pattern, and the position of the beam

is combined with the detected signal to compose images. Scanning electron microscopic examination is an ideal technique to assess various coating abnormalities on DES, which had previously been reported in a descriptive way (Figure 3 provides examples of coating irregularities of a first generation DES).[36] However, so far DES coating irregularities have not been not classified, which hampered a systematic assessment. Micro-computed tomography (micro-CT) is a high-resolution imaging modality that permits nondestructive assessment and three-dimensional reconstruction of spatial objects such as DES. The technique is similar to traditional computed tomography, as it uses X-ray to create cross-sections of an object that are used for the computer-based virtual reconstruction.[37]

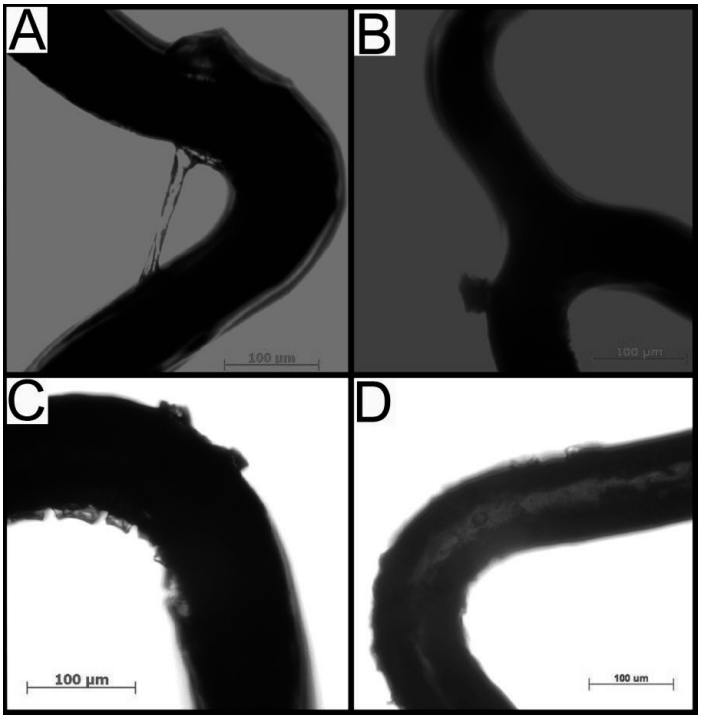

Figure 1. **Light microscopic imaging of drug-eluting stents. A**) Example of webbing in a Taxus Liberté. **B**) Fragment of coating on Xience V. **C**) Cracks and crater irregularities on Endeavor Resolute. **D**) Heterogeneity of coating of Endeavor Sprint.

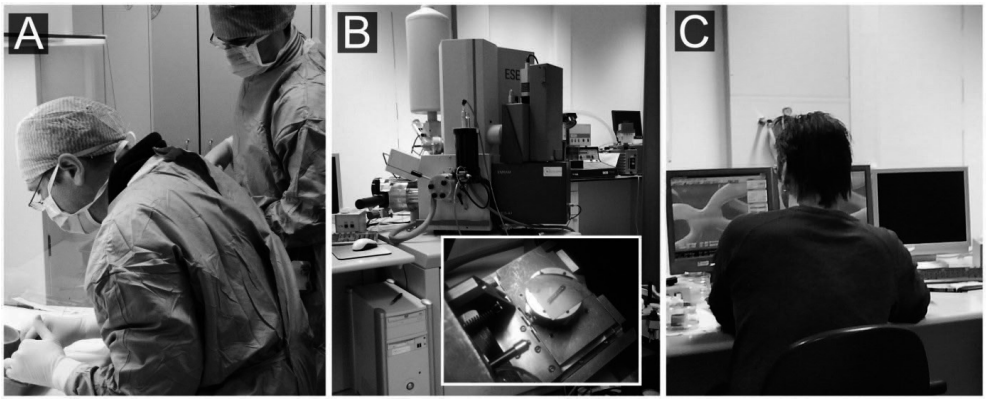

Figure 2. Sample preparation and examination.
A) Stent deployment (care was taken to avoid dust contamination). **B**) Scanning Electron microscopic examination of DES; DES sample on the examination stage of SEM (insert). **C**) Quantitative examination of coating irregularities.

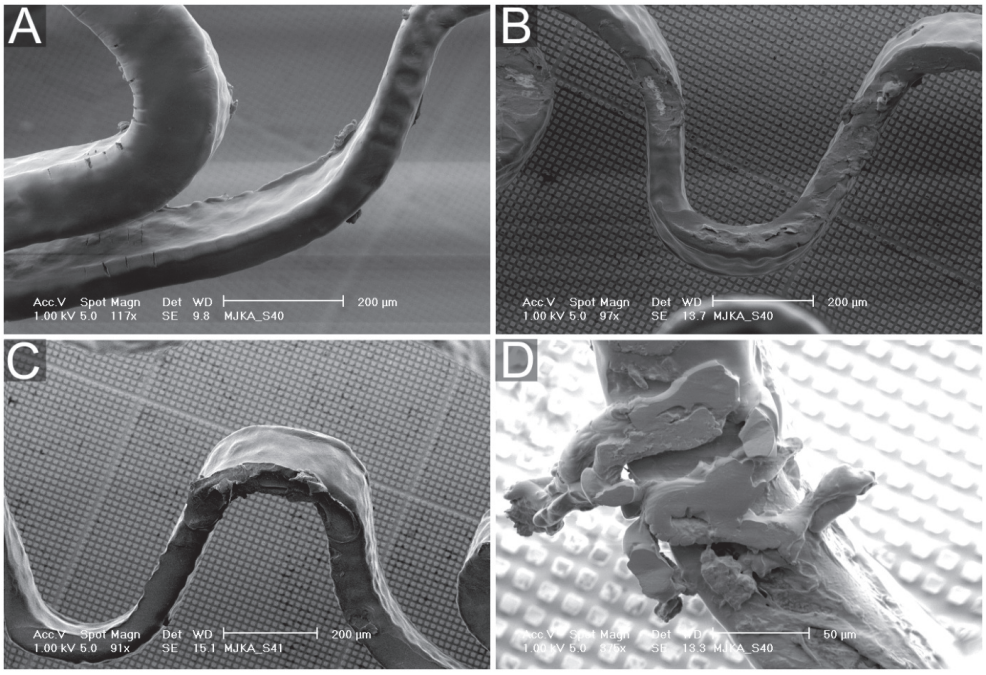

Figure 3. SEM appearance of coating irregularities on a DES with PEVA/ PBMA coating (stent expanded with a pressure of 14atm in 37°C sterile water).
A) Cracks on inner curvature. **B and C**) "Peeled polymer" with and without areas with bare metal aspect. **D**) Coarse irregular coating excess.

Bench top and clinical research in drug-eluting stents

Bench top research may provide hypothesis-generating data and valuable insights. Nevertheless, clinical research is the "gold standard" for the evaluation of safety and efficacy of medical implants. In fact, the combination of clinical and bench top research permits both, the assessment of relevant clinical scenarios in the bench top setting and the implementation of bench top-derived concepts into clinical studies. Therefore, this thesis combines bench top and clinical research examining first and second-generation DES.

An example of such bench top-derived concepts may be the assessment of the incidence of peri-procedural MI in first and second-generation DES. Second-generation DES are characterized by polymer-based coatings with presumably superior biocompatibility and– on average –better mechanical properties.[24] This could lead to more favorable clinical outcome as compared to first-generation DES.

Peri-procedural MI is one of the best-examined clinical parameters following DES implantation, and it has been related to a less favorable long-term outcome.[38-41] Several mechanisms may lead to peri-procedural MI. Such mechanisms include the formation of thrombi on stent surfaces (and their micro-embolization), which might be related to the topography of DES coatings or to the design and geometry of metallic stent platforms.[42] Based on bench top data, a lower rate of peri-procedural MI may be expected following PCI with second-generation DES. The comparison of peri-procedural MI rates of first- and second-generation DES from a registry of consecutive patients may allow to test this bench top-derived hypothesis in a clinical setting.

Randomized trials in "real world" patient populations

Analysis of registry data may help to gain insights into the clinical performance of second-generation DES. However, data obtained from randomized controlled trials are considered the most reliable source of clinical evidence. The applicability of the findings of such trials may be particularly high, if they examine "real world" patient populations. One of the major characteristics of "real world" trials is that they assess patient populations as seen in routine daily practice. Ideally, there should be no difference in characteristics and outcome of patients that are enrolled in "real world" clinical trial and the non-enrolled patients.

The TWENTE trial

TWENTE is a large, investigator-initiated, randomized controlled trial that compares the clinical outcome of two second-generation durable polymer-based DES in a "real world" population of PCI patients.[43] The two DES examined are the Xience V stent (Figure 4B,4D) that elutes everolimus from a fluoropolymer-based coating (Abbott Vascular, Santa Clara, CA) and has been shown to be superior to first-generation DES,[44] and the Resolute stent (Figure 4A,4C) that releases zotarolimus from a BioLinx coating (Medtronic, Santa Rosa,

CA) and has shown encouraging clinical results.[45-47] The widespread use of both devices in routine clinical practice, comprising a high percentage of PCI with off-label indications for DES, [48] underlines the necessity to compare these two DES in a randomized clinical trial that examines a "real world" population of PCI patients.

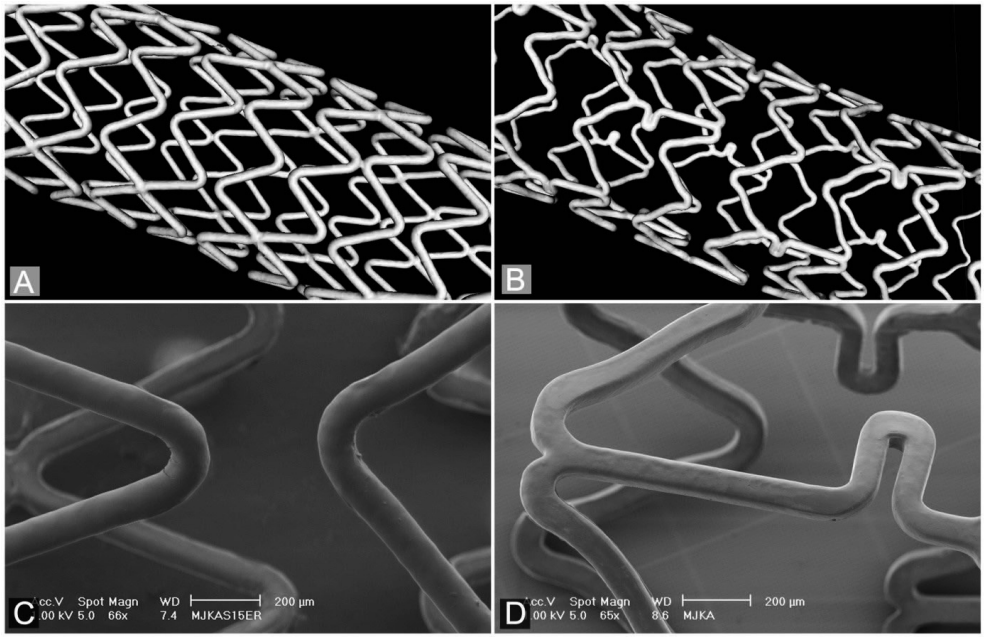

Figure 4. Geometry and surface morphology of Endeavor Resolute and Xience V. Micro-computed tomography images of Endeavor Resolute **A)** and Xience V **B).** Scanning electron microscopic images of Endeavor Resolute **C)** and Xience V **D)**

Effect of gender differences on clinical outcomes after DES implantation

Within the patient population undergoing PCI, there is a growing proportion of females. Until recently, research on cardiac disease in women did not receive sufficient attention.[49,50] As a result, most data on clinical outcome after DES implantation in women were generated from pooled analyses of multiple, small-sized, randomized studies in specific patient populations and/or large, non-randomized registries. Yet, recently there was a call for more gender-specific analyses in clinical trials, aiming at the improvement of knowledge about potential gender differences, which may ultimately improve therapeutic management of female patients.[50] Gender-stratification, as performed in the TWENTE trial, may facilitate gender subgroup analyses.[51]

Further evolution of durable polymer-based drug-eluting stents

First-generation DES consisted of established bare-metal stent (BMS) platforms, which were coated with durable polymer-based coatings to carry and deliver the drug to the vessel wall. This was followed by the development of second-generation DES, aiming at improved biocompatibility of their coatings while maintaining the antiproliferative potential of the first-generation DES.[52] In the third-generation of DES, further refinement has involved an increase in flexibility of the stent platform, which facilitates stent delivery in challenging anatomical situations and improves stent apposition to the vessel wall. Resolute Integrity (Medtronic) and Promus Element (Boston Scientific, Natick, MA) are third-generation DES, utilizing established drugs and durable polymer-based coatings [53] in combination with novel, more flexible stent designs. DUTCH PEERS (TWENTE–II) is a multicenter trial that was designed to compare the clinical outcome of these two third-generation DES in an all-comer population of PCI patients.

Aim of this thesis

While the results of large clinical trials are most significant for the evaluation of the safety and efficacy of DES, post-marketing bench top research may provide additional insights that could help to interpret clinical performance. This thesis combines bench top assessment and clinical research to evaluate the performance of several DES types.

- In **chapter 2** we used Scanning electron microscopy to investigate, classify, and quantify irregularities of coatings on contemporary durable polymer-based DES following stent expansion with regular balloon pressures.
- In **chapter 3** we use micro-CT to assess the spatial geometry of the stent platform of contemporary DES following extremely oversized partial stent post-dilatation.
- In **chapter 4** we use SEM to assess shape, type, size, and incidence of irregularities on durable polymer-based DES coatings following extremely oversized partial stent post-dilatation.
- In **chapter 5** we assess and quantify coating irregularities on unexpanded and expanded durable polymer-based DES with SEM to gain insights into the origin of coating irregularities.
- In **chapter 6** we use insights from our own work to interpret SEM findings of another research group in DES after failed implantation.
- In **chapter 7** we use SEM to assess the post-expansion morphology of the biodegradable, polylactic acid-based coating on a siolimus-eluting stent.
- In **chapter 8** we discuss advantages and disadvantages of polymer-based coatings of DES, based on recent bench-top and pre-clinical studies.
- In **chapter 9** we compare the incidence of peri-procedural myocardial infarction between first- and second-generation DES in a consecutive series of patients.

- In **chapter 10** we compare the safety and efficacy of Resolute zotarolimus-eluting stents (R-ZES) with Xience V everolimus-eluting stents (EES) at one-year follow-up of a randomized controlled trial with limited exclusion criteria and a high proportion of complex patients and lesions (TWENTE trial).
- In **chapter 11** we investigate whether eligible, non-enrolled patients differed from the randomized TWENTE trial population in baseline characteristics and one-year clinical outcome (Non-Enrolled TWENTE study).
- In **chapter 12** we assess potential differences in procedural and clinical outcome between women treated with Resolute versus Xience V stents in the TWENTE trial population. In addition, we assessed between-gender differences in outcome within this population of PCI patients treated with second-generation DES.
- In **chapter 13** we describe the design of the DUTCH-PEERS (TWENTE–II) multicenter study to compare safety and efficacy of third-generation everolimus-eluting Promus Element stents and zotarolimus-eluting Resolute Integrity stents in a Dutch all-comers population.

REFERENCES

(1) Hamm CW, Bassand JP, Agewall S et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999-3054.

(2) Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet.* 1997;349:1498-1504.

(3) DOTTER CT, JUDKINS MP. TRANSLUMINAL TREATMENT OF ARTERIOSCLEROTIC OBSTRUCTION. DESCRIPTION OF A NEW TECHNIC AND A PRELIMINARY REPORT OF ITS APPLICATION. *Circulation.* 1964;30:654-670.

(4) Gruntzig A, Schneider HJ. [The percutaneous dilatation of chronic coronary stenoses--experiments and morphology]. *Schweiz Med Wochenschr.* 1977;107:1588.

(5) Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med.* 2012;366:54-63.

(6) Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med.* 1987;316:701-706.

(7) de Feyter PJ, de Jaegere PP, Serruys PW. Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty. *Am Heart J.* 1994;127:643-651.

(8) Erbel R, Haude M, Hopp HW et al. Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. Restenosis Stent Study Group. *N Engl J Med.* 1998;339:1672-1678.

(9) Califf RM, Fortin DF, Frid DJ et al. Restenosis after coronary angioplasty: an overview. *J Am Coll Cardiol.* 1991;17:2B-13B.

(10) Serruys PW, de JP, Kiemeneij F et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med.* 1994;331:489-495.

(11) Fischman DL, Leon MB, Baim DS 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;331:496-501.

(12) Serruys PW, Unger F, Sousa JE et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-1124.

(13) 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;346:1773-1780.

(14) 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;349:1315-1323.

(15) Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation.* 2007;115:1440-1455.

(16) Daemen J, Wenaweser P, Tsuchida K et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet.* 2007;369:667-678.

(17) Kastrati A, Mehilli J, Pache J et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med.* 2007;356:1030-1039.

(18) Stettler C, Wandel S, Allemann S et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-948.

(19) Luscher TF, Steffel J, Eberli FR et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation.* 2007;115:1051.

(20) 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;115:2435.

(21) Ormiston JA, Webster MW, El Jack S et al. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. *Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions.* 2006;67:49.

(22) Baim DS, Mehran R, Kereiakes DJ et al. Postmarket surveillance for drug-eluting coronary stents: a comprehensive approach. *Circulation.* 2006;113:891.

(23) Garg S, Serruys PW. Coronary stents: current status. *Journal of the American College of Cardiology.* 2010;56:S1.
(24) Basalus MW, von Birgelen C. Benchside testing of drug-eluting stent surface and geometry. *Interventional Cardiology.* 2010;2:159-175.
(25) van der Giessen WJ, Lincoff AM, Schwartz RS et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation.* 1996;94:1690.
(26) Vroman L. The life of an artificial device in contact with blood: initial events and their effect on its final state. *Bulletin of the New York Academy of Medicine.* 1988;64:352.
(27) How TV. Mechanical properties of arteries and arterial grafts. 1992.
(28) Cook S, Ladich E, Nakazawa G et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation.* 2009;120:391.
(29) Hunter WL. Drug-eluting stents: beyond the hyperbole. *Advanced drug delivery reviews.* 2006;58:347.
(30) Kounis NG, Kounis GN, Kouni SN, Soufras GD, Niarchos C, Mazarakis A. Allergic reactions following implantation of drug-eluting stents: a manifestation of Kounis syndrome? *Journal of the American College of Cardiology.* 2006;48:592.
(31) Nebeker JR, Virmani R, Bennett CL et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *Journal of the American College of Cardiology.* 2006;47:175.
(32) Schwartz RS. Pathophysiology of restenosis: interaction of thrombosis, hyperplasia, and/or remodeling. *The American journal of cardiology.* 1998;81:14E.
(33) Hecker JF, Scandrett LA. Roughness and thrombogenicity of the outer surfaces of intravascular catheters. *Journal of biomedical materials research.* 1985;19:381.
(34) Palmaz JC, Benson A, Sprague EA. Influence of surface topography on endothelialization of intravascular metallic material. *Journal of vascular and interventional radiology: JVIR.* 1999;10:439.
(35) Enderle JD, Brozino JD Blanchard SM. *Introduction to Biomedical Engineering*. Academic Press, Elsevier (2005). 2013. Ref Type: Generic
(36) Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. *The Journal of invasive cardiology.* 2007;19:71.
(37) Paulus MJ, Gleason SS, Kennel SJ, Hunsicker PR, Johnson DK. High resolution X-ray computed tomography: an emerging tool for small animal cancer research. *Neoplasia (New York, NY).* 2000;2:62.
(38) Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. *Circulation.* 2002;106:1205.
(39) Prasad A, Singh M, Lerman A, Lennon RJ, Holmes Jr DR, Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *Journal of the American College of Cardiology.* 2006;48:1765.
(40) Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol.* 2003;42:1406-1411.
(41) Nienhuis MB, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. *Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions.* 2008;71:318.
(42) Basalus MW, von Birgelen C. Benchside testing of drug-eluting stent surface and geometry. *Interventional Cardiology.* 2010;2:159-175.
(43) Basalus MW, Tandjung K, van Houwelingen KG et al. TWENTE Study: The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente: study design, rationale and objectives. *Neth Heart J.* 2010;18:360-364.
(44) Stone GW, Lansky AJ, Johnson G et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA.* 2008;299:1903-1913.
(45) Massberg S, Byrne RA, Kastrati A et al. Polymer-free sirolimus-and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus-and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation.* 2011;124:624.

(46) Meredith IT, Worthley S, Whitbourn R et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. *JACC: Cardiovascular Interventions.* 2009;2:977-985.
(47) Yeung AC, Leon MB, Jain A et al. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. *Journal of the American College of Cardiology.* 2011;57:1778-1783.
(48) Grines CL. Off-Label Use of Drug-Eluting Stents: Putting it in PerspectiveΓüÄ. *Journal of the American College of Cardiology.* 2008;51:615-617.
(49) Kim AM, Tingen CM, Woodruff TK. Sex bias in trials and treatment must end. *Nature.* 2010;465:688.
(50) Maas AH, van der Schouw YT, Regitz-Zagrosek V et al. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *European heart journal.* 2011;32:1362.
(51) Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. *Journal of clinical epidemiology.* 1999;52:19.
(52) Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. *Lancet.* 2011;377:1241-1247.
(53) Tandjung K, Basalus MW, Sen H et al. DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity (DUTCH PEERS): rationale and study design of a randomized multicenter trial in a Dutch all-comers population. *Am Heart J.* 2012;163:557-562.

CHAPTER 2

COATING IRREGULARITIES OF DURABLE POLYMER-BASED DRUG-ELUTING STENTS AS ASSESSED BY SCANNING ELECTRON MICROSCOPY

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ABSTRACT

Aims: To classify and quantify post-expansion irregularities in durable polymer-based coatings of drug-eluting stents (DES).

Methods and results: Taxus Liberté™, Endeavor Sprint™, Endeavor Resolute™ and Xience V™ DES (three samples of each) were explored by light microscopy and scanning electron microscopy (SEM) following expansion at 14 atm in water. Incidence and size of irregularities were measured during thorough quantitative examinations of a 360 SEM images. DES types examined showed a significant difference in the incidence of irregularities ($p<0.0001$; 6.6±4.2/image at 60-fold magnification) with typical patterns specific for each DES. All types showed areas with bare metal-aspects, but incidence, shape, and size differed largely: Sprint showed the largest areas. Cracks were only found in Sprint and Resolute, while wrinkles were seen exclusively in Taxus Liberté and Xience V ($p<0.0001$). The coating of each DES type showed some inhomogeneity of distribution, but the incidence differed ($p<0.0001$) and was least in Taxus Liberté, which, on the other hand, was the only DES that showed webbing with large bare-metal exposure.

Conclusions: The incidence and size of various coating irregularities on different types of DES varied widely. These data may be considered in ongoing discussions on the differences between DES and may serve as reference to compare novel DES.

Abbreviations
DES: drug-eluting stent
SEM: scanning electron microscopy
BMS: bare metal stent

Drug-eluting stents (DES) represent a successful therapeutic strategy to minimize the rate of restenosis and the need for repeat revascularization procedures compared to bare metal stents (BMS).(1-4)However, this success is somewhat overshadowed by the ongoing debates on whether DES decrease mortality(5-8) and on the incidence of late and very late stent thrombosis in DES.(9) In the meantime, high-risk patient subsets have been identified, and DES implantation technique and anti-platelet regimen have been optimized to reduce the risk of DES thrombosis.(10)

The surface of the coating on DES, which incorporates and delivers the drug to the target area, can also promote thrombus formation, as irregularities and defects on the coating surface may increase roughness of the stent surface.(11) In addition, endothelialization of the DES struts is delayed (versus BMS) and sometimes incomplete which results in a longer – and sometimes even persistent – exposure of DES coating to blood.

Scanning electron microscopy (SEM) is a technique which allows to closely examine the coating surface of DES, but only very few SEM studies addressed the post-expansion morphology of DES so far.(12,13) Otsuka et el. demonstrated in a descriptive SEM-study the presence of defects in polymer coatings of primarily early generation DES.(13) Several novel DES have appeared in the meantime. In the present study, we used SEM to thoroughly study the post-expansion morphology of the coating layer on four types of DES. Aim of our study was to classify post-expansion irregularities in the polymer coatings and to determine their frequency and dimensions.

METHODS

DES samples examined. We examined 4 types of DES which all share the presence of a durable-polymer component. A total of 12 DES was examined: 3 Taxus Liberté™ (Boston Scientific Corp., Natick, MA, USA), 3 Endeavor Sprint™ (Medtronic Vascular, Santa Rosa, CA, USA), 3 Endeavor Resolute™ (Medtronic Vascular, Santa Rosa, CA, USA), and 3 XIENCE V™ (Abbott Vascular, Santa Clara, CA, USA). Endeavor Sprint, Endeavor Resolute, and Xience V stents were provided by the manufacturer, while Taxus Liberté stents were obtained from our own stock (all companies had been invited to provide stents). Stent dimensions were for Xience V 3.5x23mm (n=3), for Endeavor Resolute 3.5x24mm (n=3), for Endeavor Sprint 3.5x24mm (n=3), and for Taxus Liberté 3.5x28mm (n=1), and 3.5/8mm (n=2).

Taxus Liberté consists of the Liberté™ stainless steel platform (Figure 1A) with a strut thickness of 97µm covered by a 17.8µm thick coating consisting of SIBS(styrene-b-isobutylene-b-styrene) polymer and Paclitaxel.(14) Endeavor Sprint consists of the cobalt-chromium Driver™ platform (Figure 1B) with a strut thickness of 91µm covered by a 4.8µm thick coating of phosphorylcholine (10%) and Zotarolimus(90%).(15) Endeavor Resolute is also based on the Driver™ platform with Zotarolimus as the anti-proliferative drug while

the coating consists of drug plus Biolinx™ polymer (16); the coating thickness is 5.6 µm (information by manufacturer, personal communication). Xience V stents consist of the Vision™ cobalt-chromium platform (Figure 1C) with a strut thickness of 81µm, covered by a 7.8µm thick layer of a mixture of fluoropolymer and Everoliums as the anti-proliferative drug.(17)

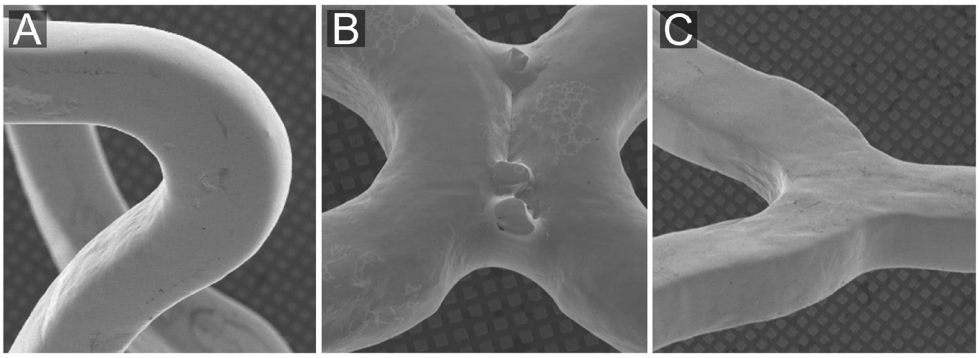

Figure 1. Scanning electron microscopic appearance of bare metal stents. The SEM-images demonstrate in general a relatively smooth surface (all three stents) as well as some irregularities at welding points (Driver stent only): **A)** Liberté stent (bare metal platform of Taxus Liberté); **B)** Driver stent (bare metal platform of Endeavor sprint and Endeavor Resolute); **C)** Vision stent (bare metal platform of Xience V).

DES expansion protocol. All stents (sterile packed; expiration date not passed) were expanded by an interventional cardiologist under sterile conditions in a sterile water bath at 37ºC. Balloon expansion of the DES was performed at 14atm, and all DES were consecutively dried under laminar air flow at room temperature. Stent expansion, drying, and examination of the samples were performed at the University of Twente in Enschede at an experimental laboratory with laminar air flow, being almost free from dust.

Light microscopy. The surface of 1 stent per DES type was examined by stereoscopic light microscopy (Zeiss Axiovert 200 inverted microscope) at 50- to 200-fold magnifications in an exploratory fashion to search for irregularities and/or defects. Digital images were taken where appropriate in order to portray typical irregularities.

Scanning electron microscopic analysis. SEM imaging was performed with a Phillips XL30/ESEM FEG scanning electron microscope (µ Candela Systems). In order to see the coating as pure as possible, all DES remained untreated (i.e., no gold layer was sprayed on DES). A 1KeV-protocol was applied (average working distance 10mm; range 6–12mm sample dependent). *Exploratory assessment.* First, one sample per DES type was examined with SEM at 50- to 60-fold magnification to detect and locate suspected irregularities.

Defining and classifying coating irregularities. Areas of coating irregularities as detected in the previous step were further examined at 200- to 500-fold magnification to characterize them and to distinguish them from artifacts. This information was used to develop a classification of coating irregularities. In addition, by zooming in on individual irregularities, the analysts learned to discriminate various types of irregularities at a lower magnification level. This was a prerequisite for measuring the incidence of individual coating irregularities.
Measurement incidence of coating irregularities. Finally, the DES surface was thoroughly scanned at 50-to-70-fold magnifications on 8 stents (2 of each type); care was taken to avoid overlap between scanned areas. A total of 360 SEM images (including both, luminal and abluminal aspect) were carefully examined to determine the incidence of all prespecified coating irregularities on different DES types. Despite some difference in stent length, the actual stent surface area examined by SEM for quantification of coating irregularities was identical in all four DES types. Data are presented as frequency of each irregularity per image field at 60-fold magnification. If individual magnifications differed slightly from this level, a correction factor was applied to normalize findings for 60-fold magnification. In addition, the dimensions of coating irregularities were measured (length x width; diameter for defects with a round appearance). In Endeavor Sprint stents (typically on the luminal aspect), bare metal zones were generally too large to permit a meaningful quantification.
Statistics: Data are presented as a mean ± one standard deviation. The incidence of various DES irregularities in the four DES types was compared by using the Kruskal-Wallis test. In cases in which the Kruskal-Wallis test demonstrated a significant difference, a Mann-Whitney test was performed between each 2 samples. P-values <0.05 were considered significant; the level of significance for the Mann-Whitney test was adjusted by Bonferroni-correction. Statistical analyses were performed with the software of SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Exploratory light microscopy. On all DES types, light microscopy detected coating irregularities (Figure 2).

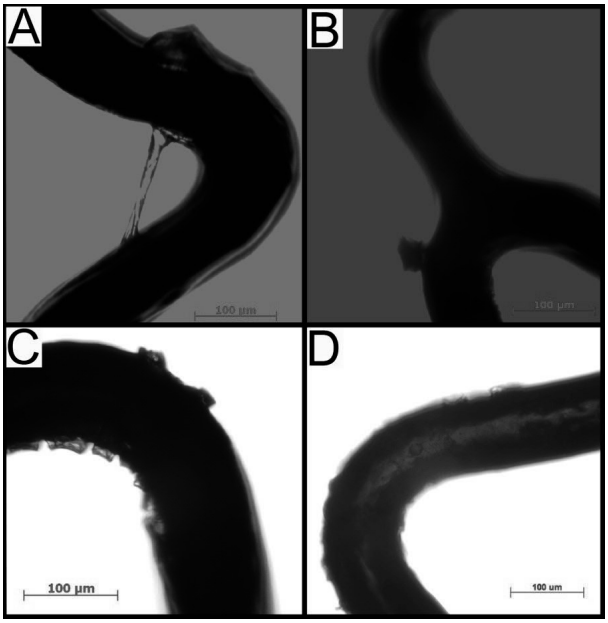

Figure 2. **Light microscopic imaging of drug-eluting stents.** **A**) Example of webbing in a Taxus Liberté. **B**) Fragment of coating on Xience V. **C**) Cracks and crater irregularities on Endeavor Resolute. **D**) Heterogeneity of coating of Endeavor Sprint.

SEM exploration and categorization of irregularities. Using 200-to-500-fold magnifications, we detected and characterized 14 types of coating irregularities. These irregularities were classified into four categories: (I) reduced thickness; (II) increased thickness; (III) inhomogeneous distribution; and (IV) displacement of coating; definitions are presented in Table 1. Examples are given in Figures 3 and 4.

Quantification of irregularities. For each of the 4 DES types, we systematically analyzed 90 non-overlapping images at 50-to-70-fold magnification (45 images of luminal and 45 of abluminal aspect). The total incidence of irregularities differed among DES types ($p<0.0001$; on average 6.6±4.2/SEM image at 60-fold magnification). The incidence of different irregularities is presented in Tables 2-5. On all 4 DES types, there were areas with visual aspect of bare metal; but incidence, shape, and size of these areas differed largely among the DES types (Table 2). Increased thickness of coating was seen in Taxus Liberté and – to a lower extent – in Xience V stents ($p=0.0001$; Table 3).

Cracks of the coating were found in Endeavor Sprint and Resolute (Table 2), while wrinkles were seen in Taxus Liberté and in Xience V only ($p<0.0001$; Table 4). Inhomogeneous distribution of coating was found on each DES type, but incidence and size differed between

DES types (Table 4). Displacement of coating was observed mainly in Taxus Liberté and Xience V – and to a much lower extent in Endeavor Resolute (Table 5).

The size of the various irregularities differed (Tables 2-5). Visual assessment revealed that areas with bare metal aspect were largest on Endeavor Sprint (too large to permit meaningful measurement, as previously mentioned). On Xience V, the incidence of areas with bare metal aspect was particularly low and their dimensions were relatively small.

Certain irregularities were found on constant locations of specific DES types, forming typical patterns of irregularities for these DES types. Cracks were generally found on the inner curvatures of crowns (curved struts), where they could be observed on both, the luminal and abluminal aspect of stents. Crater lesions were mainly detected at the apex on the outer curvature of a loop and at sites, where struts of unexpanded, crimped stents may have been in contact with each other.

Table 1. Classification of irregularities of durable polymer-based DES coatings

Categories	**Types** (within individual categories); Figure = typical example
I. Irregularities with reduced thickness of coating	**IA.** Small or big areas with aspect of bare metal, not fulfilling criteria of IB or IC (see below); Fig. 3A and 3B
	IB. Cracks, i.e. sharp-edged coating irregularity extending from the surface deep into the coating, sometimes with exposure of underlying stent/primer; Fig. 3C
	IC. Reduced thickness of DES coating at strut crossings; Fig. 3D
II. Irregularities with increased thickness of coating	**IIA.** "Auricle-shaped" excess of coating; Fig. 3E
	IIB. Ridge-shaped excess of coating connecting two facets of a strut; Fig. 1F
	IIC. Small rounded structure of excess coating; Fig. 3G
III. Irregularities with inhomogeneous coating	**IIIA.** Crater-shaped irregularity with metal exposure, i.e. circular or elliptical irregularity with centrally reduced thickness of coating (including bare metal areas) and increased thickness of coating at the peripheral zone; Fig. 3H
	IIIB. Crater-shaped irregularity without metal exposure, i.e. circular or elliptical irregularity with centrally reduced thickness of coating and increased thickness of coating at the peripheral zone; Fig. 4A and 2B
	IIIC. Small crater-shaped irregularity, i.e. irregularity with appearance of punched-out hole. (bottom not visible; Fig. 4C)
	IIID. Wrinkles, i.e. shallow minimal linear irregularities; Fig. 4D
	IIIE. Flattened coating enclosed between two linear thickenings of coating material; Fig. 4E
IV. Irregularities with displacement of coating	**IVA.** Webbing with metal exposure; Fig. 4F
	IVB. Webbing without metal exposure; Fig. 4G
	IVC. Fragments of coating, i.e. mostly detached piece of coating which keeps loosely attached to the main coating; Fig. 4H

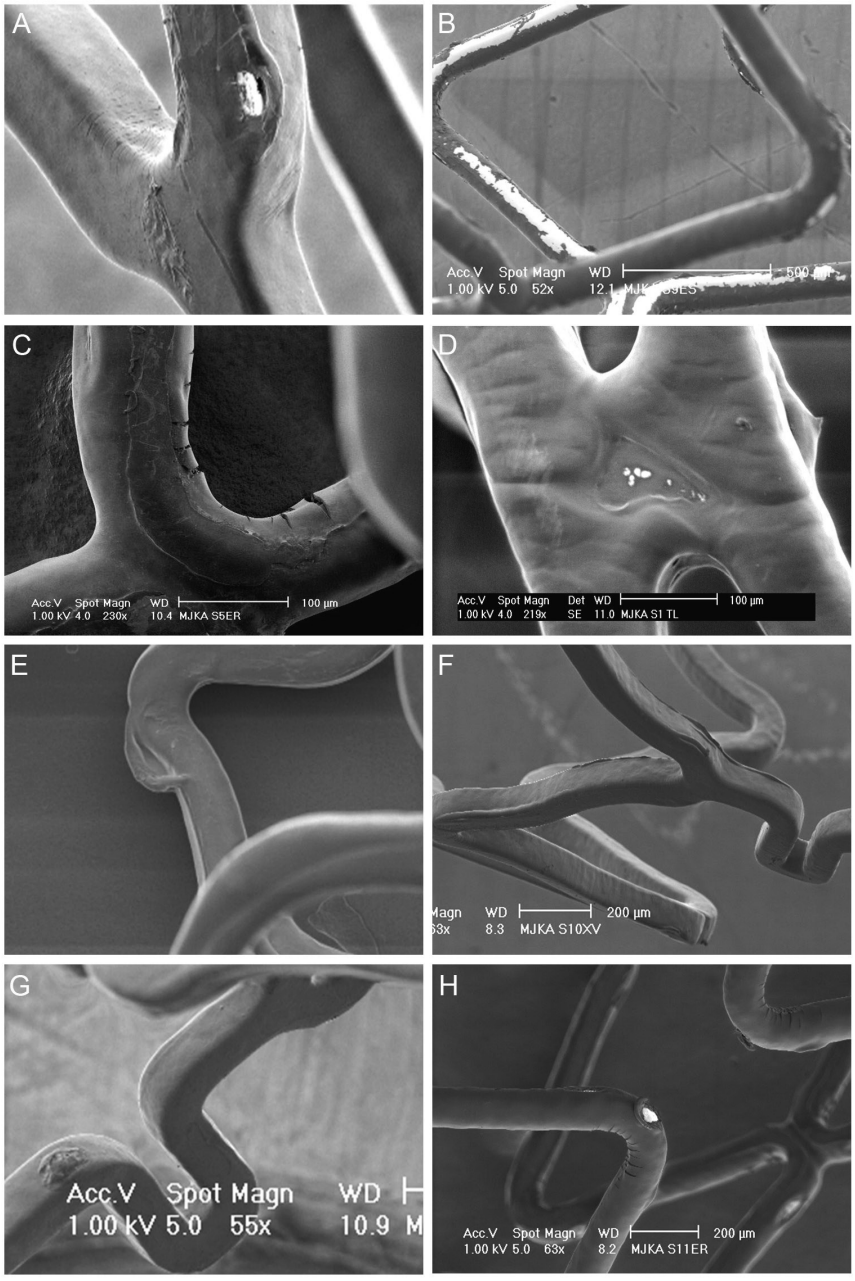

Figure 3. **Scanning electron microscopic appearance of coating irregularities (part 1).** **A**) Apparently bare-metal area on Xience V. **B**) Endeavor Sprint with visual aspect of bare-metal areas. **C**) Cracks in coating of Endeavor Resolute. **D**) Thinning of coating on crosslink of Taxus Liberté. **E**) "Auricle-shaped" excess of coating on Taxus Liberté. **F**) Ridge-like excess of coating on Xience V. **G**) Small round structure of excess coating on Xience V. **H**) Crater irregularity with apparent central bare-metal area on Endeavor Resolute.

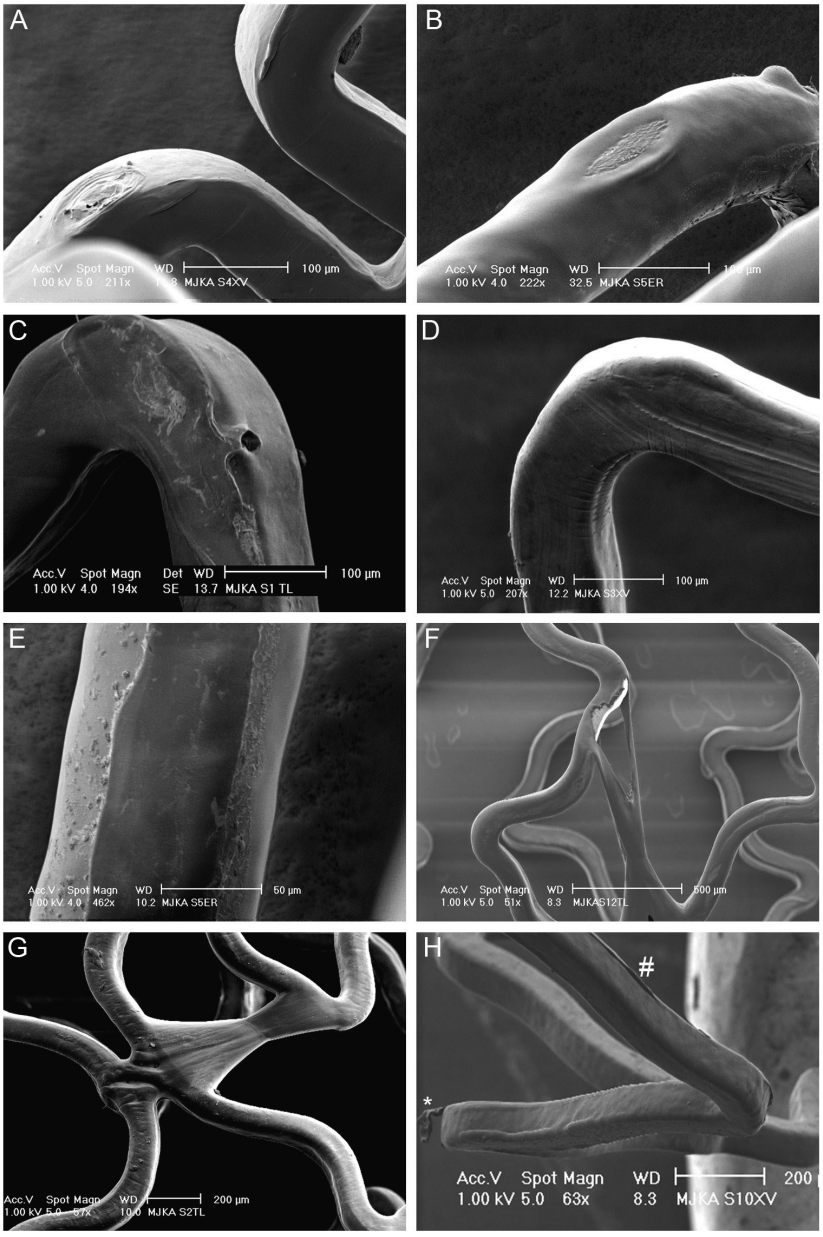

Figure 4. Scanning electron microscopic appearance of coating irregularities (part 2).

A) Crater-shaped irregularity without bare-metal exposure on Xience V. **B**) Crater-shaped irregularity without bare-metal exposure on Endeavor Resolute. **C**) Small crater-shaped irregularity on Taxus Liberté. **D**) Wrinkles on Xience V. **E**) Flattened coating on luminal surface of Endeavor Resolute. **F**) Webbing with bare-metal exposure on Taxus Liberté. **G**) Webbing without bare-metal exposure on Taxus Liberté. **H**) Detached fragment of coating (*****) and ridge-like thickening of coating (**#**) on Xience V.

Table 2. Category I DES coating irregularities (reduced thickness; frequencies and dimensions)

Types			Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
	Aspect		Luminal	Abluminal	Total	Luminal	Abluminal	Total	Luminal	Abluminal	Total	Luminal	Abluminal	Total
IA) Small or big areas of bare metal not fulfilling criteria for IB of IC. ‡,#,§, ○	**Mean frequency of irregularity per SEM field at 60-fold magnification**	**Small areas**	0.58 ±0.75	0.32 ±0.58	0.45 ±0.68	0.12 ±0.47	3.96 ±1.91	2.04 ±2.37	1.19 ±1.06	1.79 ±1.7	1.49 ±1.43	0.04 ±0.21	0.28 ±0.7	0.16 ±0.52
		Big areas	0	0	0	2.49 ±1.09	0.86 ±0.93	1.67 ±1.3	0	0	0	0	0	0
	Dimensions		135±66x46±19µm			Very large areas, too large to be measured			81±24x36±3µm			57±25x24±9µm		
IB) Cracks *,†,‡,¶,#,||	**Mean frequency /field**		0	0	0	2.34 ±0.98	2.91 ±1.15	2.62 ±1.1	3.23 ±0.78	4.02 ±1.27	3.63 ±1.12	0	0	0
	Dimensions					57±23x6±3µm			52±19x5±3µm					
IC) Reduced coating at strut crossing *,†,‡,§	**Mean frequency /field**		0.38 ±0.83	0.51 ±0.53	0.44 ±0.69	0	0	0	0	0	0	0	0	0
	Dimensions		177±38x83±58µm											

Differences in incidence of irregularities:
*difference among the stents: p<0.05
†Taxus Liberté vs.Endeavor Sprint: p<0.0125(Bonferroni)
‡Taxus Liberté vs.Endeavor Resolute: p<0.0125(Bonferroni)
§Taxus Liberté vs.Xience V: p<0.0125(Bonferroni)
||Endeavor Sprint vs.Endeavor Resolute: p<0.0125(Bonferroni)
¶Endeavor Sprint vs.Xience V: p<0.0125(Bonferroni)
#Endeavor Resolute vs.Xience V: p<0.0125(Bonferroni)

○ As the large size of type IA lesions in Endeavor Sprint stents prevented reliable quantification, this stent was excluded from direct comparison with the other DES types (this accounts for type IA lesions only).

Table 3. Category II DES coating irregularities (increased thickness; frequencies and dimensions)

Types		Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
	Aspect	**Luminal**	**Abluminal**	**Total**	**Luminal**	**Abluminal**	**Total**	**Luminal**	**Abluminal**	**Total**	**Luminal**	**Abluminal**	**Total**
IIA) Auricle-shaped excess of coating *,†,‡,§	**Mean frequency /field**	0.81 ±1.06	0.36 ±0.47	0.59 ±0.84	0	0	0	0	0	0	0	0	0
	Dimensions	118±13x57±6µm											
IIB) Ridge shaped excess of coating *,†,‡,¶,#	**Mean frequency /field**	1.26 ±0.86	1.37 ±1.02	1.31 ±0.94	0	0	0	0	0	0	0.98 ±0.84	0.79 ±0.94	0.89 ±0.89
	Dimensions	207±40x12±1µm									136±63x15±9µm		
IIC) Small rounded excess coating *	**Mean frequency /field**	0	0	0	0	0	0	0	0	0	0.09 ±0.28	0.05 ±0.23	0.07 ±0.26
	Dimensions										82±56µm (diameter)		

legend: see Table2

Table 4. Category III DES coating irregularities (inhomogeneous thickness; frequencies and dimensions)

Types		Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
	Aspect	**Luminal**	**Abluminal**	**Total**	**Luminal**	**Abluminal**	**Total**	**Luminal**	**Abluminal**	**Total**	**Luminal**	**Abluminal**	**Total**
IIIA) Crater irregularity with bare metal exposure *,†,‡,||,¶,#	**Mean frequency / field**	0	0	0	1.89 ±1.2	2.63 ±1.59	2.26 ±1.45	2.7 ±1.32	2.92 ±1.92	2.81 ±1.64	0.11 ±0.31	0	0.05 ±0.23
	Dimensions				98±7x50±17µm			90±20x46±10µm			53±17µm(diameter)		
IIIB) Crater irregularity without bare metal exposure *,‡,§,||,#	**Mean frequency / field**	0.02 ±0.14	0.04±0.29	0.03 ±0.27	0	0.06 ±0.23	0.03 ±0.17	0.26 ±0.48	0.37 ±0.59	0.32 ±0.54	0.24 ±0.43	0.58 ±0.83	0.41 ±0.68
	Dimensions					68±10µm			85±7µm			67±16µm	
IIIC) Small crater irregularity *,†,‡,¶,#	**Mean frequency / field**	0.17 ±0.42	0.23 ±0.0.51	0.2 ±0.47	0	0	0	0	0	0	0.15 ±0.42	0.15 ±0.46	0.15 ±0.44
	Dimensions		20±5µm								29±8µm		
IIID) Wrinkles *,†,‡,¶,#	**Mean frequency / field**	0.33 ±0.49	1.36 ±1.08	0.82 ±0.93	0	0	0	0	0	0	0.44 ±0.8	1.7 ±1.96	1.07 ±1.62
	Dimensions	99±51x12±2µm									43±28x3±1µm		
IIIE) Flattened coating enclosed between two linear thickenings of coating *,‡,||,#	**Mean frequency / field**	0	0	0	0	0	0	2.57 ±0.82	2.16 ±1.65	2.36 ±1.31	0	0	0
	Dimensions							Length variable x62±8µm					

legend: see Table2

Table 5. Category IV DES coating irregularities (displacement; frequencies and dimensions)

Types		Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
		Luminal	Abluminal	Total	Luminal	Abluminal	Total	Luminal	Abluminal	Total	Luminal	Abluminal	Total
IVA) Webbing with metal exposure *,†,‡,§	**Mean frequency of irregularity / image field**	0.11 ±0.30	0.26 ±0.6	0.18 ±0.48	0	0	0	0.02 ±0.15	0.03 ±0.17	0.02 ±0.16	0.02 ±0.15	0	0.01 ±0.1
	Dimensions	582±409 x 68±40µm							97x12µm			91x8µm	
IVB) Webbing without metal exposure *	**Mean frequency of irregularity / field**	0.02 ±0.14	0.11±0.31	0.06 ±0.24	0	0	0	0	0	0	0	0	0
	Dimensions		169x43µm										
IVC) Fragments of coating *,§,¶,#	**Mean frequency of irregularity/ field**	0	0	0	0	0	0	0	0	0	0.15 ±0.36	0.33 ±0.63	0.24 ±0.52
	Dimensions										29±7µm(diameter)		

legend: see Table2

DISCUSSION

Main findings. Examination of 4 commercially available types of DES demonstrated a wide range of 14 types of irregularities that were classified into four categories according to amount and homogeneity of coating. The different DES types showed certain irregularities at constant locations, forming typical patterns in panoramic SEM images. The total incidence of irregularities differed largely among DES types. All DES types showed stent areas with an aspect of bare metal; however, incidence, shape, and size differed among stent types with the largest areas being found in Endeavor Sprint. Cracks were found in Endeavor Sprint and Resolute only, while wrinkles were exclusively seen in Taxus Liberté and Xience V. Inhomogeneous distribution of coating was found on each DES type but the incidence differed between types and was least in the Taxus Liberté, which – on the other hand – was the only DES type that showed webbing associated with *large* bare-metal exposure.

Rationale of the study. Recent clinical studies suggested potential differences between DES-types in their capability to prevent restenosis. In addition, late and very late stent thrombosis continue to be important challenges. Late or incomplete endothelialization of DES increases the risk of stent thrombosis, most likely as a result of prolonged contact between blood and DES.(18)

The surface texture as well as imperfections of the distribution of the polymer may have implications with regards to safety and efficacy. While a mild degree of roughness of the surface of endovascular implants may promote endothelialization (versus perfectly smooth surfaces),(19) irregular and rough surface textures increase thrombogenicity.(20) And on polymer-based DES, a reduction in polymer thickness or the focal absence of polymer may reduce the local, drug-induced inhibition of neointimal proliferation. Therefore, in the present study we assessed the surface of 4 types of DES with SEM to document and quantify all forms of coating irregularities.

Choice of DES examined. There is development of polymer coating through DES generations, aiming at optimization of biocompatibility and release profile.(21) In this study, we examined DES of different generations which all share the presence of the durable-polymer component. We have clinical experience with the use of all four DES. According to a recent consensus for preclinical evaluation of DES, (22) we examined 3 stents per DES type.

Microscopic examination of DES coating. The two-dimensional character of light microscopic images substantially limited the visualization of some coating irregularities and was less suitable for quantification of (subtle) irregularities. Therefore, we used SEM to verify, categorize, and quantify the irregularities.

Only very few SEM-data on DES coating irregularities have been published so far. Otsuka et al. used SEM to describe polymer irregularities on first-generation DES.(13) The authors observed webbing in Taxus Express stents, however, they reported no quantitative

information on incidence and size of this and other polymer irregularities. Ormiston et al. presented data on both SEM and environmental SEM examination of some DES, including Taxus Express and Enveavor (Sprint) stents with phosphorylcholine-based coatings.(23) Some of the irregularities quantified in our study such as webbing and crater irregularities are consistent with the findings of Ormiston and coworkers. The Food and Drug Administration (FDA) recently reported the presence of microcracks in the drug-polymer layer and areas of (apparent) coating loss in Phosphorylcholine-based Endeavor (Sprint) stents.(24) This information is consistent with our findings.

Elasticity of coating and irregularity formation. The geometry of the stent platform, details of the process of coating stent, and both composition and physical characteristics of the coating (e.g., elasticity) may contribute to the reproducible shape and location of certain irregularities. DES expansion stretches the coating. This may lead to wrinkles if the elasticity of coating is high (Taxus Liberté, Xience V), while it may lead to cracks if the elasticity is low (Endeavor Sprint and Resolute). In line with this is the fact that adhesion of the polymer coating on adjacent stent struts (so-called webbing) was mainly seen in Taxus Liberté, while Endeavor Sprint, Endeavor Resolute, and (to a lower extent) Xience V showed the so-called crater lesion, which is presumably the pendant to webbing in DES with less elastic coatings.

Implications. The present in-vitro data should be interpreted cautiously, as the value of DES should be primarily judged based on clinical data. Nevertheless, in-vitro data may sometimes help to find explanations for differences in clinical outcome or surrogate endpoints by coronary angiography, intravascular ultrasound, or optical coherence tomography.

The local antiproliferative potential of DES may be reduced at sites of major polymer loss, particularly at bare metal areas. We found a relatively large size of such irregularities in Endeavor Sprint stents, which could be related to the somewhat higher restenosis rate of this stent as compared to the Cypher stent (Cordis Corporation, Miami Lakes, FL,USA);(25) nevertheless, the restenosis rate of this stent was significantly lower than that of BMS.(26)

The size of polymer irregularities was mostly smaller on the more recently introduced DES types (Endeavor Resolute, Xience V) compared to earlier DES types (Endeavor Sprint, Taxus Liberté). Irregularities with inhomogeneous or displaced polymer coating increase roughness of DES and thus thrombogenicity. In addition, detachment of coating material could be a source of microembolism; this risk may be insignificant as durable-polymer based DES were previously associated neither with increased periprocedural cardiac marker release nor with increased in-hospital major events.(2;25;27;28) Nevertheless, Virmani et al. showed that hypersensitivity reaction to durable polymer fragments can play a role in the process of late and very late in-DES thrombus formation,(29) a problem which may be partly solved by biodegradable coatings or biodegradable stents / DES.(21;30-33)

Limitations. As an inherent limitation of benchside studies, the present in-vitro study does not exactly mimic the conditions in vivo. Even DES with somewhat less favourable

SEM appearance may be clinically highly efficacious and safe. For example, a higher biocompatibility of certain DES coatings may compensate for a somewhat higher incidence of certain irregularities on these coatings. Therefore, clinical data are most important to form a prudent opinion of a DES. Nevertheless, we feel that a meticulous SEM examination of the DES surface (including quantitative assessment) is important because it adds valuable information to the overall picture of a DES and may in sometimes help to understand clinical data. During stent delivery (in clinical practice), potential **s**hear between the (abluminal) DES surface and the vessel wall may lead to additional defects that may vary depending on characteristics of target lesion and vessel (e.g., vessel tortuosity; calcification; lesion location) and characteristics of DES (e.g., stent platform; coating). Nevertheless, the assessment of this complex issue is beyond the scope of the present in vitro study. In our experimental setup, we did not implant stents in vessels or vascular phantoms; implantation in vessels or vascular phantoms might have reduced some irregularities. However, our current experimental approach avoided any additional defect that could have resulted from scratching the DES along (calcified) vessel walls or from regaining DES out of vascular phantoms or specimens. Our data were obtained in DES with a nominal diameter of 3.5 mm; findings may be somewhat different in small DES, e.g. in DES with a diameter of 2.25 or 2.5 mm.

Expansion in water followed by drying could theoretically have affected the more hydrophilic DES coatings (e.g., aggravate some coating irregularities). The use of environmental SEM may avoid this problem, however, comparing images obtained in our SEM study with illustrations of studies with environmental SEM in corresponding DES (23), we found identical irregularities with a very similar severity. But due to technical issues, environmental SEM may be less suitable for quantitative studies such as the present study.

Conclusions. Scanning electron microscopic assessment of the incidence and size of irregularities in the drug-eluting coating of four types of commercially available DES demonstrated significant differences between DES types. Our data may be considered in the ongoing discussion on between-DES differences and may serve as reference to compare novel DES.

ACKNOWLEDGEMENT

We are very grateful to Jan Feijen, MSc PhD, Professor in Biomaterials and Polymer Chemistry and Scientific Director of the Institute for Biomedical Technology (BMTI) at the University of Twente in Enschede for his valuable suggestions and for proofreading the manuscript. While free DES samples were provided by Abbott Vascular and Medtronic Inc., no financial support was obtained; the study was investigator-initiated.

REFERENCES

1. Colombo A, Drzewiecki J, Banning A et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788-94.
2. 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;349:1315-23.
3. Serruys PW, Degertekin M, Tanabe K et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL trial. Circulation 2002;106:798-803.
4. von Birgelen C, Erbel R. The stent is here to stay: a note on stenting, ultrasound imaging, and the prevention of restenosis. Eur Heart J 2002;23:595-7.
5. Stettler C, Wandel S, Allemann S et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937-48.
6. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989-97.
7. Schömig A, Dibra A, Windecker S et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373-80.
8. Kastrati A, Mehilli J, Pache J et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030-9.
9. Daemen J, Wenaweser P, Tsuchida K et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667-78.
10. 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;52:1134-40.
11. Mani G, Feldman MD, Patel D, Agrawal CM. Coronary stents: a materials perspective. Biomaterials 2007;28:1689-710.
12. Ormiston J, Webster M, Ruygrok P, et al. Polymer integrity after Cypher and Taxus stent implantation: A scanning electron microscope study. http://www.tctmd.com.
13. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. J Invasive Cardiol 2007;19:71-6.
14. FDA Summary of Safety and Effectiveness Data of Taxus Liberté. P060008. 10-10-2008. http://www.fda.gov/cdrh/pdf6/p060008b.pdf. Last accessed on 01-12-2008.
15. Pinto Slottow TL, Waksman R. Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on the endeavor zotarolimus-eluting coronary stent. Circulation 2008;117:1603-8.
16. Meredith IT, Worthley S, Whitbourn R et al. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Resolute first-in-man trial. EuroIntervention 2007;3:50-3.
17. Stone GW, Midei M, Newman W et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903-13.
18. 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;115:2435-41.
19. Palmaz JC, Benson A, Sprague EA. Influence of surface topography on endothelialization of intravascular metallic material. J Vasc Interv Radiol 1999;10:439-44.
20. Hecker JF, Scandrett LA. Roughness and thrombogenicity of the outer surfaces of intravascular catheters. J Biomed Mater Res 1985;19:381-95.
21. Daemen J, Serruys PW. Drug-eluting stent update 2007: part I. A survey of current and future generation drug-eluting stents: meaningful advances or more of the same? Circulation 2007;116:316-28.
22. Schwartz RS, Edelman ER, Carter A et al. Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. Circulation 2002;106:1867-73.
23. Ormiston J, Panther M, Pornratanarangsi S, et al. The “Pitiful polymer, scanning electron microscope observations.”. TCT 2005, http://www.tctmd.com.

24. FDA Summary of Safety and Effectiveness Data Endeavor. http://www.fda.gov/cdrh/pdf6/p060033b.pdf. P060033, 21. 10-10-2007. Last accessed on 01-12-2008.
25. Kandzari DE, Leon MB, Popma JJ et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440-7.
26. 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;48:193-202.
27. Bertrand OF, Faurie B, Larose E et al. Clinical outcomes after multilesion percutaneous coronary intervention: comparison between exclusive and selective use of drug-eluting stents. J Invasive Cardiol 2008;20:99-104.
28. Barlis P, Kaplan S, Dimopoulos K, Ferrante G, Di Mario C. Comparison of bare-metal and sirolimus- or paclitaxel-eluting stents for aorto-ostial coronary disease. Cardiology 2008;111:270-6.
29. 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;109:701–5.
30. Windecker S, Serruys PW, Wandel S et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
31. Erbel R, Di Mario C, Bartunek J, for the PROGRESS-AMS Investigators. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. Lancet 2007;369:1869–75.
32. 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;371:899–901.
33. Di Mario C, Ferrante G. Biodegradable drug-eluting stents: promises and pitfalls. Lancet 2008;371:874–5.

CHAPTER 3

MICRO-COMPUTED TOMOGRAPHIC ASSESSMENT FOLLOWING EXTREMELY OVERSIZED PARTIAL POSTDILATATION OF DRUG-ELUTING STENTS

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ABSTRACT

Aim. To assess the spatial geometry of drug-eluting stents (DES) following extremely oversized proximal postdilatation. Interventions of distal left main (LM) disease generally require stenting across the LM bifurcation with inherent vessel tapering along this segment and a high likelihood of stent malapposition, which can be avoided by such postdilations.

Methods and Results. 16 DES (four 3.5mm-samples of Cypher Select Plus, Taxus Liberté, Endeavor Resolute, Xience V) were deployed in water; 12 samples were then proximally postdilated with non-compliant 5.0-mm-balloons at 18atm. All samples were examined by micro-computed tomography. Taxus Liberté, Endeavor Resolute, and Xience V, showed increased cell areas in the transitional region (just distal to postdilated region), while Cypher Select showed its largest cells inside the postdilated region. Overall, the largest maximum cell area was observed in Endeavor Resolute while Cypher Select showed the smallest ($p<0.001$, for both). In addition, the size of the very proximal postdilated cells was relatively small in most DES except Xience V.

Conclusions. Extremely oversized partial stent postdilatation demonstrated significant between-DES differences in final spatial stent configuration and maximum cell size. These data could be of practical interest with regard to coronary interventions in LM stems with stenting across the LM bifurcation.

ABBREVIATIONS

DES: drug-eluting stent
Micro-CT: micro-computed tomography
PCI: percutaneous coronary intervention
LM: left main

There is growing evidence that – in case of a favorable anatomy – percutaneous coronary interventions (PCI) with drug-eluting stents (DES) may represent a valuable alternative to coronary artery bypass grafting for the treatment of significant left main (LM) coronary artery disease.[1,2] Recently, it has been suggested that DES use in unprotected left main disease should be considered as IIa recommendation.[3] Isolated mid LM stenoses can frequently be treated by stenting the left main stem only, while distal LM disease represents a more challenging situation as it requires stenting of the transition between the distal LM stem and a proximal segment of one of the major left coronary branches with inherent major tapering and very substantial differences in lumen size between the distal and proximal part of the coronary segment to be stented.[4] In this setting, oversized postdilatation of the proximal part of the stent (inside the LM stem) will generally be mandatory to avoid stent malapposition, which could promote DES thrombosis and restenosis.[5-8] Such partial postdilation often requires significant oversizing of the balloon compared to the nominal diameter of the implanted stent (Figure 1), which may affect the final geometrical stent configuration and the size of stent cells with potential consequences for sidebranch access.[9] The response of DES geometry to such extremely oversized postdilatation of the proximal stent segment is greatly unknown. In the present benchside study, we used micro-computed tomography (Micro-CT) to examine this issue in four types of commercially available DES.

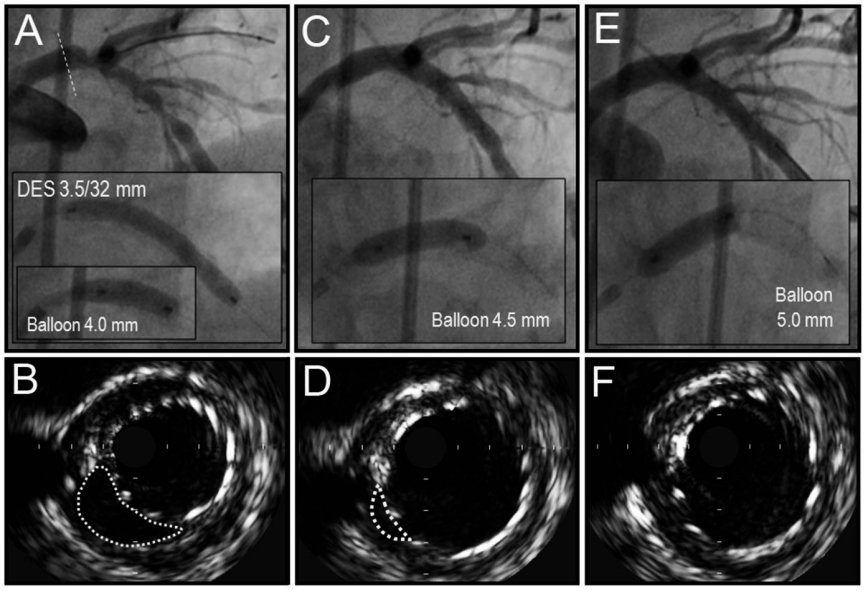

Figure 1. DES malapposition in the left main stem corrected by extremely oversized partial (proximal) postdilation of the DES. A) Implantation of 3.5/32mm DES with subsequent postdilation with 4.0mm balloon. **B)** DES malapposition in the LM stem demonstrated by intravascular ultrasound (indicated by dotted gray line). **C)** Postdilation with 4.5mm balloon. **D)** Persistence of minor malapposition. **E)** Postdilation with 5.0mm balloon. **F)** Disappearance of malapposition in the postdilated stent region.

METHODS

DES samples examined. We examined 4 types of commercially available DES.A total of 16 DES was examined: 4 Cypher Select Plus™ (Cordis Europa, Roden, Netherlands), 4 Taxus Liberté™ (Boston Scientific Corp., Natick, MA, USA), 4 Endeavor Resolute™ (Medtronic Vascular, Santa Rosa, CA, USA), and 4 XIENCE V™ (Abbott Vascular, Santa Clara, CA, USA). Stent dimensions were 3.5x23mm for Cypher Select and Xience V and 3.5x24mm for Endeavor Resolute, and Taxus Liberté.

Cypher Select is based on a laser-cut stainless steel platform (based on a modification of BX Velocity; strut thickness 140µm with 7 links between each two adjacent rings), covered with a primer layer of paralyne C and a main coating layer made of polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA) and Sirolimus.[10] Taxus Liberté is based on a laser-cut, stainless steel stent platform (Liberté™; strut thickness 97µm with 3 links between adjacent stent rings, coated with a 17.8µm-thick layer of SIBS(styrene-b-isobutylene-b-styrene) polymer and Paclitaxel.[11]

Endeavor Resolute is based on the a cobalt-chromium stent platform (Driver™; strut thickness 91µm), which is made of stent rings that are laser-welded at 2 to 3points, the stent is covered by 5.6µm-thick (information obtained from manufacturer) Biolinx™ polymer and Zotarolimus.[12]

Xience V is based on a laser-cut, cobalt-chromium stent platform (Vision™, strut thickness 81µm) that consists of stent rings that are connected by 3 multi-links, covered by a 7.8µm-thick layer of fluoropolymer and Everoliums.[13]

DES expansion protocol. All stents (sterile packed; expiration date not passed) were expanded at 14atm by an interventional cardiologist under sterile conditions in a sterile water bath at 37ºC. Consecutively, the proximal part of 12 DES sample (3 of each DES type) were postdilated at 18atm with 5.0/12mm non-compliant balloon catheters (Quantum Maverick Monorail™; Boston Scientific Corp., Natick, MA, USA). Four samples (one sample of each DES type) were not postdilated and were used as control samples. All DES were consecutively dried under laminar air flow. Stent expansion, drying, and examination of the samples were performed at the University of Twente in Enschede at an experimental laboratory with laminar air flow, being almost free from dust. Figure 2 demonstrates the location of the postdilatation balloon (and the balloon markers) in relation to the stent.

Nomenclature of stent regions: (1) distal “non-postdilated region” subjected to the 14 atm expansion pressure only; (2) proximal “postdilated region” subjected to both 14 atm implantation pressure plus postdilatation with a 5.0/12 mm noncompliant balloon at 18 atm; (3) the “transitional region” between the two aforementioned regions in which the stent diameter showed a gradual decline.

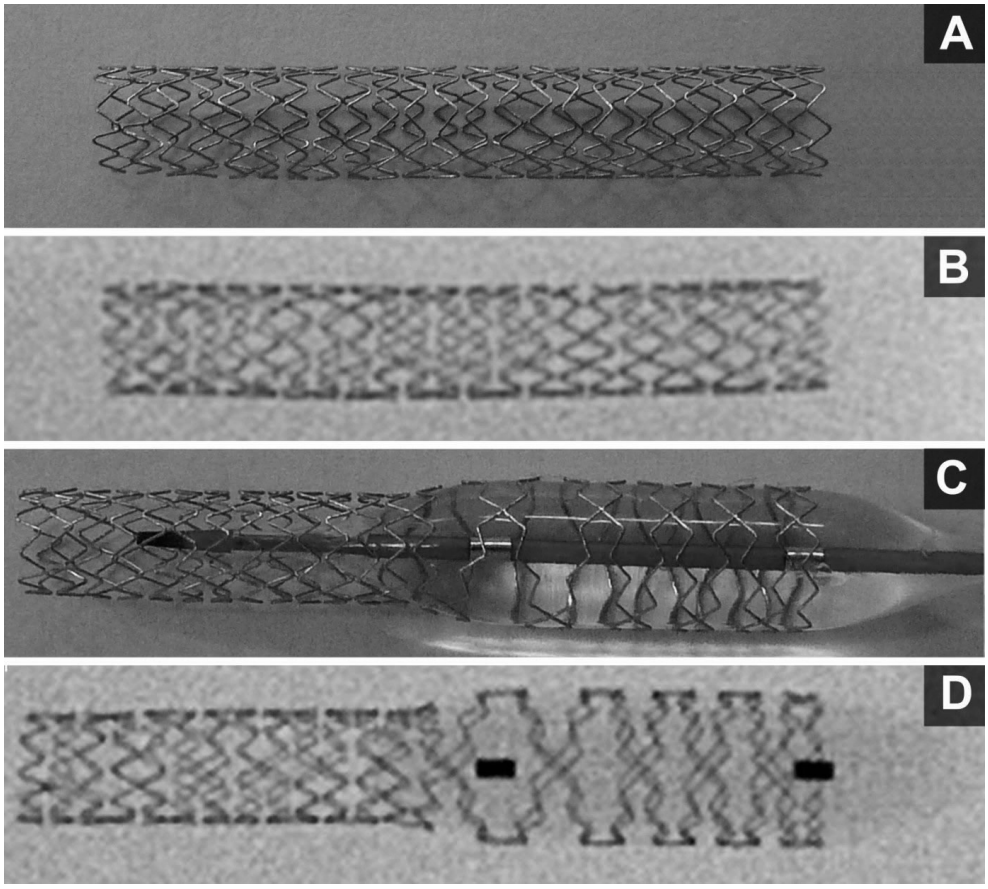

Figure 2. **DES postdilatation (example of Endeavor Resolute stent): A)** Photograph of DES after expansion at 14 atm; **B)** high resolution radiographic image of A; **C)** photograph of partial proximal postdilatation with 5 mm non-compliant balloon at 18 atm; **D)** high resolution radiographic image of C (please note the large size of stent cells at the position of the distal balloon marker).

Micro-CT examination: Four samples of each of the 4 DES types (n=16) were examined with the Explore Locus SP Micro-CT (GE Healthcare, Milwaukee, WI, USA). The grayscale image data obtained from the Micro-CT scan were thresholded to distinguish between stent voxels and space voxels. The spatial resolution applied was 8µm (voxels being 8×8×8µm^3 volume-elements). Due to the metal nature of the scanned stent samples, a copper filter was applied for optimal visualization. Visual assessment of 3D-reconstruction of each DES-sample was followed by a meticulous quantitative analysis.

The *spaces between adjacent stent rings* were numbered from proximal to distal. *Links* between adjacent stent rings (see above for details on links in description of DES samples) divided each space into 2, 3, or 7 *stent cells*. Stent diameters were measured at the middle

of each space between adjacent stent rings. In addition, at each space between adjacent stent rings we measured the size of *cell areas*. To accurately measure the area of stent cells, cells were subdivided into small triangles and measurable quadrangles which allowed the measured areas to follow the spatial structure of the stents. The areas of these shapes were subsequently measured and added up to form the total area of a stent cell; five cell area measurements for each space between adjacent stent rings for each individual DES type were performed (total of 330; 290 cells of postdilated stents and 40 cells of control stents). In addition, the *distances between adjacent stent rings* along each DES sample were measured, which permitted the quantification of longitudinal stent stretch in the transitional regions (expressed as percentage of between-ring distances in control samples).

Data analysis and statistics: Data are presented as a mean±1SD. Between-DES comparison of the areas of corresponding stent cells was performed by using Kuskal-Wallis test and Mann-Whitney test. While P-values <0.05 were generally considered significant, Bonferroni-Holm's correction was applied for multipe testing. Statistical analyses were performed with the software of SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Visual assessment of 3D-reconstructed Micro-CT image data. In animated 3D-reconstructions of the DES samples (Figure 3, Videos 1-8), the closed cell-designed Cypher Select stent showed its largest cells in the postdilated stent region, while the other DES (with an open-cell design) showed the maximum cell areas in the transitional region just distal to the postdilated region (i.e., at the level of the distal marker of the postdilatation balloon; see Figure 2). The evaluation of cell size was even facilitated when DES were virtually sliced in a longitudinal direction to eliminate overlapping stent struts (panel A of Figures 4-7). In Cypher Select, Taxus Liberté, and Endeavor Resolute, the most proximal stent cells in the postdilated stent region were somewhat smaller than other cells in that region.

Measurements of stent diameter. Stent diameter of Cypher Select, Taxus Liberté, Endeavor Resolute, and Xience was in the control samples Diameter values in controls 3.62±0.06mm, 3.75±0.16mm, 3.63±0.04mm, and 3.64±0.095mm, respectively. In the non-postdilated stent region (measured distal to the transitional region), the stent diameter measured 3.45±0.2mm,3.59±0.09mm, 3.55±0.06mm, and 3.62±0.09mm, while in the postdilated region it measured 4.88±0.04mm, 4.85±0.04mm, 4.78±0.06mm, and 4.82±0.06mm, respectively (Figures 4-7).

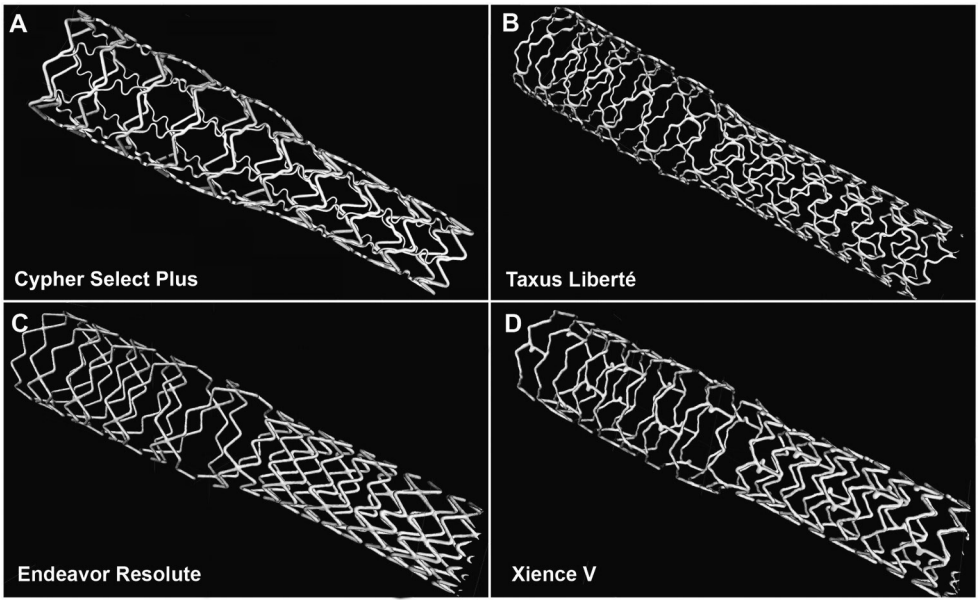

Figure 3. Micro-CT 3D-image reconstruction of the four DES examined.

Measurement of stent cell area. The measured cell area (n=40) in the control samples were: 3.48±0.29mm^2, 3.62±0.14mm^2, 6.49±0.25mm^2, 4.83±0.26 mm^2 for Cypher Select, Taxus Liberté, Endeavor Resolute, and Xience V respectively.

Measurements of 290 cell areas along the postdilated DES samples are presented in Figures 4-7. The maximum cell area (for all DES but the Cypher Select stent being located in the transitional stent region) differed between DES types ($p<0.001$): It was largest in Endeavor Resolute (14.05±0.37mm^2; 216% of the cell area of control sample; $p<0.01$); it was smallest in Cypher Select (3.48±0.27mm^2; 140% of the cell area of control sample; $p<0.01$); both Xience V (8.58±0.38mm^2; 183% of the cell area of control sample) and Taxus Liberté (6.34±0.11mm^2; 175% of the cell area of control sample) showed an intermediate size.

Distances between adjacent rings of each stent were measured to examine the longitudinal expansion of stent cells, which was found to be greatest just distal to the postdilated region (transitional region where maxium cell areas were in open-cell design DES). At that site, the between-ring distance was significantly larger ($p<0.01$) in Endeavor Resolute 3.33±0.07mm (181±4% of the distance between adjacent stent rings in the control sample) compared to both, Xience V 1.87±0.06mm (166±5%) and Taxus Liberté 2.25±0.05mm (165±3%). Only the postdilated Cypher Select did not demonstrate such pattern. In all DES but Xience V, the smallest between-ring distance of the postdilated region was noticed in the most proximal postdilated region (Figures 4-7).

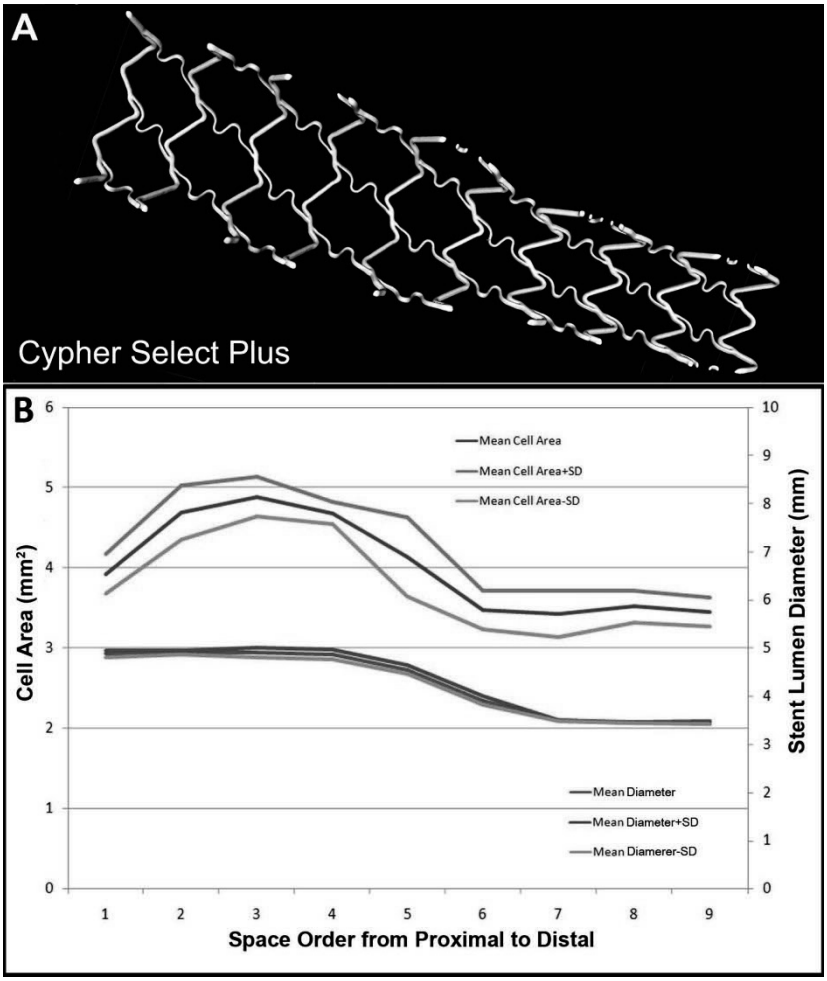

Figure 4. **Cypher Select. A)** Micro-CT image of virtually sliced DES with only slighly larger cells in the mid postdilated region. **B)** The horizontal axis represents the cell order from proximal to distal (e.g., cell 1 represents the most proximal cells, located in the space between the two most proximal stent rings). The upper curve represents area measurements of stent cells (see left vertical axis); the lower curve represents stent diameter (see right vertical axis) from the postdilated stent region (left) through the transitional region (mid) to the non-postdilated region (right).

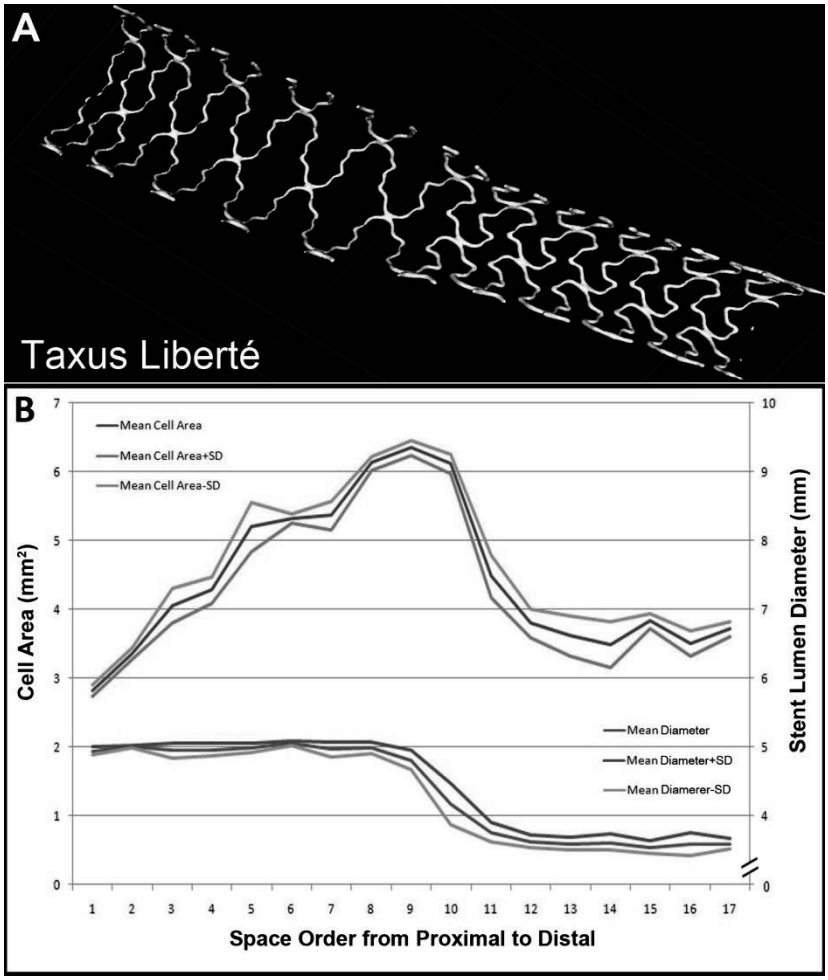

Figure 5. **Taxus Liberté. A)** Micro-CT image of virtually sliced DES with larger cells in the transitional region. The cells in the most proximal part of the postdilated region (left hand side) are smaller. **B**) See legend to Figure 4.

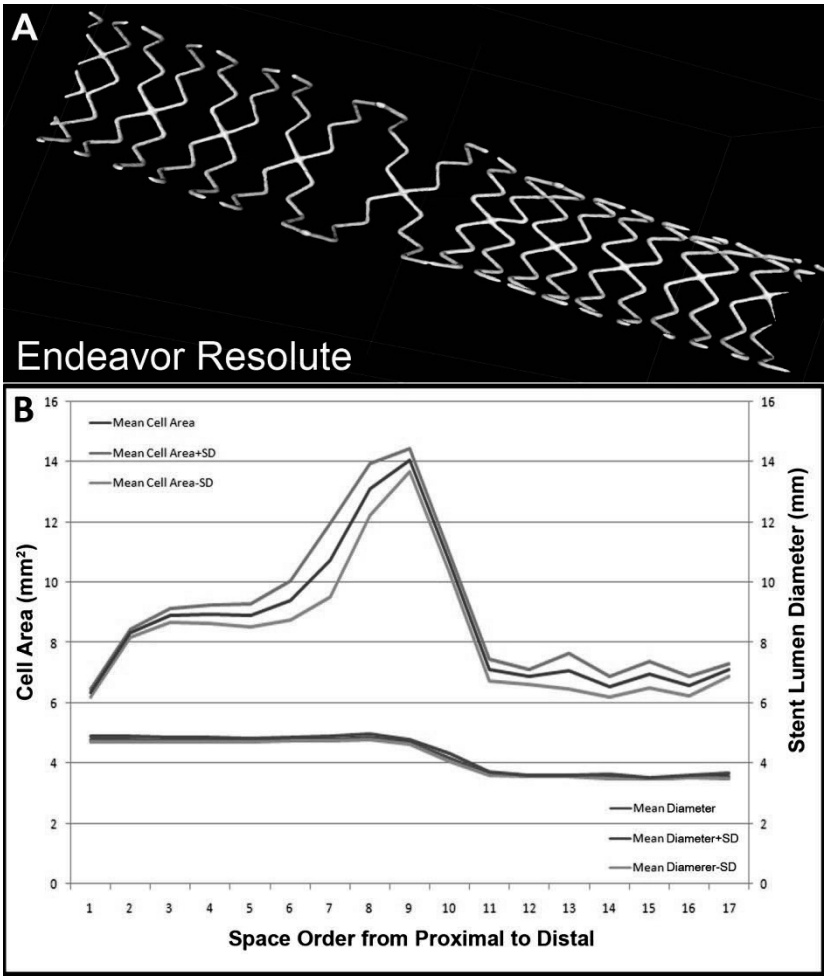

Figure 6. **Endeavor Resolute. A)** Micro-CT image of virtually sliced DES with increased cell size in transitional region and somewhat reduced cell size in the most proximal postdilated region. **B**) See legend to Figure 4.

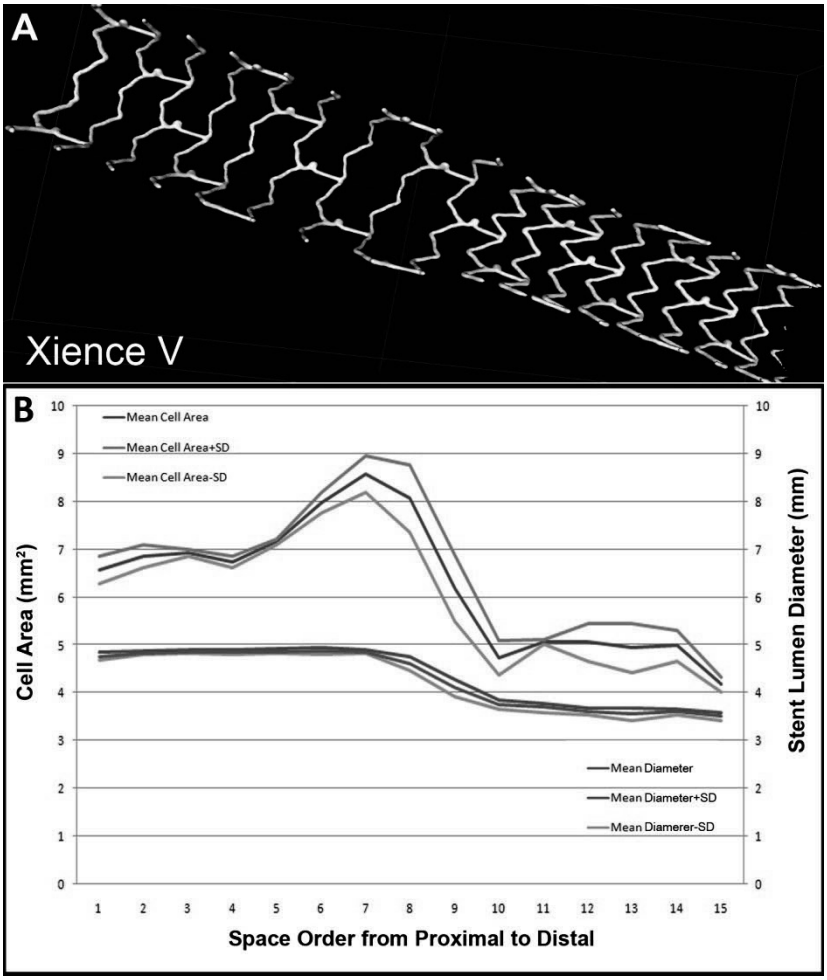

Figure 7. **Xience V. A)** Micro-CT image of virtually sliced DES with increased cell size in transitional region. **B**) See legend to Figure 4.

DISCUSSION

Rationale and design of the study. Significant LM stenoses can be observed in 6-18% of patients undergoing diagnostic coronary angiography [14,15] and involve in two thirds the *distal* LM stem.[16] In the era of DES implantation, such lesions still carry a particularly high PCI-risk (compared to lesions in proximal or mid LM stems) [17,18] as they require stenting of the transition between the distal LM stem and/or the proximal left anterior descending or circumflex artery with inherent major vessel tapering (i.e., very substantial difference in vessel size between distal and proximal parts of the segment to be stented).

The size of the proximal left anterior descending or circumflex artery will generally limit the maximum nominal stent diameter that can be safely implanted without significant risk of dissection. This will usually lead to significant undersizing and malapposition of the DES in the distal LM stem which could (if not corrected) promote DES thrombosis.[19] Therefore, significantly oversized postdilatation of the proximal part of the DES will usually be required.[5-7] However, the consequence of this practice for DES geometry are greatly unknown and may differ between various DES types.

In the present study, DES with a nominal diameter of 3.5mm were examined as this diameter corresponds well with the size of most proximal left anterior descending coronary arteries. All DES were first expanded at 14atm as in previous benchside studies;[20,21] the proximal part of all DES was then postdilated with a 5.0mm non-compliant balloon to achieve approximately 130% stent overexpansion in diameter which corresponds well with usual left main stem dimensions.[4]

Configuration of DES. Visual assessment of coronary stent configuration has provided useful information on stent deformation in the context of bifurcation stenting. [22-25] More recently, Ormiston et al. performed bench-side testing of the crush technique in DES with Micro-CT.[26] Micro-CT is a precise imaging modality that permits high resolution, nondestructive imaging and 3D-reconstruction of spatial objects to be examined.[27] The technique is very suitable to accurately measure small distances between stent struts. In this study, we used Micro-CT to visualize the struts of the stent platforms of four DES types, while structural irregularities of DES coatings are better visualized by other techniques such as scanning electron microscopy (SEM).[28]

In our present benchside study, all four DES types showed an acute increase in cell area. In Taxus Libeté, Endeavor Resolute, and Xience V, this increase was located in the transitional region (just distal to the postdilated region). Only Cypher Select showed its largest cell areas inside the postdilated stent region. Overall, the largest maximum cell area was observed in Endeavor Resolute while Cypher Select showed the smallest ($p<0.001$, for both).

In this study, we were able to demonstrate the main mechanisms that led to this increase in stent cell area. Due to the difference in stent diameter between the postdilated and the non-postdilated region, stent cells in the transitional region were exposed to forces that led to both, (1) circumferential stent expansion (gradually decreasing from proximal to distal) and (2) longitudinal stent expansion (average stretch ranged from 165% to 181% for different open-cell DES). Differences in design and material of the bare metal platform may account for between-DES differences in maximum cell area. For example, the closed cell design Cypher Select showed the smallest increase in the cell area and no longitudinal expansion between stent rings. In addition, it is very likely that stent material and design also account for the observed differences in spatial configuration of the proximal postdilated region. In fact, only Xience V showed a fairly invariable cell size along the postdilated region.

Mortier et al. used Micro-CT data of various DES for the calculation of the maximum theoretically achievable stent cell area.[9] In parallel with Mortier et al., we found the largest cell areas in Endeavor Resolute stents (DES based on Driver bare metal stent). In the present study, the measured maximum cell size differed between Taxus Liberté and Xience V, while according to calculations by Mortier et al. (based on Micro-CT data), the maximally achievable stent cell area should be the same.[9] Of note, the mechanisms that led to the maximum cell size (measured or presumed) differed between both studies (i.e., extremely oversized postdilatation of proximal part of DES only vs. postdilatation of stent cell with balloon catheter through stent struts). Therefore, *both* studies may be right; balloon dilatation through the struts of DES may thus result in similarly sized cells for Taxus Liberté and Xience V, however, after highly oversized partial postdilatation of DES (without balloon dilatation through stent struts), no such cell size was measured.

Implications. Between various DES types, there was a significant difference in the size of the largest stent cells that were for most DES types located in the transitional stent region (just distal to the postdilated region). This may be of practical interest in the context of distal LM stenting, as very large stent cells in DES provide better side branch access but can be disadvantageous with regard to plaque scaffolding and prevention of recoil and restenosis.[29] In the clinical setting, larger DES cells in the transitional region may be associated with less plaque coverage, which may have also consequences for drug distribution. Smaller stent cells – on the other hand – may provide better plaque scaffolding and prevention of recoil and restenosis while side branch access is often more difficult. An intermediate maximum cell size may represent a compromise between both extremes. The demands on a DES of choice for distal LM stenting may vary significantly between individual patients, depending on the specific lesion morphology and plaque distribution, and on sidebranch involvement with or without need for sidebranch access (e.g., in partially bypass-protected LM stems (see Figure 1) and in the presence of small or occluded LM sidebranches, access may not be required). As in the present benchside study the maximum cell size differed between DES types, it may be allowed to hypothesize that there could be a difference between DES with regard to the necessity to perform final kissing balloon inflations following DES procedures in the distal LM stem.

Changes in stent length may also have clinical implications. Partial postdilatation of open-cell design stents in the current study resulted in DES elongation in the transitional stent region. In addition, most DES types demonstrated shortening of the most proximal part of the postdilated region. Changes in stent length could result in endothelial damage, however, in the clinical setting, the stent struts will be lodged in the arterial wall which could limit changes in stent length as observed in vitro.

Limitations. The present in vitro data should be interpreted cautiously as bench side studies cannot exactly mimic conditions in vivo. Nevertheless, we feel that meticulous Micro-CT examinations are important because they add valuable information to the overall picture of a DES and may help to interpret clinical data. DES were not implanted in standard vascular phantoms as they could have limited significant partial DES oversizing, which was critically important for this study protocol. The consequences of simultaneous (kissing) balloon inflations on DES geometry were not addressed in the present study but may be subject of further research. However, as two-balloon approaches are inevitably associated with some oversized partial DES postdilatation, our present study addresses a major component of the optimization process of stents implanted along major coronary bifurcations.

Conclusions. In four commercially available DES, extremely oversized postdilatation of the proximal stent region demonstrated significant differences in final spatial configuration and maximum cell size, which was found inside the postdilated stent region of a closed-cell DES and just distal to the postdilated region in various open-cell design DES. The findings of this benchside study could be of practical interest in the context of left main interventions with stenting across the left main bifurcation, where the choice of DES may depend upon lesion morphology, plaque distribution, side-branch involvement, and the need for side-branch access.

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Media:
Videos 1-8 are accessible on http://www.pcronline.com/eurointervention/27th_issue/21/

REFERENCES

(1) Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-972.

(2) Buszman PE, Buszman PP, Kiesz RS, Bochenek A, Trela B, Konkolewska M, Wallace-Bradley D, Wilczynski M, Banasiewicz-Szkrobka I, Peszek-Przybyla E, Krol M, Kondys M, Milewski K, Wiernek S, Debinski M, Zurakowski A, Martin JL, Tendera M. Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. *J Am Coll Cardiol* 2009;54:1500-1511.

(3) Kandzari DE, Colombo A, Park SJ, Tommaso CL, Ellis SG, Guzman LA, Teirstein PS, Tamburino C, Ormiston J, Stone GW, Dangas GD, Popma JJ, Bass TA. Revascularization for unprotected left main disease: evolution of the evidence basis to redefine treatment standards. *J Am Coll Cardiol* 2009;54:1576-1588.

(4) Ge J, Erbel R, Gerber T, Gorge G, Koch L, Haude M, Meyer J. Intravascular ultrasound imaging of angiographically normal coronary arteries: a prospective study in vivo. *British Medical Journal* 1994;71:572-578.

(5) Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 2005;45:995-998.

(6) Alfonso F, Suarez A, Perez-Vizcayno MJ, Moreno R, Escaned J, Banuelos C, Jimenez P, Bernardo E, Angiolillo DJ, Hernandez R, Macaya C. Intravascular ultrasound findings during episodes of drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;50:2095-2097.

(7) Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007;115:2426-2434.

(8) Price MJ, Cristea E, Sawhney N, Kao JA, Moses JW, Leon MB, Costa RA, Lansky AJ, Teirstein PS. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. *J Am Coll Cardiol* 2006;47:871-877.

(9) Mortier P, Van Loo D, De Beule M, Segers P, Taeymans Y, Verdonck P, Verhegghe B. Comparison of drug-eluting stent cell size using micro-CT: important data for bifurcation stent selection. *EuroIntervention* 2008;4:391- 396.

(10) Serruys PW, Regar E, Carter AJ. Rapamycin eluting stent: the onset of a new era in interventional cardiology. *Heart* 2002;87:305-307.

(11) FDA Summary of Safety and Effectiveness Data of Taxus Liberté. 2008. Report No.: P060008.

(12) Meredith IT, Worthley S, Whitbourn R, Walters D, Popma J, Cutlip D, Fitzgerald P. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Resolute first-in-man trial. *EuroIntervention* 2007;3:50-53.

(13) Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 2008;299:1903-1913.

(14) Proudfit WL, Shirey EK, Sones FM, Jr. Distribution of arterial lesions demonstrated by selective cinecoronary arteriography. *Circulation* 1967;36:54-62.

(15) Sukhija R, Yalamanchili K, Aronow WS. Prevalence of left main coronary artery disease, of three- or four-vessel coronary artery disease, and of obstructive coronary artery disease in patients with and without peripheral arterial disease undergoing coronary angiography for suspected coronary artery disease. *Am J Cardiol* 2003;92:304-305.

(16) Cameron A, Kemp HG, Fisher LD, Gosselin A, Judkins MP, Kennedy JW, Lesperance J, Mudd JG, Ryan TJ, Silverman JF. Left main coronary artery stenosis: angiographic determination. *Circulation* 1983;68:484-489.

(17) Valgimigli M, Malagutti P, Aoki J, Garcia-Garcia HM, Rodriguez Granillo GA, van Mieghem CA, Ligthart JM, Ong AT, Sianos G, Regar E, Van Domburg RT, De FP, de JP, Serruys PW. Sirolimus-eluting versus paclitaxel-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: a combined RESEARCH and T-SEARCH long-term analysis. *J Am Coll Cardiol* 2006;47:507-514.

(18) Chen SL, Ye F, Zhang JJ, Liu ZZ, Lin S, Zhu ZS, Sun XW, Li F, Zhang AP, Chen JG, Ji QJ, Qian J, Chen F, Kwan TW. Distal left main coronary bifurcation lesions predict worse outcome in patients undergoing percutaneous implantation of drug-eluting stents: results from the Drug-Eluting Stent for the Treatment of Left Main Disease (DISTAL) Study. *Cardiology* 2009;113:264-273.
(19) Ramcharitar S, Ligthart J, van der Giessen WJ. Stent undersizing can result in procedure-related very late stent thrombosis. *J Invasive Cardiol* 2007;19:E276-E277.
(20) Basalus MW, van Houwelingen KG, Ankone M, de Man FH, von Birgelen C. Scanning electron microscopic assessment of the biodegradable coating on expanded biolimus-eluting stents. *EuroIntervention* 2009;5:505-510.
(21) Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. *EuroIntervention* 2009;5:157-165.
(22) Ormiston JA, Webster MW, Ruygrok PN, Stewart JT, White HD, Scott DS. Stent deformation following simulated side-branch dilatation: a comparison of five stent designs. *Catheter Cardiovasc Interv* 1999;47:258-264.
(23) Ormiston JA, Currie E, Webster MW, Kay P, Ruygrok PN, Stewart JT, Padgett RC, Panther MJ. Drug-eluting stents for coronary bifurcations: insights into the crush technique. *Catheter Cardiovasc Interv* 2004;63:332-336.
(24) Ormiston JA, Webster MW, El JS, Ruygrok PN, Stewart JT, Scott D, Currie E, Panther MJ, Shaw B, O'Shaughnessy B. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. *Catheter Cardiovasc Interv* 2006;67:49-55.
(25) Carrie D, Karouny E, Chouairi S, Puel J. "T"-shaped stent placement: a technique for the treatment of dissected bifurcation lesions. *Cathet Cardiovasc Diagn* 1996;37:311-313.
(26) Ormiston JA, Webster MWI, Webber B, Stewart JT, Ruygrok PN, Hatrick RI. The (crush) technique for coronary artery bifurcation stenting: insights from micro-computed tomographic imaging of bench deployments. *JACC: Cardiovascular Interventions* 2008;1:351-357.
(27) Ritman EL. Micro-computed tomography-current status and developments. *Annu Rev Biomed Eng* 2004;6:185-208.
(28) Basalus MW, von Birgelen C. Benchside testing of drug-eluting stentsurface and geometry. *Interventional Cardiology* 2010;2:in press.
(29) Ako J, Bonneau HN, Honda Y, Fitzgerald PJ. Design criteria for the ideal drug-eluting stent. *Am J Cardiol* 2007;100:3M-9M.

CHAPTER 4

EFFECT OF OVERSIZED PARTIAL POSTDILATATION ON COATINGS OF CONTEMPORARY DURABLE POLYMER-BASED DRUG-ELUTING STENTS: A SCANNING ELECTRON MICROSCOPY STUDY

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ABSTRACT

Background. Oversized DES postdilation is often performed to avoid stent malapposition. In stents implanted in long lesion or major bifurcations, extremely oversized partial postdilation may be required, which exposes DES coating to extreme forces. This study aims to assess shape and incidence of coating irregularities on durable polymer-based drug-eluting stents (DES) following extremely oversized partial post-dilatation.

Methods. Fifteen DES samples (3 3.5 mm stents of Cypher Select plus [Cordis Europa, Roden, the Netherlands], Taxus Liberté[Boston Scientific Corp., Natick, MA, USA], Endeavor Sprint [Medtronic Vascular, Santa Rosa, CA, USA], Endeavor Resolute [Medtronic Vascular, Santa Rosa, CA, USA], and Xience V [Abbott Vascular, Santa Clara, CA, USA]) were deployed in sterile water (37 °C) at 14 atm, followed by a proximal postdilation with noncompliant 5.0-mm balloons at 18 atm. Stents were then examined with scanning electron microscopy.

Results. Thorough examination of a total of 660 scanning electron microscopic images demonstrated that shape and incidence of coating irregularities in the postdilated and/or transitional DES regions differed only mildly from the non-postdilated regions. Cypher Select plus showed more peeling without bare metal aspect in the postdilated and transitional regions, and cracks were wider ($p<0.001$) in the postdilated and transitional regions; in Taxus Liberté one additional irregularity (*torn webbing*) and more wrinkles were observed ($p<0.05$, for both); in Endeavor Resolute wider cracks were found in the extremely postdilated region only ($p<0.001$). Endeavor Sprint and Xience V showed no differences in shape or incidence of coating irregularities between oversized and non-oversized stent regions.

Conclusions. Bench side assessment of five contemporary durable polymer-based DES with scanning electron microscopy suggests that even very aggressive stent postdilatation does not result in a significant increase in the incidence of coating irregularities.

Initially after the publication of the early beneficial drug-eluting stent (DES) data[1-3], the importance of postdilatations for the result of percutaneous coronary interventions (PCI) with DES implantation was underestimated.[4] Meanwhile, DES underexpansion and malapposition were found to be associated with unfavorable outcome, that is restenosis[5-7] and stent thrombosis.[8-12] As a consequence, the importance of DES postdilatation is nowadays increasingly recognized which is reflected in current clinical practice.[4] In both, long lesions and lesions involving major bifurcations, complete DES apposition may be particularly difficult because of significant vessel tapering along the stented segment. In this setting, oversized postdilatation of the proximal part of the stent will generally be mandatory to assure complete stent apposition. Such postdilatation maneuvers may subject DES coatings to variable shear and traction forces, which may vary widely between DES with different coatings and stent designs.[13]

Therefore, we examined in the present study the morphology of the coatings of five contemporary durable polymer-based DES after vigorous oversized partial postdilatation, which is supposed to expose DES coatings to particularly high stress.[14]

METHODS

DES samples examined. We examined 5 types of DES which all share the presence of a durable-polymer component. A total of 15 DES samples were examined: 3 Cypher Select plus (Cordis Europa, Roden, the Netherlands), 3 Taxus Liberté (Boston Scientific Corp., Natick, MA, USA), 3 Endeavor Sprint (Medtronic Vascular, Santa Rosa, CA, USA), 3 Endeavor Resolute (Medtronic Vascular, Santa Rosa, CA, USA), and 3 Xience V (Abbott Vascular, Santa Clara, CA, USA). Stent dimensions were 3.5 × 23 mm for Cypher Select plus and Xience V and 3.5 × 24 mm for Taxus Liberté, Endeavor Sprint, and Endeavor Resolute.

Cypher Select plus is based on a stainless steel platform (strut thickness 140µm) covered with a primer layer of paralyne C and a main coating layer made of polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA) and Sirolimus.[15] Taxus Liberté is based on the stainless steel Liberté bare metal platform (strut thickness 97µm) coated with a 17.8µm thick layer of SIBS(styrene-b-isobutylene-b-styrene) polymer and Paclitaxel.[16] Endeavor Sprint is based on a cobalt-chromium stent platform (Driver; strut thickness 91µm) covered by a 4.8µm thick coating of phosphorylcholine (10%) and Zotarolimus (90%).[17] Endeavor Resolute is also based on the Driver platform, covered by a 5.6 µm thick (information from manufacturer) coating of Biolinx polymer and Zotarolimus.[18] Xience V is based on a cobalt-chromium stent platform (Vision, strut thickness 81µm) covered by a 7.8µm thick layer of fluoropolymer and Everolimus.[19]

DES expansion protocol. All stents (sterile packed; expiration date not passed) were expanded at 14atm by an interventional cardiologist under sterile conditions in a sterile water bath at 37ºC. Stents were expanded in a straight fashion (Figure 1A,1B). As previously described,[13] the proximal part of each DES sample was then postdilated with 5.0/12mm non-compliant balloon catheters (Quantum Maverick Monorail; Boston Scientific Corp., Natick, MA, USA) at 18atm. A single oversized postdilatation was applied in a straight fashion (Figure 1C,1D). An example of stent final configuration is presented in Figure 2. All DES were consecutively dried under laminar airflow. Stent expansion, drying, and examination of the samples were performed at the University of Twente in Enschede at an experimental laboratory under laminar airflow (being almost free from dust).

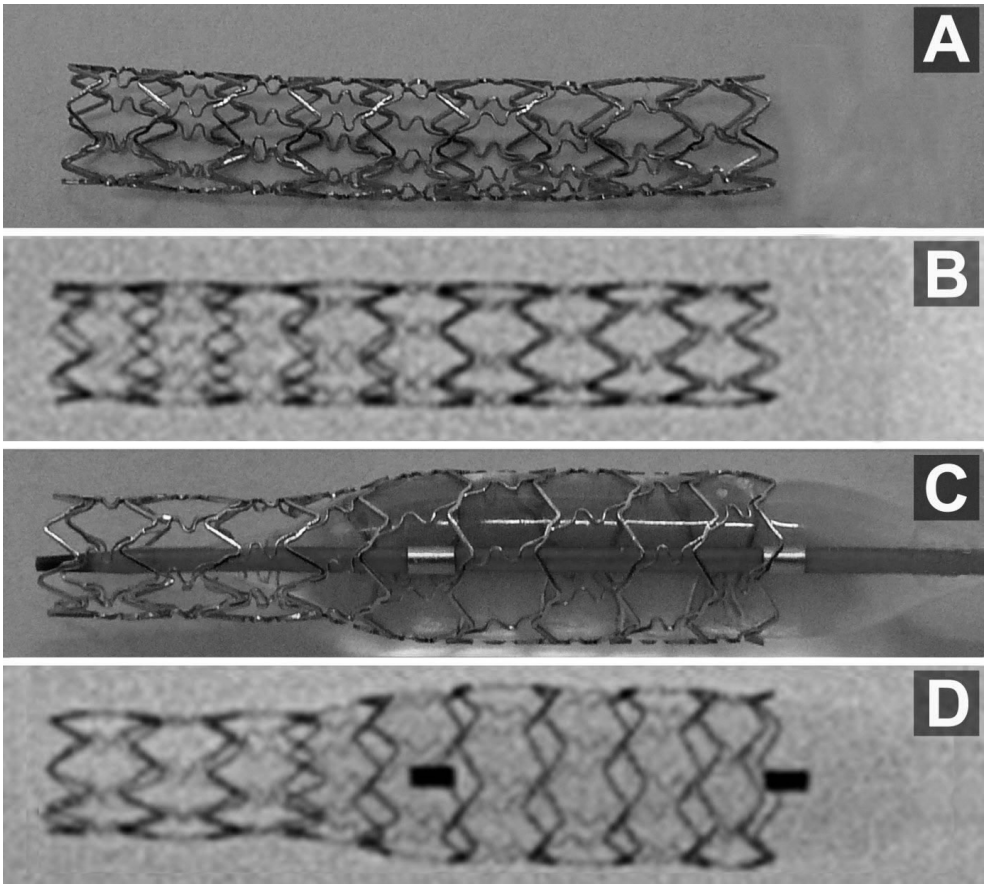

Figure 1. **DES postdilatation (example of Cypher Select stent): A)** Photograph of DES after expansion at 14 atm; **B)** high resolution radiographic image of A; **C)** photograph of partial proximal postdilatation with 5 mm non-compliant balloon at 18 atm; **D)** high resolution radiographic image of C.

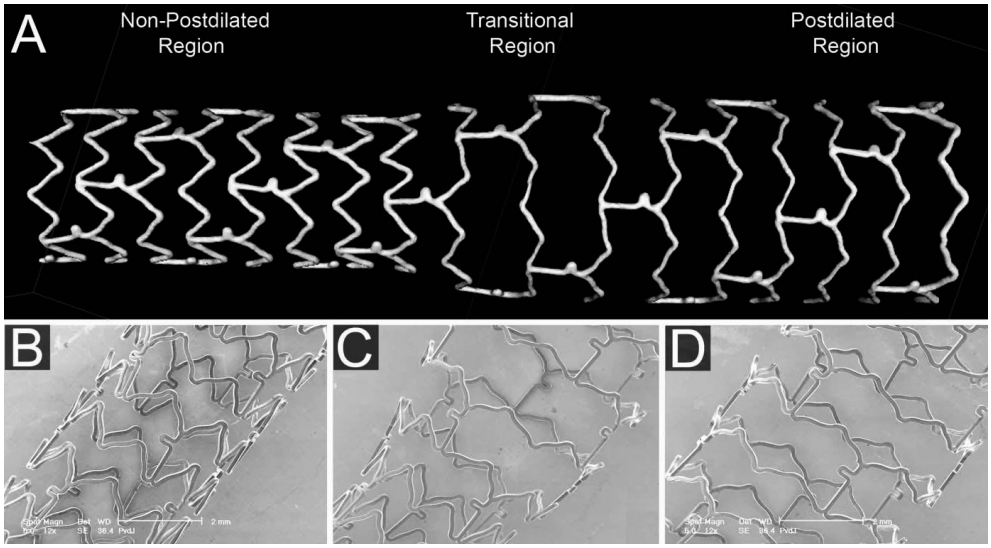

Figure 2. Example of DES configuration after oversized partial postdilatation. Micro-computed tomography image **(A)** indicating (from left to right) the location of the non-postdilated, transitional, and postdilated DES regions. Scanning electron microscopic images of non-postdilated **(B)**, transitional **(C)**, and postdilated **(D)** stent regions.

Scanning electron microscopic analysis. SEM imaging was performed with a Phillips XL30 scanning electron microscope (Phillips, Eindhoven, the Netherlands), as previously described.[20] As in previous studies[20;21], all DES samples remained untreated (i.e., no spraying of gold layer) to avoid artifacts, and a 1KeV-protocol was applied (average working distance 10mm; range 6–12mm sample dependent).

Exploratory assessment. To identify, locate, and characterize suspected irregularities, and to examine the distribution of coating irregularities one sample of each DES type was fully scanned with SEM. Scanning was performed at 50-fold to 60-fold magnification. Coating irregularities that were detected during exploratory assessment were further examined at 200-fold to 500-fold magnification in order to compare them with previously described DES coating irregularities [20-23] and to identify potential new types of coating irregularities.

Measuring incidence of coating irregularities in different DES regions. The DES surface was thoroughly scanned on 15 stent samples (3 of each DES type), generally using a 60-fold magnification (range: 50-fold to 70-fold; quantitative analyses were normalized for a 60-fold magnification as previously described); care was taken to avoid overlap between scanned areas. [20] Forty-four SEM images were randomly selected in each single stent sample for further quantitative analysis. Randomization was performed by means of separate randomization tables for each of the three predefined stent regions. This resulted in a total of 660 SEM images that were carefully examined to determine the incidence of all predefined coating irregularities on the various DES types.

Equal numbers of SEM images were prospectively taken from 3 different regions of each DES: (1) non-postdilated region only subjected to the 14atm expansion pressure; (2) postdilated region subjected to both 14atm implantation pressure plus postdilatation with a 5.0/12mm noncompliant balloon at 18atm; and (3) the transition between the two aforementioned regions in which the stent diameter showed a gradual decline (Figure 2). The frequency of each irregularity was presented as frequency per image field at 60-fold magnification. Postdilatation results in an increased stent lumen with increased space between adjacent stent struts. As a consequence, SEM-images of the postdilated region, taken with an identical magnification (i.e., an identical size of the image field) as the images of the non-postdilated region, display less struts per image field. This would lead to underestimation of polymer irregularities, if not normalized. For that reason and to allow comparison between the 3 different stent regions, we normalized data from the postdilated and transitional regions for the non-postdilated situation. Normalization, based on strut area measurements in 150 SEM images (i.e., 30 images per DES type), was performed individually for each DES type and for both postdilated and transitional regions. As a consequence, frequency data of each irregularity are presented as frequency per image field at 60-fold magnification, normalized for the non-postdilated situation (normalization applied to postdilated and transitional regions only).

Data analysis and statistics: Data are presented as a mean ±1SD. In each DES type, the incidence of various DES irregularities in the 3 different regions was compared with the Kruskal-Wallis test. In case of significant difference, a Mann-Whitney test was subsequently performed to pairwise compare individual stent regions (for each of the 3 possible comparison). While P-values <0.05 were generally considered significant, Bonferroni correction was applied for multiple testing. Statistical analyses were performed with the software of SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

SEM exploration of coating irregularities. We recognized the presence of various coating irregularities in all three stent regions (postdilated, transitional, and non-postdilated) examined. SEM exploration of DES samples demonstrated the presence of various coating irregularities. These irregularities (Table 1; Figures 3, 4, and 5) were greatly similar to DES coating irregularities as previously described by our group.[14;20] In general, there were no differences in the aspect of irregularities as observed in the different stent regions; however there were two exceptions: (1) cracks on the surface of the postdilated and transitional regions of Endeavor Resolute (Figure 4E, 4F) and Cypher Select plus (Figure 5E,5F) appeared somewhat wider compared to cracks in the non-oversized stent regions; (2) in the post-dilated and transitional region of Taxus Liberté a novel irregularity was observed, *torn webbing* of the polymer coating (Figure 3G and 3H).

Table 1. Classification of irregularities of durable polymer-based DES coatings

Categories	**Types** (within individual categories); Figure = typical example
I. Irregularities with reduced thickness of coating	**IA.** Small or big areas with aspect of bare metal, not fulfilling criteria of IB or IC (Figure 4C); **IB.** Cracks, i.e. sharp-edged coating irregularity extending from the surface deep into the coating, sometimes with exposure of underlying stent/primer (Figure 4E, 4F, 5E, 5F) ; **IC.** Reduced thickness of DES coating at strut crossings (Figure 3D;*)
II. Irregularities with increased thickness of coating	**IIA.** "Auricle-shaped" excess of coating (Figure 3G;#); **IIB.** Ridge-shaped excess of coating connecting two facets of a strut; **IIC.** Small rounded structure of excess coating; **IID.** Coarse irregular excess of coating;
III. Irregularities with inhomogeneous coating	**IIIA.** Crater-shaped irregularity with metal exposure, i.e. circular or elliptical irregularity with centrally reduced thickness of coating (including bare metal areas) and increased thickness of coating at the peripheral zone (Figure 4H); **IIIB.** Crater-shaped irregularity without metal exposure, i.e. circular or elliptical irregularity with centrally reduced thickness of coating and increased thickness of coating at the peripheral zone (Figure 5D); **IIIC.** Small crater-shaped irregularity, i.e. irregularity with appearance of punched-out hole; **IIID.** Wrinkles, i.e. shallow minimal linear irregularities (Figure 3A, 3B, 3C, 3D); **IIIE.** Flattened coating enclosed between two linear thickenings of coating material;
IV. Irregularities with displacement of coating	**IVA.** Webbing with metal exposure (Figure 3E); **IVB.** Webbing without metal exposure; **IVC.** Fragments of coating, i.e. mostly detached piece of coating which keeps loosely attached to the main coating; **IVD.** Torn webbing, i.e. redundant piece of polymer with an irregular outer surface indicating rupture of a webbing (Figure 3G, 3H); **IVE.** Peeling of polymer without bare metal exposure (Figure 5A); **IVF.** Peeling of polymer with bare metal exposure (Figure 5B);

For irregularities that can be seen in figures of this manuscript, the corresponding figure is indicated between brackets; examples of irregularities not shown in figures can be found elsewhere (reference 19).

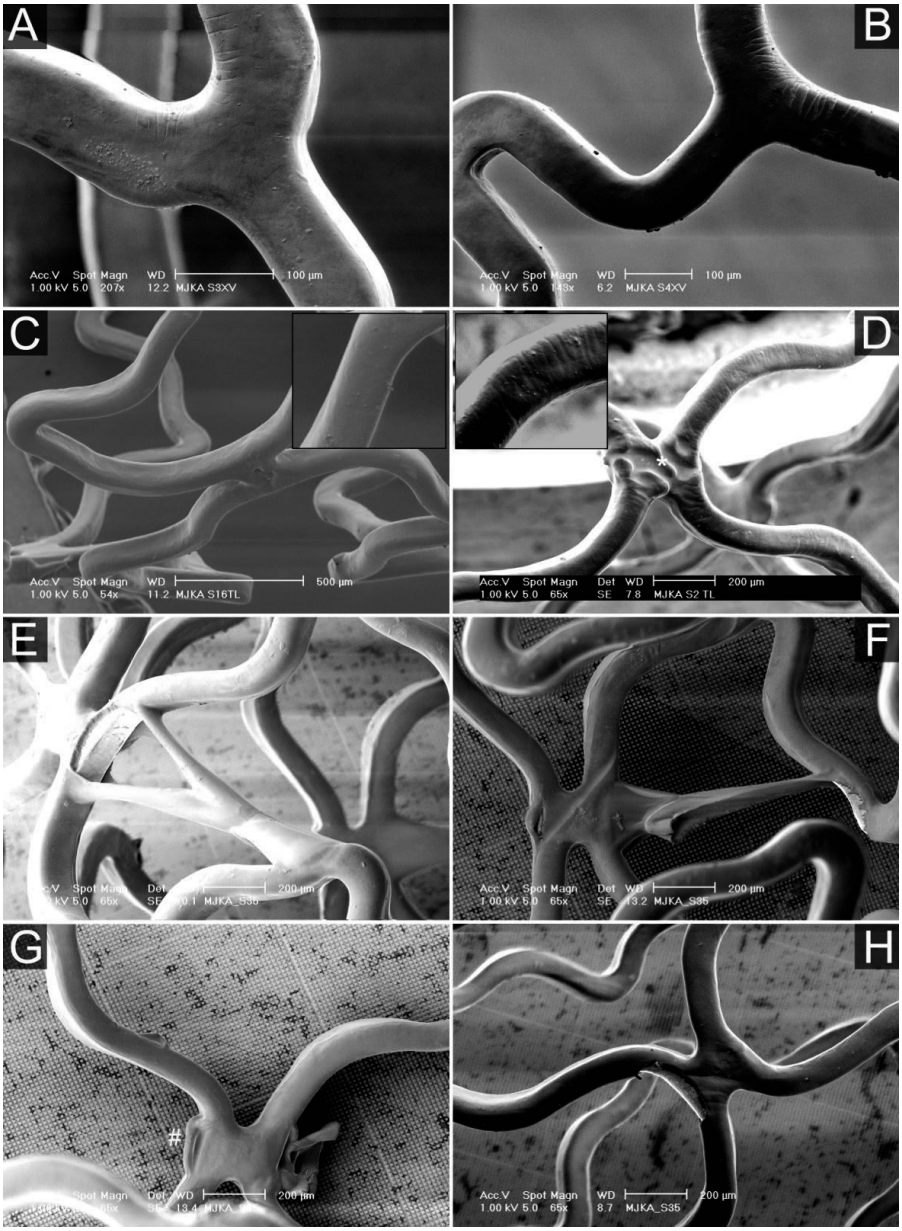

Figure 3. **SEM images of Xience V and Taxus Liberté. A)** Xience V showing wrinkles in non-postdilated region. **B**) Xience V with wrinkles in postdilated region. **C**) Taxus Liberté in non-postdilated region without wrinkles. **D**) Taxus Liberté with wrinkles in non-postdilated region. **D**) Taxus Liberté with wrinkles in postdilated region, *= reduced thickness of coating at strut crossing. **E-H**) Taxus Liberté with webbing with bare-metal exposure in non-postdilated region (E), and examples of partially torn webbing in transitional region (F), and torn webbing in post-dilated region (G and H). # in G= Auricle shaped excess of coating.

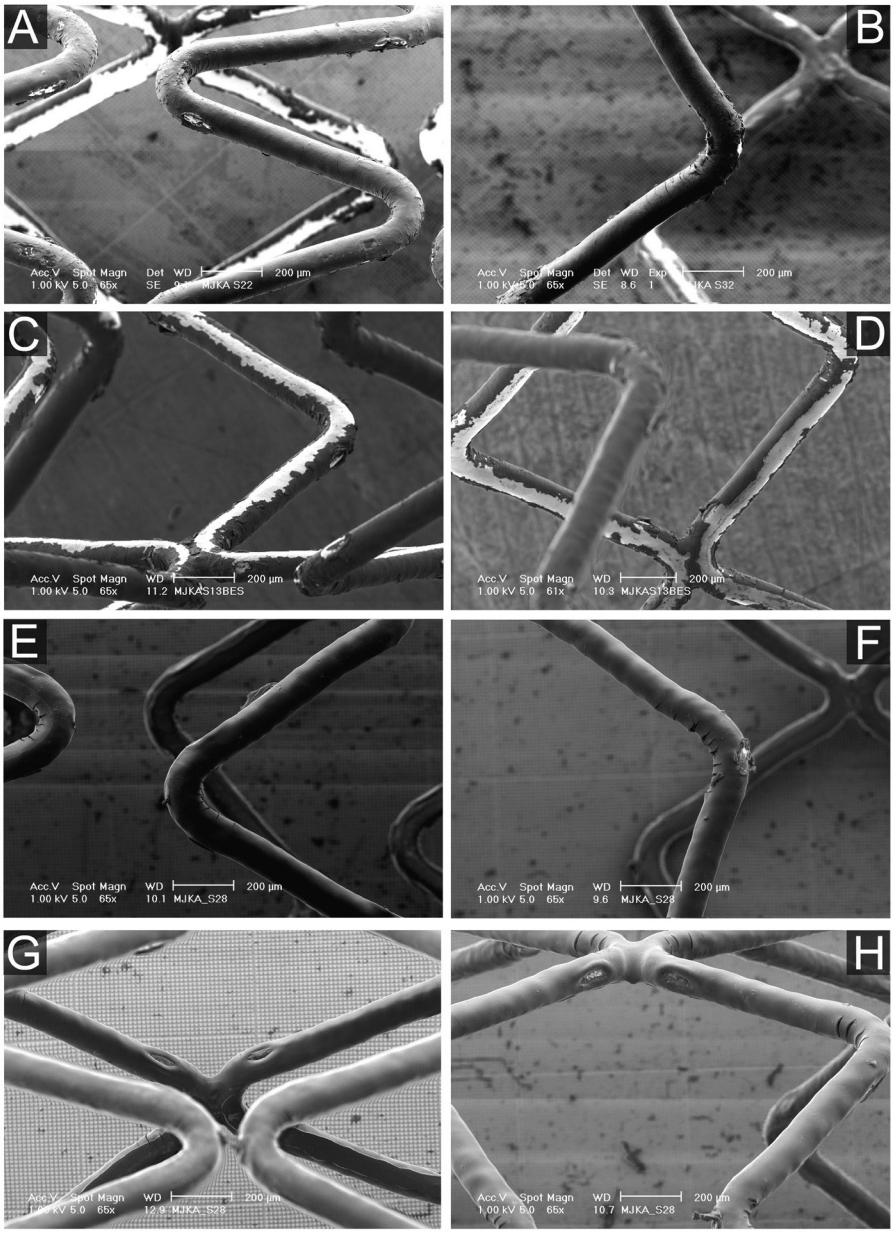

Figure 4. **SEM images of Endeavor Sprint and Resolute. A**) Endeavor Sprint with cracks in non-postdilated region. **B**) Endeavor Sprint with cracks in postdilated region. **C-D**) Very similar incidence of bare metal areas in non-postdilated and postdilated regions of Endeavor Sprint, respectively. **E**) Endeavor Resolute with cracks in non-postdilated region. **F**) Cracks and a crater irregularity on postdilated region of Endeavor Resolute. **G-H**) Endeavor Resolute with similar incidence of crater-shaped irregularity in non-postdilated and postdilated regions, respectively.

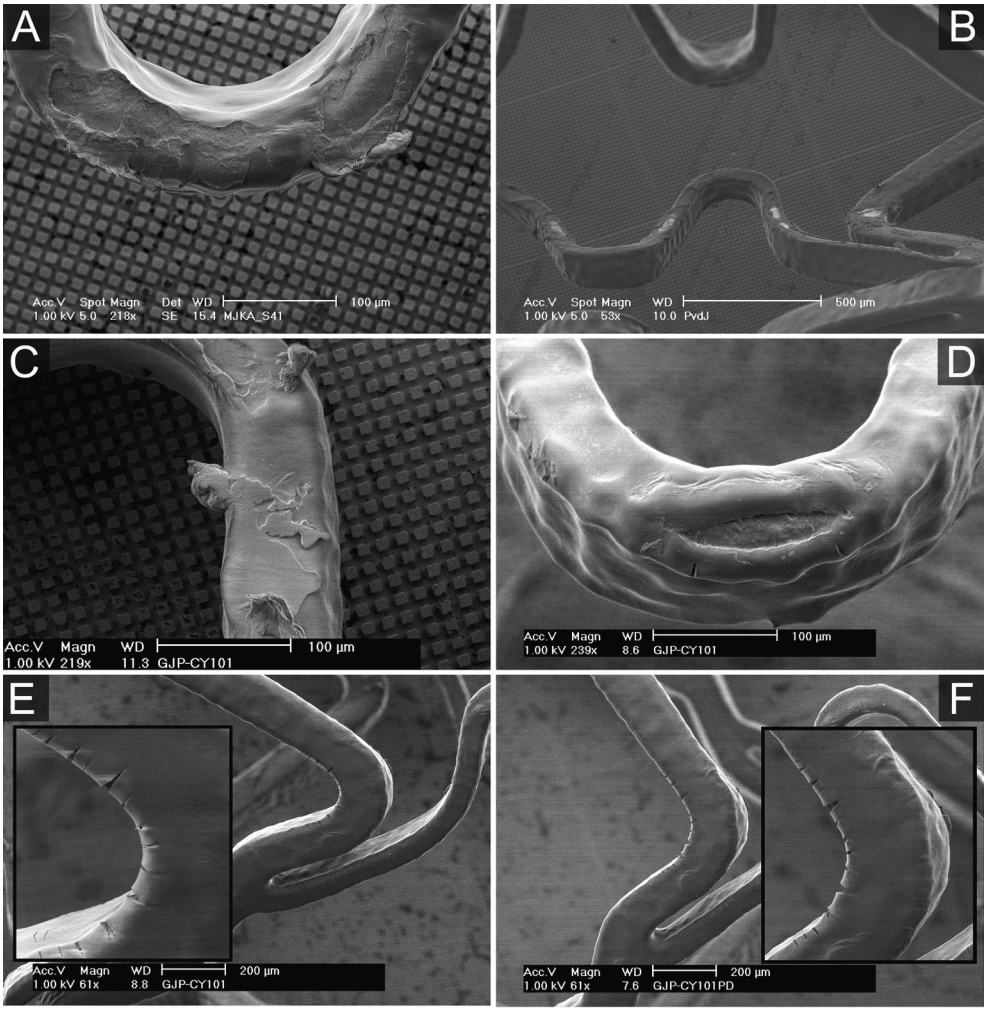

Figure 5. **SEM images of Cypher Select plus. A**) Peeling of polymer without bare metal aspect. **B**) Peeling of polymer with bare metal aspect. **C)** Coarse irregular excess of coating. **D**) Crater lesion. **E**) Cracks in the non-postdilated region of Cypher Select plus. **F)** Cracks in postdilated region of Cypher Select plus. The cracks in the postdilated stent region are wider than those in the non-postdilated region (see inserts for higher magnification).

SEM quantification of coating irregularities. The incidence of different irregularities in each region of the examined stents is presented in Tables 2-5 (data based on total of 660 non-overlapping images). Between the three regions, there were only few significant differences: (1) Cypher Select plus showed more peeling without bare metal aspect (Figure 5A) in the postdilated region vs. the non-oversized region (2) Taxus Liberté showed more wrinkles in the postdilated and transitional regions vs. the non-oversized region (Figure 3C and 3D); (3) in Taxus Liberté, torn webbing was found in the postdilated and transitional regions only.

Table 2. Category I DES coating irregularities (reduced thickness; frequencies)

Types			Cypher Select plus			Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
	Aspect		**NPR**	**TR**	**PR**	**NPR**	**TR**	**PR**	**NPR**	**TR**	**PR**	**NPR**	**TR**	**PR**	**NPR**	**TR**	**PR**
IA) Small or big areas of bare metal not fulfilling criteria for IB of IC.	**Mean frequency of irregularity per SEM field at 60-fold magnification**	**Small areas**	0	0	0	0.23 ±0.54	0.52 ±0.77	0.33 ±0.76	2.54 ±3.57	2.07 ±3.35	1.35 ±2.33	1.88 ±1.55	2.21 ±2.31	1.17 ±1.35	0.24 ±0.67	0.25 ±0.65	0.2 ±0.5
		Big areas	0	0	0	0	0	0	1.73 ±1.95	2.07 ±2.53	1.59 ±1.45	0	0	0	0	0	0
			||															
IB) Cracks (i.e, areas with cracks)	**Mean frequency /field**		0.93 ±0.92	1.2 ±1.4	0.9 ±1.21	0	0	0	2.43 ±1.58	3.02 ±1.94	2.86 ±1.21	2.61 ±0.90	2.70 ±1.71	2.77 ±1.42	0	0	0
IC) Reduced coating at strut crossing	**Mean frequency /field**		0	0	0	0.59 ±0.69	0.38 ±0.65	0.53 ±0.71	0	0	0	0	0	0	0	0	0

legend:
NPR: non-postdilated region
PR: post-dilated region
TR: transitional region
* statistically significant difference among all the regions.
† statistically significant difference between non-postdilated and transitional regions
‡ statistically significant difference between non-postdilated and postdilated regions
§ statistically significant difference between postdilated and transitional regions,
|| Bare metal areas on Cypher Select plus were in all cases related to peeling.

Table 3. Category II DES coating irregularities (increased thickness; frequencies)

Types		Cypher Select plus			Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
	Aspect	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**
IIA) Auricle-shaped excess of coating	**Mean frequency /field**	0	0	0	0.64 ±1.02	1.31 ±1.19	0.89 ±1.11	0	0	0	0	0	0	0	0	0
IIB) Ridge shaped excess of coating	**Mean frequency /field**	0.13 ±0.36	0.1 ±0.37	0.07 ±0.32	2.50 ±1.37	2.22 ±1.29	2.39 ±1.64	0	0	0	0	0	0	1.21 ±1.22	1.03 ±1.2	0.82 ±1.01
IIC) Small rounded excess coating	**Mean frequency /field**	0.02 ±0.14	0.04 ±0.22	0.05 ±0.27	0	0	0	0	0	0	0	0	0	0.13 ±0.33	0.41 ±0.75	0.28 ±0.58
IID) Coarse irregular excess coating	**Mean frequency /field**	0.02 ±0.15	0.2 ±0.17	0	0	0	0	0	0	0	0	0	0	0	0	0

legend: see Table2

Table 4. Category III DES coating irregularities (inhomogeneous thickness; frequencies)

Types		Cypher Select plus			Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
	Aspect	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**	**NPD**	**TR**	**PR**
IIIA) Crater irregularity with bare metal exposure	**Mean frequency / field**	0	0	0	0	0	0	1.44 ±1.51	2.21 ±2.13	1.74 ±1.76	2.21 ±1.97	2.49 ±2.41	1.71 ±1.8	0.03 ±0.19	0	0.07 ±0.31
IIIB) Crater irregularity without bare metal exposure	**Mean frequency / field**	0.07 ±0.26	0.07 ±0.28	0.08 ±0.34	0	0.04 ±0.29	0.03 ±0.27	0.06 ±0.37	0.11 ±0.42	0.03 ±0.19	1.26 ±1.45	1.67 ±2.1	1.39 ±1.57	0.12 ±0.36	0.1 ±0.37	0.07 ±0.31
IIIC) Small crater irregularity	**Mean frequency / field**	0.01 ±0.11	0	0	0.10 ±0.34	0.31 ±0.68	0.10 ±0.37	0	0	0	0	0	0	0.19 ±0.4	0.23 ±0.77	0.24 ±0.76
IIID) Wrinkles	**Mean frequency / field**	0.04 ±0.2	0.01 ±0.12	0.04 ±0.26	1.13 ±1.45	1.9 ±1.52	1.96 ±1.69	0	0	0	0	0	0	1.4 ±1.17	1.1 ±1.15	1.16 ±1.2
					*,†,‡ P=0.002											
IIIE) Flattened coating enclosed between two linear thickenings of coating	**Mean frequency / field**	0	0	0	0	0	0	0	0	0	2.13 ±1.56	2.41 ±2.15	1.9 ±1.7	0	0	0

legend: see Table2

Table 5. Category IV DES coating irregularities (displacement; frequencies)

Types		Cypher Select plus			Taxus Liberté			Endeavor Sprint			Endeavor Resolute			Xience V		
		NPD	TR	PR	NPD	TR	PR	NPD	TR	PR	NPD	TR	PR	NPD	TR	PR
IVA) Webbing with metal exposure	**Mean frequency / field**	0	0	0	0.21 ±0.57	0.06 ±0.31	0.07 ±0.31	0	0	0	0	0	0	0	0	0.01 ±0.1
IVB) Webbing without metal exposure	**Mean frequency / field**	0	0	0	0.08 ±0.30	0.03 ±0.25	0.03 ±0.22	0	0	0	0	0	0	0.03 ±0.19	0	0
IVC) Fragments of coating	**Mean frequency / field**	0	0	0	0.08 ±0.39	0.03 ±0.25	0.03 ±0.22	0	0	0	0	0	0	0.03 ±0.16	0	0.03 ±0.19
IVD) Torn webbing	**Mean frequency / field**	0	0	0	0	0.41 ± 0.59	0.36 ±0.57	0	0	0	0	0	0	0	0	0
					*,†,‡ (p=0.005)											
IVE) Peeling with bare metal	**Mean frequency / field**	0.18 ±0.62	0.08 ±0.34	0.14 ±0.44	0	0	0	0	0	0	0	0	0	0	0	0
IVF) Peeling without bare metal	**Mean frequency / field**	0.83 ±0.81	0.8 ±1.02	1.16 ±1.19	0	0	0	0	0	0	0	0	0	0	0	0
		‡ (p=0.01)														

legend: see Table 2

In Cypher Select plus, cracks were wider in the transitional and the postdilated regions versus the non-postdilated region (15.1±5.3µm vs.7.6±2.7µm;p<0.01). In Endeavor Resolute measurement of the diameter of cracks confirmed the observed mild difference in crack size between the postdilated and transitional regions versus the non-postdilated region (8.3±2.8µm vs. 6.1±3µm; p=0.022).

DISCUSSION

Postdilatation of DES is frequently indicated in clinical practice [4;24-26] and may be particularly important in the setting of significant vessel tapering, long lesions, calcified stenoses, or stenting across major bifurcations.[27] While the postdilatation of a bare metal stents involves an interaction between balloon and bare metal stent only, DES postdilatation implies potential interactions between balloon and both, bare metal stent platform and DES coating. The consequences of DES postdilatation for the coating are greatly unknown and may differ between various DES types, depending on coating materials and stent platforms. Homogenous oversized postdilatation of DES results in circumferential stent expansion with subsequent stress on the coating.

Partial oversized postdilatation leads to additional longitudinal forces just distal tot the postdilated region (transitional region),[13] which will expose the coating to even higher stress. In the present study, we therefore used this extreme, yet realistic, scenario of such partial oversized postdilatation (approximately 135% oversizing compared to nominal diameter) to expose DES coatings to maximum stress. *As shown by our SEM examination in five contemporary durable polymer-based DES, even such aggressive postdilatation resulted in no more than mild differences in the incidence and shape of coating irregularities between postdilated and non-postdilated stent regions.*

SEM assessment of DES coating irregularities. SEM is an imaging technique that depicts fine details of small samples with a very high resolution, which has previously been used for qualitative [21-23] and quantitative [20] assessment of DES coating irregularities. Our group previously examined homogeneously expanded DES with SEM and suggested a SEM-based classification of coating irregularities, used in the present study. [20] The characteristic coating irregularities with typical patterns for individual DES types as described in our previous work [20] were also recognized by the present SEM examinations.

In our present study, coating irregularities in the extremely oversized postdilated regions differed only little from those in the non-postdilated regions. A possible explanation for these findings is that the examined DES polymers may be either durable enough to withstand aggressive postdilatation or relatively fragile which leads to abrasion of coating in the balloon-stent contact zone already during initial deployment.

SEM demonstrated in overstretched Taxus Liberté more wrinkles and one novel coating irregularity, *torn webbing;* and in overstretched Cypher Select plus and Endeavor Resolute there were wider cracks. These findings can be interpreted as consequence of the increase in size of stent cells and the stretch upon bends of the stent struts.

Previous studies of DES coating irregularities generally examined DES after homogeneous expansion, i.e. the whole stent was deployed either to the size of the nominal diameter[23] or with very mild overstretch.[20] Ormiston and coworkers previously underlined the importance of studying DES coatings after extremely oversized DES postdilatation [22], but so far there were no quantitative data available on extremely oversized postdilation of DES.

To the best of our knowledge, the present study is the first to report quantitative SEM data on direct comparisons between different regions of the same durable polymer-based DES following exposure to different forces during deployment and/or postdilation. While our data suggest that the coating of durable polymer-based DES does not deteriorate much, DES with abluminal biodegradable coating may be less resistant to such extreme postdilatation maneuvers. [21] Totally bioabsorbable stents are subject of ongoing research and development [28;29], in which insights from SEM examination may also be valuable.

Implications. The absence of critical changes in DES coatings after aggressive postdilation at bench side suggests that postdilatation in the clinical setting may hardly affect these durable polymer-based DES coatings.

Limitations. The present in-vitro data should be interpreted cautiously as bench side studies cannot exactly mimic conditions in vivo and the clinical relevance of DES coating irregularities is not established yet. Nevertheless, we feel that meticulous SEM examinations are important because they add valuable information to the overall picture of a DES and may help to interpret clinical data.[14] Expansion in water followed by drying could theoretically have affected the more hydrophilic DES coatings (e.g. aggravate some coating irregularities); and findings may be somewhat different in small DES (e.g. in DES with a diameter 2.25 to 3.0 mm). As in previous studies, DES were not implanted in vessels or vascular phantoms [20-23],which avoided additional defects that could have resulted from scratching DES along (calcified) vessel walls[30;31] or from regaining DES out of vascular phantoms or specimens. Moreover, the use of a standard vessel phantom could have limited significant partial DES oversizing, while stent oversizing was critically important for this study protocol.

Conclusions. Bench side assessment of five contemporary durable polymer-based DES with scanning electron microscopy suggests that even very aggressive stent postdilatation does not result in a significant increase in the incidence of coating irregularities.

REFERENCES

1. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME (2003) TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 107:38-42.
2. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico, R (2002) A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 346:1773-1780.
3. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE (2003) Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 349:1315-1323.
4. Romagnoli E, Sangiorgi GM, Cosgrave J, Guillet E, Colombo A (2008). Drug-eluting stenting: the case for post-dilation. JACC Cardiovasc Interv 1:22-31.
5. Hong MK, Park SW, Mintz GS, Lee NH, Lee CW, Kim JJ, Park SJ (2000) Intravascular ultrasonic predictors of angiographic restenosis after long coronary stenting. Am J Cardiol 85:441-445.
6. Kim SW, Mintz GS, Escolar E, Ohlmann P, Pregowski J, Tyczynski P, Hassani SE, Pichard AD, Satler LF, Kent KM, Suddath WO, Waksman R, Weissman, NJ (2006) An intravascular ultrasound analysis of the mechanisms of restenosis comparing drug-eluting stents with brachytherapy. Am J Cardiol 97:1292-1298.
7. Takebayashi H, Kobayashi Y, Mintz GS, Carlier SG, Fujii K, Yasuda T, Moussa I, Mehran R, Dangas GD, Collins MB, Kreps E, Lansky AJ, Stone GW, Leon MB, Moses JW (2005) Intravascular ultrasound assessment of lesions with target vessel failure after sirolimus-eluting stent implantation. Am J Cardiol 95:498-502.
8. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S (2007) Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 115:2426-2434.
9. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB (2005) Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 45:995-998.
10. Uren NG, Schwarzacher SP, Metz JA, Lee DP, Honda Y, Yeung AC, Fitzgerald PJ, Yock PG (2002) Predictors and outcomes of stent thrombosis: an intravascular ultrasound registry. Eur Heart J 23:124-132.
11. Jeremias A, Kirtane A (2008) Balancing efficacy and safety of drug-eluting stents in patients undergoing percutaneous coronary intervention. Ann Intern Med 148:234-238.
12. Mehran R, Dangas GD (2007) Off-label use of drug-eluting stents: assessing the risk. Nat. Clin Pract Cardiovasc Med. 4:594-595.
13. Basalus MW, van Houwelingen GK, Ankone MJ, Feijen J, von Birgelen C (2010). Micro-computed tomographic assessment following extremely oversized partial postdilatation of drug-eluting stents. Eurointervention 141-148.
14. Basalus MW,von Birgelen C (2010) Bench side testing of drug-eluting stent surface and geometry. Interventional Cardiology 2: 159-175.
15. Serruys PW, Regar E, Carter AJ (2002) Rapamycin eluting stent: the onset of a new era in interventional cardiology Heart 87:305-307.
16. FDA Summary of safety and effectiveness data of Taxus Liberté. 2008;P060008. 2008.
17. Pinto Slottow TL,Waksman R. (2008) Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on the endeavor zotarolimus-eluting coronary stent. Circulation 117:1603-1608.
18. Meredith IT, Worthley S, Whitbourn R, Walters D, Popma J, Cutlip D, Fitzgerald P (2007) The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Resolute first-in-man trial. EuroIntervention 3:50-53.
19. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ (2008) Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 299:1903-1913.
20. Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C (2009) Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. EuroIntervention 5:157-165.

21. Basalus MW, van Houwelingen KG, Ankone M, de Man FH, von Birgelen C (2009) Scanning electron microscopic assessment of the biodegradable coating on expanded biolimus-eluting stents. EuroIntervention 5:505-510.
22. Ormiston J, Webster M, Ruygrok P, Stewart J, Scott D, Currie E (2004) Polymer integrity after Cypher and Taxus stent implantation: A scanning electron microscope study. http://www.tctmd.com/show.aspx?id=58632. Accessed 28 June 2010
23. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA (2007) Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. J Invasive Cardiol 19:71-76.
24. Brodie BR, Cooper C, Jones M, Fitzgerald P, Cummins F(2003) Is adjunctive balloon postdilatation necessary after coronary stent deployment? Final results from the POSTIT trial. Catheter Cardiovasc Interv 59:184-192.
25. De Benedetti E, Urban P (2007) Coronary stenting: why size matters. Heart 93:1500-1501.
26. Aziz S, Morris JL, Perry RA, Stables RH (2007) Stent expansion: a combination of delivery balloon underexpansion and acute stent recoil reduces predicted stent diameter irrespective of reference vessel size. Heart 93:1562-1566.
27. Brodie BR (2006) Adjunctive balloon postdilatation after stent deployment: is it still necessary with drug-eluting stents? J Interv Cardiol 19:43-50.
28. Erbel R, Di Mario C, Bartunek J, Bonnier J, de Bruyne B, Eberli FR, Erne P, Haude M, Heublein B, Horrigan M, Ilsley C, Bose D, Koolen J, Luscher TF, Weissman N, Waksman, R (2007) Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. Lancet 369:1869-1875.
29. Serruys PW, Ormiston JA, Onuma Y, Regar E, Gonzalo N, Garcia-Garcia HM, Nieman K, Bruining N, Dorange C, Miquel-Hebert K, Veldhof S, Webster M, Thuesen L, Dudek D (2009) A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 373:897-910.
30. Wiemer M, Butz T, Schmidt W, Schmitz KP, Horstkotte D, Langer C (2010) Scanning electron microscopic analysis of different drug eluting stents after failed implantation: From nearly undamaged to major damaged polymers. Catheter Cardiovasc Interv 75:905-911.
31. von Birgelen C, Basalus MW (2010). On the Loss of the Phosphorylcholine-based DES Coating on the Abluminal Surface of Endeavor Stents. Catheter Cardiovasc Interv DOI: 10.1002/ccd.22497.

CHAPTER 5

SCANNING ELECTRON MICROSCOPIC ASSESSMENT OF COATING IRREGULARITIES AND THEIR PRECURSORS IN *UN*EXPANDED DURABLE POLYMER-BASED DRUG-ELUTING STENTS

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ABSTRACT

Objectives. To assess and quantify coating irregularities on unexpanded and expanded durable polymer-based drug-eluting stents (DES) to gain insights into the origin of coating irregularities.

Background. Previous scanning electron microscopy (SEM) studies in various expanded DES revealed differences in frequency and size of coating irregularities between DES types and specific distribution patterns, however, the origin of these irregularities is unclear.

Methods. We assessed at bench side a total of 1,200 SEM images obtained in 30 DES samples (15 expanded and 15 unexpanded) of Cypher Select Plus, Taxus Liberté, Endeavor, Xience V, and Resolute.

Results. For most coating irregularities seen on expanded DES (72%; 23/32), a matching irregularity (n=18/24) and/or its precursor (n=11/24) was observed in unexpanded DES. Unexpanded Cypher Select showed (small) crater lesions and cracks together with precursors of 'peeling'. On unexpanded Taxus Liberté, thinning of polymer, small bare metal areas, wrinkles, and one precursor type were found. Unexpanded Endeavor showed cracks, small bare metal areas, crater lesions, and precursors of the latter. Unexpanded Xience V and Resolute mainly revealed crater lesions and their precursors. On unexpanded versus expanded DES, there was no difference in measured frequency of coating irregularities and precursors (p=ns) with the exception of more bare metal areas on expanded Taxus Liberte (p=0.01).

Conclusions. Most coating irregularities, or the potential to develop them, are inherent to the unexpanded DES. Important determinants of the formation of coating irregularities may be the stent geometry and the physical properties of the coating, while stent-balloon interaction plays no major role.

Early encouraging results of drug-eluting stent (DES) trials[1,2] led to a widespread application of DES. However, long-term follow-up data of first generation DES raised concerns about a potential increase in late (and very late) stent thrombosis [3]. Nevertheless, larger patient-based meta-analyses demonstrated no change in mortality but a reduction of morbidity after percutaneous coronary interventions (PCI) with DES vs. bare metal stents (BMS) [4-6]. This intensive research highlights the discussions on late and very late DES thrombosis, the ideal antiplatelet therapy, and probable between-DES differences in risk of stent thrombosis and re-stenosis. The use of durable polymers and the presence of coating irregularities are potentially relevant to differences in clinical performance between DES types and some DES-related problems [7,8]. Examples may be DES thrombosis and restenosis [9] as well as peri-PCI myocardial infarction, which may be related to DES coating irregularities through various mechanisms (i.e. enhanced platelet adhesion, vessel wall inflammation and hypersensitivity, delayed healing, local reduction of neointima inhibition, or embolization of polymer fragments).

Because of its capacity to provide highly magnified high-resolution images, scanning-electron microscopy (SEM) is ideal for the assessment of coating irregularities [8,10-12]. Previous SEM studies demonstrated characteristic coating irregularities with a specific distribution patterns[11], raising the question of whether manufacturing processes could be involved in their origin. Therefore, we examined both unexpanded and expanded samples of five contemporary DES with SEM to gain insights into the potential origin of coating irregularities.

METHODS

DES samples examined. Five types of contemporary, commercially available, durable polymer-based DES were examined. A total of 30 DES (15 unexpanded and 15 expanded stents) was scanned. The following stents were examined: Cypher Select plus (Cordis Europa, Roden, Netherlands;3.5x23mm), Taxus Liberté (Boston Scientific Corp., Natick, MA, USA;3.5x24mm), Endeavor Sprint (Medtronic Vascular, Santa Rosa, CA, USA;3.5x24mm), Xience V (Abbott Vascular, Santa Clara, CA, USA;3.5x24mm), and Endeavor Resolute (Medtronic Vascular, Santa Rosa, CA, USA;3.5x24mm).

Cypher Select plus is based on a stainless steel platform (strut thickness 140µm) covered with a primer layer of paralyne C and a main coating layer made of polyethylene-covinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA) and Sirolimus. Taxus Liberté is based on the stainless steel Liberté bare metal platform (strut thickness 97µm) coated with a 17.8µm thick layer of SIBS(styrene-b-isobutylene-b-styrene) polymer and Paclitaxel. Endeavor Sprint is based on a cobalt-chromium stent platform (Driver; strut thicknss 91µm) covered by a 4.8µm thick coating of phosphorylcholine (10%) and Zotarolimus (90%). Xience V is based on a cobalt-chromium stent platform (Vision, strut thickness 81µm) covered by

a 7.8µm thick layer of fluoropolymer and Everolimus. Endeavor Resolute is also based on the Driver platform covered by a 5.6 µm thick (information from manufacturer) coating of Biolinx polymer and Zotarolimus.

Experimental protocol and scanning electron microscopy. 15 DES samples (sterile packed; expiration date not passed) were examined in an unexpanded state (i.e. DES remained on balloons with the catheter shafts being truncated to allow SEM examination). The unexpanded samples were fixed at the balloon tip. The whole stent length was then scanned. This was followed by rotating the stent sample by 180°. The other 15 DES samples were expanded at 14 atm. DES expansion and examination with SEM was performed according to established methodologies [11].
To identify, locate, and characterize coating irregularities, DES samples were explored at 50 to 60-fold magnification. Coating irregularities that were detected during exploratory assessment were then further examined at 200 to 500-fold magnification. Data on characteristics and frequency of coating irregularities on expanded DES have previously been reported [11,13].

SEM image analysis. Highly magnified SEM images of the DES samples were carefully inspected to gain insight into potential mechanisms of the origin of DES coating irregularities. For that purpose, we compared predefined coating irregularities [13] that were identified on both unexpanded and expanded DES samples. In addition, in unexpanded DES samples, characteristic spots (predilection sites) of coating irregularities were carefully examined even if no evident coating defect or irregularity was observed during exploratory SEM imaging. In this context, the individual distribution pattern of coating irregularities in the various DES types was taken into account.

Measurement of frequency of coating irregularities and their precursors. The total surface of unexpanded DES was thoroughly scanned at a magnification of (in general) 60-fold. Care was taken to avoid overlap between scanned areas. In unexpanded and expanded DES samples, a total of 1,200 SEM images was examined to determine the frequency of coating irregularities and their precursors per stent ring.

Statistics: Data are presented as a mean±SD. In each DES type, the frequency of various DES irregularities on unexpanded vs. expanded stents was compared with the Mann-Whitney test. P-values <0.05 were considered significant. Statistical analyses were performed with the software of SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 1,200 SEM images of both expanded and unexpanded DES was carefully examined. Unexpanded DES, immediately examined after unpacking, demonstrated several coating irregularities (Figure 1E,1G,2A,2E,3A,3E) that were partially similar to coating irregularities as seen on expanded samples of the same DES type (Figure 1F,1H,2B,2F,3B,3F; respectively). However, some of the coating irregularities on unexpanded stents differed morphologically from those observed on the expanded samples while sharing the same characteristic location (Figure1C,2C,2G,3C,3G); we refer to them as 'precursors of coating irregularities'. For most types of coating irregularities in expanded DES (72%; 23/32), a matching irregularity (n=18/24) and/or its precursor (n=11/24) was observed in unexpanded corresponding DES. Only a few individual coating irregularities (13%; 4/32) could not be accessed in unexpanded samples, as these irregularities were typically located on the (invisible) luminal side.

Cypher Select. SEM examination of unexpanded Cypher Select demonstrated crater-shaped irregularity without bare metal exposure, small crater-shaped irregularity, coarse irregular excess of coating, and cracks. The frequency of these irregularities was similar on expanded and unexpanded stents (Table 1). In addition, a potential precursor of peeled polymer (Figure 1C) was present on unexpanded Cypher. The frequency of the potential precursor of peeling (on unexpanded stents) was lower than the frequency of peeling on the expanded stents, which was mainly seen on the luminal side of expanded Cypher.

Taxus Liberté. On unexpanded Taxus Liberté, reduced thickness of coating at strut crossings, wrinkles, and small areas with bare metal aspect were found. On expanded Taxus, there was a significantly higher frequency of bare metal areas as compared to the unexpanded Taxus DES; there was no such difference for any of the other irregularities. In unexpanded samples, adhesion between DES loops and adjacent stent struts was frequently noticed (Figure 2C). This location corresponds with the location of webbing, crater lesions, and/or "auricle" shaped irregularities on expanded Taxus DES. The frequency of precursors on unexpanded stents did not differ from the sum of webbing, crater lesions, and "auricle" shaped irregularities on expanded stents (p=ns).

PC-Based Endeavor. Similar to expanded Endeavor DES, unexpanded Endeavor showed small areas with bare metal aspect, craters, and cracks. Because of the very small dimensions of cracks on the unexpanded Endeavor, we were not able to reliably quantify them; however, frequency and severity of cracks appeared to be lower on unexpanded Endeavor. The frequency of craters and their precursors (Figure 2E) on unexpanded samples did not differ from the sum of all types of craters on expanded Endeavor DES.

Table 1 (Part 1). Frequency of coating irregularities in *un*expanded and expanded samples of five types of DES.

	Cypher Select		Taxus Liberté	
	Unexpanded	**Expanded**	**Unexpanded**	**Expanded**
IA. Small or big areas with bare metal aspect (no IB or IC criteria)	**#**	-	0.17±0.56	2.04±3.66 p=0.01
IB. Cracks	9.9±4.5	13.0±12.9 p=ns	**-**	**-**
IC. Reduced thickness of coating at strut crossings	**-**	**-**	2.75±0.64	2.64±1.38 p=ns
IIA. 'Auricle-shaped' excess of coating	**-**	**-**	(precursors: 5,31±2,69)†	3.69±5.58
IIB. Ridge-shaped excess of coating on strut edge	**#**	1.0±5.0	**-**	**-**
IIC. Small rounded structure of excess coating	**-**	0.05±0.19	**-**	**-**
IID. Coarse irregular excess of coating	0.03±0.18	0.05±0.19 p=ns	**-**	**-**

Endeavor		Xience V		Resolute	
Unexpanded	**Expanded**	**Unexpanded**	**Expanded**	**Unexpanded**	**Expanded**
2.75±2.34 *small areas*	3.96±1.91 (abluminal) *small areas(p=ns)*‡	0.2±0.6	0.29±0.93 p=ns	0.06±0.98	0.08±0.31 p=ns
Present throughout the stent	Larger, wider and more frequent	-	-	-	17.16±3.01
-	-	-	-	-	-
-	-	-	-	-	-
-	-	1.27±1.9	1.41±1.68 p=ns	-	-
-	-	0.3±0.8	0.52±1.21 p=ns	-	-
-	-	-	-	-	-

Table 1 (continued, Part 2). Prevalence of coating irregularities in *un*expanded and expanded samples of five types of DES.

	Cypher Select		Taxus Liberté	
	Unexpanded	**Expanded**	**Unexpanded**	**Expanded**
IIIA. Crater-shaped with metal exposure	-	-	-	-
IIIB. Crater-shaped without metal exposure	1.06±1.55	0.98±1.64 (p=ns)	-	0.05±0.32
IIIC. Small crater-shaped irregularity	0.03±0.18	0.05±0.2 p=ns	†	0.12±0.41
IIID. Wrinkles (shallow, minimal & linear)	-	-	7.58±3.95	9.04±11.1 p=ns
IIIE. Flattened coating on one side of a strut	-	-	-	-
IVA. Webbing with metal exposure	-	-	†	1.17±3.15
IVB. Webbing with*out* metal exposure	-	-	†(p=ns)	0.42±1.62
IVC. Fragments of coating	-	-	-	-
IVD. 'Peeled polymer'	(precursors: 1.40±1.19)*	14.14±20.0 (p= 0.000)	-	-

Legend:

- Absent.
- # Not accessible for visualization in the unexpanded state.
- * Peeling on Cypher stents was mainly noticed on the luminal surface which was not accessible for examination in the unexpanded state.
- † The precursors on the surface of unexpanded Taxus Liberté can produce different forms of irregularities i.e. webbing, "auricle shaped" excess of coating and craters. There was no statistical difference between the frequency of precursors and the sum of webbing, "auricle shaped" excess of coating and craters (p=ns).
- ‡ The areas with bare metal aspect on surface of unexpanded Endeavor stents were all small, the large areas with bare metal aspect were only seen on the luminal aspect of expanded endeavor stents.
- § Already formed craters on surface of unexpanded Endeavor stents were difficult to classify into craters with or without bare metal aspect. The precursors on Endeavor stents can produce craters with or without bare metal aspect.
- || The craters on surface of unexpanded Xience V stents were all without bare metal aspect. The precursors on surface of unexpanded Xience V stents can produce craters with or without bare metal aspect.
- ¶ Already formed craters on surface of unexpanded Resolute stents were difficult to classify into craters with or without bare metal aspect. The precursors on Resolute stents can produce craters with or without bare metal aspect.

Endeavor		Xience V		Resolute	
Unexpanded	**Expanded**	**Unexpanded**	**Expanded**	**Unexpanded**	**Expanded**
12.71±2.86 / (precursors: 6,42±2,77) § p=ns	20.5±6.25 0.3±1.2	0.27±0.93 / (precursors: 0,23± 0,64) || p=ns	0.07±0.2 0.56±1.27	10.81±3.46 / (precursors: 6.42±2.77) ¶ p=ns	13.8±9.92 4.35±5.47
-	-	-	-	-	-
-	-	-	0.33±0.72	-	-
-	-	-	-	-	-
-	-	-	-	-	-
-	-	-	-	-	-
-	-	-	0.06±0.36	-	-
-	-	-	-	-	-

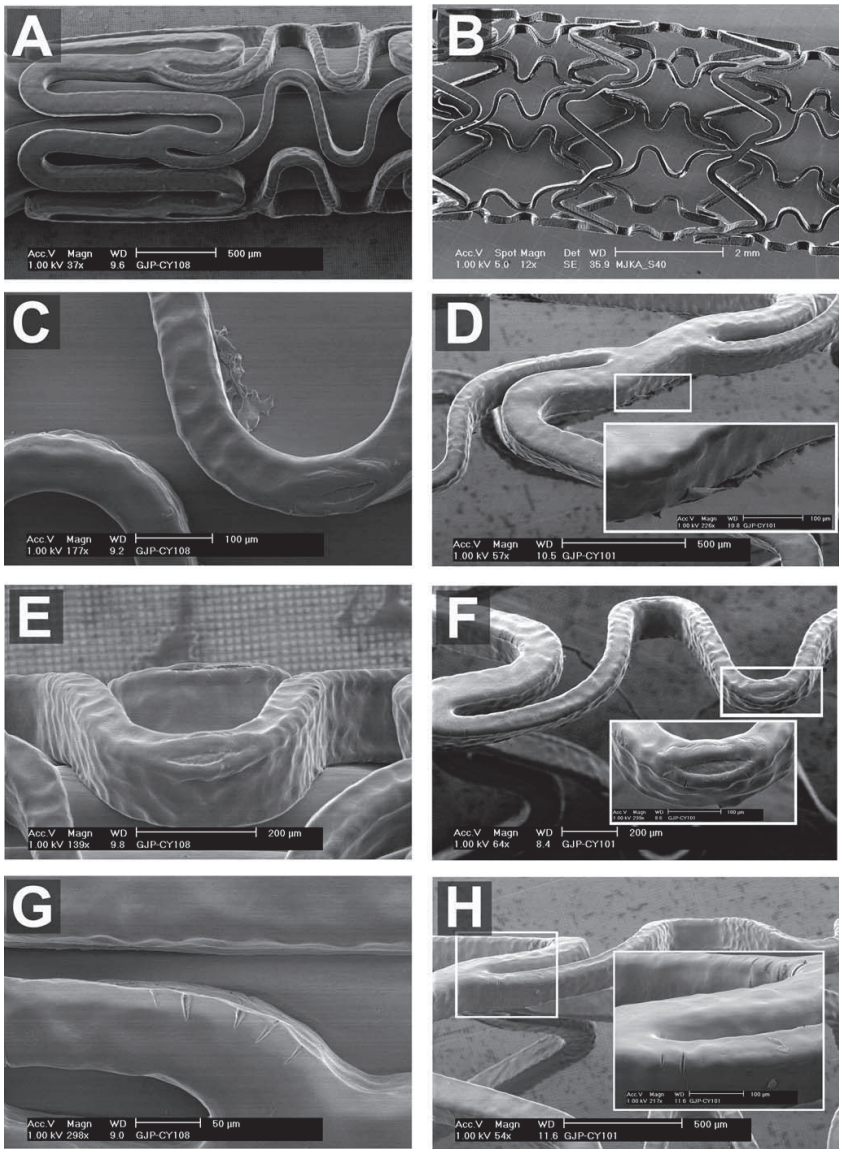

Figure 1. Scanning electron microscopic images of Cypher Select stents.
A)Unexpanded Cypher Select stent. **B**) Expanded Cypher Select stent. **C)** precursor of peeled polymer extending from stent struts to underlying balloon. **D)** Peeled polymer; a high magnification image of peeled polymer is provided in insert. **E,F)** A crater lesion present on both unexpanded and expanded Cypher stents, respectively. **G,H)** Cracks present on both unexpanded and expanded Cypher stents, respectively. A high magnification image of cracks is provided in insert.

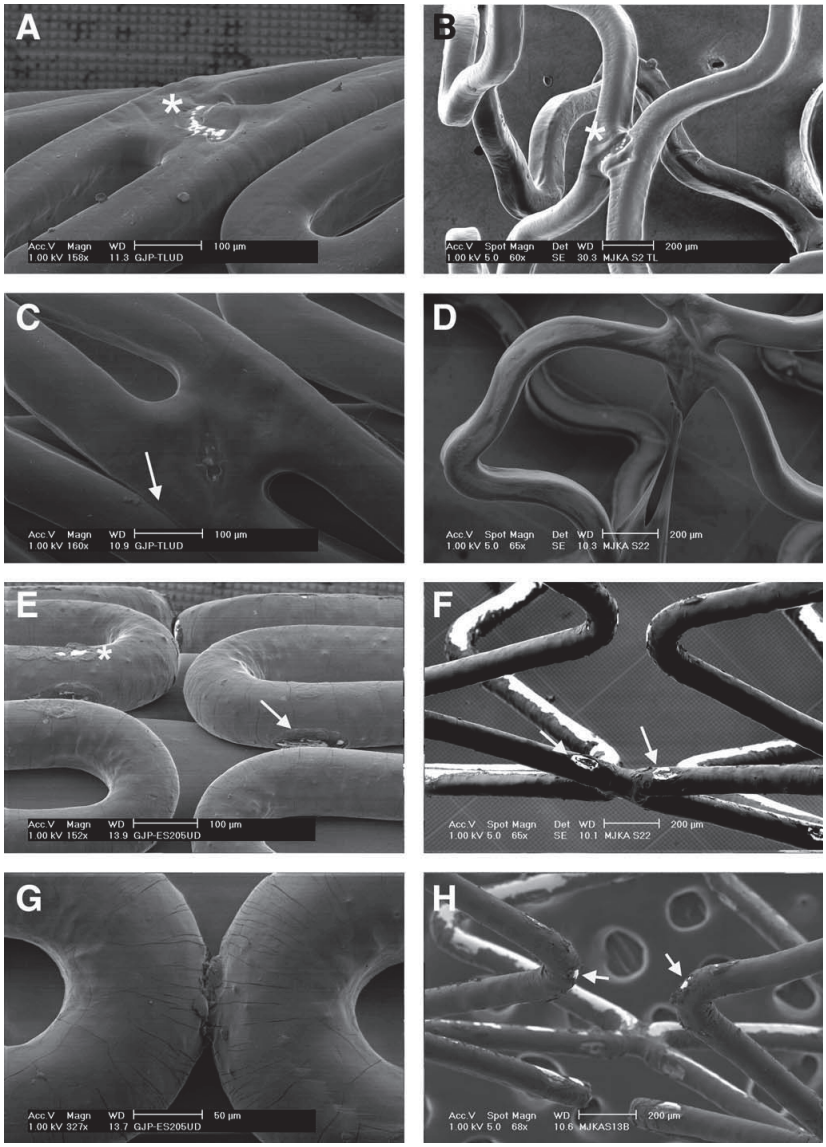

Figure 2. Scanning electron microscopic images of Taxus Liberté and Phosphorylcholine (PC)-based Endeavor stents.

A,B) Thinning of polymer at strut crossing(*) on both unexpanded and expanded stents, respectively. **C)** Adhesion of polymer coating on two adjacent struts (arrow) on unexpanded Taxus Liberté representing a precursor of webbing. **D)** Webbing on an expanded Taxus Liberté stent sharing the characteristic location with precursor seen in panel C.

E) Small bare metal area (*) and crater lesion with bare metal aspect (arrow) on unexpanded PC-based Endeavor stent **F)** Crater lesion with bare metal aspect (arrow) on expanded PC-based Endeavor stent. **G)** Mild cracks and adhesion of polymer coating on the apex of two adjacent bends on unexpanded PC-based Endeavor stent representing a precursor of crater lesions. **H)** Crater lesions (arrowheads) seen at stent bends.

Xience V. On unexpanded Xience V, we found with an overall low frequency the following irregularities: crater irregularities, small rounded excess of polymer, ridge shaped excess of coating, and small area with bare metal aspect. In addition, there was one type of precursor, located at the characteristic location of crater irregularities. The frequency of cater irregularities plus their precursors on unexpanded Xience V was similar to the frequency of crater irregularities on expanded Xience V (ns; Table 1).

Resolute. On unexpanded Resolute DES, there were small areas with bare metal aspect and crater irregularities. In addition, adhesions of coating between adjacent stent loops were found (Figure 3E,3G). Cracks were observed on expanded Resolute DES only. The frequency of crater irregularities plus their precursors on unexpanded Resolute DES was similar to the frequency of crater irregularities on expanded Resolute DES (Table 1).

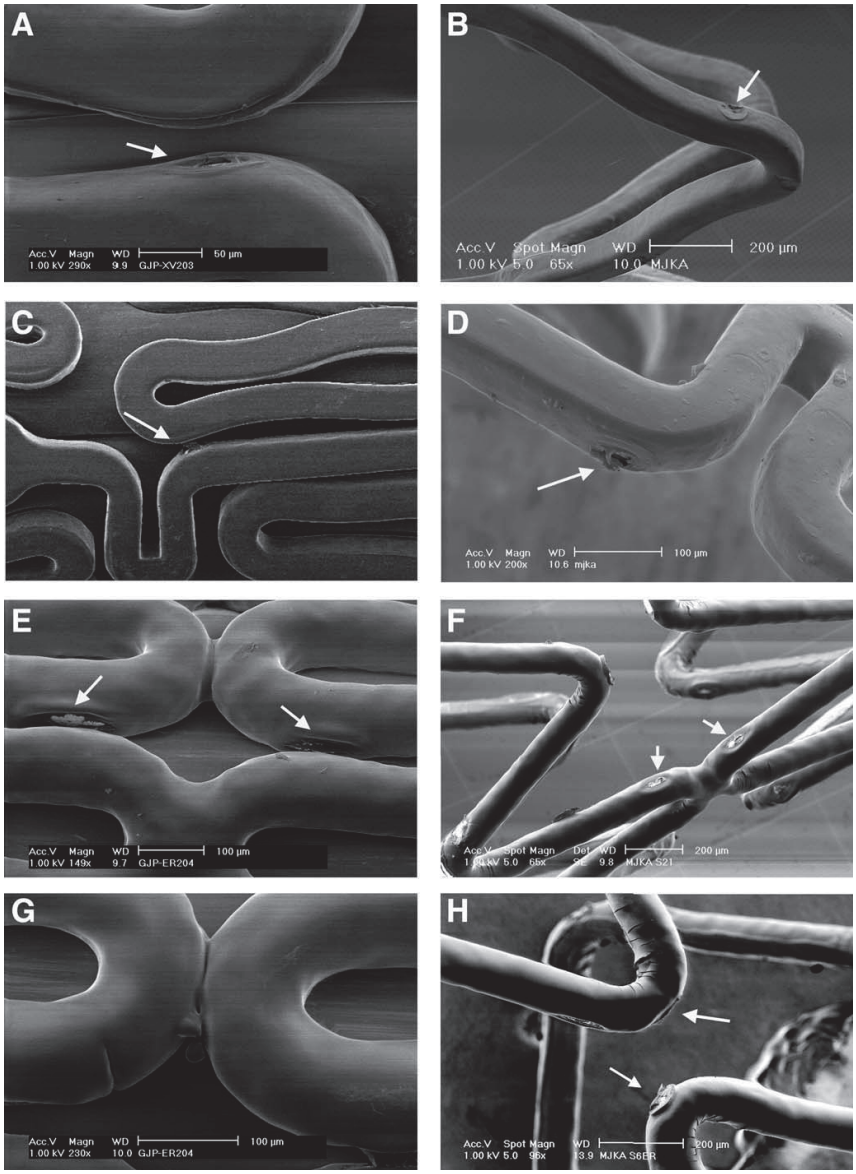

Figure 3. Scanning electron microscopic images of Xience V and Resolute stents. **A)** Crater lesion on unexpanded Xience V stent (arrow). **B)** Crater lesion (arrow) on expanded Xience V stent **C)** A precursor of crater lesion (arrow) on unexpanded Xience V stent. **D)** Crater lesion(arrow) on expanded Xience V stent seen at the same location as that of the precursor on panel C. **E)** Crater lesions (arrows) on unexpanded Endeavor Resolute stent. **F)** Crater lesions (arrowheads) on expanded Endeavor Resolute stent. **G)** A precursor of crater lesion on unexpanded Endeavor Resolute stent at a contact point of two adjacent stent bends. **H)** Crater lesions (arrowheads) on expanded Endeavor Resolute stent seen at the same location as that of the precursor on panel E. Only in the expanded state, cracks were seen at the inner curvatures of stent bends (F and G).

DISCUSSION

Certain DES coating irregularities have previously been described following bench-top deployment[8,11,12]. Theoretically, such coating irregularities could either arise from the process of DES production (i.e. irregularities should already be present on unexpanded DES samples) or during stent expansion (i.e. irregularities should be present after stent deployment only). In addition, in the clinical setting, delivery of DES through tortuous vessels and/or crossing of calcified lesions could cause major damage to the coating by scratching along the atherosclerotic vessel wall [14].

The present study sheds light on the origin of DES coating irregularities that were seen after bench top stent expansion, as it investigates and quantifies the frequency of coating irregularities in both expanded and unexpanded DES. This is the first study to systematically assess coating irregularities on unexpanded durable polymer-based DES and to compare these findings to irregularities on corresponding expanded DES samples. Examination of unexpanded Cypher Select, Taxus Liberté, and PC-based Endeavor demonstrated both some precursors of coating irregularities, and several types of coating irregularities that matched irregularities seen on expanded DES. Unexpanded Resolute showed predominantly crater lesions and their precursors in the unexpanded state. Xience V stents showed in the unexpanded state particularly few irregularities and precursors.

On unexpanded DES samples, crater lesions and their precursors (i.e. adhesions between adjacent stent bends) were found in the bend regions only. This applies to phosphorylcholine-based Endeavor, Xience V, and Resolute stents, too. On Taxus Liberté, no larger crater lesions were observed; this may be explained by the high elasticity of the SIBS-based DES coating that formed webbings or auricle-shaped irregularities at sites of adhesion between adjacent stent struts. Unexpanded Cypher Select stents showed no precursors of crater lesions, most likely because the adjacent stent bends were not close enough to each other.

The fact that precursors of irregularities were most often seen at bends demonstrates the interaction between stent geometry, polymer surface tension, and stent folding, which all may contribute to the formation of coating irregularities that were seen on the unexpanded DES. Cracks of the coating were also predominantly found at stent bends *after the expansion* of Cypher Select, PC-based Endeavor Sprint, and Resolute. Of these DES types, only the Resolute showed no cracks in its *unexpanded* state, while Cypher Select and PC-based Endeavor stent showed cracks (with milder cracks in Endeavor) in unexpanded samples. The cracks on unexpanded Cypher samples were located at other sites than cracks in corresponding expanded samples (i.e. at the outer curvatures of bends rather than at the inner curvatures). Our findings in Cypher Select and PC-based Endeavor stents suggest that cracks of the coating may be formed during both (1) drying of the polymer-drug mixture and/or stent folding on the balloon catheter, and (2) expansion of the stent during stent

deployment. In addition, the absence of cracks on the surface of unexpanded Resolute stents suggests that in this type of DES cracks are formed during stent expansion only.
Quantitative analysis of the frequencies of coating irregularities and their precursors on unexpanded versus expanded DES samples revealed no significant increase for most DES types and coating irregularities. The only exception was an increase in bare metal areas in Taxus Liberte, most likely related to traction on the webbing between adjacent stent struts during stent expansion. Cypher Select plus showed more peeling in the expanded state, however, this irregularity is predominantly located on the luminal side of the stent and cannot be reliably assessed on unexpanded stent samples.

Limitations. The findings of bench-side research should be interpreted cautiously, and clinical data are most important to judge the performance of DES. At this time, the clinical consequences of DES coating irregularities are still uncertain. Nevertheless, we feel that careful bench-side research is important as it adds valuable information to the overall picture of DES [13]. Expansion in water followed by drying could theoretically have affected the more hydrophilic DES coatings (e.g. by aggravating some coating irregularities). It was impossible to examine the same samples before and after stent deployment, as the assessment with SEM required separation of the balloon (on which the DES was mounted) from the shaft of the catheter.

Conclusions. Our data demonstrate that most coating irregularities (or the potential to develop them) are inherent to the *unexpanded* DES. Important determinants of the formation of coating irregularities may be both, the geometry of the stent platform and the physical properties of the coating, while stent-balloon interaction plays no role in the formation of most coating irregularities in the examined durable polymer-based DES.

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REFERENCES

1. Grube E, Silber S, Hauptmann KE et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003;107:38-42.
2. 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;346:1773-1780.
3. 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;27:2784-2814.
4. Kirtane AJ, Gupta A, Iyengar S et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation* 2009;119:3198-3206.
5. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020-1029.
6. Stettler C, Wandel S, Allemann S et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007;370:937-948.
7. Garg S, Serruys PW. Coronary stents: looking forward. *J Am Coll Cardiol* 2010;56:S43-S78.
8. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. *J Invasive Cardiol* 2007;19:71-76.
9. Farooq V, Gogas BD, Serruys PW. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. *Circ Cardiovasc Interv* 2011;4:195-205.
10. Basalus MW, van Houwelingen KG, Ankone M, de Man FH, von Birgelen C. Scanning electron microscopic assessment of the biodegradable coating on expanded biolimus-eluting stents. *EuroIntervention* 2009;5:505-510.
11. Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. *EuroIntervention* 2009;5:157-165.
12. Ormiston J, Webster M, Ruygrok P, Stewart J, Scott D, Currie E PMSB. Polymer integrity after Cypher and Taxus stent implantation: A scanning electron microscope study. http://www.tctmd.com. 2004.
13. Basalus MWZ, von Birgelen C. Benchside testing of drug-eluting stent surface and geometry. *Interventional Cardiology* 2010;2:159-175.
14. Wiemer M, Butz T, Schmidt W, Schmitz KP, Horstkotte D, Langer C. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: from nearly undamaged to major damaged polymers. *Catheter Cardiovasc Interv* 2010;75:905-911.

CHAPTER 6

LETTER TO THE EDITOR

LOSS OF DES COATING ON THE ABLUMINAL SURFACE OF THE ENDEAVOR STENT

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TO THE EDITOR

We enjoyed reading the article of Dr. Wiemer and co-workers describing the surface of various DES after failed attempts to implant them in calcified coronary lesions.[1] The authors managed to collect more than 60 DES to later examine these stents in non-expanded or expanded condition with scanning electron microscopy, a bench side imaging technique that was recently introduced for the assessment of DES coating irregularities.[2-3] One may honestly congratulate this group on saving all DES after failed stent implantation for further analysis.

The nature of their study is greatly descriptive, but images and preceding attempts to implant these stents in calcified vessels suggest that the relatively large abrasion of coating on the external surface of the Endeavor stents may be the result of contact between these DES and the vessel wall. However, based on data from DES after failed stent implantation only (i.e., in the absence of sufficient data in Endeavor stents without preceding manipulation in challenging lesions), it is hard to tell whether the abrasion occurred as a result of the stents' contact with the vessel wall.

Data from our recent bench side study with scanning electron microscopy in various DES demonstrate that the external (phosphorylcholine-encapsulated) coating of the Endeavor stents was greatly intact after gentle deployment in water.[4] *In fact, the difference between our findings and Dr. Wiemers data confirms their assumption that the PCI procedure accounted for the abrasion of coating on the external Endeavor surface. This example shows nicely how both, clinically oriented research and bench side studies can complement each other.* Moreover, we found during bench side testing that the largest areas with bare-metal aspect were located on the luminal surface of the Endeavor stents (where the balloon had expanded the stent), which corroborates that observation following failed stent implantation.[4] The relatively high proportion of drug to polymer of 9:1 in the Endeavor coating [5] may increase the susceptibility of the Endeavor stent to some loss of coating on contact with calcified vessel wall. Of note, the coating on the Endeavor *Resolute* stent contains the same drug but a different polymer with a different electron microscopic aspect.[4] Finally, randomized clinical studies of the Endeavor stent demonstrated - despite the microscopic findings as discussed above - the efficacy of this stent in high-risk patient subsets, such as diabetics.[6]

REFERENCES

1. Wiemer M, Butz T, Schmidt W, Schmitz KP, Horstkotte D, Langer C. Scanning electron microscopic analysis of different drug-eluting stents after failed implantation: From nearly undamaged to major damaged polymer. Cathet Cardiovasc Interv. – in press (DOI 10.1002/ccd.21373).
2. Ormiston JA, Webster M, and Ruygrok P. Polymer integrity after Cypher and Taxus stent implantation: A scanning electron microscope study. Presented at TCT 2004; http://www.tctmd.com.
3. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. J Invasive Cardiol. 2007;19:71-76.
4. Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. EuroInterv. 2009;5:157-165.
5. Leon MB, Endeavor IV-A Randomized Comparison of a Zotarolimus-Eluting Stent Endeavor IV-A Randomized Comparison of a Zotarolimus-Eluting Stent. Presented at TCT 2007; http://www.tctmd.com.
6. Kirtane AJ, Patel R, O'Shaughnessy C, Overlie P, McLaurin B, Solomon S, Mauri L, Fitzgerald P, Popma JJ, Kandzari DE, Leon MB. Clinical and angiographic outcomes in diabetics from the ENDEAVOR IV trial: randomized comparison of zotarolimus- and paclitaxel-eluting stents in patients with coronary artery disease. JACC Cardiovasc Interv. 2009;2:967-976.

CHAPTER 7

SCANNING ELECTRON MICROSCOPIC ASSESSMENT OF THE BIODEGRADABLE COATING ON EXPANDED BIOLIMUS-ELUTING STENTS

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ABSTRACT

Aims: Biodegradable coatings on drug-eluting stents (DES) may help to avoid adverse long-term effects of DES such as late/very late stent thrombosis which is partly attributed to durable polymers. As the post-expansion morphology of biodegradable coatings is greatly unknown, we investigated the polylactic acid coating on biolimus-eluting BioMatrix stents.

Methods and results: Scanning electron microscopy (SEM) was used to carefully examine five 3.5mm stents following expansion at 6–14atm (maximum 7% overstretch). SEM examination demonstrated only mild cracks of the coating after stent expansion at 6atm. Increase in expansion pressure, associated with mild stent overstretch, resulted in more severe cracks. Lifting of the coating together with few sites of partial detachment of fragments was noticed after stent expansion in water at 14atm; these irregularities further increased after aggressive oversized partial postdilatation with a 5.0mm non-compliant balloon with additional secondary cracks.

Conclusions: SEM assessment suggests a relatively low elasticity of the biodegradable coating on BioMatrix stents. At nominal pressure, stents showed predominantly mild cracks of the coating, while cracks increased after slight overstretch. Aggressive overexpansion of the stent, such as sometimes required in left main bifurcation stenting, worsened cracks and led to some detachment of fragments of the coating in vitro.

INTRODUCTION

Drug-eluting stents (DES) reduce the need for re-intervention after percutaneous coronary interventions,(1-3) however, late stent thrombosis remains an issue which is partly attributed to inflammation possibly induced by durable polymer (in DES coatings). (4-7) Biodegradable coating on DES has the promise to avoid potential adverse long-term effects of DES coating.(8) The concept of a biodegradable drug-eluting coating was tested in combination with different antiproliferative drugs.(9-11) One of these combinations is a biolimus-eluting polylactic acid (PLA) coating,(12) which has recently been investigated in the LEADERS trial.(13) The physical properties of the PLA coating on this DES may differ from that of durable polymer coatings on conventional DES. Scanning electron microscopy is an attractive modality to examine the coating morphology of DES. Only few SEM data have been published on durable polymer-based DES (14-17), while there is no published SEM-data on biodegradable polymer-coated DES. This motivated us to examine the post-expansion morphology of the coating on BioMatrix stents using scanning electron microscopy (SEM).

MATERIALS AND METHODS

Investigated stents

At the University of Twente in Enschede, we prospectively performed in vitro SEM examinations of five BioMatrix™ (Biosensors Europe SA, Morges, Switzerland) stents, being expanded in air or water at different balloon pressures, which resulted in stent dimensions that ranged from the nominal size (one sample) via mild overstretch (three samples) up to aggressive overstretch (one sample). These stents (sterile packed; expiration date not passed) were provided to us by the company Biosensors via its Dutch supplier for the purpose of SEM examination at the University of Twente. The BioMatrix stent is based on the stainless steel S-Stent™ (Biosensors International, Newport Beach, CA) platform covered with a primer of parylene C and on the abluminal side of the stent a mixture of biolimus-A9 and a PLA polymer (12)PLA coating is biodegradable and expected to be totally degraded within approximately 9 months. Of note, these stents had a subtle difference versus BioMatrix stents of the LEADERS trial; that is, Paralyne C was not used in priming the stents that were used in the LEADERS trial.

DES expansion protocol in vitro

All five stents were expanded under sterile conditions in the laboratories of the Institute for Biomedical Technology at the University of Twente under a laminar air flow hood. The experiments were performed by an experienced interventional cardiologist and a laboratory technician, assisted by a research fellow. The first two samples (samples 1 and

2) were expanded at 6 and 10atm (in air at 18ºC), which corresponds to expected stent diameters of 3.50 mm (the stent diameter at nominal pressure) and 3.62 mm (103 % of the stent diameter at nominal pressure), respectively. Three stents (sample 3,4, and 5) were expanded at 14atm (expected diameter of 3.74 mm = 107 % of the stent diameter at nominal pressure in air). Sample 3 (3.5/12mm) was expanded in a dry state (in air at 18ºC). Samples 4 and 5 (3.5/23mm) were expanded in sterile water at 37ºC after being immersed for half a minute in water. Of note, the current instruction for use document does not suggest a minimum time of immersion in water / blood before stent implantation. In sample 5, we performed an additional oversized post-dilatation at 18atm with a non-compliant Quantum Maverick™ 5.0/12mm balloon catheter (Boston Scientific, Natick, MA). In sample 5 (which was partially postdilated with an oversized balloon), the monorail sections of both stent balloon and postdilatation balloon were wired with a single 0.014" guidewire to allow alignment of the postdilatation ballon with a minimum manipulation. Following stent expansion, samples were very carefully placed in a sterile petri plate; any manipulation was minimized. Consecutively, DES were dried under laminar air flow at 18ºC; we did not perform any ethanol-based or vacuum-based drying of the samples.

Scanning electron microscopic analysis

A Phillips XL30 scanning electron microscope was used to perform standard SEM imaging; further options of the system (ESEM FEG in combination with EMRAM MCS-A1 of μ Candela Systems) were not used in this study. We avoided any pretreatment (e.g., gold sputtering). Samples were indirectly fixed on the table of the SEM (none of the SEM images presented in this manuscript was taken in the vicinity of that fixation). A 1KeV-protocol was applied (average working distance 10mm; range 6–12mm sample dependent). Samples were examined at low magnifications (14-40X) to localize areas of possible coating irregularities. This step was followed by further assessment of the irregularities at higher magnifications (80-1000X) to confirm and characterize the irregularities and to measurement their dimensions.

RESULTS

The various coating irregularities that were found are described in Table 1, which also refers to illustrative examples of each individual irregularity. Table 2 gives an overview on the presence and extent of coating irregularities in the different DES samples.

Table 1. Definitions and examples of DES coating irregularities observed.

DES coating irregularities	Definitions and examples
Primary crack	Sharp-edged coating irregularity extending from the surface deep into the coating, sometimes with exposure of underlying stent/ primer (e.g., Fig. 1A-F).
Secondary crack	Sharp-edged irregularity extending perpendicular to primary cracks (e.g., Fig. 4A and 4D).
Tiling	Local outward displacement of coating with the formation of tile-like structures resembling the ridge of a roof (e.g., Fig. 2F).
Lifting of coating	Upwards displacement of the central portion of the coating on a crosslink while still being connected with the surrounding coating (e.g., Fig. 3A)
Fragment of coating	Detached piece of coating that may or may not keep minimum contact to the rest of the coating (e.g., Fig. 2C and 3D).
Total detachment of coating	Total loss of coating with exposure of underlying stent/primer (e.g., Fig. 3E and 4C).

Table 2. Presence and extent of coating irregularities in the different DES samples.

	DES sample 1 (expanded in air at 18ºC at 6 atm without postdilatation)	**DES sample 2** (expanded in air at 18ºC at 10 atm without postdilatation)	**DES sample 3** (expanded in air at 18 ºC at14 atm without postdilatation)	**DES sample 4** (expanded in water at 37 ºC at 14 atm without postdilatation)	**DES sample 5** (expanded in water at 37ºC at 14atm followed by oversized partial postdilatation)
Primary cracks	+	++	+++	+++	++++
Secondary cracks	—	—	—	—	+
Tiling	—	—	+	+	+
Lifting of coating	—	—	—	+	++
Fragment of coating	—	—	—	+	+
Total detachment of coating	—	—	—	+	+

Legend: — : irregularity absent ; + to ++++: irregularity present with increase in severity from + to ++++.

Cracks in DES coating

The examination of a total of 130 SEM images of the BioMatrix DES demonstrated the presence of (primary) cracks in the coating which were located mainly on the inner curvature of stent loops (Fig. 1 and 2). Depending on the degree of stent overstretch, the width of cracks measured up to 64µm and the length reached up to 74µm. When examining the interior aspect of some cracks that occurred following mild overstretched of the stents, we saw sharp edges and a rough interior surface of the coating (Fig. 2D). Some cracks exposed the underlying stent/primer (Fig. 2D). In addition, relatively small polymer fragments (Fig. 2C) were noticed inside cracks and in the vicinity of cracks (visible in sample 3). There was an increase in size and number of cracks in stents expanded at increasing pressures (from 6 to 10 and 14 atm in air, respectively). Cracks tended to be larger in sample 4 (expanded in water) (Fig. 3B-C). Post-dilatation of the expanded DES with a large oversized balloon was associated with relatively large cracks (Fig. 4B and 4C). In addition, we noticed secondary cracks that showed an orientation perpendicular to the primary cracks (sample 5; Fig. 4A and 4D).

Tiling and lifting of fragments of DES coating

Following stent expansion at 14 atm in air, we occasionally noticed tiling of the coating at crosslinks between two rings up to a maximum height of 63µm (sample 3; Fig.2F) with exposure of the stent/primer at its base. In sample 4 and sample 5 (after 14 atm in water and after partial oversized postdilatation in water, respectively), there was more tiling, lifting of portions of the polymer (in particular at the crosslinks) (Fig. 3A, 3E, 4E, and 4F) in abluminal direction (which in the physiological situation would be apposed to the vessel wall). The size of the largest lifted portion of polymer measured 93x344µm.

Detachment of fragments of DES coating

In DES expanded in water, several partially detached fragments of coating were detected (maximum size 85x310µm ; Fig.3D) while there were only few sites with total loss of coating (Fig. 3E and 3F), indicating sites of total detachment of polymer fragments (maximum size 106x350µm).

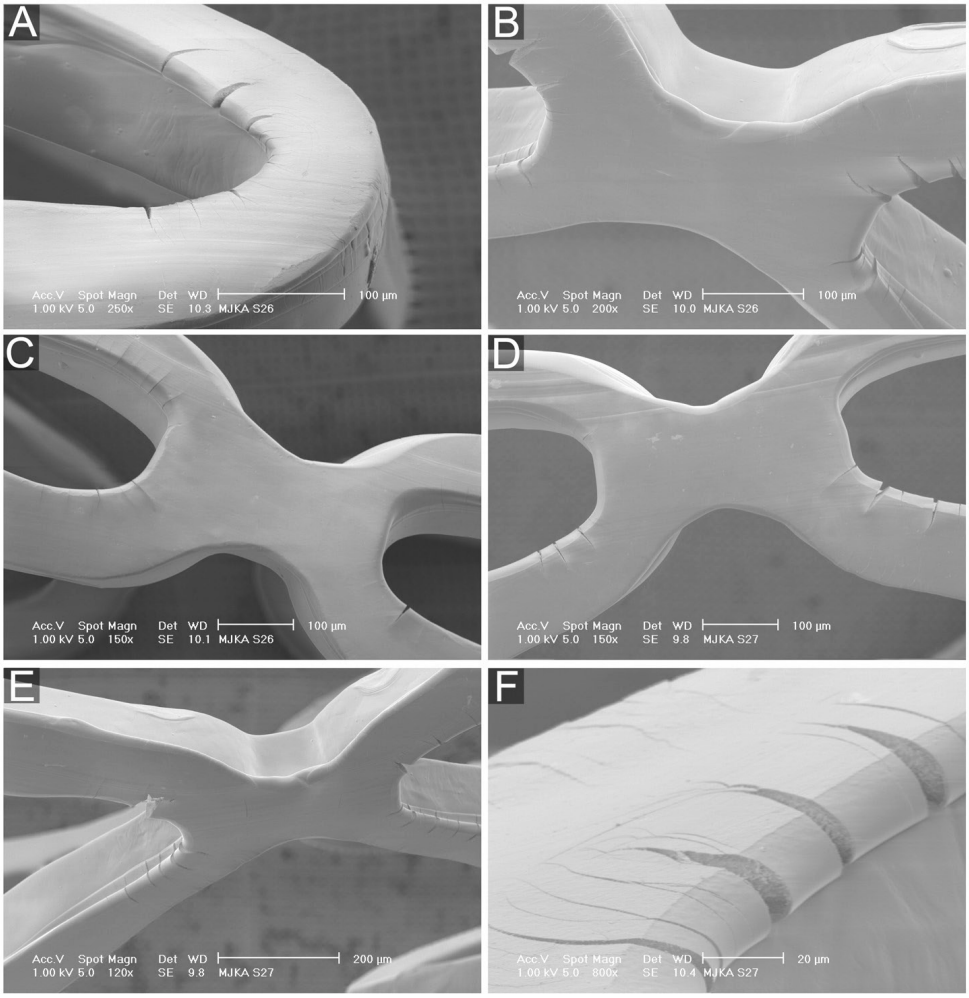

Figure 1. A,B, and C: SEM images of DES sample 1 (after 6 atm expansion in air). D,E, and F: SEM images of DES sample 2 (after 10 atm expansion in air). See results section for further details. Careful examination of panel 1C and 1D demonstrates an increase in size of cracks in sample 2 versus sample 1.

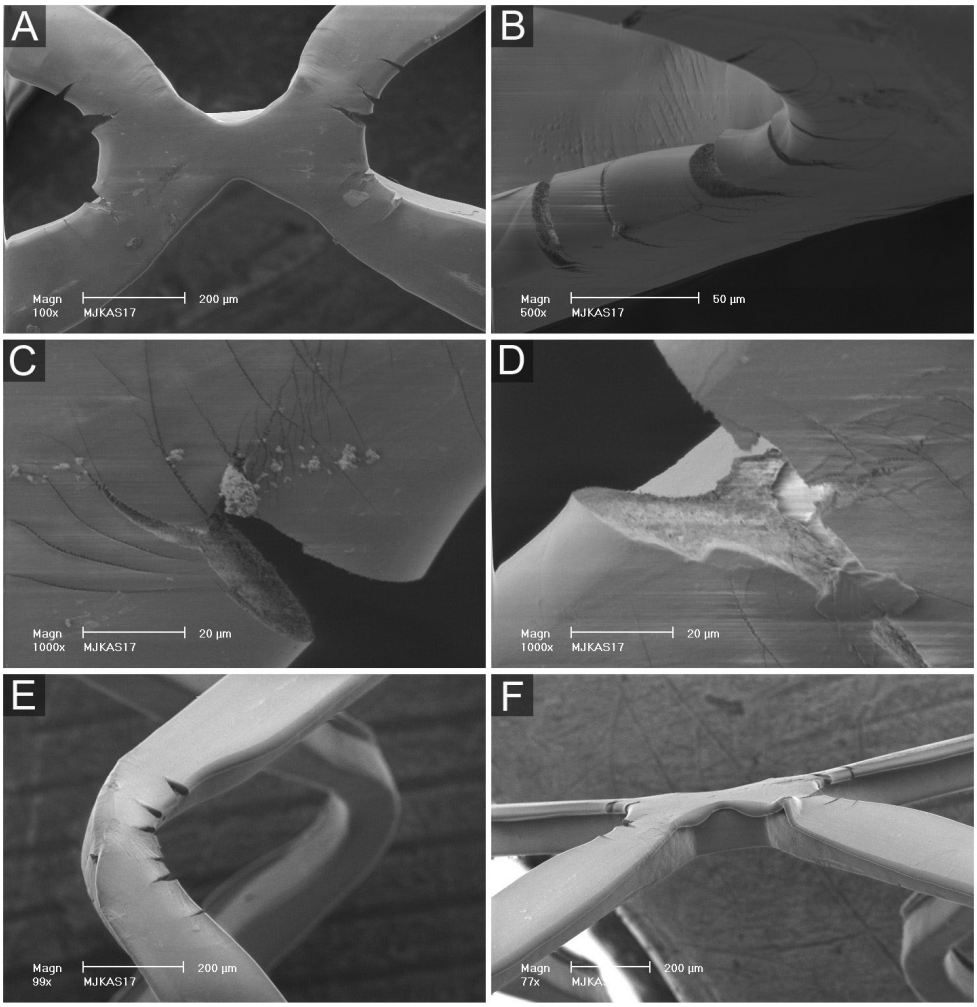

Figure 2. SEM images of DES sample 3 (expanded in air). See results section for further details.

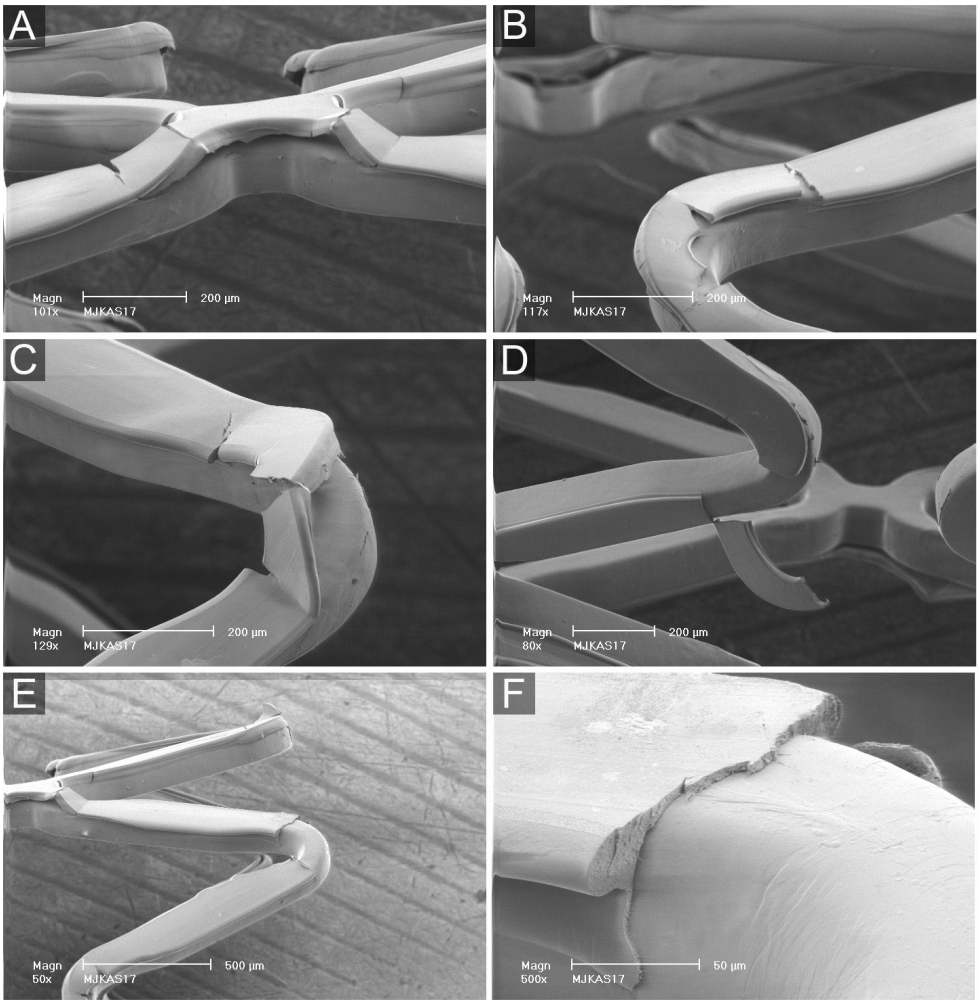

Figure 3. SEM images of DES sample 4 (expanded in water). See results section for further details.

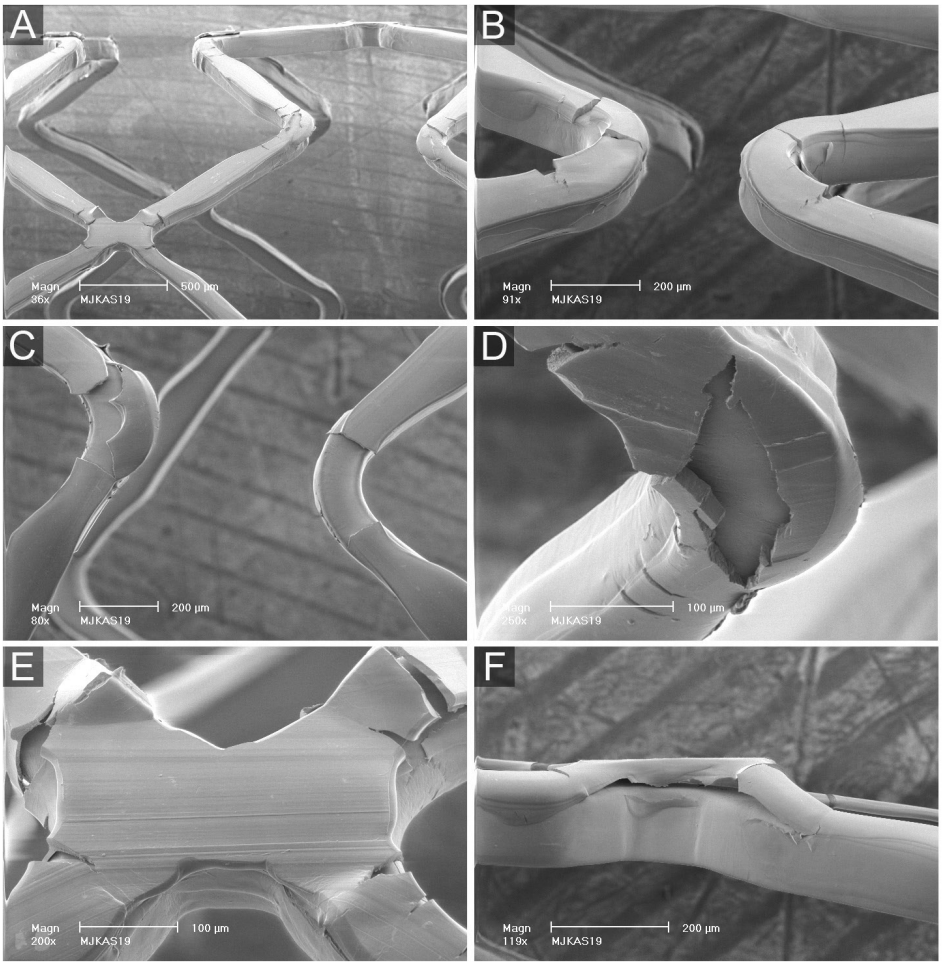

Figure 4. SEM images of DES sample 5 (after expansion in water followed by aggressive oversized partial postdilatation). See results section for further details. Of note, panel 4F demonstrates the same irregularity as panel 4E but shown from a lateral view.

DISCUSSION

The introduction of DES with biodegradable polymer coatings has the intention to reduce potential unfavorable (late) events of DES. In the LEADERS trial, the biodegradable polymer-based BioMatrix DES confirmed non-inferiority vs. the durable polymer-based Cypher stent. (13) However, the PLA-based coating of the BioMatrix stent has physical properties (e.g., elasticity that is lower than in many durable polymers) that may lead to irregularities and defects of the coating following stent expansion and/or oversized partial postdilatations, as suggested by the observations of the present study.

Elasticity of DES coating and irregularity formation

The appearance of cracks in the coating (on inner curvatures of loops) and tiling of the coating (on crosslinks) suggests a relatively low elasticity of this PLA coating in comparison to many durable polymers. This results in a higher susceptibility to the development of coating irregularities during more than mild overstretch of the stent. In particular, the inner curvature of loops is exposed to higher forces during unfolding of the stent, which may explain the predominance of cracks on the inner curvatures of loops which were found at nominal pressure (6 atm) and after very mild overstretch of the stent (103% and 107% of diameter at nominal pressure) following stent expansion at 10atm and 14atm.

In the absence of information on a minimum time of immersion in water or blood in the current instruction for use (IFU) document of the BioMatrix stent, we immersed samples 4 and 5 for 30 seconds in water to simulate the shortest feasible time required to reach and stent an easily accessible target lesion. But apparently that brief immersion in water was not sufficient to improve the elasticity of this coating. Immersion for at least 60 seconds may have been more desirable to improve its physical properties (John Shulze, CTO Biosensors; personal communication on January 29, 2009).

In BioMatrix DES, the size of the detached polymer fragments was larger than observed in conventional durable polymer-based DES. (17) As shown by our experiments, postdilatation of the BioMatrix stent with an extremely oversized non-compliant balloon may result in worsening of cracks in the coating. Even further secondary cracks may be the result of such aggressive postdilatations, which may be required in clinical scenarios when stents are implanted in the transition between the left main stem and one of its major branches.

Implications

Our in vitro observations need to be cautiously interpreted, as recent clinical data suggested that the BioMatrix DES is safe and effective,(13) and no correlation has been established between coating defects of this (or other) DES and the observed clinical performance in vivo in animals or humans.

As this PLA polymer is expected to be totally degraded within the generally advised 12 months of dual anti-platelet therapy following DES implantation, cracks and similar irregularities of the coating are unlikely to result in late unfavorable cardiac events.

The manufacturer of the BioMatrix stent recommends (in the instruction for use document) to generally select a stent diameter that results in no more than 10% overexpansion of the stent after implantation. However, it is a matter of fact that experienced interventional cardiologists occasionally apply much more aggressive partial overexpansions to DES during some of their procedures (e.g., PCI of left main bifurcation disease; major bifurcation lesions that involve considerable vessel tapering; or coronary stenoses that involve aneurysmatic coronary segments). Our overstretch test in sample 5 refers to these scenarios, showing that

some delamination of this DES could occur at sites of maximum mechanical stress if stents are overstretched in such a way.
Detachment of polymer fragments could then theoretically reduce the antiproliferative potential of DES (because of loss of antiproliferative drug). While the clinical effect of loss in antiproliferative potential may be negligible, embolization of substantial pieces of the coating could lead to luminal obstruction on microvascular level that could be associated with some degree of periprocedural cardiac marker release.
In particular, embolization of fragments of the coating is more likely if the DES is postdilated (i.e., overstretched) but partially not well apposed against the vessel wall (e.g., when covering the ostium of a large sidebranch; or in the vicinity of an excentric, calcified stenosis). Our observations are no more than hypothesis-generating; further in vitro tests in challenging and realistic vessel phantoms of coronary lesions should be performed, which may include quantitative measurements of particles released from a stent during (and following) its expansion.(18) In addition, posthoc analyses of data of the LEADERS trial may assess potential relations between periprocedural cardiac marker release and procedural details such as implantation and postdilatation pressures and degree of stent overstretch.
Nevertheless, until further data have been accumulated interventional cardiologists may consider our findings when stenting lesions that involve major bifurcations – in particular left main bifurcations with a need for final kissing balloon inflations. In the LEADERS trial, there was only a small difference in 30-days myocardial infarction rate, favoring Cypher vs. BioMatrix but that difference did not reach statistical significance.(13)

Limitations

As an inherent limitation of benchside studies, the present in vitro study does not exactly mimic the conditions in vivo. In our experimental setup, we did not implant stents in vessels or vascular phantoms that could provide some load to stabilize the stent coating against the vessel wall. Implantation in vessels or vascular phantoms might have reduced tiling and displacement of polymer fragments. On the other hand, current simulated vessel phantoms generally do not match the physiological situation of (often) rigid and calcified atherosclerotic lesions, in which we could only speculate on how high balloon pressures or “dogboning” as a result of partial stent overstretch (of the stent extremities) may affect the integrity of this stent’s coating.(19) Moreover, we avoided any additional defect that could have resulted from scratching the DES along (calcified) vessel walls or from regaining the DES out of vascular phantoms or specimens.
The design of our study is qualitative; quantification of the incidence and size of irregularities (in particular of polymer fragments) may be subject of future research. The findings of our study apply to BioMatrix stents with 9 crowns; we did not test stents with 6 crown-design (stent diameter < 3.5mm).

We cannot fully exclude that drying this DES (following expansion in water) may have modified some coating irregularities, while stent expansion in air may have worsened its physical properties. Assessment of the post-expansion DES morphology by environmental SEM may be an option to avoid such effects.
Although much effort was taken to handle stents with maximum care, we cannot exclude that an individual defect may have been aggravated (e.g., that an almost completely detached fragment of coating could have lost its final connection). However, there are scenarios in clinical practice where such stents and their coating will be exposed to much rougher actions: if for instance a used non-compliant balloon catheter is (re-)advanced into the stent; oversized high-pressure postdilatation is performed; or kissing balloon dilatation is performed at a major bifurcation (the latter represents a combination of stent overstretch and shear stress applied to the coating).

Conclusions

SEM assessment suggests a relatively low elasticity of the biodegradable coating on BioMatrix stents. At nominal pressure, stents showed predominantly mild cracks of the coating, while cracks increased after slight overstretch. Aggressive overexpansion of the stent, such as sometimes required in left main bifurcation stenting, worsened cracks and led to some detachment of fragments of the coating in vitro.

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The authors have no conflict of interest to declare.
While no financial support was obtained, free samples of DES were obtained from a Dutch supplier for the purpose of this scanning electron microscopic assessment.

REFERENCES

(1) Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003 August 19;108(7):788-94.

(2) Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003 October 2;349(14):1315-23.

(3) Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, Guagliumi G, Wijns W, Lindeboom WK, Ligthart J, de Feyter PJ, Morice MC. 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 August 13;106(7):798-803.

(4) Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007 March 8;356(10):1030-9.

(5) Schomig A, Dibra A, Windecker S, Mehilli J, Suarez de LJ, Kaiser C, Park SJ, Goy JJ, Lee JH, Di LE, Wu J, Juni P, Pfisterer ME, Meier B, Kastrati A. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007 October 2;50(14):1373-80.

(6) Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007 March 8;356(10):989-97.

(7) Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007 September 15;370(9591):937-48.

(8) Daemen J, Serruys PW. Drug-eluting stent update 2007: part I. A survey of current and future generation drug-eluting stents: meaningful advances or more of the same? Circulation 2007 July 17;116(3):316-28.

(9) Ostojic M, Sagic D, Jung R, Zhang YL, Nedeljkovic M, Mangovski L, Stojkovic S, Debeljacki D, Colic M, Beleslin B, Milosavljevic B, Orlic D, Topic D, Karanovic N, Paunovic D, Christians U. The pharmacokinetics of Biolimus A9 after elution from the Nobori stent in patients with coronary artery disease: the NOBORI PK study. Catheter Cardiovasc Interv 2008 December 1;72(7):901-8.

(10) Storger H, Grube E, Hofmann M, Schwarz F, Haase J. Clinical experiences using everolimus-eluting stents in patients with coronary artery disease. J Interv Cardiol 2004 December;17(6):387-90.

(11) Vogt F, Stein A, Rettemeier G, Krott N, Hoffmann R, vom DJ, Bosserhoff AK, Michaeli W, Hanrath P, Weber C, Blindt R. Long-term assessment of a novel biodegradable paclitaxel-eluting coronary polylactide stent. Eur Heart J 2004 August;25(15):1330-40.

(12) Grube E, Buellesfeld L. BioMatrix Biolimus A9-eluting coronary stent: a next-generation drug-eluting stent for coronary artery disease. Expert Rev Med Devices 2006 November;3(6):731-41.

(13) Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008 September 27;372(9644):1163-73.

(14) Ormiston J, Webster M, Ruygrok P, Stewart J, Scott D, Currie E, Panther M, Shaw B. Polymer integrity after Cypher and Taxus stent implantation: A scanning electron microscope study. http://www.tctmd.com. 2005.

(15) Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: comparison of BiodivYsio, Taxus and Cypher stents. J Invasive Cardiol 2007 February;19(2):71-6.

(16) Kitahara H, Kobayashi Y, Yamaguchi M, Fujimoto Y, Nameki M, Nakayama T, Kuroda N, Komuro I. Damage to polymer of undelivered sirolimus-eluting stents. J Invasive Cardiol 2008 March;20(3):130-3.

(17) Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2009;5(1):157.
(18) Conti JC, Strope E, Ramesh R, Conti C, Watkins A. A Comprehensive Protocol and Procedural Considerations Designed to Evaluate the Shedding of Particles from Drug Eluting Stents. Proceedings from the Materials & Processes for Medical Devices Conference, 2007.
(19) von Birgelen C, Mintz GS, Bose D, Baumgart D, Haude M, Wieneke H, Neumann T, Brinkhoff J, Jasper M, Erbel R. Impact of moderate lesion calcium on mechanisms of coronary stenting as assessed with three-dimensional intravascular ultrasound in vivo. Am J Cardiol 2003 July 1;92(1):5-10.

CHAPTER 8

POLYMER COATINGS ON DRUG-ELUTING STENTS: SAMSON'S HAIR AND ACHILLES' HEEL?

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Drug-eluting stents (DES) minimise the risk of in-stent restenosis by means of controlled, local delivery of anti-proliferative drugs from a thin layer of coating applied to a rigid stent backbone. In this respect, polymer coatings have proven largely indispensable for the control of drug release kinetics and the optimization of DES efficacy. Investigation of polymer-free stent platforms has typically yielded comparatively lower levels of neointimal suppression by virtue of rapid drug dissociation in the initial hours and days after stent implantation.[1] Indeed, all of the currently-available FDA-approved DES devices control drug-release by use of durable polymer coatings.[2, 3] On the other hand, polymer coatings may elicit unanticipated off-target effects – ranging from eosiniophilic hypersensitivity to foreign body reactions at one end of the spectrum,[4] to potentially favourable effects on reducing stent thrombogenicity in the acute phase.[5]

Until recently, the publicly-accessible literature provided only limited bench top data on the physical characteristics and surface integrity of different polymer coatings on devices in everyday use. Such data might be clinically important for a number of reasons. First, DES thrombogenicity could potentially be increased at regions of stent surface irregularity, due to inhomogeneous distribution or displacement of polymer coating. Coarse DES coating irregularities might promote the inflammatory reactions sometimes seen after DES implantation (Figure 1, panel A and B), which in turn act as a direct nidus for platelet activation and stent thrombosis. Second, the antiproliferative potential of DES might be locally reduced at sites of major coating loss – at such regions the DES is effectively a bare metal stent. Third, downstream microembolism of detached fragments of DES coating could lead to myocardial injury or infarction. In the current issue of Eurointervention, a study from United States researchers addresses the issue of DES coating irregularities and free particle formation after stent expansion.[6] The main findings extend observations from an earlier brief report[7] and are scientifically interesting: the expansion of stent delivery balloons topographically disturbs the polymer surfaces of all examined DES devices, and this disturbance can be complicated by the liberation of microparticles that the investigators collected from a filtered expansion chamber.

DES coating irregularities and fragments reported in the literature

Thus far, a limited body of research data has examined microscopic morphology, coating irregularities or physical properties of polymer-based DES devices.[8-11] An initial systematic classification and quantification of coating irregularities on the surface of various types of DES reported in 2009 showed that the incidence and size of various coating irregularities differed widely between different types of DES.[11] The present carefully executed study of Denardo and co-workers builds further on the available literature and confirms that important qualitative and quantitative differences in surface coating exist between approved DES

platforms that are in routine clinical use.[6] Earlier research on expanded (and post-dilated) DES demonstrated loosely-attached polymer particles with a very wide range of size, e.g. approximately 30 µm on a durable polymer-based DES coating (Figure 1, panel C) versus up to 300 µm on a biodegradable polymer-based DES coating (Figure 1, panel D);[10, 11] (these differences should not be considered as polymer class effects; preliminary data suggest that there may be equally important differences in how different biodegradable polymer coatings react upon stent expansion[12]). In addition, the identification of uncoated areas on DES may be considered as evidence of total detachment of polymer fragments (Figure 1, panels E and F), in particular if interpreted in the context of previously reported data from unexpanded DES.[13] In the present study, Denardo and co-workers went one step further, collecting and analysing totally detached particles liberated during DES expansion, by filtering the medium in which the DES were expanded. Optical microscopy and scanning electron microscopy (SEM) were used to subsequently examine the filter, aiming at qualitative and quantitative analysis of the free particles captured. In interpreting their findings, the technical challenges of the work and the translational relevance of the data should be considered.

Technical challenges of the bench top assessment of DES surfaces

The report of Denardo et al. primarily quantified stent coating irregularities based on optical microscopy, which allowed rapid handling of the samples. However, in contrast, most of the recent studies by others used systematic electron microscopy examination due to its three-dimensional properties and its capacity to obtain high magnification (>100,000-fold) images with high spatial resolution. [8-11] In addition, the FDA specifically mention SEM-based examination for visualization of acute polymer injury in published draft guidance for industry.[14] Certainly minor topographical irregularities related to manufacturing may be missed be optical microscopy, such as waviness, flattening and cratering of the polymer, as well as coating adhesion (a factor in subsequent polymer webbing observed for example with the Taxus stent). On the other hand, major polymer damage such as coating delamination, peeling, and ridging is likely to be identified with both methodologies.

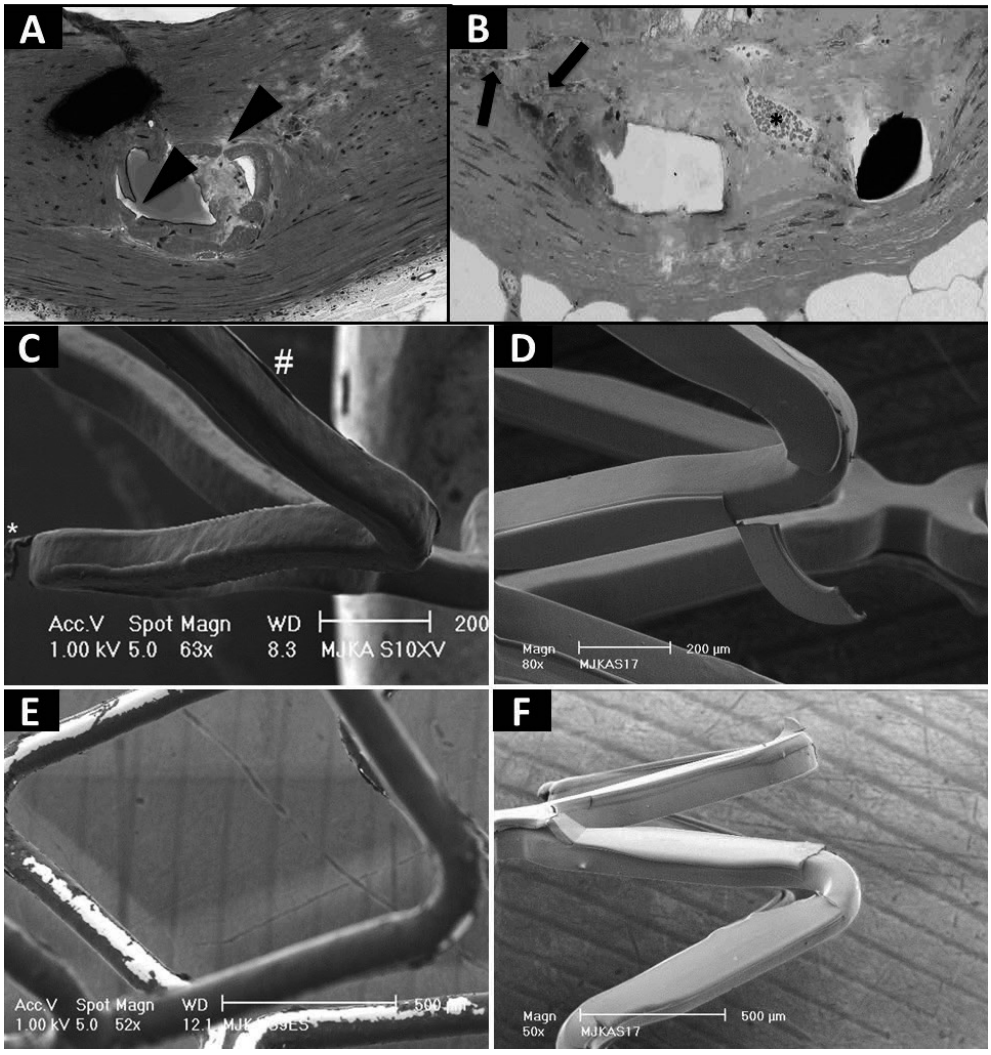

Figure 1. Representative high power (×200) magnifications of polymer-coated stent struts after Movat Pentachrome (A) and Giemsa eosin (B) staining. Note, there is presence of polymer cracking (black arrowheads) and delamination (black arrows) resulting in moderate inflammatory reaction, mostly consisting of monocyte and neutrophil infiltration. Furthermore, neovascularisation (*) is observed in the surroundings of stent struts as a sign of sustained inflammation. C) Partially detached fragment of coating (*) and ridge-like thickening of coating (#) on an everolimus-eluting XIENCE V® stent (Abbott Vascular, Santa Clara, CA, USA). D) Partially detached fragment of coating on a biolimus-eluting BioMatrix™ stent (size 85×310 µm; Biosensors International, Singapore, Singapore). E) Phosphorylcholine-based zotarolimus-eluting Endeavor® stent (Medtronic, Minneapolis, MN, USA) with visual aspect of bare metal areas. F) An area with total loss of coating on a biolimus-eluting stent, indicating total detachment of a polymer fragment. (Panels C-F modified from references 10 and 11).

A number of additional technical factors deserve consideration. First, the impact on interobserver variability must be acknowledged. Adjudication of irregularities is reliant on an analyst's experience and judgment and thus entails a certain degree of subjectivity. Semi-automated tools with image analysis software could increase reproducibility and facilitate meaningful comparisons between the findings of different research groups. Second, the FDA currently suggests in a nonbinding recommendation the use of a robust number of stents from multiple stent lots for each test (i.e. a minimum of 3 batches),[14] but the optimal number of stent samples required for individual experiments is not known. In addition, it is desirable that a minimum stent surface area is examined in order not to miss certain irregularities; this may be even more important with newer generation stents that appear to show less coating irregularities. Third, stent expansion in an aqueous medium followed by drying could theoretically create artificial cracking and splitting, preferentially affecting more hydrophilic coatings. This effect can be minimized by gradual passive drying without temperature changes, which seems to be the method employed by the authors. The use of environmental SEM might theoretically avoid the problem to some extent, but this imaging technique is very time consuming, and less suitable for studies utilizing stepwise scanning of relatively large surface area cylindrically shaped stent samples that have to be turned repeatedly.

Translational relevance of these findings?

Of course bench top studies do not accurately mimic the complex interplay of individual stent components, delivery devices and disease conditions *in vivo*. Indeed an important additional feature of the bench model of Denardo et al. is that the stents were expanded in a fluid medium without utilization of a vessel phantom. Bench-top testing of DES surfaces is mostly performed without the use of phantoms, as careful examination of the stent surface is impossible inside the phantom, and extraction of the sample from the phantom may increase the frequency and size of coating irregularities. One consequence of this approach is that the known impact of abluminal coating damage due to contact with the vessel wall as well as tracking to the lesion is not accounted for.[9] On the other hand some investigators have shown reduction in balloon expansion-related polymer damage when stents are expanded in phantoms with compliance similar to that of human coronary arteries.[15] Moreover in clinical use the majority of abluminally-derived particles liberated upon balloon expansion may remain trapped in the vessel wall behind the implanted stent. Thus the local vessel wall impact of microparticles (e.g. local inflammation, endothelial dysfunction) might be more clinically important than downstream effects (such as microvascular obstruction).

In this respect historical preclinical studies have highlighted the problem of delayed arterial healing after DES implantation and that the prolonged inflammation observed after first- and second-generation devices is most likely secondary to polymer residues especially in overlapping stented sections.[16] Infiltration of neutrophils and eosinophils was clearly increased in first generation DES compared to uncoated metal stents and the pro-inflammatory contribution of damaged polymers and delamination products in this process is likely significant (see figure 1, panel A and B). In fact the clinical implication of damaged durable polymers may have been under-recognized and may have substantial impact on clinical outcomes of patients receiving these stents.

Clinical evidence supporting the importance of topographical irregularities is difficult to evaluate. There are 2 points of view. On the one hand, it can be argued that the differences in polymer irregularities and microparticle formation between stents might have contributed to differences in peri-procedural myocardial infarction observed in some randomized clinical trials (e.g. paclitaxel-eluting versus everolimus-eluting stents,[17] and biolimus A9-eluting versus sirolimus-eluting stents[18]) as well as to the lower rates of stent thrombosis observed with newer generation durable polymer DES.[19] Nevertheless, linking such findings to free particle formation during stent deployment only may be too simplistic, as various other DES or patient-related factors may play a role.[20] Indeed it might equally be observed that the somewhat 'less favourable' appearance of some DES on the bench did not translate into detectable safety issues in large-scale randomized trials.[10, 21] It may well be that the advantages of stent macro-components (such as drug load and release kinetics, and stent superstructure) outweigh the impact of micro-components (such as surface irregularity and microparticle liberation). Accordingly, while we should be grateful for the important contribution of researchers such as Denardo and colleagues, more data is needed before we can be sure of the clinical relevance of the polymer irregularities and microparticles identified in bench studies.

Perspective

The concept of covering DES with polymer-based coatings turned out to embody both *"Samson's hair" and "Achilles' heel"* of these devices. While polymer coatings have a central role in ensuring the antirestenotic efficacy of DES devices – and may even have an acute protective role in reducing thrombogenicity – these advantages occur at the collateral cost of a significant delay in arterial healing in comparison with uncoated stents and an associated spectrum of clinicopathological events including late thrombotic stent occlusion. The present report of Denardo et al.[6] sheds further light on the issue of balloon expansion-induced polymer disruption and microparticle liberation, an effect that appeared to vary among DES types studied. Although the clinical relevance of these findings remains

to be fully elucidated, the potential relevance is such that in our opinion detailed bench evaluation of polymer coating integrity should be incorporated into European regulatory body approval processes, as is the case in the United States. In addition, we propose that use of standardized methodology and reporting, including systematic SEM examination of coating irregularities, will allow meaningful comparison of findings between studies. Further research on DES devices that are in widespread clinical use will be of great interest to the interventional cardiology community. The publication of such data in the peer reviewed literature would represent an important contribution to the further development of this technology.

DISCLOSURES

MB, MJ and RAB have no conflicts to disclose. CvB is a consultant to and has received lecture fees or travel expenses from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. The research department of Thoraxcentrum Twente has received educational and/or research grants funded by Abbott Vascular, Biotronik, Boston Scientific, and Medtronic.

REFERENCES

1. Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, Pache J, Wessely R, Schomig A, Kastrati A. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J*. 2008;29:1975-1982
2. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:254-265
3. Byrne RA, Sarafoff N, Kastrati A, Schomig A. Drug-eluting stents in percutaneous coronary intervention: A benefit-risk assessment. *Drug Saf*. 2009;32:749-770
4. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol*. 2009;57:567-584
5. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation*. 2011;123:1400-1409
6. Dernardo SJ, Carpinone PL, Vock DM, Tcheng JE, Phillips HR 3rd, Willenberg BJ, Batich CD, Pepine CJ. Detailed analysis of polymer response to delivery balloon expansion of drug-eluting stents versus bare metal stents. *EuroIntervention*. 2013;9:389-397
7. Denardo SJ, Carpinone PL, Vock DM, Batich CD, Pepine CJ. Changes to polymer surface of drug-eluting stents during balloon expansion. *JAMA*. 2012;307:2148-2150
8. Otsuka Y, Chronos NA, Apkarian RP, Robinson KA. Scanning electron microscopic analysis of defects in polymer coatings of three commercially available stents: Comparison of biodivysio, taxus and cypher stents. *J Invasive Cardiol*. 2007;19:71-76
9. Wiemer M, Butz T, Schmidt W, Schmitz KP, Horstkotte D, Langer C. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: From nearly undamaged to major damaged polymers. *Catheter Cardiovasc Interv*. 2010;75:905-911
10. Basalus MW, van Houwelingen KG, Ankone M, de Man FH, von Birgelen C. Scanning electron microscopic assessment of the biodegradable coating on expanded biolimus-eluting stents. *EuroIntervention*. 2009;5:505-510
11. Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. *EuroIntervention*. 2009;5:157-165
12. von Birgelen C. Do differences in polymer coating consistency, defects, and integrity exist (and do they matter)? *Transcatheter Cardiovascular Therapeutics (TCT) Conference*. San Francisco, CA, USA. 2012
13. Basalus MW, Tandjung K, van Westen T, Sen H, van der Jagt PK, Grijpma DW, van Apeldoorn AA, von Birgelen C. Scanning electron microscopic assessment of coating irregularities and their precursors in unexpanded durable polymer-based drug-eluting stents. *Catheter Cardiovasc Interv*. 2012;79:644-653
14. U.S. Department of Health and Human Services, Food and Drugs Administration, Center for Devices and Radiological Health. Guidance for industry and FDA staff: Non-clinical engineering tests and recommended labeling for intravascular stents and associated delivery systems. Document issued: April 18, 2010. Washington DC, USA. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071986.pdf
15. Yazdani SK, Vorpahl M, Nakano M, Su SH, Kolodgie FD, Virmani R. In vitro and in vivo characterisation of biodegradable polymer-based drug-eluting stent. *EuroIntervention*. 2011;7:835-843
16. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation*. 2005;112:270-278
17. Pervaiz MH, Sood P, Sudhir K, Hermiller JB, Hou L, Hattori K, Su X, Cao S, Wang J, Applegate RJ, Kereiakes DJ, Yaqub M, Stone GW, Cutlip DE. Periprocedural myocardial infarction in a randomized trial of everolimus-eluting and paclitaxel-eluting coronary stents: Frequency and impact on mortality according to historic versus universal definitions. *Circ Cardiovasc Interv*. 2012;5:150-156
18. Garg S, Wykrzykowska J, Serruys PW, de Vries T, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Tyczynski P, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P, Windecker S. The outcome of bifurcation lesion stenting using a biolimus-eluting stent with a bio-degradable polymer compared to a sirolimus-eluting stent with a durable polymer. *EuroIntervention*. 2011;6:928-935

19. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: Evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379:1393-1402
20. Goldstein JA. Periprocedural myocardial infarction: It's the plaque, not the stent. *Catheter Cardiovasc Interv*. 2012;80:531-532
21. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): A randomised, controlled, non-inferiority trial. *Lancet*. 2013;381:651-660

CHAPTER 9

INCIDENCE OF PERIPROCEDURAL MYOCARDIAL INFARCTION FOLLOWING STENT IMPLANTATION: COMPARISON BETWEEN FIRST AND SECOND GENERATION DRUG-ELUTING STENTS

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ABSTRACT

Background: First and second generation drug-eluting stents (DES) differ in coating materials, which may have influence on the incidence of periprocedural myocardial infarction (PMI).

Objective: To compare the incidence of PMI between first and second generation DES, using the current Academic Research Consortium (ARC) definition of PMI.

Methods: We assessed 800 patients treated with first (Taxus Liberté or Endeavor) or second generation DES (Xience V or Resolute). Each DES group consisted of 200 consecutive patients, who were treated during the transition from first to second generation DES. Routine peri-interventional assessment of cardiac biomarkers was performed to compare the incidence of PMI between DES groups according to the updated definition by the ARC: 2x upper reference limit of creatine kinase (CK), confirmed by CK-MB elevation.

Results: In 800 patients, a total of 1522 DES (363 Taxus; 385 Endeavor; 382 Xience V; 392 Resolute) were implanted to treat 1232 lesions. Patient characteristics did not differ between groups. In patients receiving second generation DES more multivessel PCI were performed ($p=0.01$). The overall incidence of PMI was 4.75%. Between first and second generation DES, there was no significant difference in PMI (5.5% vs.4.0%; $p=0.29$). In a multivariate analysis, only the total number of stents implanted ($p<0.001$) and presentation with acute coronary syndrome ($p=0.02$) were independent predictors of PMI.

Conclusion: Using the revised ARC definition, we found no significant difference in PMI between first and second generation DES. Overall, PMI occurred in 4.75%, which is 58% lower than with use of the historical PMI definition.

INTRODUCTION

In clinical studies, the incidence of periprocedural myocardial infarction (PMI) is one of the measures to assess the performance of an interventional technique and/or device implantation for the treatment of significant coronary lesions. The detection of PMI by means of the electrocardiogram requires a substantial amount of myocardial necrosis while the measurement of cardiac biomarkers is much more sensitive.(1;2) All types of percutaneous coronary intervention (PCI) are associated with a certain incidence of PMI. Bare metal stents were initially developed to treat occlusive coronary dissections following balloon angioplasty which prevented severe PMI. While the first generation drug-eluting stents (DES) minimized the restenosis problem of the bare metal stents,(3;4) they were associated with late and very late stent thrombosis.(5-7) These late coronary complications triggered the development of novel "second generation" DES with different polymeric DES coatings to improve biocompatibility.(8) As recently demonstrated, the surface of first and second generation DES differ with regards to the incidence and type of coating irregularities (9) which may have implications for DES thrombogenicity and thus the incidence of PMI.
In the literature, the incidence of periprocedural MI ranges from 2% to 22% (10-14), depending greatly on the indication for PCI and the definition of PMI used. Recently, the Academic Research Consortium (ARC) established a creatine kinase (CK)-based definition of PMI to homogenize the definition for use in stent trials and provide a generally appliable definition for reliable event adjudication, which also allows comparison with data from historical stent trials.(15)
In the present study, we used the revised definition of PMI to compare the incidence of PMI between PCI with implantation of first and second generation DES.

METHODS

Study population and design

In the present study, we assessed the data of 800 patients with stable angina, unstable angina, or NSTEMI (non-ST-elevation myocardial infarction) who were treated between February 2007 and January 2009 by implantation of DES. Patients treated with the early generation DES Taxus Liberté (Boston Scientific, Natick, MA, USA) or Endeavor (Medtronic Vascular, Santa Rosa, CA, USA) were compared to patients treated with the second generation DES Resolute (Medtronic Vascular, Santa Rosa, CA, USA) or Xience V (Abbott Vascular, Santa Clara, CA, USA). Each stent group consisted of 200 consecutive patients, who were treated within the period that our center switched to second generation DES. In other words, we retrospectively examined the last patients treated with Taxus Liberté and Endeavor and the first patients treated with Resolute and Xience V. Routine peri-interventional assessment of

cardiac biomarkers was performed to screen for PCI-induced myocardial necrosis up to 24 hours after PCI or until the highest value of CK was measured. Total CK levels were measured by CK-NAC kit and CK-MB mass by Elecsys CK-MB immunoassay (both Roche, Mannheim, Germany). Prior to PCI, informed consent for the interventional procedure was obtained as approved by the local Medical Ethical Committee.

PCI procedure

Prior to PCI, all patients received adequate loading doses of acetylsalicylic acid and clopidogrel if not pretreated, and an intravenous bolus of unfractionated heparin. The PCI procedure was performed via the femoral or radial access route. Interventional techniques and further treatment during PCI were chosen at the operators' discretion and according to current standards. In all patients, dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) was prescribed for 1 year.

Study parameters

The main outcome of this study is the incidence of PMI, defined as two times the upper reference limit of CK (URL; 99th percentile of normal reference range) confirmed by significant elevation of the MB fraction of CK (CK-MB).(15) In addition, periprocedural myocardial infarction was analyzed based on a historical definition (3x URL CK-MB).(16;17) The highest CK and CK-MB value within 24 hours post PCI was used for analysis.

Statistical analysis

Values are expressed as mean±SD or median with range. Comparison of continuous variables was performed with Student's t test or one-way analysis of variance (ANOVA), and comparison of non-parametric variables with Mann-Whitney U or Kruskal-Wallis statistical tests as appropriate. Association between categorical variables was tested with Chi-square test. Univariate and multivariate logistic regression analyses were performed to evaluate the predictors of PMI. All variables were evaluated as possible predictors, and those with p values ≤ 0.15 by univariate analysis were included in a stepwise multiple logistic regression the multivariate model. All tests were performed in a two-tailed fashion, and a p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Baseline characteristics

In the 800 patients of the study population, a total of 1522 DES (363 Taxus, 385 Endeavor, 382 Xience V, and 392 Resolute DES) were implanted to treat 1232 lesions. Patient characteristics of each of the four stent groups did not differ significantly (Table 1). Angiographic and procedure related characteristics are described in Table 2. In patients receiving second generation DES, more multivessel PCI were performed (p=0.01), while groups did not differ in various other characteristics such as the frequency of bifurcation lesions, chronic total occlusion or angiographically more complex lesions. DES groups did not differ in baseline or periprocedural medical therapy (Table 2).

Table 1. Characteristics of study population.

	Taxus Liberté (n=200)	Endeavor (n=200)	Resolute (n=200)	Xience V (n=200)	All DES (n=800)	*P*
Age	63.9±9.9	65.6±9.9	64.2±10.4	64.9±10.9	64.6±10.3	0.30
Male	134 (67.0)	138 (69.0)	146 (73.0)	143 (71.5)	561 (70.1)	0.57
Diabetes	53 (26.9)	44 (22.2)	41 (20.6)	39 (19.6)	177 (22.3)	0.31
Hypertension	103 (69.1)	89 (57.4)	110 (56.7)	122 (63.5)	424 (61.4)	0.07
Hyperchol-esterolemia	92 (65.2)	85 (56.3)	113 (58.9)	125 (67.2)	415 (61.9	0.13
Cigarette smokers	41 (31.3)	28 (21.9)	56 (29.0)	52 (27.1)	177 (27.5)	0.36
Family history of vascular disease	84 (42.0)	84 (42.0)	101 (50.5)	95 (52.5)	364 (45.5)	0.23
Stable angina pectoris	117 (58.5)	124 (62.0)	110 (55.0)	128 (64.0)	479 (59.9)	0.27
Acute coronary syndrome	83 (41.5)	76 (38.0)	90 (45.0)	72 (36.0)	321 (40.1)	0.27
Previous MI	67 (33.5)	62 (31)	73 (36.5)	78 (39)	280 (35)	0.36

Values are mean±SD, numbers of patients (percentage).
DES = drug-eluting stents. MI = myocardial infarction.

Table 2. Characteristics of lesions, PCI and periprocedural medication.

	Taxus Liberté	Endeavor	Resolute	Xience V	All DES	*P*
Target lesions						
Main stem	11 (5.5)	7 (3.5)	7 (3.5)	9 (4.5)	34 (4.3)	0.72
LAD	86 (43.0)	107 (53.5)	107 (53.5)	105 (52.5)	405 (50.6)	0.10
RCX	64 (32.0)	71 (35.5)	61 (30.5)	50 (25.0)	246 (30.8)	0.15
RCA	68 (34.0)	56 (28.0)	66 (33.0)	67 (33.5)	257 (32.1)	0.55
Graft	4 (2.0)	3 (1.5)	0 (0)	1 (0.5)	7 (0.9)	0.27
Lesion type B2	90 (31.0)	111 (36.0)	89 (28.0)	83 (26.3)	373 (30.3)	0.23
Lesion type C	113 (40.0)	125 (40.6)	117 (36.8)	114 (36.1)	469 (38.1)	0.78
Bifurcation	64 (32.0)	70 (35.0)	68 (34.0)	64 (32.0)	266 (33.3)	0.90
Chronic total occlusion	16 (8.0)	24 (12.0)	17 (8.5)	18 (9.0)	75 (9.4)	0.52
Lesion per patient	1.42±0.62	1.53±0.69	1,57±0.81	1.56±0.85	1.52±0.75	0.38
Multivessel treatment	29 (14.5)	41 (20.5)	54 (27.0)	51 (25.5)	175 (21.9)	**0.01**
Stent per patient	1.815±1.02	1.925±1.01	1.91±1.10	1.940 ±1.23	1.90±1.23	0.66
Stents per lesion	1.28±0.51	1.29±0.54	1.25±0.49	1.29±0.53	1.28±0.52	0.96
Stent length per lesion	20 (14.5-28)	20.4 (16-27)	19 (16-24)	20.5 (15-25.5)	20.25 (15-27)	0.48
Aspirin periprocedural	200	200	200	200	200	1.00
Clopidogrel periprocedural	200	200	200	200	200	1.00
Clopidogrel pretreatment	125 (62.5)	131 (65.5)	130 (65)	138 (69)	524 (65.5)	0.59
Glycoprotein IIb/IIIa inhibitors	38 (19.0)	38 (19.0)	36 (18.0)	30 (15.0)	142 (17.8)	0.69
Oral anticoagulation	19 (9.5)	21 (10.5)	18 (9.0)	11 (5.5)	69 (8.6)	0.31
Statin pretreatment	177 (88.5)	168 (84)	177 (88.5)	169 (84.5)	691 (86.4)	0.38
ACE inhibitors / ARB	95 (47.5)	97 (48.5)	95 (47.5)	82 (41)	369 (46.1)	0.35
β-blockers	175 (87.5)	176 (88.0)	161 (80.5)	167 (83.5)	679 (84.9)	0.12

Values are mean±SD, number of patients (percentage), or median (range).
DES = drug-eluting stents; PCI = percutaneous coronary intervention; Lesion type = ACC/AHA (American College of Cardiology/American Heart Association) lesion type; ACE = angiotensin-converting enzyme; ARB = Angiotensin receptor blocker.

Cardiac biomarkers and PMI

Table 3 presents the post-PCI cardiac biomarker values which did not differ between the DES groups. The overall incidence of PMI was 4.75%. Between DES types, there was also no difference (p=0.31) in PMI (2x URL CK). In addition, the incidence of PMI did not differ between first and second generation DES (5.5% vs. 4.0%; p=0.32). When using the historical definition of PMI (3x URL CK-MB), there was a 2.4-fold increase in PMI compared to use of the revised ARC definition (11.38% vs. 4.75%), and there was still no difference in PMI between first and second generation DES (11.5% vs. 11.3%, respectively; p=0.91).

Table 3. Cardiac biomarkers for each DES type and DES generation.

	Taxus Liberté	**Endeavor**	**Resolute**	**Xience V**	***P***
	First generation DES		***Second generation DES***		
Mean CK	128.5 (134.1)	161.9 (274.5)	132.9 (226.0)	133.1 (127.7)	0.32
	145.2 (216.4)		*133.0 (183.4)*		*0.39*
CK ≥ 2x	9 (4.5)	13 (6.5)	8 (4.0)	8 (4.0)	0.60
	22 (5.5)		*16 (4.0)*		*0.32*
Mean CK-MB	8.8 (19.3)	10.7 (26.9)	9.6 (23.7)	9.0 (12.0)	0.85
	9.8 (23.4)		*9.3 (18.8)*		*0.78*
CK-MB ≥ 3x	22 (11.0)	24 (12.0)	22 (11.0)	23 (11.5)	0.99
	46 (11.5)		*45 (11.3)*		*0.91*

Values are mean±SD, numbers of patients (percentage).
CK = creatine kinase; DES = drug-eluting stents.

Predictors of PMI

Predictors of PMI based on univariate analyses were: number of stents placed, multivessel PCI, and type C lesions (p≤0.01), as well as presentation with acute coronary syndrome (ACS), peripheral artery disease, diabetes mellitus, PCI in circumflex coronary artery, and bifurcation lesion (p<0.1). In a multivariate analysis, only presentation with ACS (p=0.02) and the total number of stents placed (p<0.001) were predictors of PMI. Even when correcting for these factors, neither DES type nor generation of DES were predictors of PMI (p= 0.48 and p=0.23, respectively). Further details of the regression analyses are presented in Table 4.

Table 4. Predictors of periprocedural myocardial infarction.

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Acute coronary syndrome	2.13 (1.10-4.12)	0.02	2.28 (1.16-4.47)	0.02
Diabetes	1.95 (0.95-4.03)	0.07	1.58 (0.75-3.33)	0.23
Peripheral artery disease	2.48 (0.99-6.21)	0.05	2.29 (0.89-5.86)	0.08
Multivessel treatment	2.52 (1.23-5.15)	0.01	1.32 (0.54-3.24)	0.54
RCX treated	1.83 (0.91-3.66)	0.09	1.21 (0.57-2.58)	0.63
Type C lesion	2.93 (1.35-6.35)	0.01	1.43 (0.66-3.09)	0.36
Bifurcation	1.84 (0.92-3.66)	0.09	1.32 (0.66-2.65)	0.44
Total stents placed	1.79 (1.40-2.28)	0.00	1.69 (1.34-2.14)	0.00

Odds ratio and 95% confidence intervals are presented. Predictors with a *P* value ≤0.15 are shown in the table.
OR = Odds ratio.

DISCUSSION

Several previous studies showed a relation between PMI and an increased mortality during short-term and long-term follow-up. (18-21) Nevertheless, there is still an ongoing discussion on this issue as other studies were unable to show a significant relation between PMI and clinical outcome.(22;23) The (routine) measurement of cardiac biomarkers following elective PCI has been given a class IIa recommendation in the ACC/AHA/SCAI (American College of Cardiology/ American Heart Association/Society for Cardiac Angiography and Interventions) PCI guidelines of 2005(24) and has not yet been implemented in current European guidelines for coronary revascularization, while data on PMI are considered as a marker of stent performance and used as clinical endpoint in stent trials.(16;25) In clinical practice, however, measurement of cardiac biomarkers following acute and elective PCI procedures appears to be suboptimal.(25)

With the introduction of more sensitive biomarkers such as troponin, which allows the detection of even minute myocardial damage during PCI, the joint task force of ESC/ACCF/AHA/WHF (European Society of Cardiology/ American College of Cardiology/ American Heart Association/ and World Health Foundation) in 2007 proposed definitions for PMI based on troponin or CK-MB for use in clinical stent trials,(16) while the Academic Research Consortium (ARC) preferred CK-MB.(17) Although several studies demonstrated that troponin has a correlation with late mortality(18;19), there are some concerns that troponin might be too sensitive. This enhanced sensitivity might inflate the occurrence of serious adverse events and thus make it harder to detect differences in performance between different coronary stents and/or techniques.

The ARC recently suggested a revised PMI definition for use in ongoing and future stent trials in an attempt to homogenize the PMI definition for use in selected patient groups and broad "all comer" populations,(15) in which PMI is an important component of the primary endpoint. In fact, this revised definition of PMI represents a modification of the World Health Organization criteria to establish the diagnosis of myocardial infarction.(26)

Using the revised ARC definition of PMI, the main finding of the present study is that in a broad spectrum of clinical settings the incidence of PMI was similar for first and second generation DES, despite more multivessel PCI in patients who received second generation DES.

In fact, the PMI rate of 4% in second generation DES matches quite well with the findings of the Resolute All Comers trial, which reported a similar incidence of PMI for Xience V and Resolute (~3%, both).(27) The COMPARE trial applied the same definition of PMI to perform post-PCI cardiac marker assessment in approximately 40% of patients and measure PMI rates of 2% for both Xience V and Taxus Liberté.(12) Other studies such as Endeavor III and IV as well as the Spirit III and IV generally reported lower PMI (0.6-3%) in Endeavor, Resolute, Xience V, and Taxus DES.(28-32) This may be partly attributed to the fact that these studies addressed lesions and patient populations that differed in severity from the above-mentioned all-comer trials.(12;27)

In the present study, the move from use of first to second generation DES was associated with a mild but statistically significant increase in multivessel PCI. The absence of differences in PMI between first and second generation DES groups may be unexpected as PCI of more than one vessel could be associated with a greater likelihood of periprocedural myocardial damage.(33-35) Nevertheless, in our multivariate analysis there was no significant relation between multivessel PCI and PMI. In fact, we found that the total number of stents implanted was the most significant predictor of PMI in our stepwise multivariate model; and in our study population first and second generation DES groups did not differ in total number of stents per patient implanted.

Coatings of second generation DES have a superior biocompatibility and less or smaller coating irregularities compared to first generation DES.(9) As this may reduce thrombogenicity of the DES surface, one might have expected less PMI in patients receiving second generation DES.(36;37) Nevertheless, this was not the case in the present study. In addition, stent cell size (and thus side-branch accessibility) may be a relevant factor for the incidence of PMI. But in our present study, cell size of first and second generation DES did not differ greatly, as previously demonstrated with micro-computed tomography.(38)

Use of the revised CK-based ARC definition of PMI (2x URL CK) resulted in a lower incidence of PMI compared to the historical CK-MB-based definition (3x URL CK-MB). In our study, the rate of PMI was reduced by 58% when using the revised PMI definition. Notably, most contemporary DES trials are powered for composite endpoints including PMI.(12;27;39;40)

As a consequence of the use of the revised ARC definition of PMI, comparative stent trials have to examine larger patient populations to detect differences in stent performance. On the other hand, less sensitive thresholds (e.g. 5x URL CK-MB) for the detection of PMI have previously been shown to be most relevant predictors of mortality (2;21;33;41), which supports the use of the (less-sensitive) revised ARC definition of PMI.

Limitations

This study is limited by its retrospective nature and the limited sample size of 800 patients. At any time two DES types were available while the type of DES implanted was left at the operators' discretion. As a consequence, we cannot completely exclude a potential selection bias; however, on a group level, there were no significant differences between DES groups. In the present study, patients with ST-segment elevation myocardial infarction (STEMI) were not included as bare metal stent implantation was the standard treatment in STEMI patients during this period of time. Nevertheless, in STEMI patients the assessment of PMI is challenging, as the discrimination between procedure-related myocardial damage and the natural course of the STEMI can be very difficult.

Conclusion

Using the revised ARC definition, we found no significant difference in PMI between first and second generation DES. Overall, PMI occurred in 4.75%, which is 58% lower than with use of the historical PMI definition.

Disclosure statement

This investigator-initiated study was performed without specific funding. The research department received in the past educational and/or research grants and has participated in clinical studies funded by Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Cordis, and Medtronic. Dr. von Birgelen has been a consultant to Abbott Vascular, Biosensors, Boston Scientific, Cordis, and Medtronic.

REFERENCES

(1) Califf RM, Abdelmeguid AE, Kuntz RE, Popma JJ, Davidson CJ, Cohen EA, Kleiman NS, Mahaffey KW, Topol EJ, Pepine CJ, Lipicky RJ, Granger CB, Harrington RA, Tardiff BE, Crenshaw BS, Bauman RP, Zuckerman BD, Chaitman BR, Bittl JA, Ohman EM. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998;31):241-51.

(2) Stone GW, Mehran R, Dangas G, Lansky AJ, Kornowski R, Leon MB. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. Circulation 2001;104:642-7.

(3) Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002 6;346:1773-80.

(4) Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.

(5) Schwartz RS. Pathophysiology of restenosis: interaction of thrombosis, hyperplasia, and/or remodeling. Am J Cardiol 1998;81:14E-7E.

(6) Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202.

(7) Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007 ;369:667-78.

(8) Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;56):S1-42.

(9) Basalus MW, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. EuroIntervention 2009;5:157-65.

(10) Lindsey JB, Marso SP, Pencina M, Stolker JM, Kennedy KF, Rihal C, Barsness G, Piana RN, Goldberg SL, Cutlip DE, Kleiman NS, Cohen DJ. Prognostic impact of periprocedural bleeding and myocardial infarction after percutaneous coronary intervention in unselected patients: results from the EVENT (evaluation of drug-eluting stents and ischemic events) registry. JACC Cardiovasc Interv 2009;2:1074-82.

(11) Kini AS, Lee P, Marmur JD, Agarwal A, Duffy ME, Kim MC, Sharma SK. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. Am J Cardiol 2004;93:18-23.

(12) Kedhi E, Joesoef KS, McFadden E, Wassing J, van MC, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.

(13) Testa L, Van Gaal WJ, Biondi Zoccai GG, Agostoni P, Latini RA, Bedogni F, Porto I, Banning AP. Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. QJM 2009;102:369-78.

(14) Simoons ML, van den BM, Lincoff M, Harrington R, van der WR, Vahanian A, Rutsch W, Kootstra J, Boersma E, Califf RM, Topol E. Minimal myocardial damage during coronary intervention is associated with impaired outcome. Eur Heart J 1999;20:1112-9.

(15) Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871-4.

(16) Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173-95.

(17) Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

(18) Nienhuis MB, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A meta-analysis. Catheter Cardiovasc Interv 2008;71:318-24.

(19) Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR, Jr., Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. J Am Coll Cardiol 2006;48:1765-70.
(20) Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. J Am Coll Cardiol 2003 ;42:1406-11.
(21) Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. Circulation 2002;106:1205-10.
(22) Prasad A, Gersh BJ, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Pocock SJ, McLaurin BT, Cox DA, Lansky AJ, Mehran R, Stone GW. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol 2009;54:477-86.
(23) Jeremias A, Baim DS, Ho KK, Chauhan M, Carrozza JP, Jr., Cohen DJ, Popma JJ, Kuntz RE, Cutlip DE. Differential mortality risk of postprocedural creatine kinase-MB elevation following successful versus unsuccessful stent procedures. J Am Coll Cardiol 2004;44:1210-4.
(24) Smith SC, Jr., Feldman TE, Hirshfeld JW, Jr., Jacobs AK, Kern MJ, King SB, III, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:e1-121.
(25) Wang TY, Peterson ED, Dai D, Anderson HV, Rao SV, Brindis RG, Roe MT. Patterns of cardiac marker surveillance after elective percutaneous coronary intervention and implications for the use of periprocedural myocardial infarction as a quality metric: a report from the National Cardiovascular Data Registry (NCDR). J Am Coll Cardiol 2008;51:2068-74.
(26) Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 1994;90:583-612.
(27) Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van LF, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46.
(28) Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903-13.
(29) Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-74.
(30) Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C, Overlie PA, McLaurin BT, Solomon SL, Douglas JS, Jr., Ball MW, Caputo RP, Jain A, Tolleson TR, Reen BM, III, Kirtane AJ, Fitzgerald PJ, Thompson K, Kandzari DE. A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol 2010 ;55:543-54.
(31) Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, Turco M, Applegate RJ, Gurbel PA, Midei MG, Badre SS, Mauri L, Thompson KP, LeNarz LA, Kuntz RE. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440-7.
(32) Schomig A, Dibra A, Windecker S, Mehilli J, Suarez de LJ, Kaiser C, Park SJ, Goy JJ, Lee JH, Di LE, Wu J, Juni P, Pfisterer ME, Meier B, Kastrati A. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373-80.

(33) Roe MT, Mahaffey KW, Kilaru R, Alexander JH, Akkerhuis KM, Simoons ML, Harrington RA, Tardiff BE, Granger CB, Ohman EM, Moliterno DJ, Lincoff AM, Armstrong PW, Van de WF, Califf RM, Topol EJ. Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes. Eur Heart J 2004 ;25:313-21.
(34) Lansky AJ, Goto K, Cristea E, Fahy M, Parise H, Feit F, Ohman EM, White HD, Alexander KP, Bertrand ME, Desmet W, Hamon M, Mehran R, Moses J, Leon M, Stone GW. Clinical and angiographic predictors of short- and long-term ischemic events in acute coronary syndromes: results from the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial. Circ Cardiovasc Interv 2010;3:308-16.
(35) Nienhuis MB, Ottervanger JP, Dambrink JH, Dikkeschei LD, Suryapranata H, van 't Hof AW, Hoorntje JC, de Boer MJ, Gosselink AT, Zijlstra F. Troponin T elevation and prognosis after multivessel compared with single-vessel elective percutaneous coronary intervention. Neth Heart J 2007;15:178-83.
(36) Tepe G, Wendel HP, Khorchidi S, Schmehl J, Wiskirchen J, Pusich B, Claussen CD, Duda SH. Thrombogenicity of various endovascular stent types: an in vitro evaluation. J Vasc Interv Radiol 2002;13:1029-35.
(37) Hecker JF, Scandrett LA. Roughness and thrombogenicity of the outer surfaces of intravascular catheters. J Biomed Mater Res 1985;19:381-95.
(38) Basalus MW, van Houwelingen KG, Ankone MJ, Feijen J, von Birgelen C. Micro-computed tomographic assessment following extremely oversized partial postdilatation of drug-eluting stents. EuroIntervention 2010;6:141-8.
(39) Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di MC, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163-73.
(40) Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JW, Said SA, Linssen GC, Kleijne MA, van der PJ, Huisman J, Verhorst PM, von Birgelen C. TWENTE Study: The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente: study design, rationale and objectives. Neth Heart J 2010;18:360-4.
(41) Jang JS, Hong MK, Park DW, Lee SW, Kim YH, Lee CW, Kim JJ, Park SW, Park SJ. Impact of periprocedural myonecrosis on clinical events after implantation of drug-eluting stents. Int J Cardiol 2008;129:368-72.

CHAPTER 10

A RANDOMIZED CONTROLLED TRIAL IN SECOND-GENERATION ZOTAROLIMUS-ELUTING RESOLUTE STENTS VERSUS EVEROLIMUS-ELUTING XIENCE V STENTS IN REAL-WORLD PATIENTS THE TWENTE TRIAL

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ABSTRACT

Objective The aim of this study was to compare the safety and efficacy of Resolute zotarolimus-eluting stents (ZES) (Medtronic Cardiovascular, Santa Rosa, California) with Xience V everolimus-eluting stents (EES) (Abbott Vascular Devices, Santa Clara, California) at 1-year follow-up.

Background Only 1 randomized trial previously compared these stents.

Methods This investigator-initiated, patient-blinded, randomized noninferiority study had limited exclusion criteria (acute ST-segment elevation myocardial infarctions not eligible). Patients (n = 1,391; 81.4% of eligible population) were randomly assigned to ZES (n = 697) or EES (n = 694). Liberal use of stent post-dilation was encouraged. Cardiac biomarkers were systematically assessed. The primary endpoint was target vessel failure (TVF), a composite of cardiac death, myocardial infarction not clearly attributable to non-target vessels, and clinically indicated target-vessel revascularization. An external independent research organization performed clinical event adjudication (100% follow-up data available). Analysis was by intention-to-treat.

Results Acute coronary syndromes were present in 52% and "off-label" feature in 77% of patients. Of the lesions, 70% were type B2/C; the post-dilation rate was very high (82%). In ZES and EES, TVF occurred in 8.2% and 8.1%, respectively (absolute risk-difference 0.1%; 95% confidence interval: −2.8% to 3.0%, $p_{noninferiority} = 0.001$). There was no significant between-group difference in TVF components. The definite-or-probable stent thrombosis rates were relatively low and similar for ZES and EES (0.9% and 1.2%, respectively, p = 0.59). Definite stent thrombosis rates were also low (0.58% and 0%, respectively, p = 0.12). In EES, probable stent thrombosis beyond day 8 was observed only in patients not adhering to dual antiplatelet therapy.

Conclusions Resolute ZES were noninferior to Xience V EES in treating "real-world" patients with a vast majority of complex lesions and "off-label" indications for drug-eluting stents, which were implanted with liberal use of post-dilation. (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting SteNt Study: Head-to-head Comparison of Clinical Outcome After Implantation of Second Generation Drug-eluting Stents in a Real World Scenario; NCT01066650)

ABBREVIATIONS

DES = drug-eluting stent
EES = everolimus-eluting stent
PCI = percutaneous coronary intervention
STEMI = ST-elevation myocardial infarction
TVF = target vessel failure
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent

Early trials with drug-eluting stents (DES) demonstrated a significant reduction in restenosis and reintervention rates,[1,2] which rapidly led to the adaptation of these stents for routine percutaneous coronary interventions (PCI). However, long term follow-up data of first-generation DES showed that these stents did not improve mortality.[3-5] Several factors and mechanisms have been suggested to be potentially involved. A particularly important factor may be the lack of biocompatibility of coatings on first-generation DES, some of which were shown to be associated with hypersensitivity and vessel wall inflammation that can promote stent thrombosis. In addition, deliverability and side branch access of first-generation DES were somewhat limited,[6] and the reduction in reintervention rates in patients with advanced coronary disease was less than expected.[7]

Second-generation DES with improved coatings and designs may offer solutions to the limitations of first-generation DES.[8,9] A thin-strut, open-cell, cobalt-chromium stent that releases everolimus from a thin fluoropolymer-based coating (Xience V, Abbott Vascular Devices, Santa Clara, California) has been shown to be superior to first-generation DES, which – together with other favorable data – led to its approval by regulatory bodies.[10] Recently, a thin-strut, cobalt-chromium, open-cell stent that releases zotarolimus from a thin biocompatible coating (Resolute, Medtronic CardioVascular, Santa Rosa, California) showed very promising clinical results.[11–13]

More than 2 million DES are implanted annually worldwide.[14] Both everolimus-eluting Xience stents (EES) and zotarolimus-eluting Resolute stents (ZES) represent a substantial share of them. However, published head-to-head comparison between both stents is limited to a single randomized trial.[15] Therefore, in the present study, we compared safety and efficacy of the Resolute ZES to the Xience V EES in a “real-world” patient population with advanced coronary disease and complex lesions. Interventions were performed according to our routine clinical practice, encouraging operators to make liberal use of stent postdilatation to optimize stent apposition to the vessel wall, which may facilitate drug delivery and could reduce stent thrombosis.[16]

METHODS

Study design and patients. Between June 2008 and August 2010, we undertook, at Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands, a randomized non-inferiority trial (TWENTE trial) in consecutive patients aged 18 years or older who were capable of providing an informed consent and underwent a PCI with DES implantation for the treatment of chronic stable coronary artery disease or acute coronary syndromes. To allow for the inclusion of a broad patient population, the study protocol defined no limit for lesion length, reference vessel size, and number of target lesions or vessels. The only exclusion criteria were: ST-elevation myocardial infarction (STEMI) or STEMI-equivalent, requiring primary or rescue PCI during the past 48 h; planned staged revascularization; renal failure requiring hemodialysis; serious conditions that could limit the patient's ability to participate in study procedures, in particular life expectancy <1 year; participation in investigational drug or device study; if the choice of stent type was dictated by logistic reasons (e.g. a stent with required dimensions was only available as 1 type).
The TWENTE trial complied with the Declaration of Helsinki for investigation in human beings, and was approved by the institutional ethics committee of Medisch Spectrum Twente, Enschede, the Netherlands, and the Dutch Central Committee on Research Involving Human Subjects. All patients provided written, informed consent for participation in this trial.

Randomization and study devices. After stratification for sex, randomization was performed on the basis of computer-generated random numbers (block stratified randomization V5.0 by S. Piantadosi), with sealed, opaque, sequentially numbered allocation envelopes. After passage of the guide wire or pre-dilatation (if necessary), patients were assigned in a 1:1 ratio to Resolute ZES or Xience V EES. Patients had no knowledge of the stent type they were allocated to (single-blinded design).
In our center, Resolute ZES were available in diameters of 2.25,2.50,3.00,3.50, and 4.00 mm. Stent length was 8 mm and 14 mm for stents with a diameter ≤2.5 mm; 9 mm and 15 mm for stents with a diameter of ≥3.00 mm; and 12,18,24, and 30 mm for all available stent diameters. Xience V EES were available in diameters of 2.25,2.50,3.00,3.50, and 4.00 mm, and in lengths of 8,12,15,18,23, and 28 mm.

Percutaneous intervention and medication. Interventions were performed via femoral or radial route according to standard techniques. Complete lesion coverage was attempted with one or more stent(s). Lesion pre-dilatation, direct stenting, and/or stent post-dilation were permitted at the discretion of the operators. Operators were encouraged to make liberal use of post-dilation Although planned staging of PCI was an exclusion criterion, unplanned staged procedures were permitted if the second procedure was performed within 6 weeks

after the index procedure (e.g., in unexpected lengthy procedures and/or procedures with excessive contrast use); in such cases, the allocated stent type was used during all stages. During index procedure, mixture of stents was not permitted unless the allocated study stent could not be delivered; then, crossover to another stent was permitted.
Patients who were not taking acetylsalicylic acid received ≥300 mg of acetylsalicylic acid before PCI. In addition, patients received before or at the time of PCI 300 to 600 mg of clopidogrel and at least 5,000 IU or 70 to 100 IU/kg of unfractionated heparin, according to standard protocols. Administration of glycoprotein IIb/IIIa antagonists was left at the operators' discretion.
In patients not on oral anticoagulation therapy, we prescribed at discharge the combination of 100mg of acetylsalicylic acid once daily (indefinitely) and clopidogrel 75mg once daily (12 months). In patients receiving oral anticoagulation therapy, we prescribed 100 mg of acetylsalicylic acid once daily (at least 1 month) and clopidogrel 75 mg daily (12 months) in addition to oral anticoagulation.

Laboratory and angiographic analyses. In all patients, the concentration of creatine kinase was determined before PCI, and the concentration of creatine kinase, creatine kinase-myocardial band, and troponin was measured 6 to 18 h after PCI, with subsequent serial measurements in case of relevant biomarker elevation. Twelve-lead electrocardiographs were obtained before and after PCI, prior to discharge, and at suspicion of acute ischemia.
Quantitative coronary angiography was performed offline with use of edge-detection software (QAngio XA 7.1, Medis, Leiden, the Netherlands) by experienced analysts of Thoraxcentrum Twente, who were blinded as to the type of study device used. All measurements (baseline and final) were conducted according to current standards. Standard offline measurements were obtained over the entire segment consisting of stented segment plus 5 mm proximal and distal margins. We defined percentage diameter stenosis as: ([reference vessel diameter–minimal lumen diameter]/reference vessel diameter)×100%. Lesion length was assessed, in general, by quantitative coronary angiography.

Definition of endpoints and data management. The pre-specified primary composite endpoint was the incidence of *Target Vessel Failure* (TVF) within 1 year, defined as (in hierarchical order) cardiac death, target vessel related myocardial infarction (MI), or clinically driven target vessel revascularization (TVR) by re-PCI or surgery. All clinical endpoints were defined according to the Academic Research Consortium.[17,18] Cardiac death was defined as any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Myocardial infarction was defined as previously outlined in detail. In brief, MI was defined by any creatine kinase concentration

of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker (creatine kinase-myocardial band fraction or troponin).[18] Moreover, classification of MIs and location of MIs was performed on the basis of laboratory testing, electrocardiographic parameters, angiographic information, and/or clinical data.[17,18] A TVR was defined as any repeat coronary revascularization (PCI or surgery) of any segment of the entire major coronary artery and its branches. A TVR (or target lesion revascularization [TLR]) was considered clinically indicated if the angiographic percent diameter stenosis of the then- treated lesion was ≥50% in the presence of ischemic signs or symptoms, or if the diameter stenosis was ≥70% irrespective of ischemic signs or symptoms.[17]

Secondary endpoints were the individual components of the primary endpoint; all-cause mortality; Q-wave and non-Q-wave MI; any MI; TVR by PCI, surgery, or both; clinically indicated TLR; any TLR, defined as repeated revascularization within the stented segment including 5 mm proximal and distal border-zones; stent thrombosis, defined according to Academic Research Consortium as definite, probable, or possible; *Target Lesion Failure*, defined as composite of cardiac death, target vessel-related MI, and clinically indicated T; *major adverse cardiac events*, composite of all-cause death, any MI, emergent coronary-artery bypass surgery or clinically indicated TLR; and a *patient-oriented composite endpoint*, consisting of all-cause mortality, any MI, and any repeat (target and non-target vessel) revascularization. All composite endpoints, as defined in the preceding text, are presented with the individual components in a hierarchical order. We did not pre-specify subgroup analyses but performed exploratory subgroup analyses in line with the later published Resolute All Comers Trial.[15]

In addition, we assessed *device success*, defined as achievement of a final residual diameter stenosis of <50% during the initial procedure, with the use of the assigned study stent only; *lesion success*, defined as achievement of a final residual diameter stenosis of <50% with use of any PCI approach; and *procedure success,* defined as the as achievement of a final residual diameter stenosis of <50% together with the absence of any in-hospital major adverse cardiac events.

Data management and clinical event adjudication. In-hospital adverse events were recorded prior to discharge. The 12-month clinical follow-up data were obtained at visits at outpatient clinics or, if not feasible, by telephone follow-up and/or a medical questionnaire. For any event trigger, members of the study team gathered all clinical information available from referring cardiologist, general practitioner, and/or hospital involved. If required, on-site review of the clinical chart was performed. Clinical and procedural data were stored in a database at Thoraxcentrum Twente. Staff involved in follow-up procedures and analyses were blinded to the assigned stent.

Processing of clinical data and adjudication of adverse clinical events was performed by an independent external contract research organization and core lab (Cardialysis, Rotterdam, the Netherlands). In brief, any death, potential MI, possible stent thrombosis, and revascularization procedure were independently adjudicated by an external clinical event committee (blinded). In addition, Cardialysis performed an on-site audit to assess key study data and adherence to the rules of good clinical practice. The local institutional ethics committee served as independent data and safety monitoring board.

Statistical analysis. Main outcome parameter of this noninferiority study was the incidence of TVF at 1 year with 80% power to detect noninferiority at a 1-sided type I error of 0.05. Assuming a median time to TVF of 48 months, based on the Endeavor III (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus- Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) that had an event rate of 12.8%[19], a hazard ratio of 1.35, an accrual time of 2 years, and an additional follow-up of 1 year for TVF, a total of 1380 patients was required. On basis of the aforementioned hazard ratio and assumed event rate, noninferiority would be declared if the upper limit of the 1-sided 95% confidence interval (CI) of the absolute risk difference was ≤4.48%. The Newcombe-Wilson method without continuity correction was used to calculate a confidence interval for the absolute risk difference.[20] Analyses were performed on the basis of intention-to-treat principle. Patients were censored when they did not reach any component of the composite primary endpoint. Categorical variables were assessed with use of chi-square or Fisher's exact tests, as appropriate, whereas continuous variables were assessed with the Wilcoxon rank-sum test or Student's *t*-test, as appropriate. The time to the primary endpoint and the components thereof were assessed according to the method of Kaplan-Meier, and the log-rank test was applied to compare the 2 groups. Kaplan-Meier curves were drawn in accordance with guidelines provided by Pocock *et al*.[21] Logistic regression was performed to test for interaction between subgroups and stent type with regard to the primary endpoint. A p value <0.05 was considered significant. All p values and CIs were 2-sided, except for those for noninferiority testing of the primary clinical endpoint. After noninferiority was established, we calculated regular 2-sided 95% CIs and 2-sided p values to allow conventional interpretation of results (as for a superiority design). Statistical analyses were performed with SPSS (version 15.0, SPSS, Inc., Chicago, Illinois) and SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina).

RESULTS

Study population. Figure 1 shows the trial profile. Patients (n = 1,391; 81.4% of the eligible patient population) with 2116 lesions were randomly assigned to Resolute ZES (n = 697 patients, 1080 lesions) or Xience V EES (n = 694 patients, 1036 lesions). At least 1 allocated study stent was implanted in 689 (99%) and 690 (99%) patients allocated to Resolute ZES and Xience V EES, respectively. In each study arm, 2 (0.3%) patients withdrew consent before reaching 12 months follow-up. In all other 1387 patients, complete follow-up information was obtained (100%).

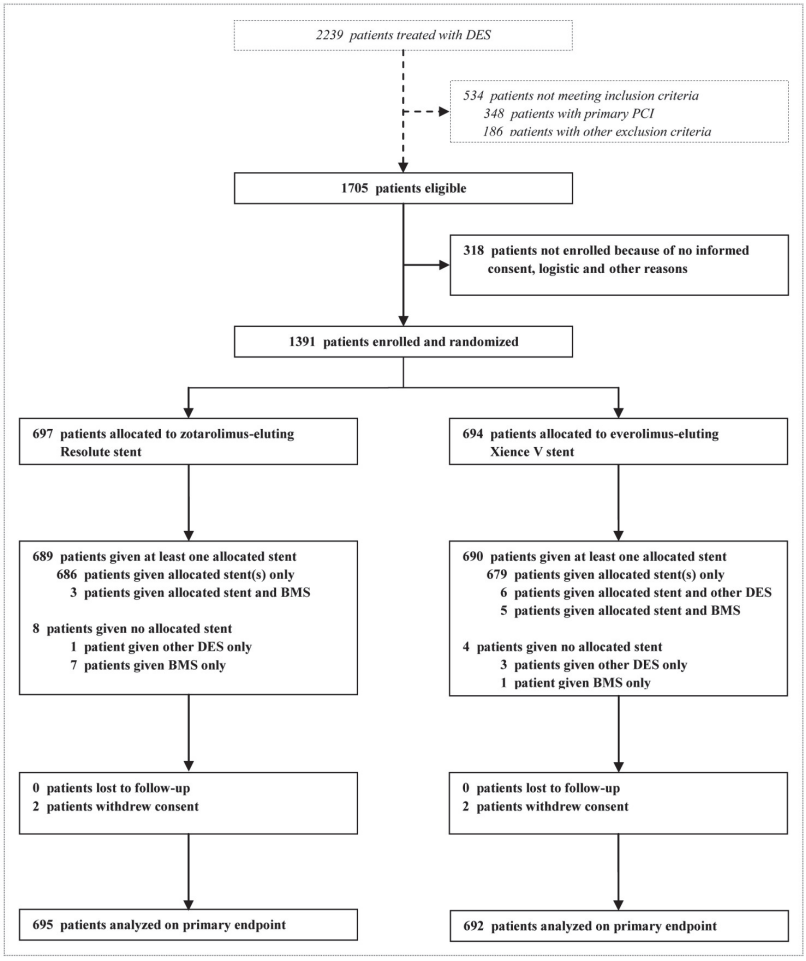


Figure 1: Trial profile.
Trial Profile
BMS = bare-metal stent(s); DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

Table 1 Baseline Characteristics of Patients

	Total Population (n = 1,391)	ZES Resolute (n = 697)	EES Xience V (n = 694)	p Value
Age (yrs)	64.2 ± 10.8 (1,391)	63.9 ± 10.9 (697)	64.5 ± 10.7 (694)	0.32
Men	1,009/1,391 (72.5)	505/697 (72.5)	504/694 (72.6)	0.94
BMI (kg/m^2)	27.7 ± 4.0 (1,391)	27.7 ± 3.9 (697)	27.8 ± 4.0 (694)	0.57
Diabetes mellitus (any)	301/1,391 (21.6)	158/697 (22.7)	143/694 (20.6)	0.35
Chronic renal failure□	38/1,391 (2.7)	19/697 (2.7)	19/694 (2.7)	0.99
Arterial hypertension	773/1,391 (55.6)	386/697 (55.4)	387/694 (55.8)	0.89
Hypercholesterolemia	803/1,357 (59.2)	392/688 (57.0)	411/669 (61.4)	0.10
Current smoker	340/1,391 (24.4)	176/697 (25.3)	164/694 (23.6)	0.48
Family history of CAD	740/1,391 (53.2)	370/697 (53.1)	370/694 (53.3)	0.93
MI (any)	450/1,391 (32.4)	213/697 (30.6)	237/694 (34.1)	0.15
Previous PCI	288/1,391 (20.7)	139/697 (19.9)	149/694 (21.5)	0.48
Previous CABG	148/1,391 (10.6)	68/697 (9.8)	80/694 (11.5)	0.28
PCI for acute coronary syndrome	717/1,391 (51.5)	362/697 (51.9)	355/694 (51.2)	0.77
Clinical indication				0.47
Stable angina pectoris	674/1,391 (48.5)	335/697 (48.1)	339/694 (48.8)	
Unstable angina	325/1,391 (23.4)	172/697 (24.7)	153/694 (22.0)	
Non–ST-segment elevation MI	392/1,391 (28.2)	190/697 (27.3)	202/694 (29.1)	
Left ventricular ejection fraction <30%†	32/1,051 (3.0)	19/529 (3.6)	13/522 (2.5)	0.30
Multivessel treatment	336/1,391 (24.2)	174/697 (25.0)	162/694 (23.3)	0.48
Total no. of lesions treated/patient				0.49
1 lesion treated	857/1,391 (61.6)	422/697 (60.5)	434/694 (62.7)	
2 lesions treated	393/1,391 (28.3)	198/697 (28.4)	195/694 (28.1)	
3 of more lesions treated	141/1,391 (10.1)	77/697 (11.0)	64/694 (9.2)	
De novo coronary lesions only‡	1,287/1,391 (92.5)	644/697 (92.4)	643/694 (92.7)	0.86
At least 1 CTO	95/1,391 (6.8)	51/697 (7.3)	44/694 (6.3)	0.47
At least 1 bifurcation	362/1,391 (26.0)	179/697 (25.7)	183/694 (26.4)	0.77
At least 1 bifurcation with side branch treatment	213/1,391 (15.3)	98/697 (14.1)	115/694 (16.6)	0.19
At least 1 in-stent restenosis	69/1,391 (5.0)	36/697 (5.2)	33/694 (4.8)	0.73
At least 1 small-vessel (RVD <2.75 mm)	874/1,391 (62.8)	445/697 (63.8)	429/694 (61.8)	0.43
At least 1 lesion length >27 mm	293/1,391 (21.1)	156/697 (22.4)	137/694 (19.7)	0.23
Glycoprotein IIb/IIIa antagonist use	193/1,391 (13.9)	90/697 (12.9)	103/694 (14.8)	0.29
At least 1 off-label indication§	1,077/1,391 (77.4)	547/697 (78.5)	530/694 (76.4)	0.35

□Chronic renal failure defined by serum creatinine level ≥130 µmol/l.
†Left ventricular ejection fraction assessed with ultrasound, magnetic resonance imaging, or left ventricular angiography.
‡Including chronic total occlusion but not grafts and in-stent restenosis.
§Off-label stent use includes renal insufficiency, an ejection fraction of <30%, the occurrence of acute myocardial infarction (MI) within the previous 72 h, more than 1 lesion/vessel, at least 2 vessels with stents, a lesion measuring more than 27 mm, bifurcation, bypass grafts, in-stent restenosis, unprotected left main artery, lesions with thrombus, or total occlusion.

Study groups had similar baseline clinical (Table 1), angiographic (Table 2), and procedural characteristics (Table 3). A total of 52% of patients presented with an acute coronary syndrome. Of The study population 22% were diabetics. In a high proportion of patients, there was advanced coronary disease with a need for multivessel treatment, bifurcation lesions, long lesions, and small-vessel disease. At least 1 off-label characteristic was present in 77% of patients, and 70% of lesions were complex (type B2/C). Between study groups, there was no difference in the proportion of left main stem and bypass treatment and of recanalization of chronic total occlusions. Direct stenting was performed in 39% of lesions. In 82% of lesions, stents were post-dilated.

Table 2 Baseline Lesion Characteristics

	Total Lesions (n = 2,116)	**ZES Resolute (n = 1,080 Lesions)**	**EES Xience V (n = 1,036 Lesions)**	**p Value**
Target lesion coronary artery				
Left main	54 (2.6)	26 (2.4)	28 (2.7)	0.67
Left anterior descending	878 (41.5)	441 (40.8)	437 (42.2)	0.53
Left circumflex	483 (22.8)	243 (22.5)	240 (23.2)	0.72
Right coronary artery	653 (30.9)	349 (32.3)	304 (29.3)	0.13
Bypass graft	48 (2.3)	21 (1.9)	27 (2.6)	0.38
ACC/AHA lesion class				0.90
A	154 (7.3)	77 (7.1)	77(7.5)	
B1	478 (22.6)	241 (22.3)	237 (22.9)	
B2	678 (32.0)	342 (31.7)	336 (32.4)	
C	806 (38.1)	420 (38.9)	386 (37.3)	
De novo lesions□	1,999 (94.5)	1,024 (94.8)	975 (94.1)	0.48
Chronic total occlusion	100 (4.7)	53 (4.9)	47 (4.5)	0.69
In stent restenosis	75 (3.5)	38 (3.5)	37 (3.6)	0.95
Aorta ostial lesion	154 (7.3)	76 (7.1)	78 (7.6)	0.66
Severe calcification	364 (17.2)	192 (17.8)	172 (16.6)	0.47
Bifurcated lesion	518 (24.5)	258 (23.9)	260 (25.1)	0.52
Thrombus present†	71 (3.4)	33 (3.1)	38 (3.7)	0.43
Total occlusion	203 (9.6)	109 (10.1)	94 (9.1)	0.43
Pre-procedural TIMI flow grade				0.82
0	120 (5.7)	63 (5.8)	57 (5.5)	
1	83 (3.9)	46 (4.3)	37 (3.6)	
2	140 (6.6)	73 (6.8)	67 (6.5)	
3	1,773 (83.8)	898 (83.1)	875 (84.5)	

□Including chronic total occlusion but not grafts and in-stent restenosis.
†Thrombus triggering use of thrombus aspiration catheters.

Table 3 Quantitative Coronary Angiography and Procedural Results

	Total Lesions (n = 2,116)	ZES Resolute (n = 1,080 Lesions)	EES Xience V (n = 1,036 Lesions)	p Value
Lesion length (mm)	14.43 (9.80–22.09)	14.51 (9.85–22.54)	14.30 (9.66–21.83)	0.35
Diameter of reference vessel (mm)	2.65 (2.29–3.06)	2.65 (2.30–3.05)	2.66 (2.28–3.07)	0.73
Baseline minimum lumen diameter (mm)	0.99 (0.72–1.29)	0.97 (0.72–1.29)	1.00 (0.73–1.29)	0.39
Baseline stenosis, lumen diameter (%)	61.92 (52.74–71.20)	62.57 (52.78–71.34)	61.26 (52.67–71.07)	0.31
Post-procedure stenosis, lumen diameter (%)	11.84 (9.05–15.34)	11.67 (8.93–14.90)	12.00 (9.18–15.64)	0.07
Post-procedure minimum lumen diameter (mm)	2.27 (1.89–2.67)	2.29 (1.89–2.69)	2.25 (1.88–2.65)	0.37
Acute gain in segment (mm)	1.25 (0.86–1.68)	1.24 (0.89–1.70)	1.25 (0.83–1.65)	0.22
Stents implanted				
Per patiënt	2.02 ± 1.18	2.03 ± 1.19	2.02 ± 1.18	0.91
Per lesion	1.33 ± 0.62	1.31 ± 0.59	1.35 ± 0.64	0.09
Total stent length (mm)				
Per patiënt	40.97 ± 26.86	41.84 ± 27.66	40.09 ± 26.02	0.22
Per lesion	26.9 ± 15.69	27.00 ± 15.39	26.85 ± 16.00	0.83
Direct stenting	824 (38.9)	416 (38.5)	408 (39.4)	0.68
Post-dilation	1,727 (81.6)	876 (81.1)	848 (82.1)	0.54
Maximal stent diameter/lesion (mm)	2.97 (0.46)	2.96 (0.452)	2.98 (0.468)	0.37
Implantation of study stent only	2,094 (99.0)	1,068 (98.9)	1,026 (99.0)	0.74
Device success□	2,074 (98.0)	1,063 (98.4)	1,011 (97.6)	0.17
Lesion success†	2,112 (99.8)	1,078 (99.8)	1,034 (99.8)	0.97
Procedure success‡	1,332/1,391 (95.8)	667/697 (95.7)	665/694 (95.8)	0.91

□Device success is defined as the attainment at the target site of a final residual diameter stenosis of <50% with only the assigned study device.
†Lesion success is defined as the attainment at the target site of a final residual diameter stenosis of <50% with any percutaneous method.
‡Procedure success is defined as the attainment at the target site of a final residual diameter stenosis of <50%, together with the absence of any in-hospital major adverse cardiac events. Abbreviations as in Table 1.

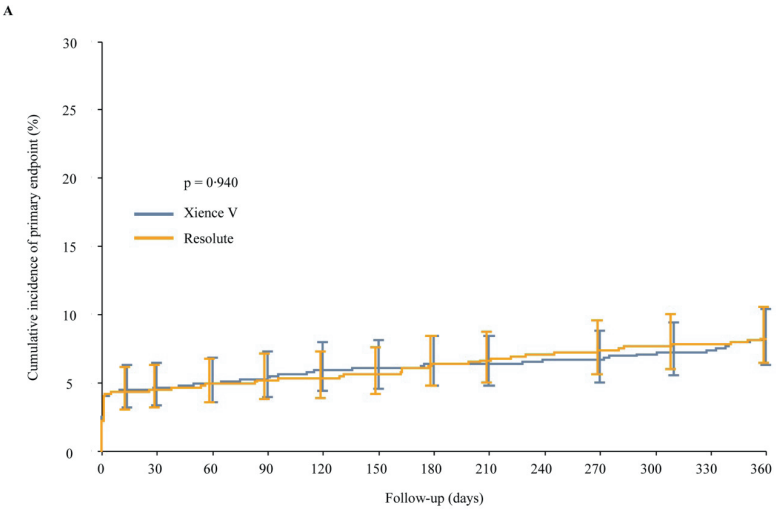
Primary and secondary endpoints. Table 4 shows the major adverse cardiac events during 1-year follow-up. Target vessel failure occurred in 57 patients (8.2%) of the Resolute ZES and in 56 patients (8.1%) of the Xience V EES groups. We established noninferiority of the ZES with an absolute risk difference of 0.1% (95% CI: −2.8% to 3.0%) and the upper limit of the 1-sided 95% CI of 2.53% (1-sided p value for noninferiority = 0.001) (Fig. 2A, Table 4).
Between Resolute ZES and Xience V EES groups, there was also no difference in the components of the primary endpoint: cardiac death (1.0% vs. 1.4%, p = 0.46); target vessel-related MI (4.6% vs. 4.6%, p = 0.99); clinically driven TVR at 12 months follow-up (3.3% vs. 2.7%, p = 0.54) (Table 4; Figs.2B to 2D).
In addition, there was no difference between groups in other secondary endpoints (Table 4) such as the incidence of death from any cause (2.2% vs. 2.0% p = 0.86).
The results of an exploratory subgroup analysis of the primary endpoint are shown in Figure 3. This analysis suggested a potential interaction between stent type and diabetes mellitus (p = 0.045) with a trend towards a lower rate of TVF in diabetics treated with EES (13.9% [22 of 158] vs. 7.7% [11 of 143], p = 0.08; relative risk: 1.81 [95% CI: 0.91 to 3.60] for Resolute ZES and Xience V EES, respectively). In nondiabetic patients, TVF did not differ significantly between stent types (6.5% [35 of 539] vs. 8.2% [45 of 551], p = 0.29; relative risk: 0.80 [95% CI: 0.52 to 1.22] for Resolute ZES and Xience V EES, respectively).

Stent thrombosis. *Definite or probable stent thrombosis* occurred in 6 patients (0.9%) of the Resolute ZES group (1 death, 4 MI, 1 repeat TVR) and 8 patients (1.2%) of the Xience V EES group (4 death, 4 MI) (p = 0.59) (Table 4, Fig.4). In the EES arm, probable stent thrombosis beyond day 8 was only observed in patients not adhering to dual antiplatelet therapy (stent thromboses on day 28 and 136) (Fig.4). The incidence of *definite stent thrombosis* was low in both study arms. It occurred in 4 patients (0.6%) of the Resolute ZES arm and in none (0%) of the patients in the Xience V EES arm (p = 0.12) (Table 4, Fig.4). One patient (day 245) was not on dual antiplatelet therapy. Three of the 4 patients with definite stent thrombosis (75%) survived this event. The only fatal event (day 5) occurred in a patient enrolled for stenting of right and left anterior descending arteries, 7 days after treatment of the circumflex artery with a bar metal stents for a large, subacute non-STEMI. Autopsy revealed thrombus formation in all three vessels, and the event was classified as definite stent thrombosis, according to the definition.

Table 4 1-Year Clinical Outcomes in the Intention-to-Treat Study Population

	Total Population (n = 1,387)	ZES Resolute (n = 695)	EES Xience V (n = 692)	Difference (95% CI)	p Value
Target vessel failure	113 (8.1)	57 (8.2)	56 (8.1)	0.1 (−2.8 to 3.0)	0.94
Death					
Any cause	29 (2.1)	15 (2.2)	14 (2.0)	0.1 (−1.3 to 1.6)	0.86
Cardiac cause	17 (1.2)	7 (1.0)	10 (1.4)	−0.4 (−1.6 to 0.7)	0.46
Target vessel-related MI					
Any	64 (4.6)	32 (4.6)	32 (4.6)	0.0 (−2.2 to 2.2)	0.99
Q-wave	11 (0.8)	5 (0.7)	6 (0.9)	−0.1 (−1.1 to 0.8)	0.76
Non–Q-wave	53 (3.8)	27 (3.9)	26 (3.8)	0.1 (−1.9 to 2.1)	0.90
Periprocedural MI	57 (4.1)	29 (4.2)	28 (4.0)	0.1 (−2.0 to 2.2)	0.91
Clinically indicated TVR					
Any	42 (3.0)	23 (3.3)	19 (2.7)	0.6 (−1.2 to 2.4)	0.54
Percutaneous	33 (2.4)	19 (2.7)	14 (2.0)	0.7 (−0.9 to 2.3)	0.39
Surgical	9 (0.6)	4 (0.6)	5 (0.7)	−0.1 (−1.0 to 0.7)	0.73
Target lesion failure	102 (7.4)	55 (7.9)	47 (6.8)	1.1 (−1.6 to 3.9)	0.42
Clinically indicated TLR					
Any	29 (2.1)	19 (2.7)	10 (1.4)	1.3 (−0.2 to 2.8)	0.09
Percutaneous	22 (1.6)	15 (2.2)	7 (1.0)	1.1 (−0.2 to 2.5)	0.09
Surgical	7 (0.5)	4 (0.6)	3 (0.4)	0.1 (−0.6 to 0.9)	0.71
Death from cardiac causes or target vessel MI	67 (4.8)	34 (4.9)	33 (4.8)	0.1 (−2.1 to 2.4)	0.92
Major adverse cardiac events□	132 (9.5)	70 (10.1)	62 (9.0)	1.1 (−2.0 to 4.2)	0.48
Patient-oriented composite endpoint†	151 (10.9)	78 (11.2)	73 (10.5)	0.7 (−2.6 to 4.0)	0.69
Definite ST (0–360 days)					
All patients	4 (0.3)	4 (0.6)	0 (0)	0.6 (0.0 to 1.1)	0.12
Acute (0–1 day)	0 (0)	0 (0)	0 (0)	—	—
Subacute (2–30 days)	1 (0.1)	1 (0.1)	0 (0)	0.1 (−0.1 to 0.4)	1.00
Late (31–360 days)	3 (0.2)	3 (0.4)	0 (0)	0.4 (0.0 to 0.9)	0.25
Probable ST (0–360 days)					
All patients	10 (0.7)	2 (0.3)	8 (1.2)	−0.9 (−1.8 to 0.0)	0.06
Acute (0–1 day)	4 (0.3)	1 (0.1)	3 (0.4)	−0.3 (−0.9 to 0.3)	0.37
Subacute (2–30 days)	4 (0.3)	0 (0.0)	4 (0.6)	−0.6 (−1.1 to 0.0)	0.06
Late (31–360 days)	2 (0.1)	1 (0.1)	1 (0.1)	0.0 (−0.4 to 0.4)	1.00
ST (0–360 days)					
Possible	6 (0.4)	4 (0.6)	2 (0.3)	0.3 (−0.4 to 1.0)	0.69
Definite or probable	14 (1.0)	6 (0.9)	8 (1.2)	−0.3 (−1.3 to 0.8)	0.59
Definite, probable, or possible	20 (1.4)	10 (1.4)	10 (1.4)	0.0 (−1.3 to 1.3)	0.99

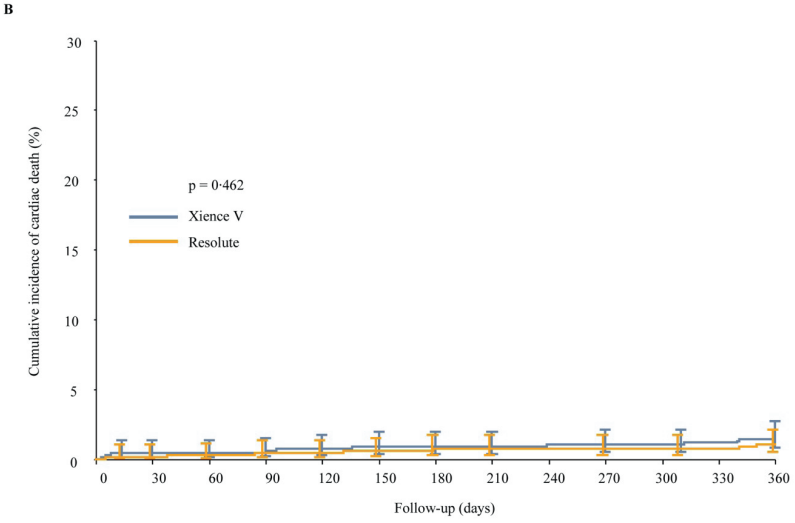
□Major adverse cardiac events are a composite of all-cause death, any myocardial infarction (MI), emergent coronary artery bypass surgery, or clinically indicated target lesion revascularization (TLR).
†Patient-oriented composite endpoint is a composite of endpoint of all-cause death, any MI, or any revascularization.



Number at risk

Xience V	694	677	662	660	656	651	648	646	646	644	643	639	637
Resolute	697	682	665	661	658	655	653	647	645	642	640	636	635

Figure 2A



Number at risk

Xience V	694	694	691	691	689	687	684	684	684	683	682	681	680
Resolute	697	697	695	693	690	688	687	685	685	685	685	683	683

Figure 2B

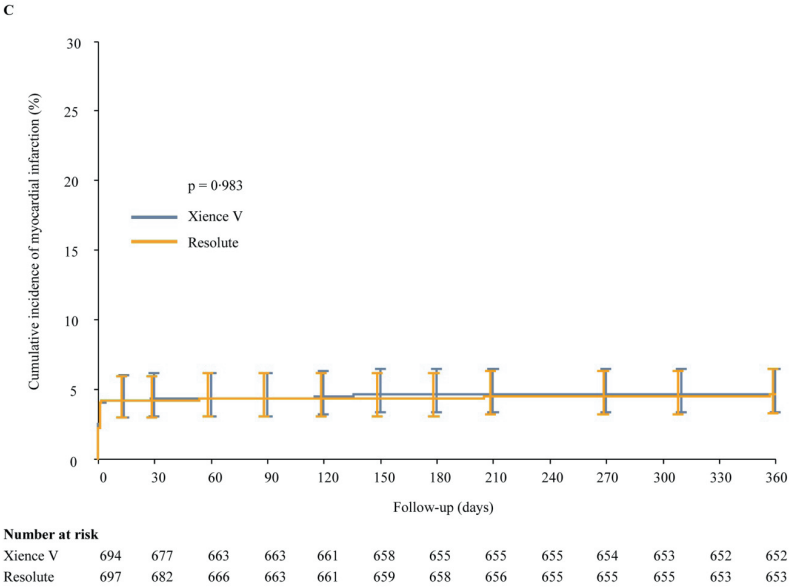


Figure 2C

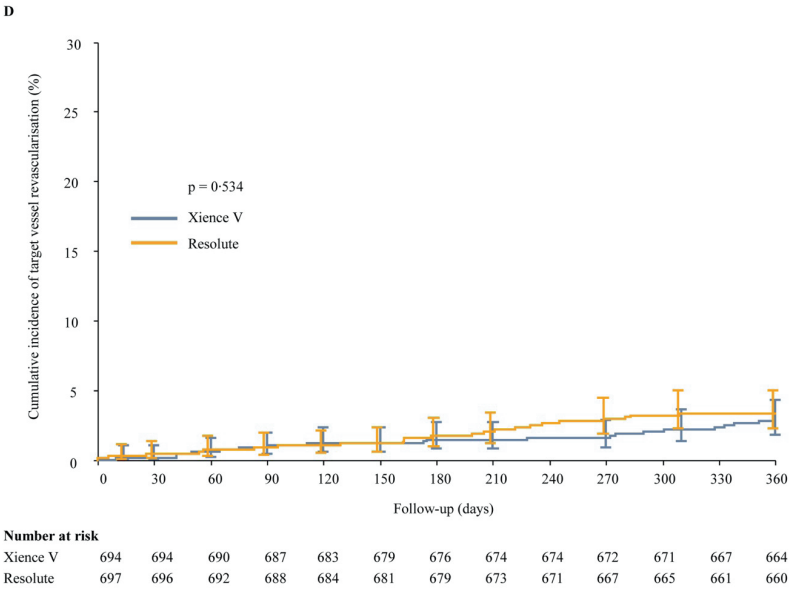


Figure 2D

Figure 2: Kaplan-Meier for Primary Endpoint and the Individual Components of the Primary Endpoint

Kaplan-Meier cumulative incidence curves at 1 year for the primary endpoint, a composite of cardiac death, target-vessel related myocardial infarction, or target-vessel revascularization **(A)**; cardiac death **(B)**; myocardial infarction **(C)**; and target-vessel revascularization **(D)** for the zotarolimus-eluting Resolute stent and the everolimus-eluting Xience V stent.

Group	zotarolimus-eluting Resolute (%)	evorolimus-eluting Xience V (%)	Relative risk (95% CI)	Relative risk (95% CI)	p Value
All patients (n=1391)	8·2 (57/697)	8·1 (56/694)		1·01 [0·71, 1·44]	0·94
Off-label indication (n=1077)	9·9 (54/547)	9·2 (49/530)		1·07 [0·74, 1·54]	0·73
Vessel diameter < 2·75 mm (n=874)	9·2 (41/445)	8·4 (36/429)		1·10 [0·72, 1·68]	0·67
NSTEMI < 72 hrs. (n=408)	6·9 (14/202)	8·7 (18/206)		0·79 [0·41, 1·55]	0·50
Multivessel PCI (n=336)	14·9 (26/174)	9·3 (15/162)		1·61 [0·89, 2·94]	0·11
Diabetes (n=301) *	13·9 (22/158)	7·7 (11/143)		1·81 [0·91, 3·60]	0·08
Overlapping stents (n=503)	10·7 (26/244)	12·4 (32/259)		0·86 [0·53, 1·40]	0·55
Bifurcation lesion (n=362)	10·1 (18/179)	8·2 (15/183)		1·23 [0·64, 2·36]	0·54
Lesion length > 27 mm (n=293)	15·4 (24/156)	13·9 (19/137)		1·12 [0·64, 1·94]	0·71
In-stent restenosis (n=69)	2·8 (1/36)	9·1 (3/33)		0·31 [0·03, 2·80]	0·34
Renal insufficiency (n=38)	10·5 (2/19)	10·5 (2/19)		1·00 [0·16, 6·39]	1·00
Bypass graft treated (n=41)	25·0 (5/20)	28·6 (6/21)		0·88 [0·32, 2·42]	0·86
Left main treated (n=52)	11·5 (3/26)	11·5 (3/26)		1·00 [0·22, 4·51]	1·00

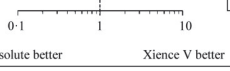


Figure 3: Subgroup analysis: Target vessel failure at one year.
Target vessel failure is a composite of cardiac death, target-vessel myocardial infarction, or clinically driven target vessel revascularization. *p = 0.045 for interaction between stent type and presence of diabetes mellitus; interaction testing was not significant for all other subgroups. CI = confidence interval; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

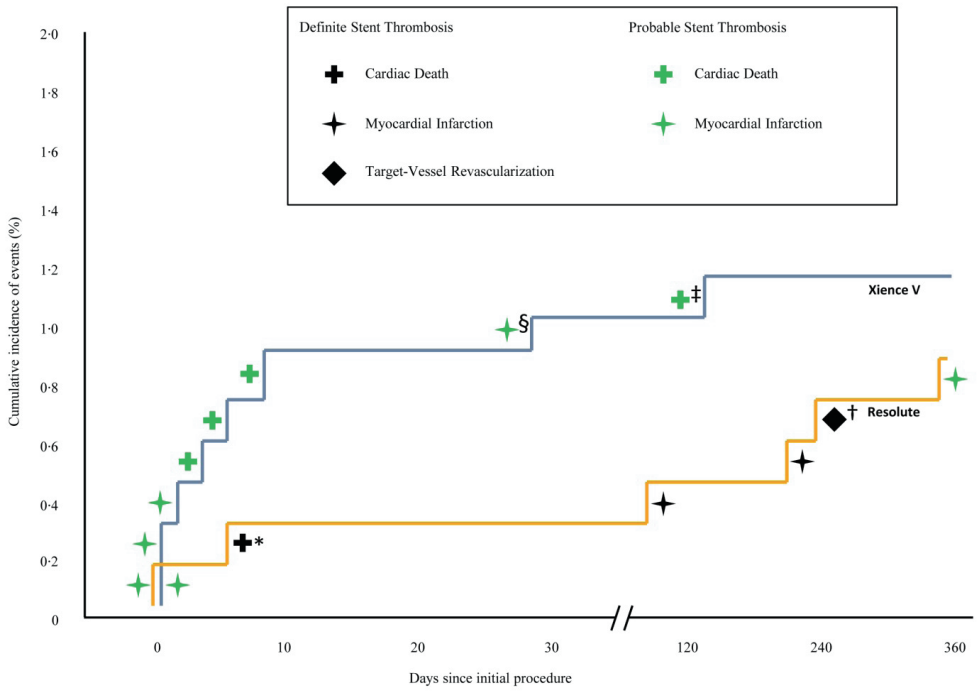


Figure 4: Cumulative incidence of definite or probable stent thrombosis.
*Cardiac death; patient enrolled for stenting of residual lesions in right and left anterior descending arteries 7 days after a non–ST-segment elevation myocardial infarction, treated with a bare-metal stent in circumflex artery. †Target vessel revascularization; patient was not receiving dual antiplatelet therapy because of intolerance to acetylsalicylic acid (patient used clopidogrel and oral anticoagulation). ‡Cardiac death; patient did not adhere to prescribed dual antiplatelet therapy (used acetylsalicylic acid only). §Non–Q-wave myocardial infarction; patient was not receiving dual antiplatelet therapy (used clopidogrel and oral anticoagulation).

DISCUSSION

In this randomized trial, which comprised a vast majority of patients with "off-label" indication for DES (77%), the Resolute ZES group and the Xience V EES group had a similar incidence of the primary composite endpoint of TVF at 12-month follow-up. As a result, the Resolute ZES met the criterion of noninferiority versus the Xience V EES. In addition, between both study groups there was no significant difference in the individual components of the primary endpoint (cardiac death, target vessel-related MI, and clinically indicated TVR).

In the present study, more than 80% of all eligible patients were enrolled. There were only a few exclusion criteria. As a consequence, the majority of patients of this "real-world" patient

population were treated in a nonelective setting, and a high proportion of patients had complex lesions and suffered from advanced coronary disease, that required multivessel PCI.

More than one-half of the patients of our study presented with acute coronary syndromes, whereas primary PCI for acute STEMI was an exclusion criterion. Nevertheless, most other patient and lesion characteristics and procedural details were similar to the few previous comparative stent studies in "all comer" populations (varying STEMI proportion of 12 to 25%).[15,22,23] Although the implantation of DES for treatment of STEMI has gained acceptance,[24] this approach was not the standard when the present study was designed.

To date, there is only 1 other published trial (Resolute All Comers)[15] with a head-to-head comparison of the same stents as in the present study. That trial assessed 1140 patients in the Resolute ZES arm and 1152 patients in the EES arm, and demonstrated noninferiority of the ZES in a patient population with minimal exclusion criteria. This was confirmed by the present trial.

The clinical event adjudication of both Resolute All Comers and TWENTE trial was performed by the same independent clinical research organization, which might facilitate meaningful comparison of clinical outcome data. In the TWENTE trial, the incidence of TVF (8.2% and 8.1%, respectively) was lower than in Resolute All Comers (9.0% and 9.6%, respectively). This was the result of lower clinically indicated TVR rates (3.3% and 2.7% versus 3.9% and 3.4%) and slightly lower rates of cardiac death (1.0% and 1.4% versus 1.3% and 1.7%), while the rates of target vessel-related MI were somewhat higher in the TWENTE trial (4.6% and 4.6% versus 4.2% and 4.1%).

The majority of target vessel related MIs occur during the periprocedural period. Therefore, the high rate of stent post-dilation in the present trial (82% of lesions) might explain the slightly higher rate of target vessel-related MIs compared with Resolute All Comers study.[15] By contrast, stent post-dilation is likely to improve stent apposition and drug delivery, which might have contributed to the somewhat lower rate of clinically indicated TVR in the present study. In fact, this rate was even lower than that of EES in SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) study (3.9%), a multicenter trial that compared EES and paclitaxel-eluting stents in 2485 and 1229 patients, respectively.[14]

In the TWENTE trial, direct stenting was performed in 39% of lesions. This is similar to the rate of direct stenting in other trials with complex lesions (30 to 40%).[15,22,23]

Intuitively, one might tend to argue that the lack of inclusion of patients with STEMI in the TWENTE trial might have contributed to a low rate of TVF. However, in Resolute All Comers trial, the 12% STEMI patients actually had *lower* rates of TVF and *fewer* major cardiac events than the overall study population.[25] This might partly be explained by the difficulty of identifying periprocedural MI in the setting of STEMI.[18] In addition, because of the generally reduced myocardial mass subtended, restenoses of infarct-related arteries are less likely

to provoke myocardial ischemia, which can have a lowering effect on the TVR rate. In the COMPARE (Trial of Everolimus-eluting Stents and Paclitaxel-eluting Stents for Coronary Revascularization in Daily Practice), which assessed 897 patients treated with EES and 903 patients treated with paclitaxel-eluting stents, clinically justified TVR in the EES arm (2.1%)[22] was even lower than in Resolute All Comers study[15] and the present study. For reasons discussed in the preceding text, the particularly high proportion of STEMI in COMPARE trial (27%) might have contributed to this difference.[22]

In the exploratory subgroup analysis of the primary endpoint, there was no difference in TVF across all different subgroups except for diabetes mellitus, which showed a significant interaction with the type of stent (p = 0.045), indicating a trend in diabetic patients towards a lower rate of TVF in the EES arm (p = 0.08). Although this finding is intriguing, it should be considered at most as hypothesis-generating. Undoubtedly, it is desirable to perform further basic and clinical research on DES in the field of diabetes mellitus.[26,27]

Our study was not statistically powered to prove potential differences in stent thrombosis, but there are several findings that are worth discussion. In the TWENTE trial, the incidence of definite stent thrombosis tended to be lower than in the Resolute All Comers trial (Relative Risk: 0.4; p = 0.09). In the Resolute ZES arm of the current trial, both the rates of definite as well as definite or probable stent thrombosis (0.6% and 0.9%) were low and one-half as high as in Resolute All Comers trial (1.2% and 1.6%, respectively).[15] In addition, we did not see any clustering of definite or probable stent thrombosis in Resolute ZES in the acute or early subacute phase, as was previously observed.[15] One patient with definite stent thrombosis on day 245 was not on dual antiplatelet therapy because of an intolerance to acetylsalicylic acid. In addition, the only fatal definite stent thrombosis occurred in a patient in whom sudden death (on day 5 after index procedure and day 12 after Non-STEMI, respectively) could have been caused by fatal post-infarction arrhythmias. Other trials have previously shown a relatively low risk of stent thrombosis in Resolute ZES; in RESOLUTE US (Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries), ISAR-TEST 5 (Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents), and Resolute All Comers trials, definite stent thrombosis rates ranged from 0.1% to 1.2%.[12,13,15]

In the present study, the Xience V EES arm showed no definite stent thrombosis at one year follow-up. The TWENTE trial is the first randomized trial that showed no definite stent thrombosis in a complex “real-world” patient population with advanced coronary disease and challenging lesions. The use of EES has previously been associated with a relatively low risk of stent thrombosis.[28] In SPIRIT III and IV, COMPARE, and Resolute All Comers trials, definite stent thrombosis rates in EES ranged from 0.3-0.8%.[10,15,22,29] In contrast to the absence of definite stent thrombosis in the Xience V study arm of the TWENTE trial, there

were 8 adverse cardiac events that were adjudicated as probable stent thromboses—4 of them being lethal. However, beyond 8 days after the index procedure, none of these probably thrombotic events occurred in a patient who adhered to dual antiplatelet therapy (the events on day 28 and day 136 occurred in patients not receiving dual antiplatelet therapy) (Fig. 4).

The strengths of the present study are the assessment of a "real-world" patient population with advanced disease and complex lesions, enrollment of more than 80% of all eligible patients, systematic post-procedural measurement of cardiac biomarkers (available in 99% of patients), absence of loss to follow-up, and verification of all patient-reported clinical event triggers from the source. We also consider the entirely clinical endpoint as a strength, because angiographic assessment of a subgroup of patients— even if performed after the 12-month clinical endpoint has been reached (e.g., angiographic assessment at 13 months)—could have an impact on the important 2-year clinical outcome data of the TWENTE population.

Study limitations

This trial was performed in a high-volume tertiary centre for PCI by 5 experienced operators with relatively uniform procedural strategies and liberal use of stent post-dilation; therefore, generalization of the results might be limited in other settings. In addition, we did not pre-specify subgroup analysis; however, to avoid a subjective post hoc selection of subgroups, we used the same subgroups as Resolute All Comers trial.[15]

Conclusion

Resolute ZES were noninferior to Xience V EES in terms of safety and efficacy for treating "real-world" patients with a vast majority of complex lesions and "off-label" indications for drug-eluting stents, which were implanted with liberal use of post-dilation.

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REFERENCES

1. 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; 346:1773-80.
2. 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; 349:1315-23.
3. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007; 356:1030-9.
4. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007; 370:937-48.
5. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007; 369:667-78.
6. Basalus MW, van Houwelingen KG, Ankone MJ, Feijen J, von BC. Micro-computed tomographic assessment following extremely oversized partial postdilatation of drug-eluting stents. EuroIntervention 2010; 6:141-8.
7. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009; 360:961-72.
8. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent:the SPIRIT II trial. EuroIntervention 2006; 2:286-94.
9. Tsuchida K, Piek JJ, Neumann FJ, et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial). EuroIntervention 2005; 1:266-72.
10. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008; 299:1903-13.
11. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. JACC Cardiovasc Interv 2009; 2:977-85.
12. Yeung AC, Leon MB, Jain A, et al. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. J Am Coll Cardiol 2011; 57:1778-83.
13. Massberg S, Byrne RA, Kastrati A, et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. Circulation 2011; 124:624-32.
14. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010; 362:1663-74.
15. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010; 363:136-46.
16. Romagnoli E, Sangiorgi GM, Cosgrave J, Guillet E, Colombo A. Drug-eluting stenting: the case for post-dilation. JACC Cardiovasc Interv 2008; 1:22-31.
17. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007; 115:2344-51.
18. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010; 363:136-46.
19. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006; 48:2440-7.
20. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998; 17:873-90.
21. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002; 359:1686-9.
22. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010; 375:201-9.

23. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008; 372:1163-73.
24. Sakhuja R, Mauri L. Controversies in the use of drug-eluting stents for acute myocardial infarction: a critical appraisal of the data. Annu Rev Med 2010; 61:215-31.
25. Windecker S. Clinical and Angiographic Outcomes in Patients with Acute Myocardial Infarction from the RESOLUTE All Comers Open Label Randomized Trial: RESOLUTE-AMI. Presented at TCT 2010, San Francisco, CA, USA on Sep 22; 2010.
26. Kereiakes DJ, Cutlip DE, Applegate RJ, et al. Outcomes in diabetic and nondiabetic patients treated with everolimus- or paclitaxel-eluting stents: results from the SPIRIT IV clinical trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System). J Am Coll Cardiol 2010; 56:2084-9.
27. Stone GW, Kedhi E, Kereiakes DJ, et al. Differential clinical responses to everolimus-eluting and Paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. Circulation 2011; 124:893-900.
28. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011; 58:1569-77.
29. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011; 377:1241-7.

CHAPTER 11

COMPARISON OF ELIGIBLE NON-ENROLLED PATIENTS AND THE RANDOMIZED TWENTE TRIAL POPULATION TREATED WITH RESOLUTE AND XIENCE V DRUG-ELUTING STENTS

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H. Sen and K.Tandjung contributed equally to this work.

ABSTRACT

Aims: The TWENTE trial recently enrolled more than 80% of all eligible patients, who were randomized to zotarolimus-eluting Resolute or everolimus-eluting Xience V stents. In the present study, we investigated whether eligible, non-enrolled patients differed from the randomized TWENTE trial population in baseline characteristics and one-year outcome.

Methods and Results: Characteristics of 1709 eligible patients were analyzed. Independent external adjudication of clinical events was likewise performed for non-enrolled (n=318) and randomized patients (n=1391). Non-enrolled and randomized patients did not differ in gender distribution, diabetes mellitus, and clinical presentation, but differed significantly in age and cardiovascular history. Nevertheless, clinical outcome after one year did not differ in the primary composite endpoint target-vessel failure (TVF; 9.8% vs. 8.1%; p=0.34), and its components cardiac death (1.6% vs. 1.2%; p=0.61), target vessel-related myocardial infarction (4.7% vs. 4.6%; p=0.92), and target-vessel revascularization (3.8% vs. 3.0%; p=0.48). Previous bypass surgery predicted TVF in non-enrolled patients (p=0.001); removal of these patients resulted in identical TVF rates for non-enrolled and randomized patients (7.3% vs. 7.3%; p=0.99).

Conclusion: Despite some differences in baseline characteristics, non-enrolled and randomized patients did not differ in one-year outcome, which was favorable for both populations and may be related to the drug-eluting stents used.

INTRODUCTION

Drug-eluting stents (DES) have been rapidly adapted for routine percutaneous coronary interventions (PCI), as they reduced the need for reinterventions.[1,2] As first-generation DES did not improve mortality,[3-6] novel stents with different coatings were developed, aimed at improved clinical outcome.[7,8] Two of these so-called second-generation DES are the zotarolimus-eluting Resolute stent (Medtronic CardioVascular) and the everolimus-eluting Xience V stent (Abbott Vascular Devices). Both DES have thin-strut, open-cell, cobalt-chromium-based stent platforms and thin, durable polymer-based coatings,[9,10] and they have shown favorable clinical results that have led to widespread use in clinical practice.[11-16] For these stents, non-inferiority with regard to safety and efficacy was recently demonstrated by TWENTE, a randomized, controlled study in a patient population with advanced coronary disease and complex lesions,[17] which confirmed with relatively low event rates the results of the RESOLUTE All Comers trial.[18] In addition, TWENTE is one of the relatively few randomized comparative DES trials that have been performed in a study population with very limited exclusion criteria to reflect routine clinical practice.[18-21]

The enrollment in the randomized TWENTE trial was high, comprising more than 80% of all eligible patients. [17] However, it is unknown whether the non-enrolled patients, who were all likewise treated with Resolute and Xience V stents, differ from the randomized TWENTE trial population in terms of baseline characteristics or – perhaps even more relevant – in clinical outcome. To answer this question, we prospectively recorded comprehensive data sets on clinical, procedural, and angiographic characteristics of all eligible but non-enrolled patients in the *Non-Enrolled TWENTE study*. To assure high-quality clinical outcome data and to facilitate meaningful comparisons with findings of the randomized TWENTE trial, an external clinical research organization performed the independent adjudication of all clinical events together in both the *Non-Enrolled TWENTE* study and randomized TWENTE trial.

METHODS

Study design and patient populations. Details of the randomized TWENTE trial, which was performed from June 18, 2008 to August 26, 2010 at Thoraxcentrum Twente in Enschede, The Netherlands, have previously been reported.[17] TWENTE is a randomized, controlled, patient-blinded DES trial, comparing Resolute and Xience V stents after 1:1 randomization (ClinicalTrials.gov NCT01066650). Patients were eligible for enrollment and randomization if they were aged 18 years or older, were capable of providing informed consent, and underwent a PCI with DES implantation for the treatment of chronic stable coronary artery disease or non-ST-elevation acute coronary syndromes (Non-STE-ACS). To include a broad study population, the study protocol defined no limit for lesion length, reference vessel

size, and number of target lesions or vessels. The only exclusion criteria were: ST-elevation myocardial infarction (STEMI) or STEMI-equivalent requiring primary or rescue PCI during the past 48 hours; planned staged revascularization; renal failure requiring hemodialysis; serious conditions that could limit the patient's ability to participate in study procedures, in particular life expectancy <1 year; participation in investigational drug or device study; if the choice of stent type was dictated by logistic reasons (e.g. a stent with required dimensions only available as one type).[17]

During the course of the randomized TWENTE trial, patients who were not enrolled were also treated with one of both, Resolute or Xience V stents, and their clinical course was prospectively registered as part of the *Non-Enrolled TWENTE study*. Operators were asked to report reasons for non-enrollment in PCI reports but incomplete documentation of this detail was not infrequent. We therefore used PCI reports, all clinical records, and interviews with the operators and other medical staff involved to obtain the most reliable estimate of the reasons for non-enrollment. The *Non-Enrolled TWENTE study* and the previously reported randomized TWENTE trial complied with the Declaration of Helsinki for investigation in human beings, and were performed after approval and supervision of our institutional ethics committee.

Intervention, medication, electrocardiography, and laboratory testing. PCI procedures were performed according to standard techniques as previously described.[17] In brief, lesion predilatation, direct stenting, and/or stent postdilatation were permitted at the operators' discretion; liberal use of stent postdilatation was encouraged. Pharmacological therapy before, during, and after PCI as well as systematic laboratory and electrocardiographic testing were performed as previously described.[17]

Definitions of clinical endpoints. Definitions of clinical endpoints have been fully described in the main report on the randomized TWENTE trial.[17] The same endpoint definitions were used in the present study. In general, the definitions of the Academic Research Consortium (ARC) were applied.[22,23] In brief, the primary endpoint *Target-Vessel Failure* (TVF) was defined as (in hierarchical order) cardiac death, target-vessel-related myocardial infarction, or clinically driven target-vessel revascularization (TVR) by re-PCI or surgery. Cardiac death was defined as any death due to proximate cardiac cause, un-witnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Classification and location of myocardial infarction was performed based on laboratory testing, electrocardiographic parameters, angiographic information, and clinical data.[17] Laboratory parameters for definition of myocardial infarction was any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker.[23] TVR was defined as any repeat coronary revascularization of the target vessel. Target-vessel (or target-lesion) revascularization was considered clinically indicated if the angiographic percent diameter stenosis of the then treated lesion

was ≥50% in the presence of ischemic signs or symptoms, or if the diameter stenosis was ≥70% irrespective of ischemic signs or symptoms.[22]

Secondary clinical endpoints are: death from any cause; Q-wave and non Q-wave myocardial infarction; any myocardial infarction; TVR by PCI, surgery, or either or both; clinically-indicated target-lesion revascularization; any target-lesion revascularization (stented segment including 5mm proximal and distal border-zones); stent thrombosis, defined according to ARC.[22] Composite parameters are (where applicable in a hierarchical order): *Target-Lesion Failure*, defined as a composite of cardiac death, target-vessel-related myocardial infarction, and clinically-indicated target-lesion revascularization; and m*ajor adverse cardiac events*, a composite of all-cause death, any myocardial infarction, emergent coronary artery bypass surgery or clinically-indicated target-lesion revascularization.

Data acquisition and follow-up. In-hospital adverse events were recorded prior to discharge. As part of our center's standard follow-up procedure, 12-month follow-up data of all patients were obtained at visits at outpatient clinics or, if not feasible, by telephone follow-up and/or a medical questionnaire. For any event trigger, members of the study team gathered all clinical information available from referring cardiologist, general practitioner, and/or hospital involved.

Independent clinical event adjudication. Processing of clinical data and adjudication of adverse clinical events of the *Non-Enrolled TWENTE* population were performed independently in the same way as for the randomized TWENTE trial (use of anonymous patient data and blinding for stent type) by Cardialysis in Rotterdam, The Netherlands. In brief, the clinical event committee adjudicated any death, potential myocardial infarction, stent thrombosis, and revascularization.

Statistical analysis. Data analysis was performed with the Statistical Package for Social Sciences (SPSS; version 17, SPSS Inc., Chicago, IL). Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean ± standard deviation for continue variables. The chi-square test and the Fisher's exact test were used as appropriate. The student's t-test was used to test normally distributed parameters. The Kaplan–Meier method was used to calculate the time to clinical endpoints and the Log-rank test was used to compare between-group differences. As non-enrolled patient populations are likely to contain more high-risk patients with a higher event rate,[24] multiple logistic regression analysis was applied to the data of the non-enrolled patient population in order to identify predictors of TVF. In a subsequent analysis, we excluded patients with these variables to correct for potential confounders. Unless otherwise specified, a two-sided P value <0.05 was considered to indicate statistical significance.

RESULTS

During the inclusion period of the randomized TWENTE trial, 2239 patients were treated with DES at Thoraxcentrum Twente, The Netherlands. A total of 1709 of these patients were eligible for study enrollment and randomization. Finally, 1391 of these 1709 patients (81.4%) with 2116 lesions were enrolled in the randomized TWENTE trial. In other words, only 318 eligible patients (18.6%, with 466 lesions) were not enrolled in the randomized trial but were assessed in the *Non-Enrolled TWENTE* study (Figure 1).

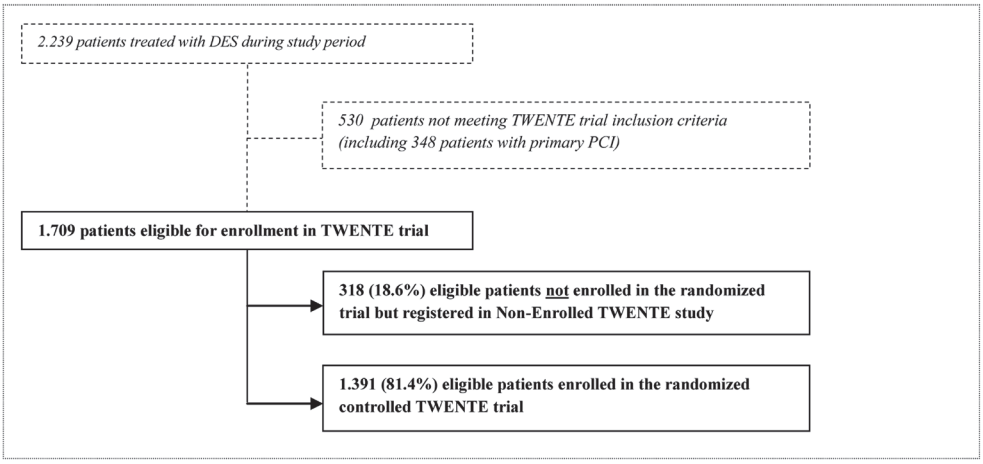


Figure 1: Flow chart of patients treated with DES during the course of the randomized TWENTE trial. Patients of the *Non-Enrolled TWENTE* study and the randomized TWENTE trial were compared. *Data of the randomized TWENTE trial have previously been reported.[17]

Reasons for non-enrollment. Reasons for non-enrollment and estimates of their incidence within the non-enrolled population were: (1) refusal of the patient to participate in the randomized trial (~10%); (2) uncertainty of the operator whether the information transfer was successful (e.g. because of language barrier, deafness, or the entire clinical condition) (~25%); (3) logistic reasons (e.g. an ACS patient is not informed prior to the catheterization, while another patient is announced for primary PCI) (~15%); and (4) omission of informing the patient about the trial prior to an elective procedure (~30%). This means that a substantial proportion of the eligible patients (~20%; i.e. ~3.7% of all eligible patients) were not enrolled without evident reason.

Patients, target lesions, and PCI procedures. Table 1 compares demographics and the procedural characteristics of both the *Non-Enrolled TWENTE study* population versus the randomized TWENTE trial population. Both study populations did not differ in the proportion of genders, diabetes mellitus, and clinical presentation (acute coronary syndromes in 52.5%

vs. 51.5%, respectively; p=0.48). Non-enrolled patients were somewhat older (66.0±10.9 vs. 64.2±10.8 years; p=0.01). There was a trend towards less multivessel treatment in the non-enrolled patients (19.2% vs. 24.2%; p=0.06), matching with a more severely impaired left ventricular (6.5% vs. 3.0%; p=0.015) and renal function (6.6% vs. 2.7%; p=0.001) in this group. In addition, non-enrolled patients had more often a history of previous MI (43.1% vs. 32.4%; p<0.001), previous PCI (28.9% vs. 20.7%; p=0.001), and previous CABG (17.0% vs. 10.6%; p=0.002; Table 1).

Table 1: Characteristics of patients and procedures.

	Non-enrolled patients (N=318)	**Randomized patients (N=1.391)**	**p Value**
Age (yrs)	66.0(10.9)	64.2(10.8)	0.01
Men	224(70.4)	1009(72.5)	0.45
Diabetes mellitus (any)	72(22.6)	301(21.6)	0.66
Chronic renal failure *	21(6.6)	38(2.7)	0.001
Arterial hypertension	185(58.2)	773(55.6)	0.40
Hypercholesterolaemia	193(60.7)	803/1357(59.2)	0.06
Current smoker	70(22.0)	340(24.4)	0.36
Family history of CAD	102/193(52.8)	740(53.2)	0.93
Myocardinfarction (any)	137(43.1)	450(32.4)	<0.001
Previous PCI	92(28.9)	288(20.7)	0.001
Previous CABG	54(17.0)	148(10.6)	0.002
Clinical characteristic			0.48
Stable angina pectoris	151(47.5)	674(48.5)	
Acute coronary syndrome	167(52.5)	717(51.5)	
Unstable angina	84(26.4)	325(23.4)	
Non-ST-elevation MI	83(26.1)	392(28.2)	
Left ventricular ejection fraction < 30% †	13/199(6.5)	32/1051(3.0)	0.015
Multivessel treatment	61(19.2)	336(24.2)	0.06
Total no lesions treated per patient			0.28
One lesion treated	203(63.8)	857(61.6)	
Two lesions treated	92(28.9)	393(28.3)	
Three of more lesions treated	23(7.2)	141(10.1)	
At least one CTO	28(8.8)	95(6.8)	0.22
At least one bifurcation	83(26.1)	362(26.0)	0.98
At least one in-stent restenosis	43(13.5)	69(5.0)	<0.001
Postdilatation	278(87.4)	1222(87.9)	0.83

Data are number (%) or mean (SD). CAD=coronary artery disease. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. MI=myocardial infarction. CTO=chronic total occlusion.

* Chronic renal failure was defined by serum creatinine level ≥ 130 µmol/L.

† Left ventricular ejection fraction was assessed with ultrasound, MRI or LV angiography.

A total of 466 and 2116 lesions were treated in the *Non-Enrolled TWENTE study* and the randomized TWENTE trial, respectively (Table 2). Target lesions of non-enrolled patients showed more often complex B2 or C lesion types (76.1% vs. 70.1%; p=0.047). In parallel with the higher incidence of a history of PCI and/or CABG in the *Non-Enrolled TWENTE* population, more target lesions were restenoses and bypass graft lesions (p<0.001 for both; Table 2).

Table 2: Lesion characteristics.

	Non-enrolled (N=466 lesions)	**Randomized (N=2.116 lesions)**	**p Value**
Target lesion coronary artery			
Left main	17(3.6)	54(2.6)	0.19
Left anterior descendens	179(38.4)	878(41.5)	0.22
Left circumflex	107(23.0)	483(22.8)	0.95
Right coronary artery	135(29.0)	653(30.9)	0.42
Bypass graft	28(6.0)	48(2.3)	<0.001
ACC-AHA lesion class			0.047
A	24(5.2)	154(7.3)	
B1	87(18.7)	478(22.6)	
B2	153(32.8)	678(32.0)	
C	202(43.3)	806(38.1)	
De novo lesions	409(87.8)	1999(94.5)	<0.001
Chronic total occlusion	30(6.4)	100(4.7)	0.13
In stent restenosis	37(7.9)	75(3.5)	<0.001
Bifurcated lesion	101(21.7)	518(24.5)	0.20

Data are number (%). ACC=American College of Cardiology.
AHA=American Heart Association. De-novo lesions include chronic total occlusion, but not grafts and in-stent restenosis.

Clinical outcome. Clinical follow-up data were available for 316 patients of the *Non-Enrolled TWENTE* study (99.4% follow-up data) and 1387 randomized TWENTE patients (100% follow-up data available; four patients withdrew consent). Table 3 and Figure 2 show various clinical outcome parameters at 1-year follow-up. Between both populations, there was no significant difference in the primary outcome parameter TVF (9.8% vs. 8.1%; p=0.34, OR 1.23 [95% CI 0.81 to 1.8]). There was also no significant difference in the components of the primary endpoint (cardiac death (1.6% vs. 1.2%; p=0.61); target vessel-related MI (4.7% vs. 4.6%; p=0.92; and clinically driven TVR (3.8% vs. 3.0%; p=0.48)), and any other clinical endpoint, such as death from any cause (2.2% vs. 2.1%; p=0.89) and major adverse cardiac events (9.5% vs. 9.5%; p=0.99; Table 3).

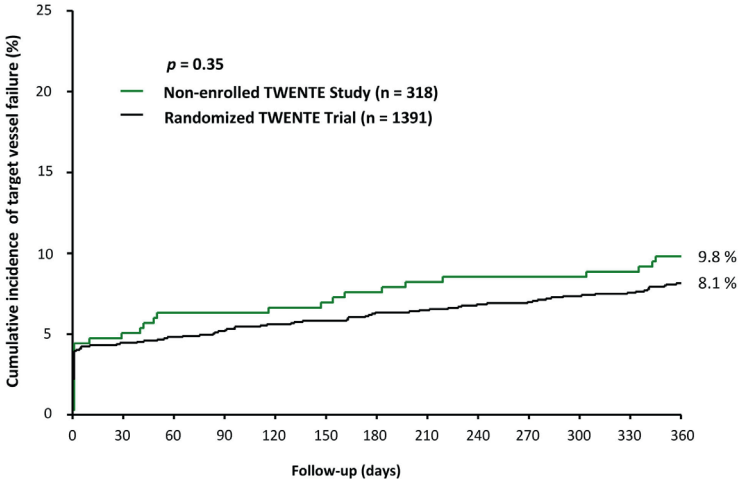
Stent thrombosis. Within the non-enrolled patient population, there was no definite stent thrombosis (Table 3). Definite or probable stent thrombosis occurred in one patient of the *Non-Enrolled TWENTE* population (one probable stent thrombosis) and in 14 patients of the randomized TWENTE trial population (0.3% vs. 1.0%; p=0.23).

Table 3: Clinical outcome after one year.

	Non-enrolled patients (N=316)	Randomized patients (N=1.387)	p Value
Target vessel failure	31(9.8)	113(8.1)	0.34
Death			
Any cause	7(2.2)	29(2.1)	0.89
Cardiac cause	5(1.6)	17(1.2)	0.61
Target vessel related MI			
Any	15(4.7)	64(4.6)	0.92
Q-wave	0	11(0.8)	0.11
Non-Q-wave	15(4.7)	53(3.8)	0.45
Periprocedural MI	13(4.1)	57(4.1)	0.99
Clinically indicated TVR			
Any	12(3.8)	42(3.0)	0.48
Percutaneous	12(3.8)	33(2.4)	0.16
Surgical	0	9(0.6)	0.15
Target lesion failure	28(8.9)	102(7.4)	0.36
Clinically indicated TLR			
Any	9(2.8)	29(2.1)	0.41
Percutaneous	9(2.8)	22(1.6)	0.13
Surgical	0	7(0.5)	0.21
Death from cardiac causes or target-vessel MI	20(6.3)	67(4.8)	0.28
Major adverse cardiac events	30(9.5)	132(9.5)	0.99
Definite ST (0-360 days)			
all patients	0	4(0.6)	0.34
Probable ST (0-360 days)			
all patients	1(0.3)	10(0.7)	0.42
ST (0-360 days)			
Possible	3(0.9)	6(0.4)	0.25
Definite or probable	1(0.3)	14(1.0)	0.23
Definite, probable or possible	4(1.3)	20(1.4)	0.81

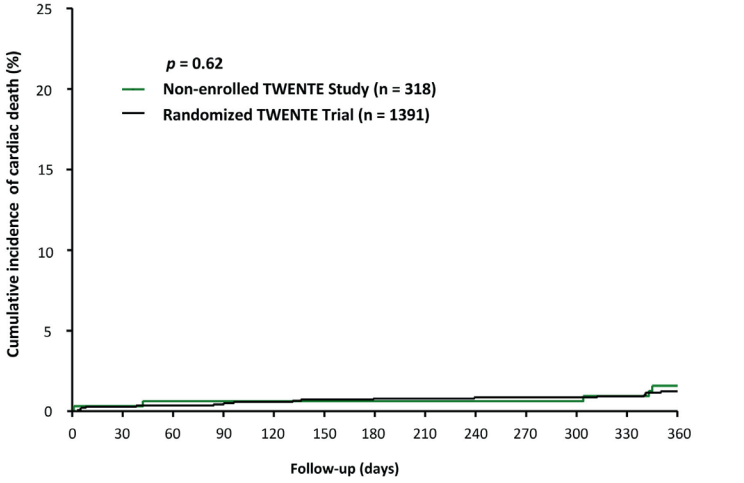
Data are number of patients (%). MI=myocardial infarction. TVR=target vessel revascularization. TLR=target lesion revascularization. ST=stent thrombosis. Major adverse cardiac events is a composite of all cause death, any myocardial infarction, emergent coronary-artery bypass surgery or clinically indicated target lesion revascularization.

A



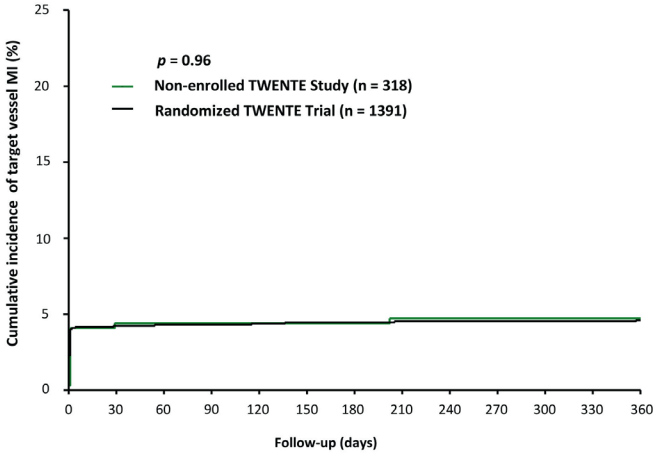
Number at risk													
Non-enrolled patients	318	300	296	296	295	294	291	289	288	288	288	287	283
TWENTE patients	1391	1327	1321	1314	1306	1301	1293	1291	1286	1283	1275	1272	1263

B



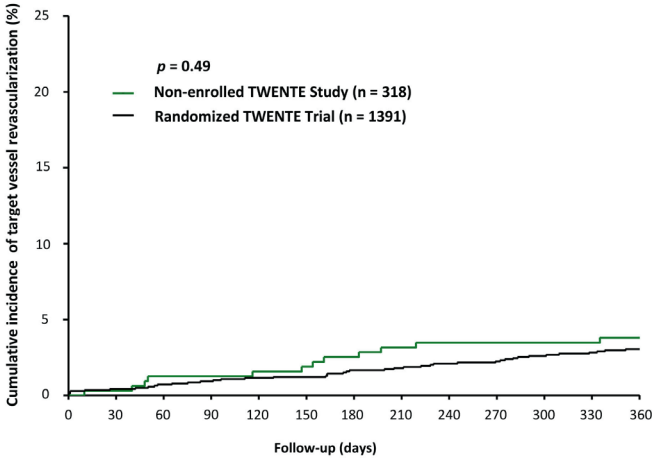
Number at risk													
Non-enrolled patients	318	315	314	314	314	314	313	313	313	313	313	312	309
TWENTE patients	1391	1386	1384	1379	1375	1371	1369	1369	1368	1367	1364	1363	1358

C



Number at risk													
Non-enrolled patients	318	303	302	302	302	302	301	300	300	300	300	299	296
TWENTE patients	1391	1329	1326	1322	1317	1313	1311	1310	1309	1308	1305	1305	1299

D



Number at risk													
Non-enrolled patients	318	316	312	312	311	310	307	305	304	304	304	303	299
TWENTE patients	1391	1382	1375	1367	1360	1355	1347	1345	1339	1336	1328	1324	1316

Figure 2: Kaplan-Meier for the primary endpoint and the individual components of the primary endpoint. Kaplan-Meier cumulative incidence curves at one year for the primary endpoint target-vessel failure, a composite of cardiac death, target-vessel related myocardial infarction, or target-vessel revascularization (A); cardiac death (B); myocardial infarction (C); and target-vessel revascularization (D) for both patients of the *Non-Enrolled TWENTE* study and the randomized TWENTE trial.

Predictors of Target-Vessel Failure. The only parameter that significantly predicted TVF in the *Non-Enrolled TWENTE* population was a history of CABG (OR 3.7, 95% CI 1.67–8.15; p=0.001). After removal of patients with a history of CABG from the analyses (54/316 non-enrolled (17%) and 148/1.386 randomized patients (10.6%)), differences in baseline characteristics were virtually unchanged: the *Non-Enrolled TWENTE* population still comprised older patients (65.3±11.1 vs. 63.7±10.9 years; p=0.03) and more patients with severely impaired left ventricular function (6.2% vs. 2.6%; p=0.02), impaired renal function (5.3% vs. 2.6%; p=0.02), history of previous MI (42.8% vs. 31.5%; p<0.001), and history of previous PCI (24.6% vs. 18.8%; p=0.03). However, removal of patients with a history of CABG resulted in identical TVF rates for *Non-Enrolled TWENTE* patients and the randomized TWENTE population (7.3% (19/262) vs. 7.3% (90/1239); p=0.99). Moreover, the slight numerical differences in other clinical endpoints continued to be statistically non-significant (major adverse cardiac events 8.0% (21/262) vs. 8.6% (106/1239); p=0.78).

DISCUSSION

In the present study, we addressed the question of whether patients, who were not enrolled in the randomized TWENTE trial [17] but were all likewise treated with Resolute or Xience V stents, differed from the enrolled and randomized patients in baseline characteristics, procedural details, or clinical outcome. During the course of the randomized TWENTE trial, only 19 percent of the eligible patients were *not enrolled* in the randomized trial.[17] To assure high-quality clinical outcome data and to facilitate meaningful comparisons, an independent external clinical research organization performed the clinical event adjudication for both *Non-Enrolled TWENTE* population and randomized TWENTE population (together in the same adjudication session). The randomized TWENTE population comprised many complex patients and advanced coronary lesions,[17] and in the *Non-Enrolled TWENTE* population many patients showed similar baseline characteristics and cardiovascular risk factors. Nevertheless, *Non-Enrolled TWENTE* patients were on average slightly older and showed more frequently a history of previous myocardial infarction and/or coronary revascularizations. As a consequence, we also identified mild but statistically significant differences in the rates of heart failure, renal failure, and lesion complexity in favor of the randomized TWENTE trial population, which comprised less bypass graft lesions and restenoses.

Despite the slight aforementioned baseline differences, *Non-Enrolled TWENTE* population and randomized TWENTE trial patients showed no significant difference in clinical outcome parameters such as TVF (9.8% vs. 8.1%; p=0.34), all-cause mortality (2.2% vs. 2.1%; p=0.89), or major adverse cardiac events (9.5% vs. 9.5%; p=0.99). Our data suggest that if all 1709 consecutive eligible patients had entered the randomized trial, the overall TVF rate could have been as low as 8.5%. In fact, this study underlines the high clinical performance of the

second-generation DES that were used. This performance appears to be greatly independent of the clinical profile of the patients.

Comparison with previous studies. Compared to RESOLUTE All Comers trial[18] and COMPARE trial,[20] two randomized studies with second-generation DES in 'real-world' patient populations, the randomized TWENTE patients showed similar or slightly higher rates of previous MI (32.4% vs. 16.5-29.7%), previous PCI (20.7% vs. 13.5-32%), previous CABG (10.6% vs. 6.5-9.8%), heart failure (3.0% vs. 2.5%), in-stent restenosis lesions (5.0% vs. 2.5-8.1%), bypass graft lesions (2.3% vs. 2.0-2.5%), and their age was similar (mean age 64.2 vs. 63.3-64.3 years). Accordingly, it is fair to state that the randomized TWENTE trial[17] is a study in a 'real-world' patient population (with the exception of acute STEMI), providing data that is highly relevant for routine clinical practice.

Analyses of randomized intervention studies that compared PCI and CABG have demonstrated that patient characteristics and the clinical outcome of these studies differed significantly from routine clinical practice.[24] Selection bias is more likely to be undetectable in studies with low enrollment rates, but in the randomized TWENTE trial the enrollment rate was particularly high. In many *Non-Enrolled TWENTE* patients there was at least one reason for non-enrollment. Nevertheless, in approximately 3.7% of all eligible patients the main reason for non-enrollment could not be identified. This leaves room for potential selection bias, and in fact, the differences in baseline characteristics between *Non-Enrolled TWENTE* study population and randomized TWENTE trial patients suggest that there could have been some selection bias. Examples of patients whom operators may deliberately not enroll in a randomized trial are patients with target vessels that supply previously (partly) infarcted myocardium because persistent electrocardiographic changes may render the diagnosis of a subsequent myocardial infarction difficult and sometimes impossible. The same may apply to certain patients with previous CABG and end-stage coronary artery disease, who likewise often have a higher cardiovascular risk profile and an advanced age.

But what is known about eligible patients who were not enrolled in other randomized, comparative DES trials with 'real-world' patient populations? In fact, such information is sparse. However, de Boer et al. recently reported for their high-volume PCI center baseline characteristics and 1-year all-cause mortality of patients who participated in two randomized multicenter trials in all comers and compared it to non-participating PCI patients (579 patients enrolled vs. 663 non-participants).[25] In that study, baseline characteristics differed significantly between trial participants and non-participants, who were older and had a higher incidence of heart failure and unstable clinical syndromes than trial participants).[25] In addition, all-cause mortality at 1-year follow-up was significantly higher in non-participants (6.9% vs. 3.1%; p=0.002).

Of note, these all-comers trials included patients with acute STEMI,[18,19,25] which – on average – have a higher mortality risk. On the contrary, the randomized TWENTE trial did

not enroll patients with acute STEMI,[17] who consequently were also not assessed in the *Non-Enrolled TWENTE* study. In addition, de Boer et al. addressed all non-participating PCI patients, including those who had clear contraindications for participation in one of the two randomized trials (e.g. patients in shock with very high mortality risk), [25] while our own study examined only eligible patients who all fulfilled the inclusion criteria of the randomized TWENTE trial.[17] This may explain differences in all- cause mortality between non-participants of the study of de Boer et al. and the *Non-Enrolled TWENTE* population. A comparison of clinical outcome parameters other than mortality was not possible, as no such data were available for non-enrolled patients of other randomized comparative DES trials.

Previous bypass surgery as predictor of outcome. In the *Non-Enrolled TWENTE* population, a history of CABG turned out to be the only predictor of TVF. In fact, the rate of TVF became identical for both patient populations after removing patients with a history of CABG from both patient populations (7.3% vs. 7.3%; p=0.99). Implication of this finding may be that particular attention should be paid to the distribution of patients with a history of CABG between the study arms of comparative DES trials.

Notably, in the randomized TWENTE trial [17] the proportion of patients with a history of CABG was similar or even higher than in some recent trials with second-generation DES in all-comer populations. [18,20]

Study limitations. This trial was performed in a high-volume tertiary center for PCI by five experienced operators with relatively uniform procedural strategies and liberal use of stent postdilatation.[17] Therefore, generalization of the results may be limited in other settings.

Conclusion. Despite some differences in baseline characteristics, non-enrolled and randomized patients did not differ in 1-year clinical outcome, which was favorable for both populations and may be related to the second-generation drug-eluting stents used.

Potential Conflict of Interest

Dr. von Birgelen is consultant to and has received lecture fees or travel expenses from Abbott Vascular, Medtronic, and Boston Scientific; he received a lecture fee from MSD. All other authors declare that they have no potential conflict of interest.

REFERENCES

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-1780.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-1323.
3. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030-1039.
4. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;369:667-678.
5. Lotan C, Meredith IT, Mauri L, Liu M, Rothman MT; E-Five Investigators. Safety and effectiveness of the Endeavor zotarolimus-eluting stent in real-world clinical practice: 12-month data from the E-Five registry. *JACC: Cardiovascular Interventions* 2009;2:1227-1235.
6. Jensen LO, Maeng M, Thayssen P, Christiansen EH, Hansen KN, Galloe A, Kelbaek H, Lassen JF, Thuesen L. Neointimal hyperplasia after sirolimus-eluting and paclitaxel-eluting stent implantation in diabetic patients. Eur Heart J 2008;29:2733-2741.
7. Tsuchida K, Piek JJ, Neumann FJ, van der Giessen,WJ, Wiemer M, Zeiher AM, Grube E, Haase J, Thuesen L, Hamm CW, Veldhof S, Dorange C, Serruys PW. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial). *EuroIntervention* 2005;1:266-272.
8. Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrie D, Thuesen L, Boone E, Miquel-Herbert K, Daemen J. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent:the SPIRIT II trial. *EuroIntervention* 2006;2:286-294.
9. Basalus MW, van Houwelingen KG, Ankone MJ, Feijen J, von Birgelen C. Micro-computed tomographic assessment following extremely oversized partial postdilatation of drug-eluting stents. *EuroIntervention* 2010;6:141-148.
10. Basalus MW, Ankone MJ, van Houwelingen KG, de Man FAHF, von Birgelen C. Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy. *EuroIntervention* 2009;5:157-165.
11. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Mahaffey KW, Cutlip DE, Fitzgerald PJ, Sood P, Su X, Lansky AJ. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 2008;299:1903-1913.
12. Meredith IT, Worthley S, Whitbourn R, Walters DL, McClean D, Horrigan M, Popma JJ, Cutlip DE, DePaoli A, Negoita M, Fitzgerald PJ. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. *JACC: Cardiovascular Interventions* 2009;2:977-985.
13. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;362:1663-1674.
14. Yeung AC, Leon MB, Jain A, Tolleson TR, Spriggs DJ, Mc Laurin BT, Popma JJ, Fitzgerald PJ, Cutlip DE, Massaro JM, Mauri L. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. J Am Coll Cardiol 2011;57:1778-1783.
15. Massberg S, Byrne RA, Kastrati A, Schulz S, Pache J, Hausleiter J, Ibrahim T, Fusaro M, Ott I, Schomig A, Laugwitz KL, Mehilli J. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation* 2011;124:624-632.

16. Meredith IT, Worthley SG, Whitbourn R, Walters D, McClean D, Ormiston J, Horrigan M, Wilkins GT, Hendriks R, Matsis P, Muller D, Cutlip DE. Long-term clinical outcomes with the next-generation Resolute Stent System: a report of the two-year follow-up from the RESOLUTE clinical trial. EuroIntervention 2010;5:692-697.
17. von Birgelen C, Basalus WMZ, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JW, Linssen GCM, Saïd SAM, Kleijne MAWJ, Sen H, Löwik MM, van der Palen J, Verhorst PMJ, de Man FHAF. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: The TWENTE Trial. *J Am Coll Cardiol* 2012;59:1350-61.
18. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;363:136-46.
19. Windecker S, Serruys PW, Wandel S, Buszman P,Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;372:1163-1173.
20. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 2010;375:201-209.
21. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. *Lancet* 2011;377:1241-1247.
22. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-2351.
23. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention* 2010;5:871-874.
24. Hordijk-Trion M, Lenzen M, Wijns W, de Jaegere P, Simoons ML, Scholte op Reimer WJM, Bertrand ME, Mercado N, Boersma E. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. *Eur Heart J* 2006;27:671-678.
25. de Boer SPM, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011;32:2161-2167.

CHAPTER 12

WOMEN TREATED WITH SECOND-GENERATION ZOTAROLIMUS-ELUTING RESOLUTE STENTS AND EVEROLIMUS-ELUTING XIENCE V STENTS: INSIGHTS FROM THE GENDER-STRATIFIED, RANDOMIZED, CONTROLLED TWENTE TRIAL

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ABSTRACT

Background: Women are underrepresented in clinical research, and few data are available from randomized head-to-head comparisons of second-generation drug-eluting stents (DES) in female patients. Aim of this study was to assess safety and efficacy of two second-generation DES in women. In TWENTE—a prospective, randomized, comparative DES trial—"real-world" patients were stratified for gender before randomization for Resolute or Xience V stents.

Methods: Target vessel failure (TVF; cardiac death, target vessel-related myocardial infarction, and clinically indicated target vessel revascularization) after 1 year was the predefined endpoint.

Results: Among 1,391 patients, 382 (27.5%) women were randomized to Resolute (n = 192) and Xience V (n = 190). Baseline and procedural characteristics were similar for females in both study arms, except for smaller vessel and stent diameters in Resolute-treated lesions. After 1 year, TVF (8.9 vs. 8.4%; adjusted odds ratio [OR]: 0.95, 95% confidence interval [CI]: 0.41–2.20, P = 0.91) and a patient-oriented composite endpoint (13.0 vs. 12.1%, P = 0.79) did not differ significantly between women in both arms. Women were older than men (P < 0.01) and had more often diabetes mellitus (26.4 vs. 19.8%, P = 0.01) and hypertension (63.6 vs. 52.5%, P < 0.01), but there was no significant gender difference in TVF (adjusted OR: 1.18, 95% CI: 0.73–1.92, P = 0.50).

Conclusions: This gender-stratified TWENTE trial analysis resulted in no significant difference in safety and efficacy outcomes between Resolute- and Xience V-treated females.

INTRODUCTION

In many countries with a Western lifestyle, cardiovascular disease is a leading cause of death for both genders. However, women are often underrepresented in cardiovascular research [1-3]. Less than one-third of all cardiovascular clinical trials report sex-specific results, and most trials include fewer women [4, 5]. Percutaneous coronary intervention (PCI) trials previously demonstrated an improvement in clinical outcome in women with first-generation drug-eluting stents (DES) as compared to bare metal stents [6-8]. Second-generation DES were developed, such as the Resolute zotarolimus-eluting stent and the Xience V everolimus-eluting stent, which aimed at enhanced biocompatibility and an improved clinical outcome [9-12]. To date, gender-specific data have only been published for Xience V, which showed prolonged clinical benefit compared to Taxus [13, 14].

This study reports gender-specific data of Resolute and Xience V from the randomized TWENTE trial, which recently compared these DES in 1,391 "real-world" PCI patients and applied a gender stratification prior to randomization [12, 15]. The aim of this analysis of the TWENTE trial was to assess potential differences in procedural and clinical outcome between women treated with Resolute versus Xience V stents. In addition, we assessed between-gender differences in outcome within this population of contemporary practice PCI patients treated with second-generation DES.

METHODS

Study design and patient population. The TWENTE trial (ClinicalTrials.gov NCT01066650) has been previously described in detail [12]. In brief, TWENTE was an investigator-initiated, patient-blinded, randomized noninferiority study with limited exclusion criteria in a "real-world" study population with a majority of complex lesions and "off-label" indications for DES. The study was performed between June 2008 and August 2010 at Thoraxcentrum Twente, Enschede, The Netherlands. Patients capable of providing informed consent with an indication for PCI with DES were randomized for treatment with Resolute (Medtronic, Santa Rosa, CA) or Xience V stents (Abbott Vascular, Santa Clara, CA) in a ratio of 1:1 after stratification for gender. There was no limit for lesion length, reference vessel size, and number of target lesions or vessels. The most important exclusion criterion was a recent stent thrombosis (ST)-elevation myocardial infarction (STEMI) [12]. The TWENTE trial was approved by the institutional ethics committee and complied with the Declaration of Helsinki.

Intervention, medication, and in-hospital course. Lesion predilatation, direct stenting, stent postdilatation, and/or use of glycoprotein IIb/IIIa antagonists were permitted at the operators' discretion. Operators were encouraged to make liberal use of postdilatation. All patients were pretreated with acetylsalicylic acid and clopidogrel. At discharge, the combination of 100 mg of acetylsalicylic acid once daily indefinitely and clopidogrel 75 mg once daily for 1 year was prescribed. Cardiac biomarkers and electrocardiograms were systematically assessed in all patients before and after PCI to identify periprocedural myocardial infarction [12].

Definitions of clinical endpoints. Definitions of all clinical endpoints have been described previously in detail [12]. In brief, the prespecified primary clinical endpoint was the incidence of target vessel failure (TVF) within 1 year, a composite endpoint that was defined as cardiac death, target-vessel-related myocardial infarction (or not attributable to a nontarget vessel), or clinically driven target-vessel revascularization.

Prespecified secondary endpoints included the individual components of the primary endpoint as well as target lesion failure, defined as composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-lesion revascularization; Major Adverse Cardiac Events (MACE), a composite of all-cause death, any myocardial infarction, emergent coronary-artery bypass surgery or clinically indicated target-lesion revascularization; and a patient-oriented composite endpoint, consisting of all-cause mortality, any myocardial infarction, and any repeat revascularization. All clinical endpoints were defined according to the Academic Research Consortium [16, 17].

Acquisition and Analysis of Clinical Data. Clinical follow-up data were obtained at visits at outpatient clinics, or, if not feasible, by telephone follow-up and/or medical questionnaire. For any potential event trigger, members of the study team gathered all clinical information from the referring cardiologist, general practitioner, and/or hospital involved (100% follow-up data available). Processing of clinical data and adjudication of all adverse clinical events were performed by an independent external contract research organization (Cardialysis, Rotterdam, The Netherlands). Analyses were performed based on the principle of intention-to-treat.

Statistical Analysis. Statistical analyses were performed with SPSS vers.15.0 (SPSS, Chicago, IL). Categorical variables were assessed with use of $\chi 2$ or Fisher's exact tests, as appropriate, whereas continuous variables were assessed with the Wilcoxon rank-sum test or Student's t-test, as appropriate. The primary endpoint TVF was assessed in both genders by $\chi 2$, and also differences between treatment groups with 95% CIs are reported. The time to the primary endpoint and to the components thereof was assessed according to the method of Kaplan–Meier, and the log-rank test was applied to compare the two groups. Logistic regression was performed to test for interaction between gender and stent type with regard

to TVF. In addition, multivariate logistic regression analyses were performed to adjust for baseline variables showing differences ($P \leq 0.15$) between the comparators in each stratum (between Resolute and Xience V in women stratum, or between Resolute and Xience V in men stratum, or between women and men stratum), that is age, diabetes, renal failure, smoking status, hypertension, peripheral artery disease, previous coronary bypass surgery, acute coronary syndrome, bifurcation treatment, in-stent restenosis lesion, small vessels, long lesions, use of glycoprotein IIb/IIIa antagonist, off-label indication, left main lesion, lesion in right coronary artery or right circumflex, graft lesions, chronic total occlusion, aorta-ostial lesion, severe calcified lesion, the presence of thrombus, preprocedural reference vessel diameter, baseline stenosis, direct stenting, maximal stent diameter, postdilatation, number of stents placed, and total stent length. Unless otherwise specified, P-values and confidence intervals were two-sided. A P-value ≤0.05 was considered significant.

RESULTS

Gender Populations. Among the 1,391 patients enrolled in the TWENTE trial, there were 382 women (27.5%) of whom 192 were treated with Resolute and 190 with Xience V. The trial also comprised 1,009 men (72.5%) of whom 505 were treated with Resolute and 504 with Xience V. All women and all but four men completed the study (there were four withdrawals of consent).

Women Treated With Resolute Versus Xience V. Demographics, angiographic details, and procedural characteristics were similar for women treated with Resolute versus Xience V. However, in the Resolute arm there was more small vessel disease ($P = 0.04$) with smaller lumen dimensions in the target lesion and the reference segment ($P = 0.02$ for both), resulting in a smaller maximum stent diameter ($P = 0.04$; Tables 1-3). There was no significant difference in clinical outcome at 1-year follow-up between women treated with Resolute versus Xience V. The primary outcome measure TVF (8.9 vs. 8.4%, $P = 0.88$) (log-rank test, $P = 0.87$, Fig. 1) and the patient-oriented composite endpoint were similar between groups (13.0 vs. 12.1%, $P = 0.79$). There was a nonsignificant trend for less definite-or-probable stent thrombosis in women treated with Resolute versus Xience V (0 vs. 2.1%, $P = 0.06$), whereas there was no definite stent thrombosis in women.

Men Treated With Resolute Versus Xience V. Male patients treated with Resolute were slightly younger ($P = 0.05$) and had longer target lesions ($P = 0.02$; Table 1) than males treated with Xience V. No significant difference in angiographic or procedural characteristics was observed between both arms (Tables 2 and 3). Clinical outcome measures at 1-year follow-up were similar for males in both treatment arms (Table 4). The primary outcome measure TVF occurred in 8.0% of the males in both treatment arms ($P = 0.99$) (log-rank test, $P = 0.99$, Fig. 2). Definite stent thrombosis occurred in none of the male patients treated with Xience V and in four males treated with Resolute stents ($P = 0.12$).

Table 1: Baseline characteristics of patients

	Total population (N = 1391)			Women (N = 382)			Men (N = 1009)		
	Women (N = 382)	Men (N = 1009)	p Value	Resolute (N = 192)	Xience V (N = 190)	p Value	Resolute (N = 505)	Xience V (N = 504)	p Value
Age (yrs)	67.6 (10.3)	62.9 (10.7)	<0.01	68.3 (9.9)	66.8 (10.6)	0.18	62.2 (10.8)	63.6 (10.6)	0.05
Body mass index (kg/m²)	27.8 (4.8)	27.7 (3.6)	0.72	27.5 (4.5)	28.1 (5.1)	0.30	27.7 (3.7)	27.7 (3.5)	0.91
Diabetes mellitus (any)	101 (26.4)	200 (19.8)	0.01	56 (29.2)	45 (23.7)	0.22	102 (20.2)	98 (19.4)	0.76
Diabetes mellitus requiring insulin	41 (10.7)	74 (7.3)	0.04	25 (13.0)	16 (8.4)	0.15	34 (6.7)	40 (7.9)	0.46
Chronic renal failure *	6 (1.6)	32 (3.2)	0.10	1 (0.5)	5 (2.6)	0.12	18 (3.6)	14 (2.8)	0.48
Arterial hypertension	243 (63.6)	530 (52.5)	<0.01	120 (62.5)	123 (64.7)	0.65	266 (52.7)	264 (52.4)	0.93
Hypercholesterol aemia	223/373 (59.8)	580/984 (58.9)	0.78	109/192 (56.8)	114/181 (63.0)	0.22	283/496 (57.1)	297/488 (60.9)	0.23
Current smoker	83 (21.7)	257 (25.5)	0.15	42 (21.9)	41 (21.6)	0.94	134 (26.5)	123 (24.4)	0.44
Family history of CAD	211 (59.6)	529 (55.4)	0.17	102 (53.1)	109 (57.4)	0.40	268 (53.1)	261 (51.8)	0.68
Peripheral artery disease	19/984 (5.1)	85/369 (8.6)	0.03	8/187 (4.3)	11/182 (6.0)	0.44	43/496 (8.7)	42/488 (8.6)	0.97
Myocardinfarction (any)	105 (27.5)	345 (34.2)	0.17	50 (26.0)	55 (28.9)	0.53	163 (32.3)	182 (36.1)	0.20
Previous PCI	72 (18.8)	216 (21.4)	0.29	36 (18.8)	36 (18.9)	0.96	103 (20.4)	113 (22.4)	0.43
Previous CABG	29 (7.6)	119 (11.8)	0.02	11 (5.7)	18 (9.5)	0.17	57 (11.3)	62 (12.3)	0.62
Clinical Indication			0.08			0.88			0.52
Stable angina pectoris	178 (46.6)	496 (49.2)		88 (45.8)	90 (47.4)		247 (48.9)	249 (49.4)	
Unstable angina	105 (27.5)	325 (23.4)		55 (28.6)	50 (26.3)		117 (23.2)	103 (20.4)	
Non-ST-elevation MI	99 (25.9)	293 (29.0)		49 (25.5)	50 (26.3)		141 (27.9)	152 (30.2)	
Clinical indication: Acute coronary syndrome	204 (53.4)	178 (50.8)	0.39	104 (54.2)	100 (52.6)	0.76	258 (51.1)	255 (50.6)	0.88
Left ventricular ejection fraction < 30% †	10 (3.3)	22 (2.9)	0.75	4 (2.6)	6 (4.1)	0.47	15/374 (4.0)	7/375 (1.9)	0.08
Multivessel treatment	84 (22.0)	252 (25.0)	0.25	47 (24.5)	37 (19.5)	0.24	127 (25.1)	125 (24.8)	0.90

Total no lesions treated per patient			0.33			0.57			0.60
One lesion treated	243 (63.6)	614 (60.9)		122 (63.5)	121 (63.7)		300 (59.4)	314 (62.3)	
Two lesions treated	97 (25.4)	296 (29.3)		46 (24.0)	51 (29.3)		152 (30.1)	144 (28.6)	
Three of more lesions treated	42 (11.0)	99 (9.8)		24 (12.5)	18 (9.5)		53 (10.5)	46 (9.1)	
De novo coronary lesions only ‡	352 (92.1)	935 (92.7)	0.74	179 (93.2)	173 (91.1)	0.43	465 (92.1)	470 (93.3)	0.47
At least one CTO	32 (8.4)	63 (6.2)	0.16	17 (8.9)	15 (7.9)	0.74	34 (6.7)	29 (5.8)	0.52
At least one bifurcation	89 (23.3)	273 (27.1)	0.15	44 (22.9)	45 (23.7)	0.86	135 (26.7)	138 (27.4)	0.82
At least one bifurcation with side-branch treatment	42 (11.0)	171 (16.9)	0.01	18 (9.4)	24 (12.6)	0.31	80 (15.8)	91 (18.1)	0.35
At least one in-stent restenosis	26 (6.8)	43 (4.3)	0.05	11 (5.7)	15 (7.9)	0.40	25 (5.0)	18 (3.6)	0.28
At least one small-vessel (RVD <2.75mm)	250 (65.4)	624 (61.8)	0.22	135 (70.3)	115 (60.5)	0.04	310 (61.4)	314 (62.3)	0.77
At least one lesion length > 27mm	75 (19.6)	218 (21.6)	0.42	31 (16.1)	44 (23.2)	0.09	125 (24.8)	93 (18.5)	0.02
Glycoprotein IIb/IIIa antagonist	44 (11.5)	149 (14.8)	0.12	18 (9.4)	26 (13.7)	0.19	72 (14.3)	77 (15.3)	0.65
At least one off label indication §	289 (75.7)	788 (78.1)	0.33	141 (73.4)	148 (77.9)	0.31	406 (80.4)	382 (75.8)	0.08

Data are number (%) or mean (SD).

* chronic renal failure defined by serum creatinine level ≥ 130 µmol/L

† left ventricular ejection fraction assessed with ultrasound, MRI or left ventricular angiography

‡ including chronic total occlusion, but not grafts and in-stent restenosis

§ off label stent use includes renal insufficiency, an ejection fraction of less than 30%, the occurrence of acute myocardial infarction within the previous 72 hours, more than one lesion per vessel, at least two vessels with stents, a lesion measuring more than 27 mm, bifurcation, bypass grafts, in-stent restenosis, unprotected left main artery, lesions with thrombus, or total occlusion

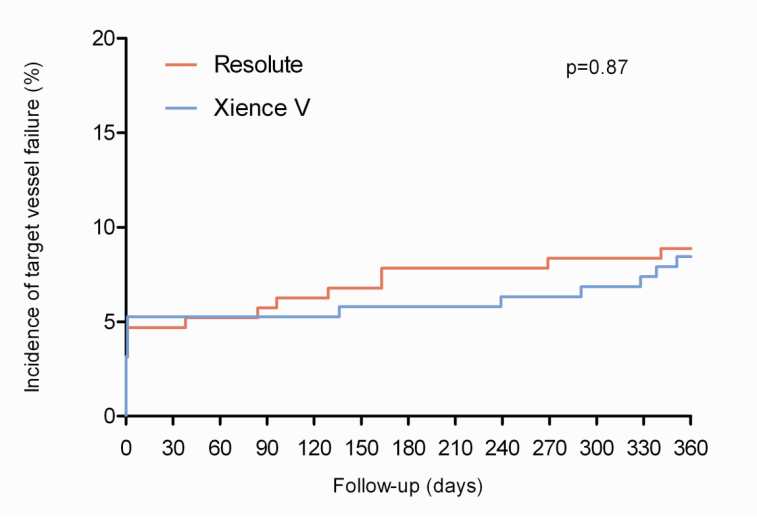
CABG = coronary artery bypass grafting. CAD = coronary artery disease. CTO = chronic total occlusion. MI = myocardial infarction. PCI = percutaneous coronary intervention. RVD = reference vessel diameter.

Table 2: Baseline lesion characteristics

	Total lesions (N = 2116)			Women (N = 578)			Men (N = 1568)		
	Female (N = 578)	Male (N = 1538)	p Value	Resolute (N = 295)	Xience V (N = 283)	p Value	Resolute (N = 785)	Xience V (N = 783)	p Value
Target lesion coronary artery									
Left main	12 (2.1)	42 (2.7)	0.40	9 (3.1)	3 (1.1)	0.09	17 (2.2)	25 (3.3)	0.17
Left anterior descendens	228 (39.4)	650 (42.3)	0.24	112 (38.0)	116 (41.0)	0.46	329 (41.9)	321 (42.6)	0.78
Left circumflex	124 (21.5)	359 (23.3)	0.36	72 (24.4)	52 (18.4)	0.08	171 (21.8)	188 (25.0)	0.14
Right coronary artery	208 (36.0)	445 (28.9)	<0.01	99 (33.6)	109 (38.5)	0.22	250 (31.8)	195 (25.9)	0.01
Bypass graft	6 (1.0)	42 (2.7)	0.02	3 (1.0)	3 (1.1)	0.96	18 (2.3)	24 (3.2)	0.28
ACC-AHA lesion class			0.77			0.98			0.72
A	40 (6.9)	114 (7.4)		21 (7.1)	19 (6.7)		56 (7.1)	58 (7.7)	
B1	129 (22.3)	349 (22.7)		67 (22.7)	62 (21.9)		174 (22.2)	175 (23.2)	
B2	195 (33.7)	483 (31.4)		100 (33.9)	95 (33.6)		242 (30.8)	241 (32.0)	
C	214 (37.0)	592 (38.5)		107 (36.3)	107 (37.8)		313 (39.9)	279 (37.1)	
De novo lesions*	545 (94.3)	1454 (94.5)	0.82	280 (94.9)	265 (93.6)	0.51	744 (94.8)	710 (94.3)	0.67
Chronic total occlusion	34 (5.9)	66 (4.3)	0.12	18 (6.1)	16 (5.7)	0.82	35 (4.5)	31 (4.1)	0.74
In stent restenosis	29 (5.0)	46 (3.0)	0.03	13 (4.4)	16 (5.7)	0.49	25 (3.2)	21 (2.8)	0.65
Aorta ostial lesion	60 (10.4)	94 (6.1)	<0.01	24 (8.1)	36 (12.7)	0.07	52 (6.6)	42 (5.6)	0.39
Severe calcification	112 (19.4)	252 (16.4)	0.10	64 (21.7)	48 (17.0)	0.15	128 (16.3)	124 (16.5)	0.93
Bifurcated lesion	117 (20.2)	401 (26.1)	<0.01	57 (19.3)	60 (21.2)	0.57	201 (25.6)	200 (26.6)	0.67
Thrombus present†	14 (2.4)	57 (3.7)	0.14	9 (3.1)	5 (1.8)	0.32	24 (3.1)	33 (4.4)	0.17
Total occlusion	59 (10.2)	144 (9.1)	0.56	32 (10.8)	27 (9.5)	0.60	77 (9.8)	67 (8.9)	0.54

Preprocedural TIMI flow (grade)			0.42		0.71		0.89
0	35 (6.1)	85 (5.5)	19 (6.4)	16 (5.7)	44 (5.6)	41 (5.4)	
1	24 (4.2)	59 (3.8)	13 (4.4)	11 (3.9)	33 (4.2)	26 (3.5)	
2	30 (5.2)	110 (7.2)	18 (6.1)	12 (4.2)	55 (7.0)	55 (7.3)	
3	489 (84.6)	1284 (83.5)	245 (83.1)	244 (86.2)	653 (83.2)	631 (83.8)	

Data are number (%).
* including chronic total occlusion, but not grafts and in-stent restenosis
† thrombus triggering use of thrombus aspiration catheters
ACC = American College of Cardiology. AHA = American Heart Association.
TIMI = thrombolysis in myocardial infarction.



Days	0	90	180	270	360
Number at risk					
Resolute	192	180	176	175	173
Xience V	190	180	178	177	173

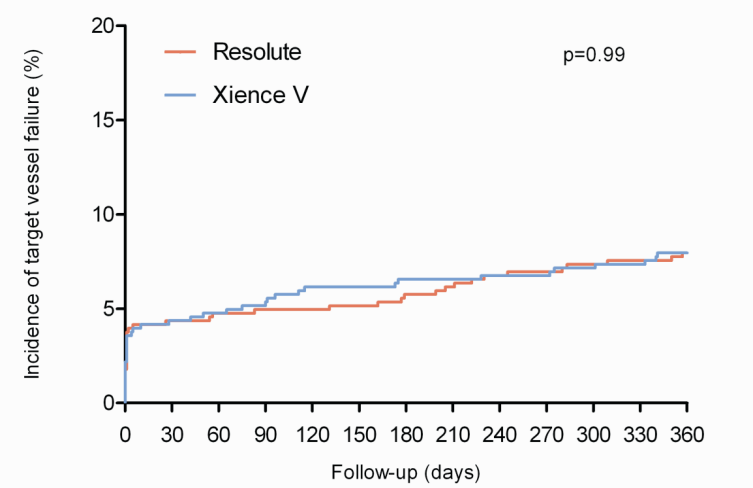
Figure 1. Cumulative incidence of target vessel failure in women.
Target vessel failure was a composite of cardiovascular death, target vessel myocardial infarction or target vessel revascularization. P value is calculated by logrank test.

Table 3: Quantitative coronary angiography and procedural results

	Total lesions (N = 2116)			Women (N = 578)			Men (N = 1568)		
	Female (N = 578)	Male (N = 1538)	p Value	Zotarolimus-Eluting Resolute stent (N = 295)	Everolimus-Eluting Xience V stent (N = 283)	p Value	Zotarolimus-Eluting Resolute stent (N = 785)	Everolimus-Eluting Xience V stent (N = 783)	p Value
Lesion length (mm)	14.61 (10.05-21.86)	14.31 (9.61-22.15)	0.70	14.94 (10.04-21.67)	14.39 (10.05-22.19)	0.63	14.40 (9.81-22.80)	14.26 (9.43-21.63)	0.16
Diameter of reference vessel (mm)	2.60 (2.23-2.99)	2.68 (2.31-3.09)	0.01	2.58 (2.17-2.95)	2.64 (2.26-3.05)	0.02	2.69 (2.36-3.09)	2.66 (2.28-3.09)	0.33
Baseline minimum lumen diameter (mm)	0.99 (0.75-1.33)	0.98 (0.72-1.27)	0.25	0.95 (0.70-1.29)	1.05 (0.78-1.37)	0.02	0.97 (0.72-1.28)	0.99 (0.71-1.27)	0.70
Baseline stenosis (lumen diameter, %)	60.66 (51.60-70.26)	62.36 (53.13-71.49)	0.13	61.5 (52.1-70.66)	60.23 (50.84-69.3)	0.14	63.15 (53.08-71.54)	61.76 (53.36-71.49)	0.77
Post procedure stenosis (lumen diameter, %)	12.13 (8.97-15.34)	11.72 (9.07-15.33)	0.78	12.08 (8.97-15.26)	12.17 (8.94-15.39)	0.84	11.52 (8.90-14.81)	11.95 (9.26-15.74)	0.05
Postprocedure minimum lumen diameter (mm)	2.23 (1.83-2.64)	2.25 (1.92-2.68)	0.05	2.21 (1.80-2.61)	2.27 (1.88-2.66)	0.18	2.30 (1.94-2.70)	2.25 (1.88-2.65)	0.06
Acute gain in segment (mm)	1.22 (0.85-1.59)	1.27 (0.88-1.72)	0.03	1.21 (0.85-1.65)	1.22 (0.85-1.55)	0.60	1.27 (0.91-1.72)	1.27 (0.82-1.69)	0.26
Number of stents implanted (mean, SD)									
Per patient	2.04 (1.24)	2.08 (1.16)	0.78	1.99 (1.23)	2.08 (1.25)	0.46	2.04 (1.18)	1.99 (1.15)	0.53
Per lesion	1.35 (0.67)	1.32 (0.60)	0.45	1.29 (0.59)	1.40 (0.74)	0.06	1.31 (0.59)	1.33 (0.61)	0.46
Total stent length (mm) (mean, SD)									
Per patient	40.78 (27.36)	41.04 (26.68)	0.55	39.98 (26.82)	41.58 (27.95)	0.57	42.54 (27.96)	39.52 (25.26)	0.07
Per lesion	27.0 (16.5)	26.9 (15.4)	0.97	26.0 (15.1)	27.9 (17.8)	0.82	27.4 (15.5)	26.5 (15.3)	0.24
Direct stenting	206 (35.6)	618 (40.2)	0.06	101 (34.2)	105 (37.1)	0.47	315 (40.1)	303 (40.2)	0.96
Post dilatation	483 (83.6)	1244 (80.9)	0.16	239 (81.0)	244 (86.2)	0.09	637 (81.1)	607 (80.6)	0.79

Maximal stent diameter per lesion (mm) (mean, SD)	2.94 (0.46)	2.99 (0.46)	0.04	2.90 (0.45)	2.98 (0.47)	0.04	2.99 (0.45)	2.98 (0.47)	0.82
Implantation of study stent only	573 (99.1)	1521 (98.9)	0.63	294 (99.7)	279 (98.6)	0.21	774 (98.6)	747 (99.2)	0.26
Device success *	566 (97.9)	1508 (98.0)	0.85	292 (99.0)	274 (96.8)	0.07	771 (98.2)	737 (97.9)	0.63
Lesion success †	577 (99.8)	1535 (99.8)	0.92	295 (100)	282 (99.6)	0.49	783 (99.7)	752 (99.9)	0.59
Procedure success ‡	362/382 (94.8)	970/1009 (96.1)	0.26	183/192 (95.3)	179/190 (94.2)	0.63	484/505 (95.8)	486/504 (96.4)	0.63

Data are median (IQR) or number (%), unless otherwise stated.
* = Device success is defined as the attainment at the target site of a final residual diameter stenosis of < 50% using only the assigned study device
† = Lesion success is defined as the attainment at the target site of a final residual diameter stenosis of <50% using any percutaneous method
‡ = Procedure success is defined as the attainment at the target site of a final residual diameter stenosis of <50%, together with the absence of any in-hospital major adverse cardiac events



Days	0	90	180	270	360
Number at risk					
Resolute	505	478	471	465	458
Xience V	504	477	468	466	459

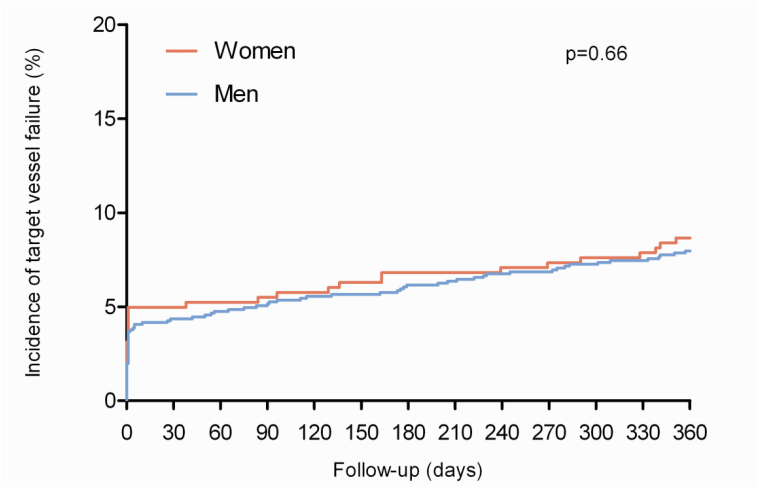
Figure 2. Cumulative incidence of target vessel failure in men.
Target vessel failure was a composite of cardiovascular death, target vessel myocardial infarction or target vessel revascularization. P value is calculated by logrank test.

Table 4: One-year clinical outcomes

	Total population (N = 1387)				Women (N= 382)				Men (N= 1005)			
	Women (N= 382)	Men (N= 1005)	Difference (95% CI)	p value	Zotarolimus-Eluting Resolute stent (N = 192)	Everolimus-Eluting Xience V stent (N = 190)	Difference (95% CI)	p value	Zotarolimus-Eluting Resolute stent (N = 503)	Everolimus-Eluting Xience V stent (N = 502)	Difference (95% CI)	p value
Target vessel failure	33 (8.6)	80 (8.0)	0.7 (-2.5 to 3.9)	0.68	17 (8.9)	16 (8.4)	0.4 (-5.2 to 6.1)	0.88	40 (8.0)	40 (8.0)	0.0 (-3.3 to 3.3)	0.99
Death												
Any cause	12 (3.1)	17 (1.7)	1.4 (-0.2 to 3.1)	0.09	6 (3.1)	6 (3.2)	0.0 (-3.6 to 3.5)	0.99	9 (1.8)	8 (1.6)	0.2 (-1.4 to 1.8)	0.81
Cardiac cause	8 (2.1)	9 (0.9)	1.2 (-0.1 to 2.5)	0.09	3 (1.6)	5 (2.6)	-1.1 (-4.0 to 1.8)	0.50	4 (0.8)	5 (1.0)	-0.2 (-1.4 to 1.0)	0.75
Target vessel related MI												
Any	20 (5.2)	44 (4.4)	0.9 (-1.6 to 3.3)	0.50	9 (4.7)	11 (5.8)	-1.1 (-5.6 to 3.4)	0.63	23 (4.6)	21 (4.2)	0.4 (-2.1 to 2.9)	0.76
Q-wave	3 (0.8)	8 (0.8)	0.0 (-1.1 to 1.0)	1.00	0 (0.0)	3 (1.6)	-1.5 (-3.4 to 0.2)	0.12	5 (1.0)	3 (0.6)	0.4 (-0.7 to 1.5)	0.48
Non-Q-wave	17 (4.5)	36 (3.6)	0.9 (-1.4 to 3.1)	0.45	9 (4.7)	8 (4.2)	0.5 (-3.7 to 4.6)	0.82	18 (3.6)	18 (3.6)	0.0 (-2.3 to 2.3)	1.00
Periprocedural MI	19 (5.0)	38 (3.8)	1.2 (-1.1 to 3.5)	0.32	9 (4.7)	10 (5.3)	-0.6 (-5.0 to 3.8)	0.80	20 (4.0)	18 (3.6)	0.4 (-2.0 to 2.8)	0.75
Clinically indicated TVR												
Any	10 (2.6)	32 (3.2)	- 0.6 (-2.6 to 1.4)	0.58	6 (3.1)	4 (2.1)	1.0 (-2.2 to 4.2)	0.75	17 (3.4)	15 (3.0)	0.4 (-1.8 to 2.6)	0.72
Percutaneous	7 (1.8)	26 (2.6)	-0.8 (1.0 to -2.6)	0.41	5 (2.6)	2 (1.1)	1.5 (-1.2 to 4.3)	0.45	14 (2.8)	12 (2.4)	0.4 (-1.6 to 2.4)	0.70
Surgical	3 (0.8)	6 (0.6)	0.2 (-0.8 to 1.1)	0.70	1 (0.5)	2 (1.1)	-0.5 (-2.3 to 1.2)	0.62	3 (0.6)	3 (0.6)	0.0 (-1.0 to 1.0)	1.00
Target lesion failure	31 (8.1)	71 (7.1)	1.1 (-2.0 to 4.1)	0.50	17 (8.9)	14 (7.4)	1.5 (-4.0 to 7.0)	0.60	38 (7.6)	33 (6.6)	1.0 (-2.2 to 4.2)	0.54
Clinically indicated TLR												
Any	7 (1.8)	22 (2.2)	-0.4 (-2.0 to 1.3)	0.68	5 (2.6)	2 (1.1)	1.6 (-1.2 to 4.3)	0.45	14 (2.8)	8 (1.6)	1.2 (-0.6 to 3.0)	0.20
Percutaneous	5 (1.3)	17 (1.7)	-0.4 (-1.9 to 1.1)	0.61	4 (2.1)	1 (0.5)	1.6 (-0.7 to 3.8)	0.37	11 (2.2)	6 (1.2)	1.0 (-0.6 to 2.6)	0.22
Surgical	2 (0.5)	5 (0.5)	0.0 (-0.8 to 0.9)	1.00	1 (0.5)	1 (0.5)	0.0 (-1.5 to 1.5)	1.00	3 (0.6)	2 (0.4)	0.2 (-0.7 to 1.1)	1.00
Death from cardiac causes or target-vessel MI	22 (5.8)	45 (4.5)	1.3 (-1.2 to 3.8)	0.32	12 (6.3)	10 (5.3)	1.0 (-3.7 to 5.7)	0.68	22 (4.4)	23 (4.6)	-0.2 (-2.8 to 2.4)	0.87
Major adverse cardiac events	39 (10.2)	93 (9.3)	1.0 (-2.5 to 4.4)	0.59	21 (10.9)	18 (9.5)	1.5 (-4.6 to 7.6)	0.64	49 (9.7)	44 (8.8)	1.0 (-2.6 to 4.6)	0.59
Patient-oriented composite end-point	48 (12.6)	103 (10.2)	2.3 (-1.4 to 6.0)	0.22	25 (13.0)	23 (12.1)	0.9 (-5.8 to 7.6)	0.79	53 (10.5)	50 (10.0)	0.6 (-3.2 to 4.3)	0.76

Definite ST (0-360 days)												
all patients	0 (0)	4 (0.4)	-0.4 (-1.0 to 0.2)	0.58	0 (0)	0 (0)	-	-	4 (0.8)	0 (0)	0.8 (-0.0 to 1.6)	0.12
acute (0-1 day)	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-
subacute (2-30 days)	0 (0)	1 (0.1)	-0.1 (-0.4 to 0.2)	1.00	0 (0)	0 (0)	-	-	1 (0.2)	0 (0)	0.2 (-0.2 to 0.6)	1.00
late (31-360 days)	0 (0)	3 (0.3)	-0.3 (-0.8 to 0.2)	0.56	0 (0)	0 (0)	-	-	3 (0.6)	0 (0)	0.6 (-0.0 to 1.2)	0.25
Probable ST (0-360 days)												
all patients	4 (1.0)	6 (0.6)	0.5 (-0.5 to 1.4)	0.48	0 (0)	4 (2.1)	-2.1 (-4.1 to 0.0)	0.06	2 (0.4)	4 (0.8)	-0.4 (-1.4 to 0.6)	0.45
acute (0-1 day)	1 (0.3)	3 (0.3)	0.0 (-0.7 to 0.6)	1.00	0 (0)	1 (0.5)	-0.5 (-1.6 to 0.5)	0.50	1 (0.2)	2 (0.4)	-0.2 (-0.9 to 0.5)	0.62
subacute (2-30 days)	2 (0.5)	2 (0.2)	0.3 (-0.3 to 1.0)	0.31	0 (0)	2 (1.1)	-1.0 (-2.5 to 0.4)	0.25	0 (0)	2 (0.4)	-0.4 (-1.0 to 0.2)	0.25
late (31-360 days)	1 (0.3)	1 (0.1)	0.2 (-0.3 to 0.6)	0.48	0 (0)	1 (0.5)	-0.5 (-1.6 to 0.5)	0.50	1 (0.2)	0 (0)	0.2 (-0.2 to 0.6)	1.00
ST (0-360 days)												
Possible	2 (0.5)	4 (0.4)	0.1 (-0.6 to 0.9)	0.67	1 (0.5)	1 (0.5)	0.0 (-1.5 to 1.5)	1.00	3 (0.6)	1 (0.2)	0.4 (-0.4 to 1.2)	0.62
Definite or probable	4 (1.0)	10 (1.0)	0.0 (-1.1 to 1.2)	1.00	0 (0)	4 (2.1)	-2.1 (-4.1 to 0.0)	0.06	6 (1.2)	4 (0.8)	0.4 (-0.8 to 1.6)	0.75
Definite, probable or possible	6 (1.6)	14 (1.4)	0.2 (-1.2 to 1.6)	0.80	1 (0.5)	5 (2.6)	-2.1 (-4.6 to 0.4)	0.12	9 (1.8)	5 (1.0)	0.8 (-0.7 to 2.2)	0.28

Data are number of patients (%).
MI = myocardial infarction. ST = stent thrombosis. TLR = target lesion revascularization. TVR = target vessel revascularization. Major adverse cardiac events is a composite of all-cause death, any myocardial infarction, emergent coronary-artery bypass surgery or clinically indicated target lesion revascularization. Patient-oriented composite endpoint is a composite of endpoint of all-cause death, any myocardial infarction or any revascularization. P values are calculated by chi-square test.



Days	0	90	180	270	360
Number at risk					
Men	1009	955	939	931	917
Women	382	360	354	352	346

Figure 3. Cumulative incidence of target vessel failure stratified for gender. Target vessel failure was a composite of cardiovascular death, target vessel myocardial infarction or target vessel revascularization. P value is calculated by logrank test.

Women Versus Men. Women were almost 5 years older than men (P < 0.01) and had a higher prevalence of diabetes mellitus (26.4 vs. 19.8%, P = 0.01) and hypertension (63.6 vs. 52.5%, P < 0.01). In addition, women had less often a history of previous coronary bypass surgery (7.6 vs. 11.8%, P = 0.02), suffered less often from peripheral artery disease (5.1 vs. 8.6%, P = 0.03), and their target lesions involved less often bifurcations with side-branch treatment (11.0 vs. 16.9%, P < 0.01). Aorta-ostial lesions (10.4 vs. 6.1%, P < 0.01) and right coronary lesions (36.0 vs. 28.9%, P < 0.01) were more common in women than in men, whereas bypass lesions were less common (1.0 vs. 2.7%, P = 0.02, Table 2). Women had somewhat smaller target vessels, resulting in smaller lumen dimensions after PCI (P = 0.04) and less acute gain (P = 0.03, Table 3). The primary outcome measure TVF was similar for women and men (8.6 vs. 8.0%, P = 0.68) (log-rank test, P = 0.66, Fig. 3). Various other clinical outcome parameters showed no significant difference between women and men, but in women there was a trend toward a higher cardiac (2.1 vs. 0.9%, P = 0.09) and all-cause mortality at 1-year follow-up (3.1 vs. 1.7%, P = 0.09) (Table 4). Definite stent thrombosis only occurred in four male patients.

After adjustment for differences in baseline variables, stent type was not a significant predictor of TVF in both women (adjusted OR: 0.95, 95% CI: 0.41–2.20, P = 0.91), and men

(adjusted OR: 0.92, 95% CI: 0.58–1.46, P = 0.72), comparing Resolute versus Xience V. When analyzing all patients in a multivariate model, female gender was not associated with TVF (adjusted OR: 1.18, 95% CI: 0.73–1.92, P = 0.50) or other clinical outcome measures. In addition, logistic regression analysis showed no significant interaction between stent type and gender with regard to TVF (P = 0.90) or other clinical endpoints.

DISCUSSION

There has recently been a call for more gender-specific analyses in clinical trials, which should improve our knowledge about potential gender differences and may ultimately improve cardiovascular health of the female patients [1]. The study design of the randomized TWENTE trial recognized the value of gender-specific data by employing a gender stratification step prior to randomization for type of DES [15]. Gender stratification ensured a randomization between DES types that was balanced within both women and men. This prespecified gender analysis of the TWENTE trial data demonstrated that there was no significant difference in clinical safety and efficacy between female patients treated with Resolute or Xience V stents.

Female populations of previous DES studies. In the present gender analysis, both Resolute and Xience V showed high procedural success and relatively low clinical event rates in women, despite a relatively high patient and lesion complexity in TWENTE.

The female population of several major DES trials in all comer populations ranged from 23.1 to 29.3% [9, 10, 18]. The TWENTE trial, which enrolled patients between 2008 and 2010, comprised 27.5% women. This proportion of female patients in TWENTE matches the routine clinical practice in the Netherlands (28% in 2009) [19] as well as a trend that was observed from the analysis of 33 prospective European stent trials: the proportion of women gradually increased from 22% (in 1995–1997) to 26% (in 2003–2006) [20]. The increase in female patients during that period reflected daily clinical practice as more women suffered from obstructive coronary disease. In addition, it paralleled a progress in stent technology (e.g., improved stent material, stent design, delivery system, and development of DES), which facilitated stent implantation in coronary vessels with small lumen dimensions that are more frequent in women [13, 21].

Previous studies established an angiographic [22] and clinical benefit [8, 21, 23, 24] of first-generation DES over bare metal stents in women. Endeavor, the first-generation zotarolimus-eluting stent that had a polymer-based coating that differed significantly from that of the second-generation Resolute, was recently shown to be particularly efficient in women in suppressing neointimal ingrowth and preventing binary restenosis [22].

Recent studies demonstrated in patient populations that also comprised women the superiority of second-generation Xience V over first-generation paclitaxel-eluting stents [9, 11]. Pooled data analysis of SPIRIT II and III, studies in well-defined patient and lesion populations, found fewer MACE and TVF at 2-year follow-up in women treated with Xience V as compared to women treated with paclitaxel-eluting stents. Also, women treated with Xience V had after 8 months a somewhat higher binary restenosis rate compared to male patients. However, that difference was statistically nonsignificant [25].

Gender and PCI outcome. In the present era, female gender was associated with an inferior outcome after PCI [26-28], which has been partly related to the often higher cardiovascular risk profile and on average smaller vessel size [14, 29]. On the contrary, studies with first-generation DES show no clear relationship between gender and outcome [7, 8, 23, 30]. Only in one DES study, female gender was associated with less favorable clinical outcome as a result of more repeat revascularization procedures [13, 14]. In the "real-world" study population of TWENTE, there was also no relationship between gender and clinical outcome after treatment with one of the second-generation DES. Although target vessel size was significantly smaller in women, outcome measures did not differ between women and men. This was despite the fact that women were on average 5 years older than men ($P < 0.01$), which matches exactly a difference of 5 years in age (63 vs. 68 years) that was recently reported for the Netherlands, based on the data from all PCI in 2009 [19]. In addition, women had a higher incidence of diabetes mellitus and hypertension ($P \leq 0.01$), and a lower incidence of previous bypass surgery ($P = 0.02$). Only all-cause and cardiac mortality rates tended to be slightly higher in women ($P = 0.09$). Although women had a higher cardiovascular risk profile and smaller target vessels, no significant gender difference in clinical outcome was observed in this study.

Gender and stent thrombosis in DES. Stent thrombosis is a potentially lethal complication of coronary stenting that is relatively rare in second-generation DES [9-12, 31]. The incidence of stent thrombosis is assumed to be similar for both genders [7, 23, 32-34]. In TWENTE, stent thrombosis was rare both in the overall study population and in the female subpopulation.

Limitations of the study. Despite gender-stratification, this study was statistically not powered to confirm noninferiority of the study stents in women. The results cannot be applied to women receiving DES in the setting of an acute STEMI, as this clinical syndrome was an exclusion criterion.

Conclusions. In this prespecified analysis of the gender-stratified TWENTE trial, there was no significant difference in safety and efficacy between female patients treated with Resolute and Xience V stents. Despite a higher cardiovascular risk profile and smaller target vessels in women, no significant gender difference in clinical outcome was observed.

REFERENCES

1. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, Ten CH, Nilsson PM, Huisman MV, Stam HC, Eizema K, Stramba-Badiale M. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. Eur Heart J 2011;32:1362-1368.
2. Chieffo A, Hoye A, Mauri F, Mikhail GW, Ammerer M, Grines C, Grinfeld L, Madan M, Presbitero P, Skelding KA, Weiner BH, Mehran R. Gender-based issues in interventional cardiology: a consensus statement from the Women in Innovations (WIN) initiative. EuroIntervention 2010;5:773-779.
3. Mehran R, Kini AS. Sex-related outcomes after drug-eluting stent: should we "never mind" or "mind" the gap?. JACC Cardiovasc Interv 2010;3:1260-1261.
4. WomenHeart and the Society for Women's Health Research. 2*011 10Q Report: Advancing Women's Heart Health Through Improved Research, Diagnosis, and Treatment* 2011.
5. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, Dolor RJ, Douglas PS, Mark DB, Newby LK. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes 2010;3:135-142.
6. Lansky AJ, Costa RA, Mooney M, Midei MG, Lui HK, Strickland W, Mehran R, Leon MB, Russell ME, Ellis SG, Stone GW. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol 2005;45:1180-1185.
7. Onuma Y, Kukreja N, Daemen J, Garcia-Garcia HM, Gonzalo N, Cheng JM, van Twisk PH, van DR, Serruys PW. Impact of sex on 3-year outcome after percutaneous coronary intervention using bare-metal and drug-eluting stents in previously untreated coronary artery disease: insights from the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. JACC Cardiovasc Interv 2009;2:603-610.
8. Solinas E, Nikolsky E, Lansky AJ, Kirtane AJ, Morice MC, Popma JJ, Schofer J, Schampaert E, Pucelikova T, Aoki J, Fahy M, Dangas GD, Moses JW, Cutlip DE, Leon MB, Mehran R. Gender-specific outcomes after sirolimus-eluting stent implantation. J Am Coll Cardiol 2007;50:2111-2116.
9. Kedhi E, Joesoef KS, McFadden E, Wassing J, van MC, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-209.
10. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van LF, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-146.
11. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-1674.
12. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, Linssen GC, Said SA, Kleijne MA, Sen H, Lowik MM, van der Palen J, Verhorst PM, de Man FH. A Randomized Controlled Trial in Second-Generation Zotarolimus-Eluting Resolute Stents Versus Everolimus-Eluting Xience V Stents in Real-World Patients: The TWENTE Trial. J Am Coll Cardiol 2012;59:1350-1361.
13. Lansky AJ, Ng VG, Mutlu H, Cristea E, Guiran JB, Midei M, Newman W, Sanz M, Sood P, Doostzadeh J, Su X, White R, Cao S, Sudhir K, Stone GW. Gender-based evaluation of the XIENCE V everolimus-eluting coronary stent system: clinical and angiographic results from the SPIRIT III randomized trial. Catheter Cardiovasc Interv 2009;74:719-727.
14. Ng VG, Lansky AJ, Hermiller JB, Farhat N, Applegate RJ, Yaqub M, Sood P, Su X, Simonton CA, Sudhir K, Stone GW. Three-year results of safety and efficacy of the everolimus-eluting coronary stent in women (from the SPIRIT III randomized clinical trial). Am J Cardiol 2011;107:841-848.
15. Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JW, Said SA, Linssen GC, Kleijne MA, van der PJ, Huisman J, Verhorst PM, von Birgelen C. TWENTE Study: The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente: study design, rationale and objectives. Neth Heart J 2010;18:360-364.

16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-2351.
17. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871-874.
18. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di MC, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163-1173.
19. Vaartjes I, van Dis I, Visseren FLJ, Bots ML. Cardiac and vascular diseases in the Netherlands 2011, data on lifestyle and risk factors, prevalence of disease, and mortality 2012:23-32.
20. Vranckx P, Boersma E, Garg S, Valgimigli M, van Es GA, Goedhart D, Serruys PW. Cardiovascular risk profile of patients included in stent trials; a pooled analysis of individual patient data from randomised clinical trials: insights from 33 prospective stent trials in Europe. EuroIntervention 2011;7:859-871.
21. Brown RA, Williams M, Barker CM, Mauri L, Meredith IT, Fajadet J, Wijns W, Leon MB, Kandzari DE. Sex-specific outcomes following revascularization with zotarolimus-eluting stents: comparison of angiographic and late-term clinical results. Catheter Cardiovasc Interv 2010;76:804-813.
22. Nakatani D, Ako J, Tremmel JA, Waseda K, Otake H, Koo BK, Miyazawa A, Hongo Y, Hur SH, Sakurai R, Yock PG, Honda Y, Fitzgerald PJ. Sex differences in neointimal hyperplasia following endeavor zotarolimus-eluting stent implantation. Am J Cardiol 2011;108:912-917.
23. Mikhail GW, Gerber RT, Cox DA, Ellis SG, Lasala JM, Ormiston JA, Stone GW, Turco MA, Joshi AA, Baim DS, Colombo A. Influence of sex on long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent: results of the "TAXUS Woman" analysis. JACC Cardiovasc Interv 2010;3:1250-1259.
24. Mehta RH, Leon MB, Sketch MH,Jr. The relation between clinical features, angiographic findings, and the target lesion revascularization rate in patients receiving the endeavor zotarolimus-eluting stent for treatment of native coronary artery disease: an analysis of ENDEAVOR I, ENDEAVOR II, ENDEAVOR II Continued Access Registry, and ENDEAVOR III. Am J Cardiol 2007;100:62M-70M.
25. Seth A, Serruys PW, Lansky A, Hermiller J, Onuma Y, Miquel-Hebert K, Yu S, Veldhof S, Sood P, Sudhir K, Stone GW. A pooled gender based analysis comparing the XIENCE V(R) everolimus-eluting stent and the TAXUS paclitaxel-eluting stent in male and female patients with coronary artery disease, results of the SPIRIT II and SPIRIT III studies: two-year analysis. EuroIntervention 2010;5:788-794.
26. Kelsey SF, James M, Holubkov AL, Holubkov R, Cowley MJ, Detre KM. Results of percutaneous transluminal coronary angioplasty in women. 1985-1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. Circulation 1993;87:720-727.
27. Malenka DJ, O'Connor GT, Quinton H, Wennberg D, Robb JF, Shubrooks S, Kellett MA,Jr., Hearne MJ, Bradley WA, VerLee P. Differences in outcomes between women and men associated with percutaneous transluminal coronary angioplasty. A regional prospective study of 13,061 procedures. Northern New England Cardiovascular Disease Study Group. Circulation 1996;94:II99-104.
28. Watanabe CT, Maynard C, Ritchie JL. Comparison of short-term outcomes following coronary artery stenting in men versus women. Am J Cardiol 2001;88:848-852.
29. Berger JS, Sanborn TA, Sherman W, Brown DL. Influence of sex on in-hospital outcomes and long-term survival after contemporary percutaneous coronary intervention. Am Heart J 2006;151:1026-1031.
30. Kovacic JC, Mehran R, Karajgikar R, Baber U, Suleman J, Kim MC, Krishnan P, Dangas G, Sharma SK, Kini A. Female gender and mortality after percutaneous coronary intervention: Results from a large registry. Catheter Cardiovasc Interv 2011.
31. Hodgson JM, Stone GW, Lincoff AM, Klein L, Walpole H, Bottner R, Weiner BH, Leon MB, Feldman T, Babb J, Dehmer GJ. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. Catheter Cardiovasc Interv 2007;69:327-333.
32. Abbott JD, Vlachos HA, Selzer F, Sharaf BL, Holper E, Glaser R, Jacobs AK, Williams DO. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). Am J Cardiol 2007;99:626-631.

33. Hoffmann R, Klinker H, Adamu U, Kelm M, Blindt R. The risk of definitive stent thrombosis is increased after "off-label" stent implantation irrespective of drug-eluting stent or bare-metal stent use. Clin Res Cardiol 2009;98:549-554.
34. Jensen LO, Tilsted HH, Thayssen P, Kaltoft A, Maeng M, Lassen JF, Hansen KN, Madsen M, Ravkilde J, Johnsen SP, Sorensen HT, Thuesen L. Paclitaxel and sirolimus eluting stents versus bare metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. EuroIntervention 2010;5:898-905.

CHAPTER 13

DURABLE POLYMER-BASED STENT CHALLENGE OF PROMUS ELEMENT VERSUS RESOLUTE INTEGRITY (DUTCH PEERS): RATIONALE AND STUDY DESIGN OF A RANDOMIZED MULTICENTER TRIAL IN A DUTCH ALL-COMERS POPULATION

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SUMMARY

Background: Drug-eluting stents (DES) are increasingly used for the treatment of coronary artery disease. An optimized DES performance is desirable to successfully treat various challenging coronary lesions in a broad population of patients. In response to this demand, third-generation DES with an improved deliverability were developed. Promus Element and Resolute Integrity are two novel third-generation DES for which limited clinical data is available. Accordingly, we designed the current multicenter study to investigate in an all-comers population whether the clinical outcome is similar after stenting with Promus Element versus Resolute Integrity.

Methods: DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity (DUTCH PEERS) is a multicenter, prospective, single-blinded, randomized trial in a Dutch all-comers population. Patients with all clinical syndromes who require percutaneous coronary interventions (PCI) with DES implantation are eligible. In these patients, the type of DES implanted will be randomized in a 1:1 ratio between Resolute Integrity versus Promus Element. The trial is powered based on a noninferiority hypothesis. For each stent arm, 894 patients will be enrolled, resulting in a total study population of 1788 patients. The primary endpoint is the incidence of target vessel failure at 1-year follow-up.

Summary: DUTCH PEERS is the first randomized multicenter trial with a head-to-head comparison of Promus Element and Resolute Integrity to investigate the safety and efficacy of these third-generation DES.

BACKGROUND

Drug-eluting stents (DES) were developed to improve invasive treatment of coronary artery disease by reducing the rate of restenosis and the need for repeat revascularization. First-generation DES consisted of established bare metal stent (BMS) platforms and durable polymer coatings that delivered the drug to the vessel wall. While the early DES studies proved the efficacy of DES to reduce morbidity,(1) these devices had no positive impact on mortality. This was greatly attributed to a somewhat increased incidence of stent thrombosis (compared to BMS).(2-4) Second-generation DES were then developed, aiming at improved biocompatibility of the coatings while maintaining the antiproliferative potential of first-generation DES.(5) Further refinement of DES involved an increase in flexibility of the stent platform, which was realized in third-generation DES. Stent flexibility facilitates both stent delivery in challenging anatomical situations and apposition of DES to the vessel wall with optimal drug delivery.

Resolute Integrity (Medtronic Vascular, Santa Rosa, CA, USA) and Promus Element (Boston Scientific, Natick, MA, USA) are third-generation DES, based on established and previously tested drugs and durable polymer-based coatings(6) in combination with a novel stent design to increase flexibility. DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity (DUTCH PEERS) is a multicenter trial to evaluate the clinical outcome of these third-generation DES in a real-world, all-comers setting.

Investigational products

Promus Element

Promus Element is a Conformité Européenne and recently Food and Drug Administration–approved-DES eluting everolimus as anti-proliferative agent from a fluoropolymer coating. It has, at minimum, a strut thickness of 81 μm and a coating thickness of 7 μm. The Promus Element was shown to be highly effective to reduce neointimal proliferation.(7;8) The stent platform is laser cut and made from a platinum chromium alloy. It consists of serpentine rings connected by links (Fig. 1) and has been designed for improved deliverability and visibility (i.e. higher radiopacity).

Resolute Integrity

Resolute Integrity is a Conformité Européenne-certified DES which elutes zotarolimus as antiproliferative agent from the BioLynx polymer system consisting of a blend of three different polymers (hydrophobic C10 polymer, hydrophilic C19 polymer, and polyvinyl pyrro-lidinone). This coating is also used in the Resolute DES, which was shown to be highly effective to reduce neointimal proliferation.(9) Resolute Integrity is based on a new flexible stent platform (Fig. 1) made from a cobalt-chromium alloy that increases stent deliverability

and conformability. Resolute Integrity has a strut thickness of 91 µm and a coating thickness of 6 µm.

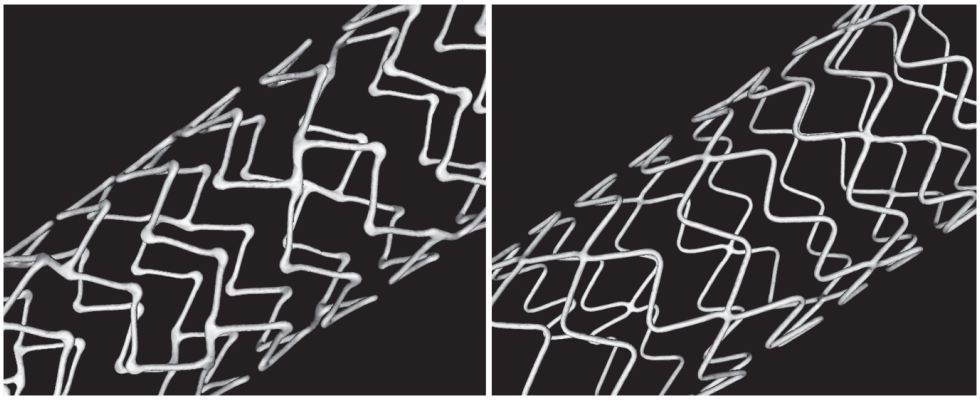

Figure 1. Micro computed tomography images of DES compared in DUTCH PEERS. Promus Element (left panel) and Resolute Integrity (right panel); images from ongoing bench side studies performed by C. von Birgelen and coworkers, University of Twente, Enschede, The Netherlands.

METHODS

Study hypothesis/ objective and design

The main objective of the DUTCH PEERS (ClinicalTrials.gov no. NCT01331707) is to compare the safety and efficacy of the Resolute Integrity to Promus Element in an all-comers population with complex lesions. The study hypothesis is that Resolute Integrity is not inferior to Promus Element. DUTCH PEERS is a multicenter, prospective, single-blinded, randomized clinical trial in an all-comers population. Randomization will involve the type of DES used. Patients will be blinded as to the type DES received. It is an investigator-initiated trial, planned and performed by cardiologists of the participating PCI centers. Boston Scientific and Medtronic provided equal financial support of the entire study.

Study population

A total of 1788 patients will be studied, which is equal to 894 patients per treatment arm. Patients with a minimum age of 18 years who undergo PCI with DES implantation are eligible for enrollment in the study. All clinical syndromes are permitted, including acute myocardial infarctions (MIs) such as ST-elevation myocardial infarctions (STEMI) and non-STEMI.

There are very few exclusion criteria in order to assess the performance of both DES in a real-world, all-comers setting, as seen in routine clinical practice. Exclusion criteria are: 1) participation in another randomized drug or device study before reaching primary endpoint;

2) planned surgery within 6 months of PCI unless dual antiplatelet therapy is maintained throughout the peri-surgical period; 3) intolerance to a P2Y12 receptor antagonist that results in the patient's inability to adhere to dual-antiplatelet therapy, or intolerance to aspirin, heparin, or components of the two DES examined; 4) known pregnancy; and 5) life expectancy of less than 1 year. Table 1 shows an overview of the inclusion and exclusion criteria.

The study complies with the Declaration of Helsinki and was approved by the local ethics committees. All patients provide written informed consent for participation in the trial. Enrollment takes place at four individual study sites in the Netherlands (Thoraxcentrum Twente at Medisch Spectrum Twente, Enschede; Scheper Hospital, Emmen; Hospital Rijnstate, Arnhem; Medisch Centrum Alkmaar, Alkmaar). The first patient was enrolled on November 25, 2010; enrollment is expected to be completed in spring 2012.

Table 1. DUTCH PEERS inclusion and exclusion criteria.

Inclusion criteria 1. Minimum age of 18 years; 2. Coronary artery disease and lesion(s) eligable for treatment with drug eluting stents according to clinical guidelines and/or the operators' judgement; 3. Patient is willing and able to cooperate with study procedures and required follow-up visits; and patient has been informed and agrees on the participation by signing an approved written informed consent.
Exclusion criteria 1. Participation in another randomized drug or device study before reaching primary endpoint; 2. Planned surgery within 6 months of PCI unless dual antiplatelet therapy is maintained throughout the peri-surgical period; 3. Intolerance to a P2Y12 receptor antagonist that results in the patient's inability to adhere to dual-antiplatelet therapy, or intolerance to aspirin, heparin, or components of the two DES examined 4. Known pregnancy; 5. Life expectancy of less than 1 year.

Study protocol, patient demographics, and medical data

Patient demographics and baseline data are collected by the investigators and entered in a database at Thoraxcentrum Twente in Enschede. Laboratory tests will be performed in the local laboratories of the participating centers as part of their clinical routine practice. In all patients, cardiac biomarkers measurement will be scheduled prior to PCI and 6-18 hours after PCI, with subsequent serial measurements in case of relevant biomarker elevation or complaints until the peak elevation has been measured.

Percutaneous coronary intervention procedures are performed according to routine clinical practice. The use of pre or postdilatation and intravascular ultrasound or optical coherence tomography is left to the operator's discretion. If an operator is unable to insert the study

stent despite various measures, crossover to a non-study stent of choice is permitted (BMS or DES). It is preferred to treat all significant coronary lesions within a single PCI procedure; however, staged procedures (defined as procedures planned at the time of the index procedure and performed within 6 weeks with the allocated type DES) are permitted. In case of unplanned revascularization procedures requiring stent implantation, it is recommended that physicians use the allocated type of DES. Coronary angiographic imaging is performed according to current guidelines to obtain high quality angiographic images that permit reliable quantitative analyses with quantitative coronary angiography.

Medical therapy during PCI does not differ from current routine medical treatment; the use of glycoprotein IIb/IIIa inhibitors is left at the operator's discretion. Patients who are not on oral aspirin therapy will receive a loading dose of at least 300mg prior to PCI. A loading dose of clopidogrel will be given before PCI (at least 300mg); if prasugrel is used, patients will receive a loading dose of 60mg. Following the index PCI procedure, patients are generally maintained on aspirin ≥80mg daily. In addition, clopidogrel 75mg daily is generally prescribed for a period of 1 year. If patients require oral anticoagulation therapy (e.g. for atrial fibrillation), clopidogrel is prescribed for 1 year, and aspirin ≥80mg daily for at least 1 month. Further medical treatment is performed according to current medical guidelines, clinical standards, and the judgment of the referring physicians.

Follow-up data collection

Follow-up data will be collected during routine visits to the outpatient clinic, or if not feasible, by telephone follow-up and/or a medical questionnaire. Staff, blinded to the allocated treatment arm, will conduct the phone calls during follow-up. During outpatient visits or telephone calls, patients will be interviewed regarding rehospitalizations, revascularization procedures, and myocardial infarctions during follow-up. In case of death, information will be obtained from the patient's medical chart, general practitioner, and/or cardiologist. Follow-up data after 1 month, 12(±1) months, and 24(±1) months will be collected.

Clinical endpoints and definitions

The primary endpoint of the study will be target vessel failure (TVF) at 12 months as defined by the Academic Research Consortium (ARC).(10) Target vessel failure is a composite endpoint to assess device efficacy as well as patient safety. Components of the primary endpoint are cardiac death, target vessel related MI, and clinically driven repeated target vessel revascularization.

Cardiac death is defined as any death due to proximate cardiac cause (e.g. MI, low-output failure, or fatal arrhythmia), unwitnessed death, death of unknown cause, and all procedure-related deaths, including those related to concomitant therapy. In brief, all deaths are considered cardiac, unless an unequivocal noncardiac cause can be established.

Target vessel-related MI (Q-wave or non-Q-wave MI) is defined as an MI that can be related to the target vessel or cannot be related to another vessel. Myocardial infarction is defined according to the revised ARC definition of myocardial infarction, including periprocedural myocardial infarction.(11) Clinically driven repeated target vessel revascularization includes revascularization procedures by means of coronary bypass graft or PCI.
Secondary endpoints will include all-cause death, target-lesion failure (TLF) (a composite of cardiac death, target vessel MI and clinically driven target lesion revascularization), a patient-oriented composite endpoint (a composite of all-cause death, any MI, any revascularization) and stent thrombosis, which will be assessed according to the ARC.(10)

Sample size calculation

The main outcome parameter is the difference in TVF between the two treatment arms after 12 months, analyzed by $\chi 2$ test. We applied a noninferiority margin of 3.6%, expecting an event rate of 10%, based on data of the RESOLUTE All Comers and TWENTE trial.(12;13) If the upper limit of the 1-sided 95% confidence interval of the difference in the primary endpoint is less than the prespecified noninferiority margin 3.6%, Resolute Integrity will be considered noninferior to Promus Element. Considering the aforementioned parameters, 894 patients per group (total study population: 1788 patients) would allow to demonstrate noninferiority, taking into account a maximum loss to follow-up of 3%. The power to detect a true difference will be at least 80%(14), and statistical significance is set at 5%.

Randomization

Patients will be randomized by a computer program (block stratified randomization V5.0 by S. Piantadosi) after diagnostic catheterization. The randomization will be performed in blocks of 8 and 4 in random order. Patients will be assigned either a Resolute Integrity stent or Promus Element stent on a 1:1 basis.

Statistical considerations

Baseline characteristics will be reported as mean±SD or as percentage for categorical and dichotomous variables. If variables are not normally distributed, values are reported as median with corresponding range. Between-group differences in (TVF) rate at 12 months will be analyzed by means of $\chi 2$ tests. In addition, the primary endpoint will be analyzed by the log-rank test by comparing the time to the primary endpoint using the Kaplan-Meier method. Subgroup analyses will be performed for, but will not be limited to, diabetes mellitus, age, gender, recent MI, in-stent restenosis, known renal insufficiency, bifurcation lesion, left main stenting, bypass graft lesion treated, multivessel stenting, number of implanted stents, lesion length, small vessels, and number of treated lesions in which the primary and secondary endpoints will be analyzed. The subgroup analyses will be performed to assess

consistency of treatment effect across different subsets and are considered hypothesis generating. We will perform even more detailed analyses in important subgroups such as patients with STEMI and diabetics. The principal analyses will be performed based on the principles of intention-to-treat.

Trial organization

Trial coordination and data management will be performed by Cardio Research Enschede, Enschede, The Netherlands. Study monitoring will be carried out by an independent external contract research organization (Diagram, Zwolle, The Netherlands). An independent clinical events committee (Cardialysis, Rotterdam, The Netherlands) will adjudicate all adverse clinical events.

DISCUSSION

The use of DES in daily clinical practice has gradually been extended to so-called "off-label indications", including its use in angiographically complex coronary lesions. This is supported by data that demonstrated similar safety and efficacy of DES (compared to BMS) for off-label indications (15) such as STEMI (16-18), bifurcations (19;20), left main lesions (21), long lesions (22), small vessels (23), bypass grafts (24-26), and chronic total occlusions (27). While officially reported data on the penetration of DES in clinical practice is scarce, current estimates of the mean DES penetration vary from 64% in the UK to 80% in the US.(28-30)

So far, very few data are available on the clinical performance of third-generation Promus Element and Resolute Integrity DES. Other DES, which have major similarities employing the same coating and polymer but different stent platforms, are the second-generation Xience V and Resolute. Several randomized trials demonstrated a superior outcome following PCI with these second-generation DES compared to first-generations DES (31-33). An example may be SPIRIT IV, which provided interesting insights into the safety and efficacy of Xience V compared to Taxus Liberté.(32) In the Xience V study arm, the primary end point TLF at 1-year follow-up (a composite of cardiac death, target vessel MI, and target lesion revascularization) occurred 38% less often compared with Taxus Liberté (4.2% vs 6.8%, P = 0.001). In addition, rates of definite-or-probable stent thrombosis according to ARC were lower in Xience V than in Taxus (0.3% vs 1.1%, P = 0.004).

Similar to DUTCH PEERS, some recent randomized comparative DES trials were "all-comers studies" that comprised a significant proportion of challenging lesions in complex patients with various clinical syndromes including STEMI. The results of such trials are particularly valuable, as they reflect the performance of DES in routine clinical practice. As a consequence, their results may be generalizable to most PCI centers. The COMPARE trial and RESOLUTE All Comers trial are such studies, which examined Xience V and Resolute in an all-comer patient population.(12;31)

In the COMPARE trial, superiority of Xience V over Taxus Liberté was shown.(31) In this prospective, randomized, controlled single-center trial, the primary endpoint – a composite of all-cause mortality, non-fatal myocardial infarction, and target vessel revascularization at 1 year – occurred in 6.2% in the Xience V arm as compared to 9.1% in the Taxus Liberté arm(P = 0.02). Lower rates of definite-or-probable stent thrombosis (0.7% vs. 2.5%) contributed to this difference.

The Resolute All Comers trial compared the clinical performance of Resolute and Xience V stents.(12) In this pivotal, prospective, randomized, controlled multicenter trial, Resolute proved to be noninferior to Xience V with similar safety and efficacy of both DES. The primary endpoint TLF at 12 months was 8.2% and 8.3% for Resolute and Xience V, respectively ($P_{noninferiority}$ <0.001). In addition, TVF rates at 12 months were non-significantly different (9.0% vs. 9.6%) with stent thrombosis rates of 1.6% and 0.7% for both DES. Noninferiority of Resolute versus Xience V was maintained at 2-year follow-up.(5) The randomized TWENTE trial recently confirmed noninferiority of Resolute vs. Xience V in a patient population with minimal exclusion criteria and with a majority of complex lesions and 'off-label' indications for DES use.(13)

Although second-generation DES employ novel coatings, aiming at increased biocompatibility, third-generation DES make use of stent platforms that were designed specifically for use in DES. Advantages of such platforms may be an improved stent flexibility and conformability, a more homogeneous drug delivery to the vessel wall, and/or an improved visibility of the stent. However, for both Resolute Integrity and Promus Element there are only limited data available from large randomized multicenter trials in third-generation DES on more complex lesions and clinical endpoints. Recently, the PLATINUM trial showed noninferiority of the third-generation Promus Element stent compared to the second-generation Xience V stent.(8) In that study, patients with stable angina, unstable angina, and silent ischemia with one or two de-novo lesions were examined, revealing for Promus Element and Xience V at 1-year follow-up TLF rates of 3.5% and 3.2% and TVF rates of 4.2% and 4.0%, respectively. Definite-or-probable stent thrombosis occurred in 0.4% in each group. Promus Element is the first third-generation DES that was approved for clinical use in the United States. So far, for the third-generation Resolute Integrity stent, no information is available from randomized comparative trials, but clinical performance is generally assumed to be at least similar to that of Resolute. Nevertheless, Promus Element will be considered as the reference device in DUTCH PEERS as (1) more clinical data have been reported on its clinical performance; (2) it was recently shown to be noninferior to the second-generation Xience V stent in the PLATINUM trial (8); (3) it recently received approval by the US Food and Drug Administration. It will be interesting to investigate whether changes in stent platform made in third-generation DES will affect clinical outcome in diabetic patients. The question whether there is a clear relation between DES type and clinical outcome in the presence of diabetes mellitus has not

been definitely answered yet. A pooled analysis showed an interaction between diabetes and DES type.(34) Everolimus-eluting stents may be less effective in diabetic patients in reducing neointimal formation than in non-diabetics. As zotarolimus is also a rapamycin analogue, Resolute Integrity theoretically could have the same interaction with diabetes mellitus. In fact, in the RESOLUTE All Comers trial Xience V showed no significant difference compared to Resolute in patients with diabetes (P = 0.25) and there was no substantial difference between the two DES types in inhibiting neointima.(12) Because the DUTCH PEERS trial will include a significant number of diabetic patients, the subanalysis of diabetics may provide more insight in this matter. Nevertheless, as in many other randomized stent trials, subgroup analyses may be considered as hypothesis-generating only, as they are often not powered to draw sound conclusions.

Because both devices share (different) changes in stent platform for improved flexibility and conformability, this study may not be able to assess a potential negative impact of these design changes in clinical practice. A major safety issue of one of both devices is likely to be detected in DUTCH PEERS. However, the assessment of small between-device differences in certain rare events may require pooling of data from more than 1 randomized trial. Nevertheless, the great acceptance of both devices in clinical practice and the fact that worldwide many operators use these stents as their “workhorse” stent(s) make the comparison of DUTCH PEERS clinically interesting and relevant.

Thus, Resolute Integrity and Promus Element are third-generation DES of which so far no head-to-head comparison has been performed. In the randomized DUTCH PEERS multicenter trial, we therefore compare both devices with regard to safety and efficacy in a large all-comers population, assuming noninferiority of Resolute Integrity compared to Promus Element.

Disclosures

CvB is consultant to and has received lecture fees or travel expenses from Boston Scientific, Medtronic, and Abbott Vascular; he received lecture fees from MSD. All other authors declare that they have no conflict of interest.

REFERENCES

(1) 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; 346(23):1773-1780.

(2) Jensen LO, Maeng M, Kaltoft A, Thayssen P, Hansen HH, Bottcher M et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007; 50(5):463-470.

(3) Planer D, Beyar R, Almagor Y, Banai S, Guetta V, Miller H et al. Long-term (>3 Years) outcome and predictors of clinical events after insertion of sirolimus-eluting stent in one or more native coronary arteries (from the Israeli arm of the e-Cypher registry). Am J Cardiol 2008; 101(7):953-959.

(4) Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation 2004; 109(16):1930-1932.

(5) Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011; 377(9773):1241-1247.

(6) Basalus MW, Tandjung K, VAN Apeldoorn AA, Ankone MJ, Von Birgelen C. Effect of Oversized Partial Postdilatation on Coatings of Contemporary Durable Polymer-Based Drug-Eluting Stents: A Scanning Electron Microscopy Study. J Interv Cardiol 2010.

(7) Meredith IT, Whitbourn R, Scott D, El-Jack S, Zambahari R, Stone GW et al. PLATINUM QCA: a prospective, multicentre study assessing clinical, angiographic, and intravascular ultrasound outcomes with the novel platinum chromium thin-strut PROMUS Element everolimus-eluting stent in de novo coronary stenoses. EuroIntervention 2011; 7(1):84-90.

(8) Stone GW, Teirstein PS, Meredith IT, Farah B, Dubois CL, Feldman RL et al. A Prospective, Randomized Evaluation of a Novel Everolimus-Eluting Coronary Stent The PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions) Trial. J Am Coll Cardiol 2011; 57(16):1700-1708.

(9) Leon MB, Mauri L, Popma JJ, Cutlip DE, Nikolsky E, O'Shaughnessy C et al. A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. J Am Coll Cardiol 2010; 55(6):543-554.

(10) Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007; 115(17):2344-2351.

(11) Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010; 5(7):871-874.

(12) Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE et al. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. N Engl J Med 2010; 363(2):136-146.

(13) Von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JW et al. TWENTE: A Randomized Controlled Trial in Second-Generation Zotarolimus-Eluting Resolute Stents Versus Everolimus-Eluting Xience V Stents in 'Real-World' Patients *(The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente)*. Paper presented at TCT (Transcatheter Cardiovascular Therapeutics) as a Late Breaking Clinical Trial; 11 November 2011; San Francisco, CA.

(14) Cohen J. Statistical Power Analysis for the Behavioral Sciences. Ed. 2. Hillsdale, New Jersey: Lawrence Erlbaum; 1988.

(15) Marroquin OC, Selzer F, Mulukutla SR, Williams DO, Vlachos HA, Wilensky RL et al. A comparison of bare-metal and drug-eluting stents for off-label indications. N Engl J Med 2008; 358(4):342-352.

(16) Greenhalgh J, Hockenhull J, Rao N, Dundar Y, Dickson RC, Bagust A. Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. Cochrane Database Syst Rev 2010; 5:CD004587.

(17) Piscione F, Piccolo R, Cassese S, Galasso G, De RR, D'Andrea C et al. Effect of drug-eluting stents in patients with acute ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: a meta-analysis of randomised trials and an adjusted indirect comparison. EuroIntervention 2010; 5(7):853-860.

(18) Violini R, Musto C, De FF, Nazzaro MS, Cifarelli A, Petitti T et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (sirolimus-eluting stent versus bare-metal stent in acute myocardial infarction) trial. J Am Coll Cardiol 2010; 55(8):810-814.
(19) Ferenc M, Gick M, Kienzle RP, Bestehorn HP, Werner KD, Comberg T et al. Long-term outcome of percutaneous catheter intervention for de novo coronary bifurcation lesions with drug-eluting stents or bare-metal stents. Am Heart J 2010; 159(3):454-461.
(20) Burzotta F, Trani C, Todaro D, Mariani L, Talarico GP, Tommasino A et al. Prospective randomized comparison of sirolimus- or everolimus-eluting stent to treat bifurcated lesions by provisional approach. JACC Cardiovasc Interv 2011; 4(3):327-335.
(21) Buszman PE, Buszman PP, Kiesz RS, Bochenek A, Trela B, Konkolewska M et al. Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. J Am Coll Cardiol 2009; 54(16):1500-1511.
(22) Kim YH, Park SW, Lee CW, Hong MK, Gwon HC, Jang Y et al. Comparison of sirolimus-eluting stent, paclitaxel-eluting stent, and bare metal stent in the treatment of long coronary lesions. Catheter Cardiovasc Interv 2006; 67(2):181-187.
(23) Bonello L, Buch AN, De Labriolle A, Roy P, Steinberg DH, Pinto Slottow TL et al. Clinical outcomes after implantation of small diameter (=2.5 mm) sirolimus- versus paclitaxel-eluting stents. Int J Cardiol 2009.
(24) Latib A, Ferri L, Ielasi A, Cosgrave J, Godino C, Bonizzoni E et al. Comparison of the Long-Term Safety and Efficacy of Drug-Eluting and Bare-Metal Stent Implantation in Saphenous Vein Grafts. Circ Cardiovasc Interv 2010.
(25) Sanchez-Recalde A, Jimenez VS, Moreno R, Barreales L, Lozano I, Galeote G et al. Safety and efficacy of drug-eluting stents versus bare-metal stents in saphenous vein grafts lesions: a meta-analysis. EuroIntervention 2010; 6(1):149-160.
(26) Lee MS, Yang T, Kandzari DE, Tobis JM, Liao H, Mahmud E. Comparison by meta-analysis of drug-eluting stents and bare metal stents for saphenous vein graft intervention. Am J Cardiol 2010; 105(8):1076-1082.
(27) Colmenarez HJ, Escaned J, Fernandez C, Lobo L, Cano S, del Angel JG et al. Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55(17):1854-1866.
(28) Garg S, Serruys PW. Drug-eluting stents: a reappraisal. Heart 2010; 96(7):489-493.
(29) Ludman PF. BCIS Audit Returns. Adult Interventional Procedures [online], http://www.bcis.org.uk/resources/BCIS_Audit_2009_data_version_08-10-2010_for_web.pdf (2011).
(30) Maluenda G, Lemesle G, Waksman R. A critical appraisal of the safety and efficacy of drug-eluting stents. Clin Pharmacol Ther 2009; 85(5):474-480.
(31) Kedhi E, Joesoef KS, McFadden E, Wassing J, van MC, Goedhart D et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010; 375(9710):201-209.
(32) Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010; 362(18):1663-1674.
(33) Park DW, Kim YH, Yun SC, Kang SJ, Lee SW, Lee CW et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. J Am Coll Cardiol 2010; 56(15):1187-1195.
(34) Stone GW, Kedhi E, Kereiakes DJ, Parise H, Fahy M, Serruys PW et al. Differential clinical responses to everolimus-eluting and Paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. Circulation 2011; 124(8):893-900.

CHAPTER 14

SUMMARY AND CONCLUSIONS

SUMMARY

The development of drug-eluting stents (DES) has improved the invasive treatment of obstructive coronary artery disease by reducing both, restenosis rate and need for reinterventions. This success resulted in a widespread utilization of DES in clinical practice and entailed many clinical research programs. In addition, numerous laboratory examinations of DES have been performed. The majority of this in vitro and pre-clinical research was performed by the DES-developing companies. Only occasionally such data are fully accessible for the public.

Chapter 1 provides an introduction to this thesis, briefly introduces the techniques and potential of bench top research for the assessment of DES, but leaves no doubt that the results of large clinical trials are most important for the evaluation of safety and efficacy of medical implants. Nevertheless, as demonstrated in this thesis, post-marketing bench top research may provide additional insights that can help interpret clinical DES performance and may be used to improve implantation techniques. **Chapter 2** focuses on the scanning electron microscopic (SEM) examination of DES and presents the results of a quantitative analysis of coating irregularities on the surface of 4 contemporary durable polymer-based DES. **Chapter 3 and 4** report on how aggressive partial oversized post-dilatation may affect DES geometry and DES coating integrity. **Chapter 5** compares coating irregularities on expanded and unexpanded durable polymer-based DES to provide insights into the mechanisms involved in the formation of DES coating irregularities. **Chapter 6** utilizes findings of previous chapters to help interpret the observations of another research group, which examined various DES after failed implantation with SEM. **Chapter 7** focuses on SEM assessment of a biodegradable polymer coating-based biolimus-eluting DES. **Chapter 8** discusses recent bench top and pre-clinical studies on the polymer-based coatings of DES. **Chapter 9** then proceeds to clinical research settings as it compares the incidence of peri-procedural myocardial infarction following the implantation of 4 different DES types (the same DES types as examined in chapter 2). **Chapters 10-12** focus on the clinical performance of the second-generation everolimus-eluting Xience V and zotarolimus-eluting Resolute stents, examined in the randomized TWENTE trial. **Chapter 10** presents the main findings of the TWENTE trial at one-year follow-up. **Chapter 11** investigates whether the enrolled patients of the TWENTE trial represent a patient population that is similar to daily clinical practice, as it compares baseline characteristics and one-year clinical outcome of eligible but non-enrolled patients and the enrolled (and randomized) patient population of the randomized trial. **Chapter 12** assesses potential gender differences in procedural and clinical outcome between women and men in the TWENTE trial, and it compares the outcome of women treated with Resolute versus Xience V stents. Treatment of more and more challenging coronary anatomies increased the demands upon clinical DES performance, which resulted

in the development of so-called third-generation DES that are characterized by a particularly high stent deliverability. **Chapter 13** presents the rationale and design of the DUTCH-PEERS (TWENTE II) multicenter trial, which investigates in all-comer patients the safety and efficacy of the third-generation Promus Element and Resolute Integrity DES.

Chapter 2 classifies and quantifies post-expansion irregularities on durable polymer-based DES coatings. A thorough SEM examination of four types of DES (Taxus Liberté, Endeavor, Resolute, and Xience V) was performed. On 360 images, 14 types of coating irregularities were classified into four categories according to the amount and the homogeneity of coating. Incidence and size of various coating irregularities in different DES types varied widely. Certain DES types showed specific coating irregularities at constant locations, resulting in typical patterns. *This chapter presents the first published quantitative data on DES coating irregularities. Data provided in this chapter may be considered in ongoing discussions on between-DES differences and may serve as reference for future research.*

In **Chapter 3,** micro-computed tomography (micro-CT) was used to assess the spatial geometry of DES (Cypher Select Plus, Taxus Liberté, Resolute, and Xience V) following extremely oversized post-dilatation of the proximal stent segment. In clinical practice, such post-dilatations are regularly applied in stents that are implanted across the left main bifurcation (or other major coronary bifurcations) in order to resemble physiological tapering of the vessel and to avoid stent mal-apposition. This study demonstrates significant differences between the various DES types in final spatial stent configuration and maximum cell size. *Differences in final cell size between the various DES types, demonstrated in this chapter, may have clinical implications for plaque scaffolding and restenosis. These data could be of interest when planning stent implantation across the left main bifurcation.*

In **Chapter 4**, we examined the effect of an extremely oversized partial post-dilatation of DES on the coatings of five durable polymer-based DES. Incidence and shape of coating irregularities after post-dilatation differed only mildly between the post-dilated and non-post-dilated DES regions. *Data presented in this chapter suggest that even very aggressive stent post-dilatation has no more than a slight effect on the coatings of various durable polymer-based DES.*

Chapter 5 presents quantitative data on DES coating irregularities based on a thorough SEM examination of both expanded and unexpanded durable polymer-based DES. We assessed a total of 1.200 images obtained in 30 DES samples (15 expanded and 15 unexpanded) of Cypher Select Plus, Taxus Liberté, Endeavor, Xience V, and Resolute. For most coating irregularities seen on expanded DES a matching irregularity and/or its precursor was

observed on unexpanded DES. *This chapter shows that most coating irregularities, or the potential to develop them, are inherent to the unexpanded DES. Important determinants of the formation of coating irregularities may be the stent geometry and the physical properties of the coating, while stent-balloon interaction plays no major role.*

Chapter 6 uses the findings from chapter 2 to explain the mechanism of a significant coating delamination of phophorylcholine based zotarolimus-eluting Endeavor stents that was revealed by others with SEM following failed attempts to implant these stents in tortuous and calcified human coronary arteries in vivo. *This chapter shows how both, clinically oriented research and bench top studies can complement each other.*

In **Chapter 7,** SEM was used to examine the biodegradable polylactic acid coating on biolimus-eluting stents. At nominal pressure, stents showed predominantly mild cracks of the coating, while cracks increased after slight overstretch. Aggressive overexpansion of one stent, as sometimes required in left main bifurcation stenting, worsened the cracks and led to some detachments of fragments of coating. *The findings of this chapter maybe considered by interventional cardiologists while applying post-dilatation to the examined biolimus-eluting stent, as this may lead to detachment of larger fragments of coating. This is of particular interest in major coronary bifurcations, as at the ostium of a large side branch the DES is not entirely constrained by the vessel wall.*

Chapter 8 addresses findings of recent bench top and pre-clinical studies that assessed the polymer-based coatings of several types of DES. The chapter elaborates on technical challenges, translational relevance, and perspective of these studies. *This chapter discusses benefits and disadvantages of covering DES with polymer-based coatings. In addition, it calls for some standardization of bench top protocols, used to examine DES coatings, and for the incorporation of these protocols into European regulatory body approval processes.*

Chapter 9 compares the incidence of peri-procedural myocardial infarction between first and second-generation DES as assessed in 800 patients treated with first (Taxus Liberté or Endeavor) or second-generation DES (Xience V or Resolute). There was no significant difference in peri-procedural myocardial infarction between first and second-generation DES (5.5% vs. 4.0%, p=0.29). *This chapter demonstrated that the increase in multi-vessel treatment, which paralleled the introduction of second-generation DES, was not associated with an increase in peri-procedural myocardial infarction as compared to first- generation DES.*

Chapter 10 presents the main one-year follow-up results of the TWENTE trial (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting SteNt Study: Head-to-head Comparison of Clinical Outcome After Implantation of Second Generation Drug-eluting Stents in a Real World Scenario; NCT01066650). The TWENTE trial is an investigator-initiated, patient-blinded, randomized study that compares the safety and efficacy of Resolute zotarolimus-eluting stents with Xience V everolimus-eluting stents in 1.391 patients with limited exclusion criteria. The primary endpoint of target vessel failure (TVF; composite of cardiac death, myocardial infarction not clearly attributable to non-target vessels, and clinically indicated target-vessel revascularization) occurred in 8.2% and 8.1%, respectively ($p_{non\text{-}inferiority} = 0.001$). The definite-or-probable stent thrombosis rates were relatively low and similar for both DES (0.9% and 1.2%, respectively, p = 0.59). *The findings of this large randomized clinical trial demonstrated that Resolute stents were non-inferior to Xience V stents in treating "real-world" patients with a majority of complex lesions and off-label indications for DES. In addition, an overall low rate of stent thrombosis in both arms of the trial was demonstrated.*

The TWENTE trial enrolled a "real world" patient population consisting of more than 80% of all eligible patients. **In Chapter 11** we investigate whether eligible, non-enrolled patients differed from the randomized TWENTE trial population in baseline characteristics and one-year outcome. Baseline characteristics of 1.709 eligible patients were analyzed (318 non-enrolled and 1.391 randomized patients). Non-enrolled and randomized patients differed only in age and cardiovascular history. But clinical outcome after one year, and in particular the primary composite endpoint TVF (9.8% vs. 8.1%, p=0.34), did not differ significantly. *The findings of this chapter show that despite some differences in baseline characteristics, non-enrolled and randomized patients did not differ in one-year outcome, which was favorable for both populations and may be related to the drug-eluting stents used.*

Chapter 12 presents a pre-specified sub-analysis of the gender-stratified TWENTE study with the aim to assess safety and efficacy of Resolute and Xience V DES in women. TVF after 1 year was the predefined endpoint. Among 1.391 patients, 382 (27.5%) women were randomized to Resolute and Xience V. Baseline and procedural characteristics were similar for females in both study arms, except for smaller vessel and stent diameters in Resolute-treated lesions. After 1 year, TVF (8.9 vs. 8.4%, p=0.91) and a patient-oriented composite endpoint (13.0 vs. 12.1%, p=0.79) did not differ significantly between women in both stent arms. In addition, women treated in the TWENTE trial were older than men and had more often diabetes mellitus and arterial hypertension, but there was no significant gender difference in TVF (adjusted OR: 1.18, p = 0.50). *The findings of this chapter demonstrate no significant difference in safety and efficacy outcomes between Resolute and Xience V-treated women.*

DES have been increasingly used for the treatment of complex lesions in challenging coronary anatomies, such as tortuous and calcified coronary vessels, which made more demands on DES in terms of stent deliverability. In response to these demands, third-generation DES with particularly flexible designs and improved deliverability were recently developed. **Chapter 13** describes rationale and design of a multicenter, prospective, single-blinded, randomized trial to compare the clinical outcomes of third-generation Resolute Integrity zotarolimus-eluting stents and Promus Element everolimus-eluting stents (DUrable Polymer-based STent CHallenge of Promus Element Versus ReSolute Integrity in an All Comers Population; DUTCH PEERS). In DUTCH PEERS (TWENTE II), a total study population of at least 1.788 all-comer patients will be examined. The primary end point is the incidence of target vessel failure at one-year follow-up (non-inferiority hypothesis). *This chapter described the rationale and design of the first randomized multicenter trial with a head-to-head comparison of Promus Element and Resolute Integrity stents to investigate the safety and efficacy of these two third-generation DES.*

CONCLUSIONS

Bench top research with SEM and micro-CT can provide valuable insights into the surface morphology and stent geometry of DES. While aggressive, oversized, partial post-dilatation of DES had almost no impact on the morphology of the coatings, DES differed significantly in their final spatial stent configuration and maximum cell size, which was generally larger in second-generation DES. In addition, DES coating morphologies were mostly favorable in second-generation DES. The positive bench top data of second-generation DES were paralleled by a favorable clinical outcome in the “real-world” patient population of the randomized TWENTE trial, subpopulations thereof, eligible but non-enrolled patients, and a clinical registry. The integration of even more flexible and deliverable stent designs represents the next step of refinement of durable coating-based DES. This will be carefully evaluated by the randomized DUTCH PEERS (TWENTE II) multi-center trial that will compare two third-generation DES in an all-comers population.

SAMENVATTING EN CONCLUSIES

Samenvatting

De ontwikkeling van drug-eluting stents (DES) heeft de invasieve behandeling van obstructief coronairlijden verbeterd door de hoeveelheid aan restenosis en de behoefte aan re-interventies te reduceren. Dit succes heeft tot een wereldwijde gebruik van DES in de klinische praktijk geleidt en heeft veel klinische onderzoeksprogramma's voortgebracht. Daarnaast zijn talrijke laboratoriumonderzoeken op DES verricht. De meerderheid van deze in vitro en preklinische onderzoeken werden uitgevoerd door de bedrijven welke DES ontwikkelen. Dergelijke gegevens zijn daarom slechts bij gelegenheid volledig openbaar toegankelijk.

Hoofdstuk 1 voorziet in een inleiding in deze thesis, introduceert beknopt de technieken en het potentieel van bench-top onderzoek voor de beoordeling van DES, maar laat er geen twijfel over bestaan dat de resultaten van omvangrijke klinische trials van groot belang zijn voor de beoordeling van veiligheid en werking van medische implantaten. Niettemin, zoals aangetoond in deze thesis, kan post-marketing bench top research additionele inzichten opleveren die kunnen bijdragen tot het duiden van klinische DES prestaties en kan worden gebruikt om implantatie technieken te verbeteren. **Hoofdstuk 2** legt de focus op het scanning electron microscopic (SEM) onderzoek van DES en presenteert de resultaten van een kwantitatieve analyse van onregelmatigheden van de coating aan de oppervlakte van vier moderne permanente polymeer gebaseerde DES. In **hoofdstuk 3 en 4** wordt vermeld hoe gedeeltelijke overmatige post-dilatatie van invloed kan zijn op de DES geometrie en de integriteit van de DES coating. **Hoofdstuk 5** vergelijkt de onregelmatigheden van de coating van geëxpandeerd en niet geëxpandeerd permanente polymeer gebaseerde DES om inzicht te verschaffen in de mechanismen die betrokken zijn bij de vorming van DES coating onregelmatigheden. **Hoofdstuk 6** maakt gebruik van de resultaten van de voorgaande hoofdstukken om de observaties van een andere onderzoeksgroep, namelijk Wiemer et al, die verschillende DES hebben onderzocht na mislukte implantatie met SEM, te kunnen interpreteren. **Hoofdstuk 7** legt de focus op SEM beoordeling van een op biologisch afbreekbaar polymeer coating gebasseerd biolimus-eluting DES. **Hoofdstuk 8** bespreekt recente bench top en preklinische studies over de op polymeer gebaseerde coatings van DES. **Hoofdstuk 9** gaat verder met klinische onderzoekskaders met de vergelijking van de frequentie van peri-procedurele myocard infarct na de implantatie van vier verschillende DES types (dezelfde DES types die in hoofdstuk 2 onderzocht zijn). In de **hoofdstukken 10-12** wordt de nadruk gelegd op de klinische prestaties van de tweede generatie everolimus-eluting Xience V en zotarolimus-eluting Resolute stents, welke zijn geanalyseerd in de gerandomiseerde TWENTE studie. **Hoofdstuk 10** presenteert de belangrijkste bevindingen

van het TWENTE onderzoek na één jaar van follow-up. **Hoofdstuk 11** onderzoekt of het aantal participerende patiënten van de TWENTE studie een patiënten populatie representeert die vergelijkbaar is aan de dagelijkse klinische praktijk. De basis karakteristieken worden vergeleken tezamen met de klinische resultaten van één jaar van in aanmerking komende, maar niet participerende patiënten en de participerende (en gerandomiseerde) patiënten populatie van het gerandomiseerde onderzoek. **Hoofdstuk 12** beoordeelt potentiële geslachtsverschillen in procedurele en klinische resultaten tussen vrouwen en mannen in de TWENTE studie en het vergelijkt de resultaten van vrouwen behandeld met Xience V versus Resolute stents.
De behandeling van steeds complexer coronaire anatomie ligt meer eisen op de klinische prestatie van DES. Dit heeft geresulteerd in de ontwikkeling van een zogeheten derde generatie DES, deze worden gekenmerkt door een bijzonder hoge stent plaatsbaarheid. **Hoofdstuk 13** presenteert de rationale en het ontwerp van het DUTCH-PEERS (TWENTE II) multicenteronderzoek welke de veiligheid en de werking van de derde generatie Promus Element en Resolute Integrity DES in een “alledaagse” patiënten populatie.

Hoofdstuk 2 classificeert en kwantificeert post-dilatatie onregelmatigheden aan de oppervlakte van op permanente polymeer gebaseerde DES coatings. Er is een grondig SEM onderzoek van vier types DES (Taxus Liberté, Endeavor, Resolute, and Xience V) uitgevoerd. Op 360 beelden zijn 14 types coating onregelmatigheden gerangschikt naar vier categorieën op basis van de hoeveelheid en de homogeniteit van de coating. De incidentie en grootte van de verschillende coating onregelmatigheden lopen bij verschillende DES types sterk uiteen. Bepaalde DES types tonen specifieke coating onregelmatigheden op dezelfde plaats, wat in specifieke patronen resulteert. Dit hoofdstuk presenteert de eerste gepubliceerde kwantitatieve gegevens over DES coating onregelmatigheden. Verstrekte gegevens in dit hoofdstuk kunnen in huidige discussies over de verschillen tussen de verschillende stents in overweging worden genomen en kunnen dienen als naslagwerk voor toekomstig onderzoek.

In **hoofdstuk 3,** is een micro computertomografie (micro-CT) gebruikt om de ruimtelijke geometrie van DES (Cypher Select Plus, Taxus Liberté, Resolute, and Xience V) te beoordelen na extreme post-dilatatie van het proximale stent segment. In de klinische praktijk worden dergelijke post-dilataties regelmatig toegepast bij stents die geïmplanteerd zijn langs de bifurcatie van de hoofdstam (of andere grote coronaire bifurcaties) om een gelijke conditie te creëren met het fysiologische geleidelijke afnemende bloedvatdiameter en om een onjuiste stent appositie te vermijden. Deze studie toont significante verschillen tussen de verschillende DES types in uiteindelijke ruimtelijke stent configuratie en maximale celgrootte. Verschillen in uiteindelijke celgrootte tussen de verschillende DES types, aangegeven in dit hoofdstuk, kunnen klinische implicaties op het gebied van ‘plaque scaffolding’ en restenosis

hebben. Deze gegevens kunnen van belang zijn bij de besluitvorming omtrent stent implantatie langs de bifurcatie van de hoofdstam.

In **hoofdstuk 4** hebben we het effect van een buitengewoon gedeeltelijke overmatige post-dilatatie op de coatings van vijf typen beproefde op polymeer gebaseerde DES onderzocht. De incidentie en de vorm van de onregelmatigheden van de coating na post-dilatatie liepen slechts gering uiteen tussen de post-gedilateerde en niet post-gedilateerde DES zones. In dit hoofdstuk verstrekte gegevens impliceren dat zelfs zeer aggressieve stent post-dilatatie slechts een gering effect op de coatings van verschillende beproefde op polymeer gebaseerde DES heeft.

Hoofdstuk 5 geeft kwantitatieve gegevens over DES coating onregelmatigheden weer gebaseerd op een gedetailleerd SEM onderzoek naar zowel geëxpandeerd als niet geëxpandeerde permanente polymeer gebaseerde DES. Er zijn in totaal 1.200 beelden onderzocht, die verkregen zijn uit 30 DES monsters (15 geëxpandeerd en 15 niet geëxpandeerd) van Cypher Select Plus, Taxus Liberté, Endeavor, Xience V en Resolute. Voor de meeste coating onregelmatigheden die aangetroffen zijn op geëxpandeerde DES geldt dat er een overeenkomstige onregelmatigheid en/of de precursor op de niet geëxpandeerde DES waargenomen werd. Dit hoofdstuk toont dat de meeste coating onregelmatigheden, of het potentieel om deze te ontwikkelen, inherent zijn aan de niet geëxpandeerde DES. Belangrijke determinanten voor de vorming van coating onregelmatigheden zijn mogelijk de stent geometrie en de fysieke eigenschappen van de coating, daarentegen speelt de interactie van de stent-ballon geen cruciale rol.

Hoofdstuk 6 bouwt voort op de bevindingen uit het 2^{e} hoofdstuk om de mechanismen uit te leggen van significante coating delaminering van phophorylcholine gebaseerde zotarolimus afgevende Endeavor stents, hetgeen door anderen aan het licht werd gebracht middels SEM bij mislukte pogingen deze stents te implanteren bij tortueuse en gecalcificeerde menselijke coronaire arteriën in vivo. Dit hoofdstuk laat zien hoe zowel klinisch georiënteerd onderzoek als bench top studies elkaar kunnen aanvullen.

In **Hoofdstuk 7** wordt SEM gebruikt om de biologisch afbreekbare polymelkzuur coating te onderzoeken bij biolimus afgevende stents. Bij normale implantatiedrukken toonden stents overwegend milde scheurtjes van de coating terwijl deze toenamen bij lichte oprekking. Agressieve overexpansie van een stent zoals dit soms nodig is bij hoofdstam bifurcatie letsel, verergerde de scheurtjes en zorgde voor enige loslating van coating fragmenten. De resultaten van dit hoofdstuk kunnen gebruikt worden door interventie cardiologen bij het toepassen van post-dilatatie van de onderzochte biolimus afgevende stent aangezien dit kan

leiden tot loslating van grotere delen van de coating. Dit laatste is met name van belang bij grote coronaire bifurcatie laesies alsmede bij het ostium van grote zijtakken alwaar DES niet volledig begrensd wordt door de vaatwand.

In **Hoofdstuk 8** wordt aandacht geschonken aan resultaten van recent bench top en pre-klinisch onderzoek met betrekking tot de polymeer gebaseerde coatings van diverse typen DES. Het hoofdstuk gaat in op technische uitdagingen, vertaling naar klinische relevantie en geboden perspectieven op basis van deze studies. Daarnaast worden voor- en nadelen besproken van het gebruik van polymeer gebaseerde coatings in DES. Voorts is er aandacht voor het standaardiseren van bench top onderzoeksprotocollen voor de analyse van DES coatings en het verwerken van deze protocollen in Europese toelatingsprocedures.

Hoofdstuk 9 vergelijkt de incidentie van peri-procedurele myocard infarcten tussen eerste en tweede generatie DES bij 800 patiënten welke werden behandeld met een eerste (Taxus Liberté of Endeavor) of tweede (Xience V of Resolute) generatie DES. Er was geen significant verschil in het optreden van een peri-procedureel infarct tussen de eerste en tweede generatie DES (5,5% vs. 4,0% p=0,29). Dit hoofdstuk toont aan dat de toename van meervats behandeling samengaand met de introductie van tweede generatie DES niet geassocieerd is met een toename van peri-procedurele myocard infarcten in vergelijking met eerste generatie DES.

Hoofdstuk 10 geeft een weergave van de belangrijkste één jaars follow-up resultaten van de TWENTE trial (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting SteNt Study: Head-to-head Comparison of Clinical Outcome After Implantation of Second Generation Drug-eluting Stents in a Real World Scenario; NCT01066650). De TWENTE trial is een onderzoeker geïnitieerde, patiënt geblindeerde, gerandomiseerde studie welke de veiligheid en effectiviteit van de Resolute zotarolimus-eluting stent en de Xience V everolimus-eluting stent vergelijkt bij 1.391 patiënten met beperkte exclusie criteria. Het primaire eindpunt Target Vessel Faillure (TVF; samengesteld uit cardiale dood, myocard infarct niet duidelijk toe te schrijven aan non-target vessels en klinisch geïndiceerde target vessel revascularisatie) deed zich voor in 8,2% en 8,1% respectievelijk ($p_{\text{non-inferiority}}$ = 0,001). Het aantal definitieve of mogelijke stent trombose aantallen was relatief laag en vergelijkbaar voor beide DES (0,9% en 1,2%, respectievelijk, p = 0,59). De bevindingen van deze grote gerandomiseerde klinische trial toonden aan dat Resolute stents non-inferieur zijn ten op zichte van de Xience V stents bij de behandeling van “alledaagse” patiënten met een meerderheid aan complexe laesies en off-label indicaties voor DES. Daarnaast werd een algemeen lage incidentie van stent trombose gezien in beide armen van de studie.

De TWENTE trial includeerde een “alledaagse” patiëntenpopulatie bestaande uit meer dan 80% van alle geschikte patiënten. In **Hoofdstuk 11** onderzoeken we of geschikte, niet-geïncludeerde patiënten, verschillen van de gerandomiseerde TWENTE trial populatie met betrekking tot baseline karakteristieken en één jaars uitkomsten. Baseline karakteristieken van 1.709 geschikte patiënten werden geanalyseerd (318 niet-geïncludeerde en 1.391 gerandomiseerde patiënten). Niet-geïncludeerde en gerandomiseerde patiënten verschilden alleen in leeftijd en cardiovasculaire voorgeschiedenis. Echter de klinische uitkomst na één jaar, en in het bijzonder het primair samengestelde eindpunt TVF (9,8% vs. 8,1%, p=0,34), verschilde niet significant. De bevindingen van dit hoofdstuk laten zien dat ondanks enkele verschillen in baseline karakteristieken, niet geïncludeerde en gerandomiseerde patiënten niet verschillen in één jaars uitkomst, hetgeen ten faveure was voor beide populaties en mogelijk gerelateerd aan de gebruikte drug-eluting stents.

Hoofdstuk 12 toont een vooraf gedefinieerde subanalyse van de geslachts gestratificeerde TWENTE studie met als doel de veiligheid en effectiviteit van de Resolute en Xience V DES in vrouwen te beoordelen. TVF na 1 jaar was het vooraf gedefinieerde eindpunt. Van de 1.391 patiënten werden 382 (27,5%) vrouwen gerandomiseerd naar een Resolute of Xience V stent. Baseline en procedurele karakteristieken waren vergelijkbaar voor vrouwen in beide studie armen, behalve voor kleinere vaten en stent diameter bij de met een Resolute behandelde laesies. Na 1 jaar was TVF (8,9 vs. 8,4%, p=0,91) en het patiënt georiënteerde samengestelde eindpunt (13,0 vs. 12,1%, p=0,79) niet significant verschillend voor vrouwen in beide stent armen. Tevens waren vrouwen behandeld in de TWENTE trial ouder dan mannen en hadden zij frequenter diabetes mellitus en arteriële hypertensie, maar was er geen significant verschil in geslacht voor wat betreft TVF (gecorrigeerde OR: 1,18, p = 0,50). De bevindingen van dit hoofdstuk laten zien dat er geen significant verschil is met betrekking tot veiligheid of effectiviteit in uitkomst tussen de met een Resolute of Xience V behandelde vrouwen.

DES wordt toenemend gebruikt voor de behandeling van complexe laesies bij een uitdagende coronaire anatomie zoals tortueuse en gecalcificeerde coronaire vaten hetgeen meer eist van de DES in termen van stent positionering. Als antwoord op deze vraag zijn recentelijk derde generatie DES ontwikkeld met meer flexibele designs en verbeterde mogelijkheden met betrekking tot specifieke positionering. **Hoofdstuk 13** beschrijft de gedachte en het design van een multicenter, prospectieve, enkel blind, gerandomiseerde trial ter vergelijking van de klinische uitkomsten van een derde generatie Resolute Integrity zotarolimus-eluting stents and Promus Element everolimus-eluting stents (DUrable Polymer-based STent CHallenge of Promus Element Versus ReSolute Integrity in an All Comers Population; DUTCH PEERS). In de DUTCH PEERS (TWENTE II) zal een brede populatie van tenminste 1.788 patiënten

worden onderzocht. Het primaire eindpunt is de incidentie van TVF na een jaar follow-up (non-inferiority hypothese). Dit hoofdstuk beschrijft de rationale en ontwerp van de eerste gerandomiseerde multicenter trial met een directe vergelijking tussen de Promus Element en de Resolute Integrity stent om de veiligheid en effectiviteit van deze derde generatie DES te onderzoeken.

Conclusies

Bench top analyse middels SEM en micro-CT kan waardevolle inzichten verschaffen in de oppervlakte morfologie en stent geometrie van DES. Hoewel agressieve, oversized, gedeeltelijke post-dilatatie van DES bijna geen effect heeft op de morfologie van de coating, verschilt DES significant in de uiteindelijke ruimtelijke stent configuratie en cel grootte, welke met name aanzienlijk groter zijn bij tweede generatie DES. Daarnaast waren DES coating morfologiën het meest gunstig in tweede generatie DES. De positieve bevindingen van bench top onderzoek bij tweede generatie DES werden ondersteund door de gunstige klinische uitkomsten van de “alledaagse” patiëntenpopulatie van zowel de gerandomiseerde TWENTE trial, als de subpopulatie van niet geïncludeerde maar wel geschikte patiënten. De integratie van meer flexibelere en beter positioneerbare stent designs vormt de volgende stap in de verbetering van de op duurzame coating gebaseerde DES. Dit zal zorgvuldig worden onderzocht in de gerandomiseerde DUTCH PEERS (TWENTE II) multi-center trial waarin twee derde generatie DES worden vergeleken in een brede populatie.

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Six months later, I started as a research fellow in the interventional cardiology research group on two projects: bench top research on drug-eluting stents and the randomized TWENTE trial, both initiated and supervised by Prof. Clemens von Birgelen. Dear Clemens, it has been a privilege working for you. I am very grateful for the opportunity you gave me to conduct clinical and laboratory research and to learn from your experience as an eminent expert in interventional cardiology research. I also thank you for encouraging me to walk new paths, to be creative, and to use my skills in mathematics – a favorite subject and previous hobby of mine – to develop (in the absence of any standard) approaches of quantitative assessment of bench top images of coronary stents. I thank you for being my promotor and mentor. After years of working together, I have not just gained a PhD, but I have also gained a valued friend.
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CURRICULUM VITAE

Mounir Basalus was born on August 28, 1977, in Cairo, Egypt. He completed medical and clinical training at the faculty of medicine, Ain Shams university. Since 2008 he worked as a member of the interventional cardiology research group, chaired by Prof. von Birgelen at Medisch Spectrum Twente in Enschede, the Netherlands. Since 2010, he is being trained at Medisch Spectrum Twente as a cardiologist. Mounir is married to Foekje and has a son called Damian.

PUBLICATION LIST

1. **Basalus MW**, Joner M, von Birgelen C, Byrne RA.
Polymer coatings on drug-eluting stents: Samson's hair and Achilles' heel?
EuroIntervention. 2013;9:302-5.

2. Tandjung K, Sen H, Lam MK, **Basalus MW**, Louwerenburg JH, Stoel MG, van Houwelingen KG, de Man FH, Linssen GC, Saïd SA, Nienhuis MB, Löwik MM, Verhorst PM, van der Palen J, von Birgelen C. Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial.
J Am Coll Cardiol. 2013;61:2406-16.

3. Tandjung K, **Basalus MW**, Sen H, Stoel MG, van Houwelingen KG, Louwerenburg JH, de Man FH, Linssen GC, Saïd SA, Kleijne MA, van der Palen J, von Birgelen C.
Women treated with second-generation zotarolimus-eluting resolute stents and everolimus-eluting xience V stents: insights from the gender-stratified, randomized, controlled TWENTE trial.
Catheter Cardiovasc Interv. 2013;82:396–405.

4. Tandjung K, van Houwelingen KG, Jansen H, **Basalus MW**, Sen H, Löwik MM, Stoel MG, Louwerenburg JH, de Man FH, Linssen GC, Nijhuis R, Nienhuis MB, van der Palen J, Stolk RP, von Birgelen C.
Comparison of frequency of periprocedural myocardial infarction in patients with and without diabetes mellitus to those with previously unknown but elevated glycated hemoglobin levels (from the TWENTE Trial).
Am J Cardiol. 2012;110:1561-7.

5. de Man FH, Tandjung K, Hartmann M, van Houwelingen KG, Stoel MG, Louwerenburg HW, **Basalus MW**, Sen H, Löwik MM, von Birgelen C.
Usefulness and safety of the GuideLiner catheter to enhance intubation and support of guide catheters: insights from the Twente GuideLiner registry.
EuroIntervention. 2012;8:336-44.

6. Sen H, Tandjung K, **Basalus MW**, Löwik MM, van Houwelingen GK, Stoel MG, Louwerenburg HW, de Man FH, Linssen GC, Nijhuis R, Nienhuis MB, Verhorst PM, van der Palen J, von Birgelen C.
Comparison of eligible non-enrolled patients and the randomised TWENTE trial population treated with Resolute and Xience V drug-eluting stents.
EuroIntervention. 2012;8:664-71.

7. Tandjung K, **Basalus MW**, Sen H, Jessurun GA, Danse PW, Stoel M, Linssen GC, Derks A, van Loenhout TT, Nienhuis MB, Hautvast RW, von Birgelen C.
DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity (DUTCH PEERS): rationale and study design of a randomized multicenter trial in a Dutch all-comers population.
Am Heart J. 2012;163:557-62.

8. von Birgelen C, **Basalus MW**, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, Linssen GC, Saïd SA, Kleijne MA, Sen H, Löwik MM, van der Palen J, Verhorst PM, de Man FH.
A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial.
J Am Coll Cardiol. 2012;59:1350-61.

9. Tandjung K, **Basalus MW**, Muurman E, Louwerenburg HW, van Houwelingen KG, Stoel MG, de Man FH, Jansen H, Huisman J, Linssen GC, Droste HT, Nienhuis MB, von Birgelen C.
Incidence of periprocedural myocardial infarction following stent implantation: comparison between first- and second-generation drug-eluting stents.
Catheter Cardiovasc Interv. 2012;80:524-30.

10. **Basalus MW**, Tandjung K, van Westen T, Sen H, van der Jagt PK, Grijpma DW, van Apeldoorn AA, von Birgelen C.
Scanning electron microscopic assessment of coating irregularities and their precursors in unexpanded durable polymer-based drug-eluting stents.
Catheter Cardiovasc Interv. 2012;79:644-53.

11. **Basalus MW**, Said SA, Stassen CM, Fast JH.
Clinical and diagnostic features of partially anomalous pulmonary venous connection in an adult female patient: a case report and review of the literature.
Neth Heart J. 2011;19:256-8.

12. **Basalus MW**, Tandjung K, Van Apeldoorn AA, Ankone MJ, Von Birgelen C.
Effect of oversized partial postdilatation on coatings of contemporary durable polymer-based drug-eluting stents: a scanning electron microscopy study.
J Interv Cardiol. 2011;24:149-61.

13. **Basalus MW**, Tandjung K, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JW, Saïd SA, Linssen GC, Kleijne MA, van der Palen J, Huisman J, Verhorst PM, von Birgelen C.
TWENTE Study: The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente: study design, rationale and objectives.
Neth Heart J. 2010;18:360-4.

14. von Birgelen C, **Basalus MW.**
On the loss of the phosphorylcholine-based DES coating on the abluminal surface of Endeavor stents.
Catheter Cardiovasc Interv. 2010;76:158-9.

15. **Basalus MW**, van Houwelingen KG, Ankone MJ, Feijen J, von Birgelen C.
Micro-computed tomographic assessment following extremely oversized partial postdilatation of drug-eluting stents.
EuroIntervention. 2010;6:141-8.

16. Huisman J, Hartmann M, Mattern ES, Mintz GS, **Basalus MW**, van Houwelingen GK, Verhorst PM, von Birgelen C.
Impact of analyzing less image frames per segment for radiofrequency-based volumetric intravascular ultrasound measurements in mild-to-moderate coronary atherosclerosis.
Int J Cardiovasc Imaging. 2010;26:487-97.

17. **Basalus M**, Louwerenburg JW, van Houwelingen KG, Stoel MG, von Birgelen C.
Primary percutaneous coronary intervention in the left main stem of a monocoronary artery.
Neth Heart J. 2009;17:274-6.

18. **Basalus MW**, van Houwelingen KG, Ankone M, de Man FH, von Birgelen C.
Scanning electron microscopic assessment of the biodegradable coating on expanded biolimus-eluting stents.
EuroIntervention. 2009;5:505-10.

19. **Basalus MW**, Ankone MJ, van Houwelingen GK, de Man FH, von Birgelen C.
Coating irregularities of durable polymer-based drug-eluting stents as assessed by scanning electron microscopy.
EuroIntervention. 2009;5:157-65.

20. **Basalus MW**, Tandjung K, Sen H, van Apeldoorn A A , Grijpma D W , von Birgelen C.
Recent insights from scanning electron microscopic assessment of durable polymer-coated drug-eluting stents
Interventional Cardiology. 2012; 4: 661-74.

21. **Basalus MW**, Clemens von Birgelen
Benchside testing of drug-eluting stent surface and geometry
Interventional Cardiology. 2010;2: 159-75.

PROPOSITIONS

Belonging to the dissertation

Drug-eluting Stents: From Bench-top to Clinical Research

1. Coating defects of particular drug-eluting stents are as distinctive as fingerprints. *(this thesis)*
2. Coating defects of drug-eluting stents typically result from built-in weaknesses. *(this thesis)*
3. The results of the TWENTE trial distinguish both, examined stents and medical care for patients with coronary disease in the region of Twente. *(this thesis)*
4. Peri-procedural myocardial infarctions may result either from lesions or from stents. *(this thesis)*
5. Everything we hear is an opinion, not a fact. Everything we see is a perspective, not the truth. *(Marcus Aurelius)*
6. Using highly flexible thin-strut stents for easily accessible, simple coronary lesions may feel like driving with a Formula 1 sports car through a pedestrian priority area. *(my promotor)*
7. An advantage of the locality of Enschede is the relatively long train journey that is required to reach it from the western metropolitan areas.
8. You can tell whether a man is clever by his answers. You can tell whether a man is wise by his questions. *(Naguib Mahfouz, Egyptian writer who won in 1988 the Nobel Prize for Literature)*