Clinical Assessment of Drug-Eluting Stents

TWENTE Trial and Beyond

Kenneth Tandjung

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TWENTE TRIAL AND BEYOND

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Chapter 1
General Introduction

Introduction

Until 1977, obstructive coronary artery disease could only be treated by pharmacotherapy or by surgery with coronary artery bypass grafting (CABG). Andreas Grüntzig then introduced the use of miniaturized inflatable balloon catheters to perform percutaneous transluminal coronary angioplasty (PTCA) procedures in humans,[1, 2] thereby launching a new revolutionary field of medicine that nowadays is called interventional cardiology.

From balloon angioplasty to bare metal stents

By PTCA, which is also called plain old balloon angioplasty (POBA), the narrowed coronary arterial segment is stretched and dilated, in order to improve coronary blood flow. POBA was quite often successful to treat focal coronary stenoses. However, it was hampered by both, the risk of acute vessel closure, which occurred mainly as a result of major dissections, and the high incidence of restenosis (i.e., recurrence of the obstruction) due to early elastic recoil, proliferative growth of the intimal layer, and procedure-induced late constrictive remodeling of the coronary vessel wall.[3, 4]

Over the years, the technique of percutaneous coronary intervention (PCI) has been improved in several ways. The introduction of stents,[5] which are metallic mesh tubes, resulted in an impressive improvement. Stents were initially only inserted to treat or prevent acute vessel closure following POBA, because of their scaffolding properties that could counteract the early elastic recoil of the vessel wall after balloon deflation and prevent dissections from obstructing the lumen.[6] The development and clinical use of feasible balloon-expandable coronary stents[7] and the knowledge from randomized trials that PCI with stents had a lower incidence of restenosis and better clinical outcome than POBA gave rise to a triumphant progress of PCI and coronary stenting.[8-10] Intravascular ultrasound imaging has played an important role in this context, as it demonstrated that use of larger balloon diameters and higher inflation pressures were safe and resulted in superior clinical outcome.[11-13]

While the early stents significantly reduced the incidence of restenosis by virtually abolishing elastic recoil of the vessel wall, they did not completely eliminate the restenosis problem.[14-17] Balloon and strut-induced injuries to the vessel wall often caused a substantial proliferation of neointima,[18] which in approximately 30% of cases resulted in a significant instent restenosis that required re-intervention.[19] As PCI of instent restenosis was associated with a much lower success rate than PCI of de-novo coronary lesions, the problem of instent restenosis remained the foremost limitation of PCI with bare metal stents.[20, 21] Various attempts to overcome this limitation by systemic or intracoronary application of drugs were made but failed.[22]

Drug-eluting stents

At last, durable polymer coatings, loaded with drugs that interfere with pathways involved in neointimal proliferation, were attached onto the bare metal stents in order to prevent restenosis. The anti-proliferative drugs that were locally delivered from the drug-eluting stents (DES) either blocked the cell cycle (mainly of vascular smooth muscle cells) from the G1 to the S phase (e.g. sirolimus)[23] or stabilized microtubules to inhibit cell division in the G0/G1 and G2/M phases (e.g. paclitaxel).[24] The polymer coating on the metal stent was employed to carry the anti-proliferative drug and to guarantee controlled drug-release kinetics. For this purpose, DES were generally composed of a bare metal stent platform, a polymer coating, and an anti-proliferative drug.[25]

In first-generation DES, sirolimus was employed as anti-proliferative drug in the Cypher stent (Cordis Europa, Roden, Netherlands) and paclitaxel in the Taxus stent (Boston Scientific Corp., Natick, MA, USA). Both DES showed in the first clinical trials very promising results and were clearly superior to conventional bare metal stents.[26, 27] The restenosis rates dropped dramatically following the use of DES, which were readily adopted into clinical practice by the interventional community. In 2006, however, there was a growing concern about the long-term safety of DES.[28, 29] Stent thrombosis (ST), an acute thrombotic occlusion of coronary stents that often results in myocardial infarction and sometimes death, was more often seen in DES than in bare metal stents.[28] Several clinical, anatomical, procedural, and stent-related factors were identified to increase the risk of ST, among them being the premature cessation of dual anti-platelet therapy,[30] PCI for acute coronary syndromes,[31] PCI of bifurcations with side branch stenting, and suboptimal stent deployment with significant malapposition of the stent (i.e., a significant number of stent struts is not well-apposed to the coronary artery wall).[32] In addition, it was hypothesized that the limited biocompatibility of the durable polymer coatings of first-generation DES promoted thrombus formation by causing delayed strut endothelialization, hypersensitivity reactions, and a prolonged inflammatory response. [33, 34]

Second-generation DES

To overcome the limitations related to the limited biocompatibility of the durable coatings of first-generation DES, more biocompatible polymer coatings were developed and subsequently used in second-generation DES. The Resolute stent (Medtronic Vascular, Santa Rosa, CA, USA) and the Xience V stent (Abbott Vascular, Santa Clara, CA, USA) are two second-generation DES. Both employ cobalt-chromium bare metal stent platforms, which are characterized by a higher flexibility as compared to stainless steel stents. The Resolute stents elute the anti-proliferative drug zotarolimus from a coating that further consists of a special blend of three different polymers.[35] The Xience V stent elutes everolimus from a thin fluoropolymer-based coating and was also available under the trade name Promus (Boston Scientific).[36]

In order to assess the safety and efficacy of newly developed stents (prior to registration by the regulatory bodies), stents were usually studied in patients with so-called "on-label" indications for stenting. These patients represent a low-risk patient population with typically less challenging coronary anatomies and clinical syndromes. However, such study population does not necessary reflect the average patients seen in daily practice, as more than half of the PCI patients have at least one "off-label" criterion (e.g. bifurcation lesion, long lesion, presentation with a myocardial infarction).[37] Therefore, more recent stent trials enrolled increasingly complex patients, leading ultimately to "all-comer trials". In these trials, only very few exclusion criteria in order to thoroughly evaluate the safety and efficacy of novel devices in "real-world" patient populations.[38] While the two aforementioned second-generation DES had been compared to first-generation DES, no data on the randomized head-to-head comparison of both DES were available.

In real-world patient populations, interventional cardiologists are confronted with challenging coronary anatomies due to advanced coronary disease and age of patients with an increased prevalence of risk factors. The tortuous coronary vessels and complex lesion anatomies (e.g. long, calcified, distal, and/or bifurcated lesions) that are encountered in such patient populations sometimes require measures to increase the back-up of the guiding catheter, meticulous lesion preparation, and stent postdilatation, in order to deliver and optimally implant stents. One of the measures to increase the back-up of the guiding catheter is the GuideLiner catheter (Vascular Solutions Inc., Minneapolis, MN, USA), a guiding catheter extension that can be deeply advanced into target vessels.[39] Only a limited number of reports and case series with use of this system were published, showing promising results.[40] Particularly in long lesions and bifurcated lesions with considerable vessel tapering along the stented segment, postdilatation of stents can be helpful to optimize stent strut apposition to the vessel wall, which may reduce the incidence of restenosis and stent thrombosis.[41]

TWENTE trial

The TWENTE trial, which enrolled patients from June 2008 to August 2010, was the first large randomized controlled stent study of the interventional cardiology department of Thoraxcentrum Twente and one of the first clinical trials to investigate two second-generation DES in a real-world patient population. Safety and efficacy of the two devices was assessed in 1391 patient with various expressions of coronary artery disease and many off-label indications for DES use, who were randomized for treatment with one of both DES. As women are often underrepresented in cardiovascular research[42, 43] and less than one-third of all cardiovascular clinical trials report sex-specific results,[44] the TWENTE trial employed gender stratification to allow for gender-specific subgroup analyses in order to gain more insight in the potential impact of gender on the outcome of PCI with second-generation DES.

DES and the risk of periprocedural myocardial infarction

One of the parameters that characterize the short-term performance of PCI is the incidence of periprocedural myocardial infarction (MI), which is a procedure-related adverse event that contributes to composite clinical endpoints of clinical stent trials. Several studies have shown a relation between the occurrence of periprocedural MI and mortality. Nevertheless, the clinical value of periprocedural MI is a matter of ongoing debate. Factors that have been associated with an increased risk of periprocedural MI are related to the general atherosclerotic burden; examples may be: multivessel disease, lesion eccentricity, lesion calcification, intraluminal thrombus, advanced age, and overt diabetes mellitus. Diabetic patients may be particularly prone to periprocedural MI as diabetes is associated with dyslipidemia, increased coagulability, higher atherosclerotic burden, and more vessel wall inflammation and vulnerable plaques.[45] Unfavorable device characteristics of DES may also contribute to the occurrence of periprocedural MI. For instance, displacement of DES coating of a relevant size may lead to microvascular obstruction and periprocedural myocardial necrosis.[46]In addition, increased roughness of the DES surface might increase thrombogenicity and the risk of stent thrombosis.[47]

Third-generation DES

The design of DES is constantly evolving. While the main alteration in second-generation DES was the use of more biocompatible durable polymer coatings, third-generation DES employed refined highly flexible stent platforms to improve DES deliverability in order to facilitate PCI in challenging lesions that are increasingly seen in routine clinical practice. However, these modifications in stents design may have potential drawbacks such as a reduced longitudinal stability of the device, which may increase the risk of certain procedure-related complications such as a longitudinal stent deformation.[48]

The zotarolimus-eluting Resolute Integrity stent (Medtronic) is a third-generation DES. It employs a novel, sinusoidal-formed, helically wrapped design of the cobalt-chromium stent for increased flexibility and deliverability; the coating is the same as used in the second-generation Resolute stent. The everolimus-eluting Promus Element stent (Boston Scientific) uses a platinum-chromium alloy-based stent platform, consisting of short serpentine rings connected by helically distributed links. The stent is designed for improved deliverability and visibility and is covered by the same coating as used in second-generation Xience V / Promus stents.[49]

In the DUTCH PEERS trial (TWENTE II), the safety and efficacy of Resolute Integrity and Promus Element stents was evaluated in an all-comer patient population. While some studies on Promus Element stents had been performed in patients with mild-to-moderate clinical risk,[50] no such data were available for the Resolute Integrity stent. DUTCH PEERS was the

first randomized trial to investigate the Resolute Integrity stent and the first randomized trial to compare these two third-generation DES with each other.

Biodegradable polymer DES

Besides the refinement of permanent polymer coatings as used in second and third-generation DES, biodegradable DES coatings were developed to address the risk of very late stent thrombosis that was seen in first-generation DES. Such biodegradable polymer DES leave after degradation of the coating only a bare metal stent in the vessel wall, which does not induce a prolonged inflammation of the vessel wall.[51, 52] Randomized studies with these devices have shown non-inferiority or even superiority of early generation biodegradable polymer DES as compared to first-generation permanent polymer DES.[53, 54] However, there are also contradictory data, as one study failed to show non-inferiority of a biodegradable polymer DES compared to the first-generation Cypher stent.[55]

So far, no large randomized study has been published that compares biodegradable polymer DES to current generation permanent polymer DES. At present, modern biodegradable coating DES are clinically used that employ highly flexible stent platforms and different approaches regarding the speed of degradation and the spatial distribution of the biodegradable coating.[56] The Orsiro stent (Biotronik, Bülach, Switzerland) elutes sirolimus from a circumferential biodegradable coating, and the Synergy stent (Boston Scientific) elutes everolimus from an abluminal biodegradable coating.[57] In the ongoing randomized multicentric BIO-RESORT trial (TWENTE III), these two biodegradable coating DES are compared with the permanent polymer-based DES Resolute Integrity in a total of 3560 all-comer patients.

Outline of this thesis

As DES are constantly being refined and newer-generation DES enter the clinical arena with limited data on clinical performance, this thesis provides insight into the safety and efficacy of newer-generation DES, including data obtained in so-called real-world patient populations.

- **Chapter 1** serves as an introduction to this thesis and provides background information on DES and their development.
- In **Chapter 2**, we examine the safety and efficacy of the second-generation Resolute zotarolimus-eluting stents and the Xience V everolimus-eluting stents at one-year follow-up in the TWENTE trial, a randomized controlled trial with limited exclusion criteria and a high proportion of complex patients and lesions.
- In **Chapter 3**, we evaluate the real-world nature of the TWENTE trial

by comparing baseline characteristics and clinical outcome of patients enrolled in the TWENTE trial with eligible patients who were not enrolled in the randomized trial but treated with the same DES.

- In **Chapter 4**, we analyze the data of the gender-stratified TWENTE trial to assess potential differences in procedural and clinical outcome between women treated with Resolute and Xience V stents; in addition, we assess potential gender differences.
- In **Chapter 5**, we assess the two-year outcome data of the TWENTE trial, in which patients followed a stringent discontinuation of dual anti-platelet therapy after 12 months from stenting.
- In **Chapter 6**, we evaluate with scanning electron microscopy in a bench top setting the effects of stent postdilatation on the coatings of durable polymer DES.
- In **Chapter 7**, we assess the occurrence of periprocedural myocardial infarction following the implantation of first and second-generation DES, and analyze risk factors of periprocedural myocardial infarction.
- In **Chapter 8**, we use scanning electron microscopy to study and quantify coating irregularities and their precursors in unexpanded durable polymer DES to gain insight in the origin of coating irregularities.
- In **Chapter 9**, we investigate the effects of previously unrecognized and untreated diabetes on the risk of periprocedural myocardial infarction.
- In **Chapter 10**, we evaluate the relation between the Syntax Score, an angiographic scoring system that quantifies the coronary disease burden, and clinical outcome after PCI with second-generation DES in the prospective, randomized TWENTE trial.
- In **Chapter 11**, we assess the effect of coronary artery dominancy on the risk of adverse clinical events following PCI with second-generation DES.
- In **Chapter 12**, we provide insight into our center's clinical experience with the use of the GuideLiner, a guiding catheter extension system that enhances intubation and support of guiding catheters.
- In **Chapter 13**, we demonstrate an example of the challenging coronary lesions that interventional cardiologist encounter in daily clinical practice and show the aspiration of an intact coronary bifurcation thrombus in a patient with ST-elevation myocardial infarction, who was consecutively treated with a Resolute Integrity DES.
- In **Chapter 14**, we describe the design of the DUTCH PEERS trial (TWENTE II), the first randomized multicenter trial to investigate the Resolute Integrity stent and the first trial to compare the third-generation Resolute Integrity and Promus Element DES with each other.

- In **Chapter 15**, we describe the one-year clinical outcome of the randomized DUTCH PEERS trial to assess the safety and efficacy of the two third-generation DES in all-comer patients; in addition we assess the incidence and consequences of longitudinal stent deformation in this study population.
- In **Chapter 16**, we perform a comprehensive network meta-analysis to compare the safety and efficacy of biolimus-eluting biodegradable polymer stents with first and second-generation durable polymer DES.
- In **Chapter 16**, we describe the design of the BIO-RESORT trial (TWENTE III), a large, prospective, randomized, multicenter trial with three arms, comparing the Orsiro sirolimus-eluting stent with circumferential biodegradable coating, Synergy everolimus-eluting stent with abluminal biodegradable coating, and Resolute Integrity zotarolimus-eluting stent with durable coating.

References

1. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet. 1978 Feb 4;1(8058):263.
2. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: Percutaneous transluminal coronary angioplasty. N Engl J Med. 1979 Jul 12;301(2):61-8.
3. Holmes DR,Jr, Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): A report from the PTCA registry of the national heart, lung, and blood institute. Am J Cardiol. 1984 Jun 15;53(12):77C-81C.
4. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med. 1991 Jan 3;324(1):13-7.
5. 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 Mar 19;316(12):701-6.
6. Serruys PW, Strauss BH, van Beusekom HM, van der Giessen WJ. Stenting of coronary arteries: Has a modern pandora's box been opened? J Am Coll Cardiol. 1991 May;17(6 Suppl B):143B-54B.
7. Erbel R, Schatz R, Dietz U, Nixdorff U, Haude M, Aichinger S, et al. Balloon dilatation and coronary vascular stent implantation. Z Kardiol. 1989 Feb;78(2):71-7.
8. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. benestent study group. N Engl J Med. 1994 Aug 25;331(8):489-95.
9. Kiemeneij F, Serruys PW, Macaya C, Rutsch W, Heyndrickx G, Albertsson P, et al. Continued benefit of coronary stenting versus balloon angioplasty: Five-year clinical follow-up of benestent-I trial. J Am Coll Cardiol. 2001 May;37(6):1598-603.
10. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. stent restenosis study investigators. N Engl J Med. 1994 Aug 25;331(8):496-501.
11. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation. 1995 Mar 15;91(6):1676-88.
12. 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 Apr;23(8):595-7.
13. von Birgelen C, Gil R, Ruygrok P, Prati F, Di Mario C, van der Giessen WJ, et al. Optimized expansion of the wallstent compared with the palmaz-schatz stent: On-line observations with two- and three-dimensional intracoronary ultrasound after angiographic guidance. Am Heart J. 1996 Jun;131(6):1067-75.
14. Haude M, Erbel R, Issa H, Meyer J. Quantitative analysis of elastic recoil after balloon angioplasty and after intracoronary implantation of balloon-expandable palmaz-schatz stents. J Am Coll Cardiol. 1993 Jan;21(1):26-34.
15. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol. 1993 Jan;21(1):15-25.
16. de Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. Circulation. 1999 Oct 26;100(17):1777-83.
17. Serruys PW, Kay IP, Disco C, Deshpande NV, de Feyter PJ. Periprocedural quantitative coronary angiography after palmaz-schatz stent implantation predicts the restenosis rate at six months: Results of a meta-analysis of the BElgian NEtherlands stent study (BENESTENT) I, BENESTENT II pilot, BENESTENT II and MUSIC trials. multicenter ultrasound stent in coronaries. J Am Coll Cardiol. 1999 Oct;34(4):1067-74.
18. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, et al.

Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. J Am Coll Cardiol. 1992 Feb;19(2):267-74.
19. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med. 2001 Apr 12;344(15):1117-24.
20. Colombo A, Ferraro M, Itoh A, Martini G, Blengino S, Finci L. Results of coronary stenting for restenosis. J Am Coll Cardiol. 1996 Oct;28(4):830-6.
21. Gruberg L, Hong MK, Mintz GS, Mehran R, Waksman R, Dangas G, et al. Optimally deployed stents in the treatment of restenotic versus de novo lesions. Am J Cardiol. 2000 Feb 1;85(3):333-7.
22. de Feyter PJ, Vos J, Rensing BJ. Anti-restenosis trials. Curr Interv Cardiol Rep. 2000 Nov;2(4):326-31.
23. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest. 1996 Nov 15;98(10):2277-83.
24. Axel DI, Kunert W, Goggelmann C, Oberhoff M, Herdeg C, Kuttner A, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation. 1997 Jul 15;96(2):636-45.
25. Stefanini GG, Holmes DR,Jr. Drug-eluting coronary-artery stents. N Engl J Med. 2013 Jan 17;368(3):254-65.
26. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002 Jun 6;346(23):1773-80.
27. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004 Jan 15;350(3):221-31.
28. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: A cause for concern. Circulation. 2007 Mar 20;115(11):1440,55; discussion 1455.
29. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in sweden. N Engl J Med. 2007 Mar 8;356(10):1009-19.
30. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, et al. Predictors of coronary stent thrombosis: The dutch stent thrombosis registry. J Am Coll Cardiol. 2009 Apr 21;53(16):1399-409.
31. Kimura T, Morimoto T, Nakagawa Y, Kawai K, Miyazaki S, Muramatsu T, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: Five-year outcome of the j-cypher registry. Circulation. 2012 Jan 31;125(4):584-91.
32. Uren NG, Schwarzacher SP, Metz JA, Lee DP, Honda Y, Yeung AC, et al. Predictors and outcomes of stent thrombosis: An intravascular ultrasound registry. Eur Heart J. 2002 Jan;23(2):124-32.
33. Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, et al. Drug-eluting stent and coronary thrombosis: Biological mechanisms and clinical implications. Circulation. 2007 Feb 27;115(8):1051-8.
34. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological correlates of late drug-eluting stent thrombosis: Strut coverage as a marker of endothelialization. Circulation. 2007 May 8;115(18):2435-41.
35. Meredith IT, Worthley S, Whitbourn R, Walters D, Popma J, Cutlip D, et al. The next-generation endeavor resolute stent: 4-month clinical and angiographic results from the endeavor resolute first-in-man trial. EuroIntervention. 2007 May;3(1):50-3.
36. Ruygrok PN, Desaga M, Van Den Branden F, Rasmussen K, Suryapranata H, Dorange C, et al. One year clinical follow-up of the XIENCE V everolimus-eluting stent system in the treatment of patients with de novo native coronary artery lesions: The SPIRIT II study. EuroIntervention. 2007 Nov;3(3):315-20.
37. Beohar N, Davidson CJ, Kip KE, Goodreau L, Vlachos HA, Meyers SN, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA. 2007 May 9;297(18):1992-2000.

38. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, 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 Sep 27;372(9644):1163-73.
39. Mamas MA, Fath-Ordoubadi F, Fraser DG. Distal stent delivery with guideliner catheter: First in man experience. Catheter Cardiovasc Interv. 2010 Jul 1;76(1):102-11.
40. Farooq V, Mamas MA, Fath-Ordoubadi F, Fraser DG. The use of a guide catheter extension system as an aid during transradial percutaneous coronary intervention of coronary artery bypass grafts. Catheter Cardiovasc Interv. 2011 Nov 15;78(6):847-63.
41. Romagnoli E, Sangiorgi GM, Cosgrave J, Guillet E, Colombo A. Drug-eluting stenting: The case for post-dilation. JACC Cardiovasc Interv. 2008 Feb;1(1):22-31.
42. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, 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. Eur Heart J. 2011 Jun;32(11):1362-8.
43. Chieffo A, Hoye A, Mauri F, Mikhail G, Ammerer M, Grines C, et al. Gender-based issues in interventional cardiology: A consensus statement from the women in innovations (WIN) initiative. Rev Esp Cardiol. 2010 Feb;63(2):200-8.
44. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes. 2010 Mar;3(2):135-42.
45. Berry C, Noble S, Gregoire JC, Ibrahim R, Levesquie S, Lavoie MA, et al. Glycaemic status influences the nature and severity of coronary artery disease. Diabetologia. 2010 Apr;53(4):652-8.
46. 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 May;5(1):157-65.
47. Hecker JF, Scandrett LA. Roughness and thrombogenicity of the outer surfaces of intravascular catheters. J Biomed Mater Res. 1985 Apr;19(4):381-95.
48. Williams PD, Mamas MA, Morgan KP, El-Omar M, Clarke B, Bainbridge A, et al. Longitudinal stent deformation: A retrospective analysis of frequency and mechanisms. EuroIntervention. 2012 Jun 20;8(2):267-74.
49. Kereiakes DJ, Cannon LA, Feldman RL, Popma JJ, Magorien R, Whitbourn R, et al. Clinical and angiographic outcomes after treatment of de novo coronary stenoses with a novel platinum chromium thin-strut stent: Primary results of the PERSEUS (prospective evaluation in a randomized trial of the safety and efficacy of the use of the TAXUS element paclitaxel-eluting coronary stent system) trial. J Am Coll Cardiol. 2010 Jul 20;56(4):264-71.
50. 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 Apr 19;57(16):1700-8.
51. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet. 2011 Dec 3;378(9807):1940-8.
52. Raber L, Kelbaek H, Ostojic M, Baumbach A, Heg D, Tuller D, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: The COMFORTABLE AMI randomized trial. JAMA. 2012 Aug 22;308(8):777-87.
53. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: Final 5-year report of the LEADERS (limus eluted from A durable versus ERodable stent coating) randomized, noninferiority trial. JACC

Cardiovasc Interv. 2013 Aug;6(8):777-89.
54. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): A randomised, controlled, non-inferiority trial. Lancet. 2013 Feb 23;381(9867):651-60.
55. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, et al. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: A randomized, controlled, noninferiority trial. J Am Coll Cardiol. 2013 Jul 16;62(3):181-90.
56. Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrie D, et al. Primary endpoint results of the EVOLVE trial: A randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol. 2012 Apr 10;59(15):1362-70.
57. Meredith IT, Verheye S, Weissman NJ, Barragan P, Scott D, Valdes Chavarri M, et al. Six-month IVUS and two-year clinical outcomes in the EVOLVE FHU trial: A randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. EuroIntervention. 2013 Jul;9(3):308-15.

Efficacy and safety of second-generation drug-eluting stents

Chapter 2

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.

Introduction

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%).

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.

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.

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.

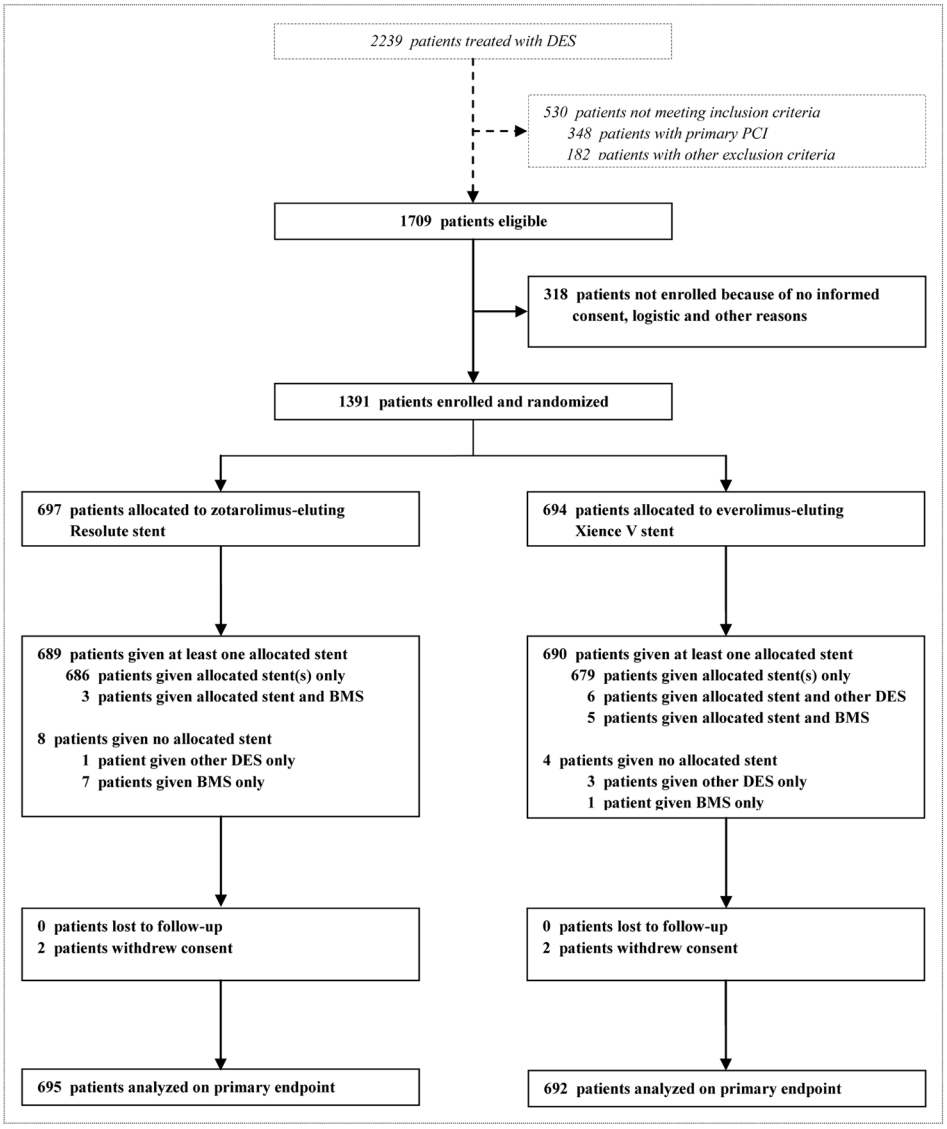
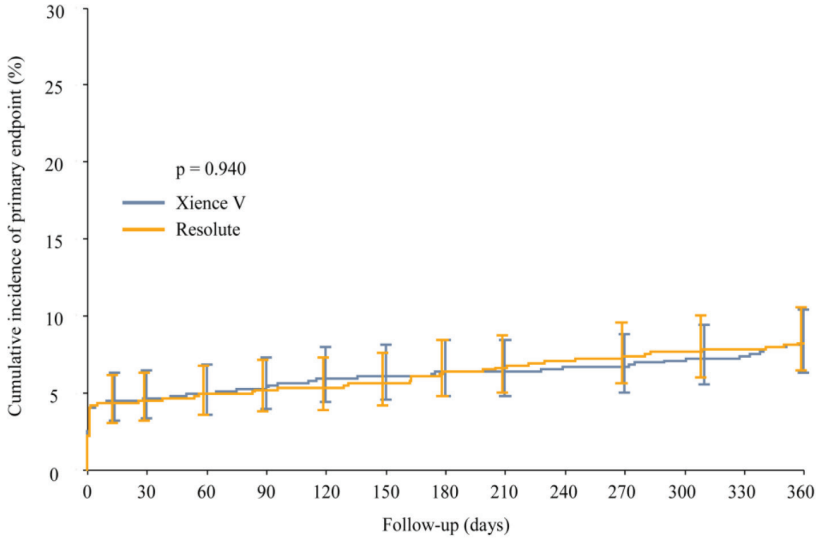


Figure 1. Trial profile

BMS = bare-metal stent(s); DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

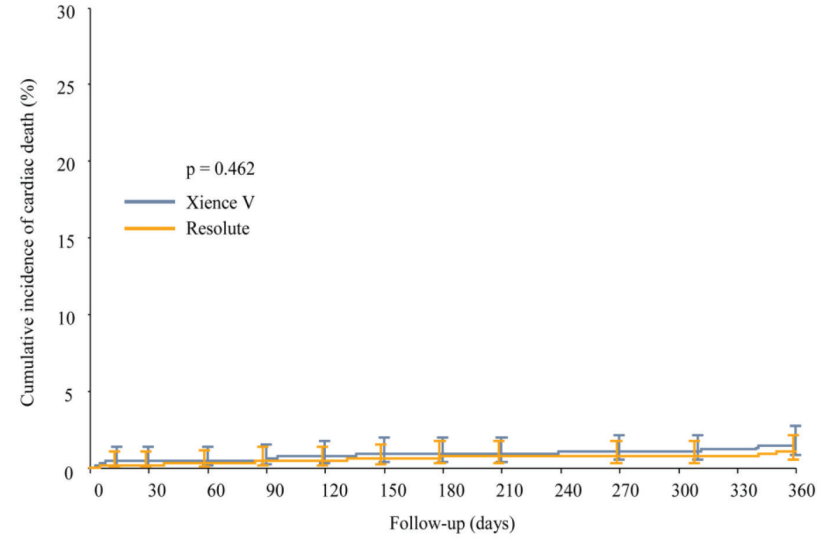
A



Number at risk

Xience V	694	662	660	656	651	648	646	646	644	643	639	637	632
Resolute	697	665	661	658	655	653	647	645	642	640	636	635	631

B



Number at risk

Xience V	694	691	691	689	687	684	684	684	683	682	681	680	678
Resolute	697	695	693	690	688	687	685	685	685	685	683	683	680

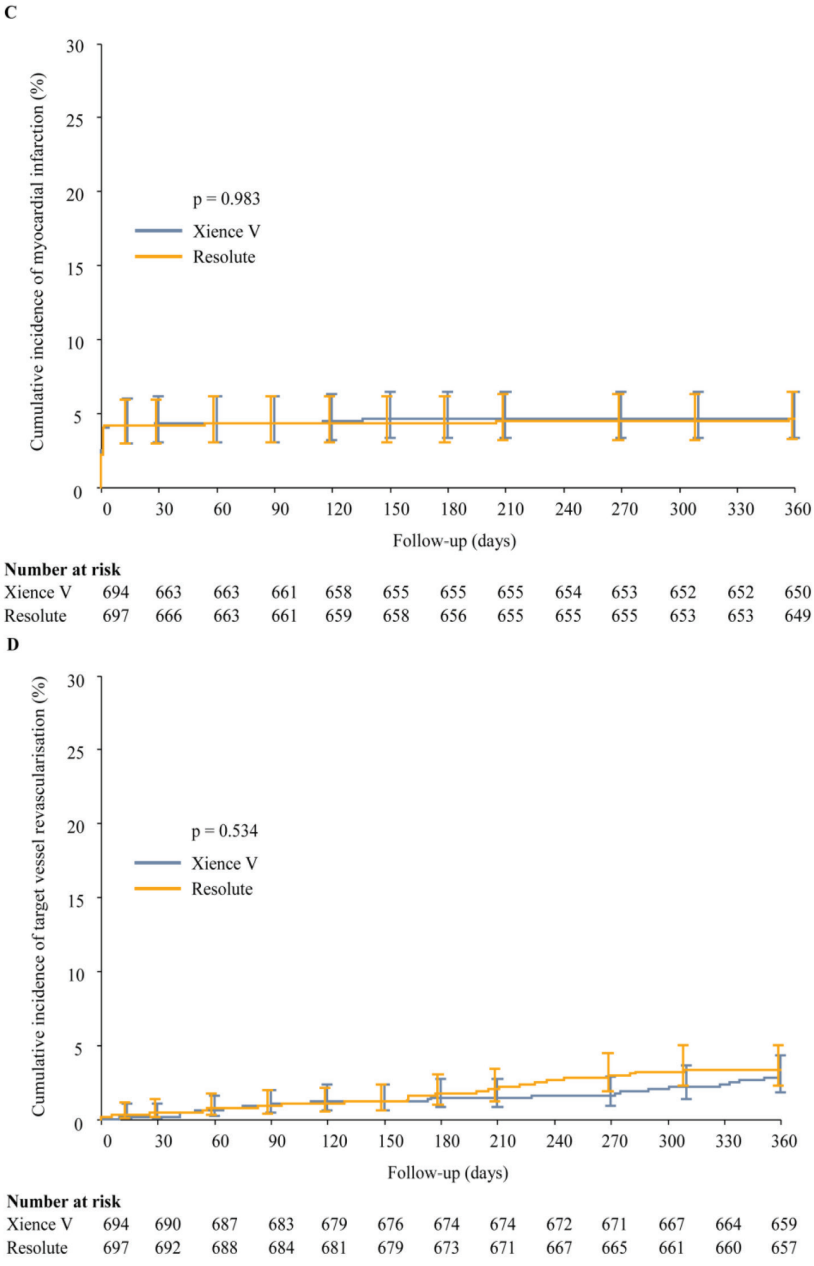


Figure 2. Kaplan-Meier for Primary Endpoint and the Individual Components of the Primary Endpoint

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.

	Zotarolimus-eluting Resolute	Everolimus-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
On-label indication (n=314)	2.0 (3/150)	4.3 (7/164)		0.47 [0.12, 1.78]	0.25
Vessel diameter < 2.75 mm (n=874)	9.2 (41/445)	8.4 (36/429)		1.10 [0.72, 1.68]	0.67
Vessel diameter ≥ 2.75 mm (n=517)	6.3 (16/252)	7.5 (20/265)		0.84 [0.45, 1.59]	0.59
NSTEMI < 72 hrs. (n=408)	6.9 (14/202)	8.7 (18/206)		0.79 [0.41, 1.55]	0.50
No NSTEMI < 72 hrs. (n=983)	8.7 (43/495)	7.8 (38/488)		1.16 [0.73, 1.70]	0.61
Multivessel PCI (n=336)	14.9 (26/174)	9.3 (15/162)		1.61 [0.89, 2.94]	0.11
Single vessel PCI (n=1055)	5.9 (31/523)	7.7 (41/532)		0.77 [0.49, 1.21]	0.25
Diabetes (n=301) *	13.9 (22/158)	7.7 (11/143)		1.81 [0.91, 3.60]	0.08
No diabetes (n=1090)	6.5 (35/539)	8.2 (45/551)		0.80 [0.52, 1.22]	0.29
Overlapping stents (n=503)	10.7 (26/244)	12.4 (32/259)		0.86 [0.53, 1.40]	0.55
No overlapping stents (n=888)	6.8 (31/453)	5.5 (24/435)		1.24 [0.74, 2.08]	0.41
Bifurcation lesion (n=362)	10.1 (18/179)	8.2 (15/183)		1.23 [0.64, 2.36]	0.54
No bifurcation lesion (n=1029)	7.5 (39/518)	8.0 (41/511)		0.94 [0.62, 1.43]	0.77
Lesion length > 27 mm (n=293)	15.4 (24/156)	13.9 (19/137)		1.12 [0.64, 1.94]	0.71
Lesion length ≤ 27 mm (n=1098)	6.1 (33/541)	6.6 (37/557)		0.92 [0.58, 1.45]	0.71
In-stent restenosis (n=69)	2.8 (1/36)	9.1 (3/33)		0.31 [0.03, 2.80]	0.34
No in-stent restenosis (n=1322)	8.5 (56/661)	8.0 (53/661)		1.06 [0.74, 1.51]	0.76
Renal insufficiency (n=38)	10.5 (2/19)	10.5 (2/19)		1.00 [0.16, 6.39]	1.00
No renal insufficiency (n=1353)	8.1 (55/678)	8.0 (54/675)		1.01 [0.71, 1.45]	0.94
Bypass graft treated (n=41)	25.0 (5/20)	28.6 (6/21)		0.88 [0.32, 2.42]	0.80
No bypass graft treated (n=1350)	7.7 (52/677)	7.4 (50/673)		1.03 [0.71, 1.50]	0.86
Left main treated (n=52)	11.5 (3/26)	11.5 (3/26)		1.00 [0.22, 4.51]	1.00
No left main treated (n=1339)	8.0 (54/671)	7.9 (53/668)		1.01 [0.71, 1.46]	0.94

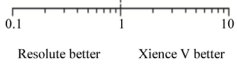


Figure 3. Subgroup analysis: Target vessel failure at one year.
Target vessel failure is a composite of cardiac death, target-vessel myocardial infarction, or clinically driven target vessel revascularization. *p = 0.045 for interaction between stent type and presence of diabetes mellitus; interaction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

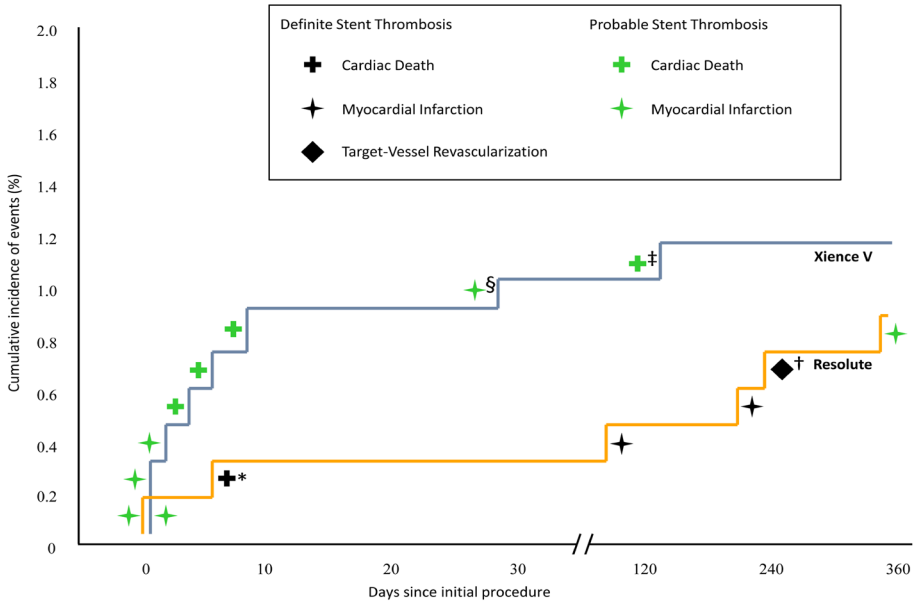


Figure 4. Cumulative incidence of definite or probable stent thrombosis.
*Cardiac death; patient enrolled for stenting of residual lesions in right and left anterior descending arteries 7 days after a non–ST-segment elevation myocardial infarction, treated with a bare-metal stent in circumflex artery. †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).

Table 1. Baseline Characteristics of Patients

	Total Population (n = 1,391)	ZES Resolute (n = 697)	EES Xience (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

	Total Population (n = 1,391)	ZES Resolute (n = 697)	EES Xience (n = 694)	p Value
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.

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.

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 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.

Chapter 3

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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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).

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). 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).

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).

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.

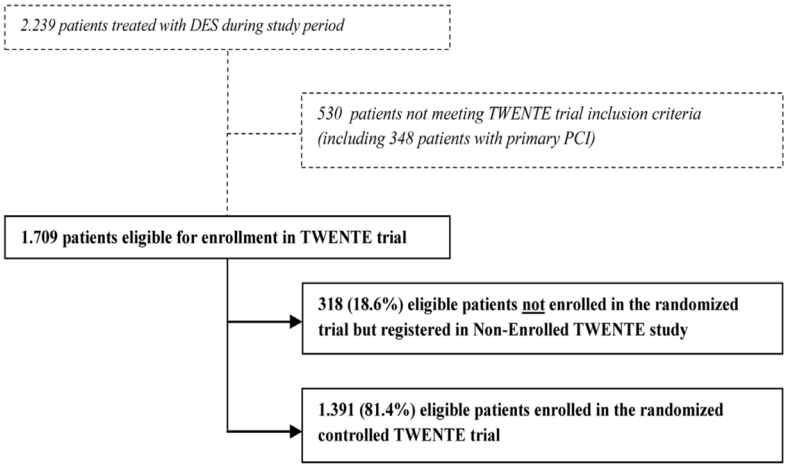

Figure 1. Flow chart of patients treated with DES during the course of the randomized TWENTE trial. Patients of the *Non-Enrolled TWENTE* study and the randomized TWENTE trial were compared. *Data of the randomized TWENTE trial have previously been reported.[17]

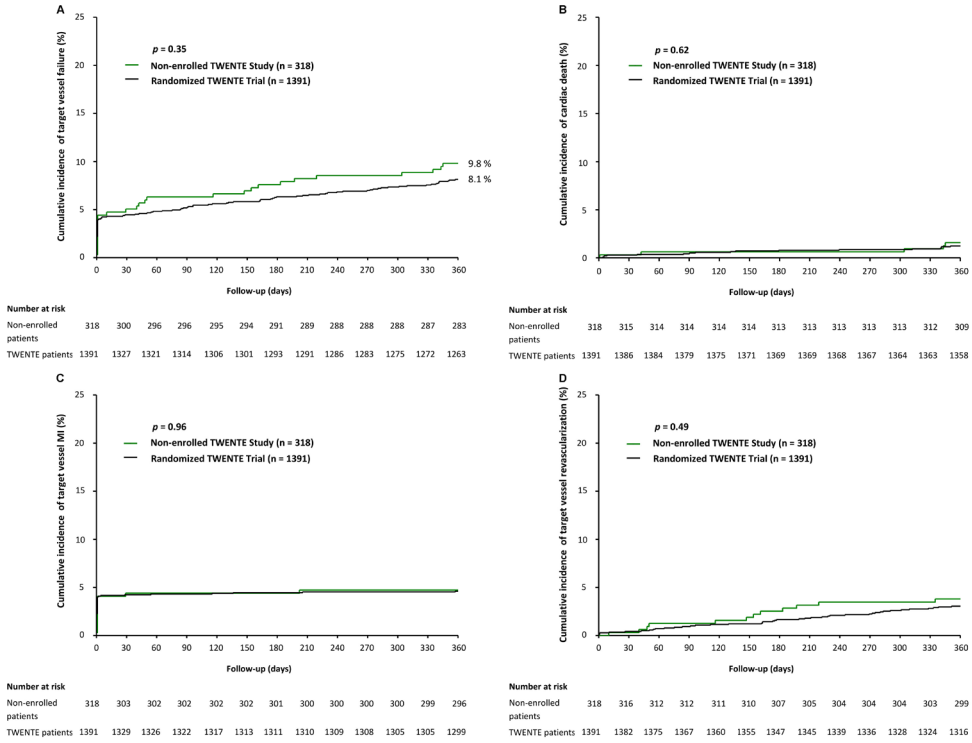

Figure 2. Kaplan-Meier for the primary endpoint and the individual components of the primary endpoint. Kaplan-Meier cumulative incidence curves at one year for the primary endpoint target-vessel failure, a composite of cardiac death, target-vessel related myocardial infarction, or target-vessel revascularization (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.

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.

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.

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.

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 4

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, randomised, comparative DES trial – 'real-world' patients were stratified for gender before randomization for Resolute or Xience V stents.
Methods: Clinical endpoints were adjudicated by an independent clinical events committee. 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 1391 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 OR: 0.95, 95%-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 of both arms. No definite stent thrombosis was observed in women. Probable stent thrombosis occurred in 0% of Resolute and 2.1% of Xience V-treated women (p=0.06). 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).
Conclusion: In this analysis of the gender-stratified TWENTE trial there was no significant difference in safety and efficacy between women treated with Resolute and Xience V.

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]

The present study reports gender-specific data of Resolute and Xience V from the randomized TWENTE trial, which recently compared these DES in 1391 '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 previously been described in detail.[12] In brief, TWENTE was an investigator-initiated, patient-blinded, randomized non-inferiority 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 Inc., Santa Rosa, CA) or Xience V stents (Abbott Vascular, Santa Clara, CA) in a 1:1 ratio 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 ST-elevation myocardial infarction (STEMI).[12] The TWENTE trial was approved by the institutional ethics committee and complied with the Declaration of Helsinki. Patients provided written informed consent.

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 pre-treated with acetylsalicylic acid and clopidogrel. At discharge, the combination of 100mg of acetylsalicylic acid once daily indefinitely and clopidogrel

75mg 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]

Quantitative coronary angiography. Quantitative coronary angiographic analyses were performed offline by experienced analysts at Thoraxcentrum Twente, using edge-detection software (QAngio XA 7.1, Medis, Leiden, the Netherlands). Measurements (baseline and final) were conducted according to current standards over entire segments, consisting of stented segment plus proximal and distal margins (each 5mm long).

Definitions of clinical endpoints. Definitions of all clinical endpoints have previously been described in detail.[12] In brief, the pre-specified 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 non-target vessel), or clinically driven target-vessel revascularization.

Pre-specified 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, including stent thrombosis, 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 practicioner, 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 Inc., 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 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), i.e. age, diabetes, renal failure, smoking status, hypertension, peripheral artery disease, previous CABG, 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, presence of thrombus, preprocedural reference vessel diameter, baseline stenosis, direct stenting, maximal stent diameter, postdilatation, number of stents placed, 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 1391 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 1009 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 4 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 1,2, and 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, Figure 1) and the patient-oriented composite endpoint were similar between groups (13.0% vs. 12.1%, p=0.79). There was a non-significant trend for less definite-or-probable stent thrombosis in women treated with Resolute versus Xience V (0% vs. 2.1%, p=0.06), while 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. However, there was no significant difference in angiographic or procedural characteristics (Table 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 of both treatment arms (p=0.99)(log-rank test p=0.99, Figure 2). Definite stent thrombosis occurred in none of the male patients treated with Xience V and in 4 males treated with Resolute stents (p=0.12).
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, while 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, Figure 3). Various other clinical outcome parameters showed no significant difference between women and men, but in women there was a trend towards 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 male patients (n=4) but not in women (p=0.58).

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 to 2.20, p=0.91), and men (adjusted OR: 0.92, 95%-CI: 0.58 to 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 to 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

In the past, cardiovascular research has paid insufficient attention to the investigation of heart disease in women.[1,18] For that reason, 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 (retrospective) registries. However, clinical evidence should preferably be derived from large, randomized clinical trials in relatively unselected patient populations.[19] As a consequence, 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, which permitted our present analysis. This pre-specified 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, although the vessel size at baseline was somewhat smaller in the Resolute arm. In addition, there was a trend towards fewer definite-or-probable stent thromboses in women treated

with Resolute versus Xience V (p=0.06); this was related to probable stent thromboses only (as no definite stent thrombosis occurred in this female population).

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. No gender-specific data from other head-to-head comparisons of Resolute and Xience V stents have been reported yet.

The female population of several major DES trials in all comer populations ranged from 23.1% to 29.3%.[9,10,20] 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)[21] as well as a trend that was observed from the analysis of 33 prospective European stent trials between 1995 and 2006: the proportion of women gradually increased from 22% (in 1995-1997) to 24% (in 1998-2002) and finally to 26% (in 2003-2006).[22] 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 strong progress in stent technology (e.g. improved stent material, stent design, delivery system, and development of drug-eluting stents), which facilitated stent implantation in coronary vessels with small lumen dimensions that are more frequent in women.[13,23]

Previous studies established an angiographic[24] and clinical benefit[8,25] 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.[24] This finding was consistent with results obtained from pooled data analyses of several ENDEAVOR studies and registries.[23,26]

Recent clinical 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, two 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. In that study, women treated with Xience V had after 8 months a somewhat higher binary restenosis rate compared to male patients. However, that difference was statistically non-significant.[27] As a matter of fact, the SPIRIT II-IV studies enrolled particularly high rates of women that ranged from 27% to 32.2%.[11,27]

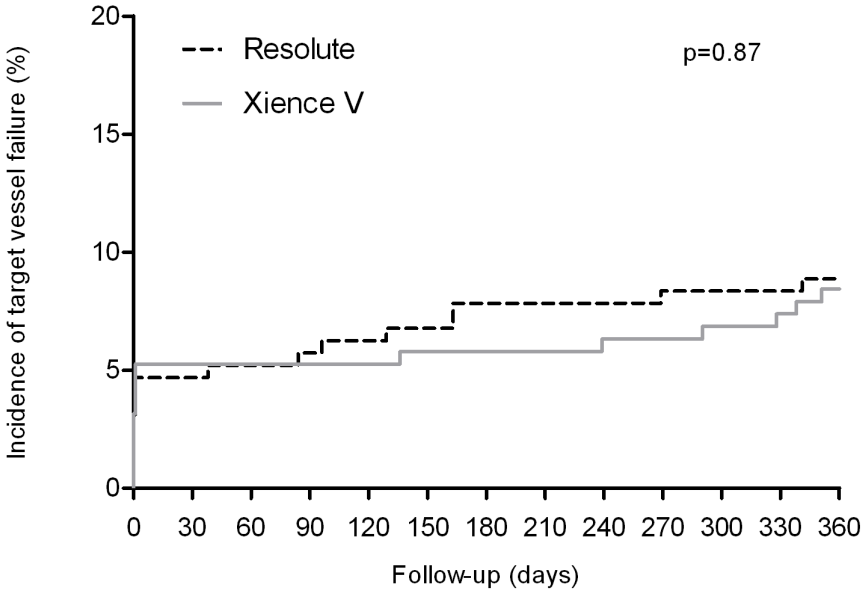
Gender and PCI outcome. In the pre-stent era, female gender was associated with an inferior outcome following PCI,[28-30] which has been partly related to the often higher cardiovascular risk profile and on average

smaller vessel size.[14,31] On the contrary, studies with first-generation DES show no clear relation between gender and outcome.[7,8,25,32] Only in one DES study, was female gender 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 relation between gender and clinical outcome after treatment with one of both 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 years vs. 68 years) that was recently reported for the Netherlands, based on data from all PCI in the year 2009.[21] In addition, women had a higher incidence of diabetes mellitus and hypertension ($p\leq0.01$), 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 ($p=0.09$).

Gender and stent thrombosis in DES. Stent thrombosis is a potentially lethal complication of coronary stenting that is relatively rare in second-generation DES.[9-12,33] The incidence of stent thrombosis is assumed to be similar for both genders.[7,25,34-36] Nevertheless, because of the low incidence of stent thrombosis in routine clinical practice and clinical trials, it is very difficult to draw a sound conclusion on this adverse event. This is even more difficult when addressing subpopulations such as female patients, who are generally underrepresented in trials.[1] In TWENTE, stent thrombosis was also rare both in the overall study population and in the female subpopulation. Nevertheless, it is quite remarkable that there was no definite stent thrombosis in women treated with one of both second-generation DES. The number of patients examined does not allow definite conclusions but suggest that there may be no excess risk of stent thrombosis in women treated with one of both DES (compared to male patients). The trend towards more probable stent thromboses in the Xience V study arm (0% vs. 2.1%; $p=0.06$) should be interpreted with much caution, as this difference was based on 4 events only. The observed low definite and probable stent thrombosis rates in the female patients of the TWENTE trial are in line with the stent thrombosis rates found in the SPIRIT women trial, which investigated the clinical results of 1573 women treated with Xience V.[37] However, more post-marketing registries and pooled analyses of randomized trials will be required to get further insight into the issue of stent thrombosis in women.

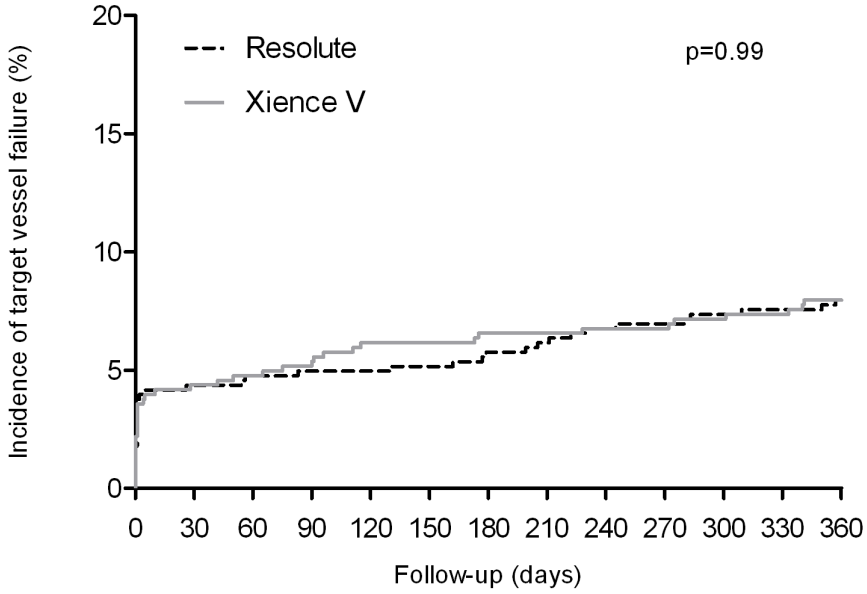
Limitations of the study. Despite gender-stratification, this study was statistically not powered to confirm non-inferiority of the study stents in women. The findings of this analysis have to be considered as hypothesis generating. The results cannot be applied to women receiving second-generation DES in the setting of an acute STEMI, as this clinical syndrome was an exclusion criterion in the TWENTE trial.

Conclusions. In this pre-specified 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.



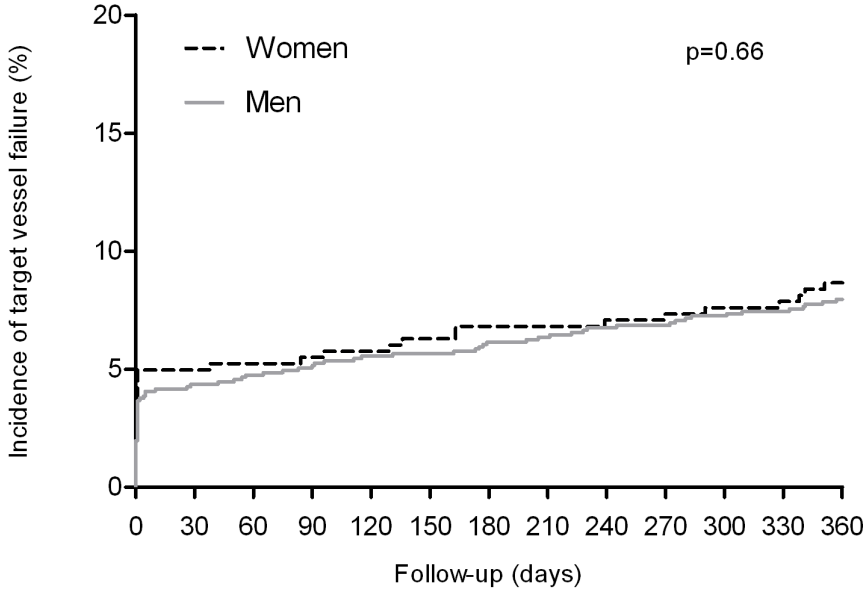
Days	0	90	180	270	360
Number at risk					
Resolute	192	180	176	175	173
Xience V	190	180	178	177	173

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.



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.



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.

	Total population (*N* = 1,391)			Women (*N* = 382)			Men (*N* = 1,009)		
	Women (*N* = 382)	Men (*N* = 1,009)	*P*-value	Resolute (*N* = 192)	Xience V (*N* = 190)	*P*-value	Resolute (*N* = 505)	Xience V (*N* = 504)	*P*-value
Age (years)	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/m^2)	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[a]	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
Hypercholesterolaemia	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%[b]	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[c]	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, <2.75 mm)	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 >27 mm	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[d]	289 (75.7)	788 (78.1)	0.33	141 (73.4)	148 (77.9)	0.31	406 (80.4)	382 (75.8)	0.08

Table 1. Baseline characteristics of patients

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

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

b) left ventricular ejection fraction assessed with ultrasound, MRI or left ventricular angiography

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

d) 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.

	Total lesions ($N = 2,116$)			Women ($N = 578$)			Men ($N = 1,568$)		
	Female ($N = 578$)	Male ($N = 1,538$)	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[a]	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[b]	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)	

Table 2. Baseline lesion characteristics

Data are number (%).

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

b) thrombus triggering use of thrombus aspiration catheters ACC = American College of Cardiology. AHA = American Heart Association. TIMI = thrombolysis in myocardial infarction.

sis of <50%, together with the absence of any in-hospital major adverse cardiac events

	Total lesions ($N=2,116$)			Women ($N=578$)			Men ($N=1,568$)		
	Female ($N=578$)	Male ($N=1,538$)	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
Postdilatation	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[a]	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[b]	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[c]	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

Table 3. Quantitative coronary angiography and procedural results

Data are median (IQR) or number (%), unless otherwise stated.

a) 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

b) Lesion success is defined as the attainment at the target site of a final residual diameter stenosis of <50% using any percutaneous method

c) 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

	Women (N= 382)	Men (N= 1,005)	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

Table 4. One-year clinical outcomes

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. Patient-oriented composite endpoint is a composite of endpoint of all-cause death, any myocardial infarction or any revascularization

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. 2011 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. Kim AM, Tingen CM, Woodruff TK. Sex bias in trials and treatment must end. Nature 2010;465:688-689.
19. Silber S. A new and rapid scoring system to assess the scientific evidence from clinical trials. J Interv Cardiol 2006;19:485-492.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.

29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. Morice MC, Mikhail GW, Mauri l Ferre F, Modena ME, Strasser RH, Grinfeld L, Sudhir K, Stuteville M, Papeleu P, Li D, Rutledge D, Windecker S. SPIRIT Women, evaluation of the safety and efficacy of the XIENCE V everolimus-eluting stent system in female patients: referral time for coronary intervention and 2-year clinical outcomes. EuroIntervention 2012;8:325-335.

Chapter 5

Clinical Outcome Following Stringent Discontinuation of Dual Anti-Platelet Therapy After 12 Months in Real-World Patients Treated With Second-Generation Zotarolimus-Eluting Resolute and Everolimus-Eluting Xience V Stents: Two-Year Follow-up of the Randomized TWENTE Trial

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Abstract

Objectives: The aim of this study was to assess safety and efficacy of the implantation of Resolute zotarolimus-eluting stents (ZES) and Xience V everolimus-eluting stents (EES) following strict discontinuation of dual anti-platelet therapy (DAPT) after 12 months.
Background: Only limited long-term follow-up data are available from head-to-head comparisons of second-generation drug-eluting stents (DES).
Methods: The randomized TWENTE (the real-world endeavor Resolute versus Xience V drug-eluting stent study in Twente) is an investigator-initiated study performed in a population with many complex patients and lesions, and only limited exclusion criteria. Patients were 1:1 randomly assigned to ZES (n=697) or EES (n=694).
Results: Two-year follow-up information on all patients were available. The rate of DAPT continuation beyond 12 months was very low (5.4%). The primary endpoint target-vessel failure (TVF), a composite of cardiac death, target-vessel-related myocardial infarction, and target-vessel revascularization did not differ between ZES and EES (10.8% vs. 11.6, p=0.65), despite fewer target-lesion revascularizations in EES (2.6% vs. 4.9%, p=0.03). The patient-oriented composite endpoint was similar (16.4% vs. 17.1%, p=0.75). Two-year definite-or-probable stent thrombosis rates were 1.2% and 1.4% (p=0.63), respectively. Very late definite-or-probable stent thrombosis occurred only in 2 patients of each study arm (0.3% vs. 0.3%, p=1.00).
Conclusion: After 2 years of follow-up and stringent discontinuation of DAPT beyond 12 months, Resolute ZES and Xience V EES showed similar results in terms of safety and efficacy for treating patients with a majority of complex lesions and off-label indications for DES.

Introduction

Second-generation DES such as the Xience V everolimus-eluting stent (EES) and the Resolute zotarolimus-eluting stent (ZES) were developed to improve clinical outcome by overcoming the limitations of first-generation DES.(1, 2) The TWENTE (The real-world endeavor RESOLUTE versus XIENCE V drug-eluting stent study in Twente) trial is an investigator-initiated randomized study that compares safety and efficacy of the Resolute ZES with that of the Xience V EES in a large patient population with complex coronary artery disease (3) that reflects routine clinical practice as has recently been underlined by the findings of the Non-Enrolled TWENTE study.(4) In the TWENTE trial at 1 year, the rates of the primary endpoint target-vessel failure (TVF), a composite of cardiac death, target-vessel-related myocardial infarction (MI), and clinically indicated target-vessel revascularization (TVR), were favorable and similar for Resolute ZES and Xience V EES. In addition, both stents did not significantly differ in the rates of several other secondary endpoints, such as stent thrombosis and patient-oriented composite endpoint.

Only few long-term data have been reported from randomized trials that compared second-generation DES in routine clinical practice. While for Xience V EES long-term data are available from several comparative DES studies (5-8), only a single randomized study reported long-term outcome of the Resolute ZES.(9) In addition, there is even less knowledge on the clinical performance of these DES after stringent dual anti-platelet therapy (DAPT) discontinuation at 12 months. DAPT was continuated beyond 1 year in 13 to 69% of patients in previous comparative DES trials.(5, 8, 10) In TWENTE, however, a strict policy of DAPT discontinuation after 12 months was followed which is of interest for the present pre-specified 2-year analysis of clinical outcome in the TWENTE trial.

Methods

Study design and patient population. The TWENTE trial (ClinicalTrials.gov NCT01066650) has previously been described in detail.(3), (11) In brief, TWENTE is an investigator-initiated, patient-blinded, randomized, comparative DES trial with limited exclusion criteria in a 'real-world' study population with a majority of complex lesions and 'off-label' indications for DES. Study enrolment was performed between June 2008 and August 2010 at Thoraxcentrum Twente, Enschede, the Netherlands. Patients capable of providing informed consent with an indication for percutaneous coronary intervention (PCI) with DES were randomized for treatment with Resolute (Medtronic Inc., Santa Rosa, CA) or Xience V stents (Abbott Vascular, Santa Clara, CA) in a 1:1 ratio. There was no limit for lesion length, reference vessel size, and number of target lesions or vessels. The main exclusion criterion was a recent ST-elevation myocardial infarction (STEMI). The study was approved by the institutional ethics committee and complied with the

Declaration of Helsinki. All patients provided written informed consent.

Intervention, medication, and in-hospital course. Patients were pre-treated with acetylsalicylic acid and clopidogrel. At discharge, the combination of 100mg of acetylsalicylic acid once daily indefinitely and clopidogrel 75mg once daily for 12 months was prescribed. Use of DAPT was determined by patient questionnaire and/or information from the patients' general practicioner or pharmacy. Lesion predilatation, direct stenting, stent postdilatation, and/or use of glycoprotein IIb/IIIa antagonists were permitted at the operators' discretion. Liberal use of postdilatation was encouraged. Cardiac biomarkers and electrocardiograms were systematically assessed in all patients before and after PCI to identify periprocedural myocardial infarction.

Definitions of clinical endpoints. Definitions of all clinical endpoints have previously been described in detail.(3) The primary clinical endpoint was the incidence of target-vessel failure (TVF) at 1 year, a composite endpoint that was defined as cardiac death, target-vessel-related myocardial infarction (or not attributable to a non-target vessel), or clinically driven target-vessel revascularization (TVR). The pre-specified secondary endpoints included TVF at 2-year follow-up, all-cause mortality, stent thrombosis, target-lesion failure (TLF), major adverse cardiac events (MACE), and a patient-oriented composite endpoint (POCE), consisting of all-cause mortality, any MI, and any repeat revascularization. All clinical endpoints, including stent thrombosis, were defined according to the Academic Research Consortium (ARC), including the addendum on definition of myocardial infarction.(12, 13)

Acquisition and analysis of clinical data. Clinical follow-up data were obtained at visits to outpatient clinics, or, if not feasible, by telephone follow-up and/or medical questionnaire. Follow-up data were available in all but 4 patients, who withdrew informed consent during the course of the study (2 Resolute ZES and 2 Xience V EES patients). 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 Inc., 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 time to the primary endpoint and to the components thereof was assessed according to the Kaplan-Meier method, and the log-rank test was applied to compare the two groups. A landmark analysis was performed at 1 year for various events. For each event type, patients were excluded from the landmark analysis if the specific event or death occurred in the first year. Unless otherwise specified, p values and CIs were two-sided. A p value

< 0.05 was considered significant.

Results

A total of 1391 patients were randomized for treatment with Resolute ZES (n=697) or Xience V EES (n=694). Apart from 4 patients, who withdrew their consent during the first year of follow-up, 2-year follow-up information was obtained from all patients (Figure 1). Baseline clinical, angiographic, and procedural characteristics of all study patients are summarized in Table 1.

At 2-year follow-up, the composite primary endpoint TVF occurred in 75 (10.8%) patients of the Resolute ZES and in 80 (11.6%) patients of the Xience V EES group, and did not differ significantly between groups (absolute difference -0.8 [-4.1 to 2.6], p=0.65, Table 2, Figure 2). The patient-oriented composite endpoint rates were also similar for patients treated with ZES and EES; this endpoint occurred in 114 (16.4%) versus 118 (17.1%) patients, respectively. For the individual components of the composite primary endpoint TVF – cardiac death (1.6% vs. 2.7%, p=0.14), target-vessel-related MI (5.3% vs. 5.6%, p=0.80), and clinically driven TVR (5.6% vs. 5.1%, p=0.65) – there was also no significant difference at 2 years. The results of an exploratory subgroup analysis at 2-year follow-up with regard to TVF are shown in figure 3. The subgroup analysis showed consistent results across different subgroups. Compared to Resolute ZES, the use of Xience V EES was associated with a lower clinically indicated target- lesion revascularization (TLR) (4.9% vs. 2.6%, p=0.03), but this did not result in a significant difference in the device-oriented composite endpoint TLF (10.5% vs. 9.8%, p=0.68).

Table 3 shows the outcome difference between 1 and 2-year follow-up. No significant difference was observed for various endpoints. However, there was numerically more cardiac deaths in Xience V EES (0.6% vs. 1.3%, p=0.16) and numerically more clinically indicated TLR in Resolute ZES (2.3% vs. 1.2%, p=0.13).

In accordance with national and European guidelines, the per-protocol duration of DAPT was 1 year following PCI. Table 4 presents the actual DAPT usage. At 1-year follow-up, 623 (91.6%) patients in the Resolute ZES arm and 621 (91.6%) Xience V EES patients were on DAPT (p=0.94), of those 73 (5.4%) of all patients continued DAPT beyond 12 months. At 2-year follow-up, 51 (7.7%) Resolute ZES patients and 40 (6.2%) Xience V EES patients were still on DAPT.

ARC definite stent thrombosis (0.9% vs 0.1%, p=0.12) and definite-or-probable stent thrombosis rates (1.2% vs 1.4%, p=0.63) at 2-year follow-up were low and similar for both Resolute ZES and Xience V EES (Figure 4). Very late definite-or-probable stent thrombosis was seen in 2 patients of both study arms (0.3% vs 0.3%, p=1.00), resulting in an MI in all 4 cases (Table 5). Of the 14 patients with definite-or-probable stent thrombosis in the first year of follow-up, 11 (78.6%) were on DAPT. All 4 patients with very late definite-or-

probable ST were on acetylsalicylic acid monotherapy beyond 1 year, and there was no clear relation between stent thrombosis and discontinuation of DAPT with a period of at least 79 days between very late stent thrombosis and discontinuation of DAPT. -

Discussion

At the 2-year follow-up of the TWENTE trial, which followed a stringent approach of DAPT discontinuation beyond 12 months, Resolute ZES and Xience V EES showed similar and beneficial results in terms of safety and efficacy for treating 'real-world' PCI patients with a vast majority of complex lesions and 'off-label' indications for DES use. Both study arms showed similar rates of TVF and its components: cardiac death, target-vessel-related MI, and clinically indicated TVR. The absence of a difference in TVF at 2-year follow-up was consistent across several subgroups. Despite a lower clinically indicated TLR in the Xience V EES, there was no significant difference between groups in the device-oriented composite endpoint TLF and the more patient-oriented composite clinical endpoints (MACE and POCE).

Resolute ZES and Xience V EES are both second-generation DES that employ cobalt-chromium stent platforms and elute limus analogues from durable polymer-based coatings with improved biocompatibility.(14, 15) This improvement in coating was considered desirable as the limited biocompatibility of coatings on first-generation DES(16-18) was found to be associated with hypersensitivity and local vascular inflammation that could induce intraluminal thrombus formation.(19-21)

In several *randomized* comparisons with first-generation DES, Xience V EES has proven that its safety and efficacy is sustained beyond 1 year, which has lead to wide acceptance in clinical practice. In SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System IV), treatment with Xience V EES was associated with a lower TLF rate after 2 years (6.9% vs. 9.9%, p = 0.003) compared with the paclitaxel-eluting Taxus stent.(8) Superiority of Xience V EES over Taxus was also seen in the 2-year results of COMPARE (A trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) with TLF rates of 7.4% vs. 11.3%, p=0.004.(5) In SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) Xience V EES had similar and low TLF rates at 2-year follow-up, but showed non-inferiority compared with the first generation sirolimus-eluting stent Cyper Select+ (Cordis, Bridgewater, New Jersey).(6)

Only a single *randomized* study, the RESOLUTE All Comers trial, has reported long-term outcome data for the Resolute ZES. After 2 years, Resolute ZES was equivalent to Xience V EES with regard to both TVF (12.6% vs. 12.2%, p=0.85) and POCE (20.6% vs. 20.5%, p=0.96).(9)

The current 2-year data of TWENTE generally support the findings of RESOLUTE All Comers and show that Resolute ZES has a long-term safety profile that is similar to Xience V EES, which was previously shown to be superior to the Taxus stent in SPIRIT IV and COMPARE.(5, 8) While in RESOLUTE All Comers, the TLR rates for Resolute and Xience V were similar (5.7% and 5.1%, respectively), in TWENTE the TLR rate of Xience V was particularly low, resulting in a statistically significant difference (4.9% vs. 2.6%, p=0.03). However, this difference did not translate into a difference in the device-oriented composite endpoint TLF, due to a numerically higher cardiac death rate in Xience V (1.4% vs. 2.6%, p=0.14). In fact, the Kaplan-Meier cumulative event curves of cardiac death tend to diverge after approximately 10 months, but a landmark analysis revealed only a non-significant difference in cardiac death during the second year of follow-up (0.6% vs.1.3%, p=0.16). Nevertheless, these data suggest that further assessment of this critical outcome parameter may be warranted beyond the present 2-year follow-up.

At 2-year follow-up of TWENTE, the rates of 2-year definite-or-probable stent thrombosis (1.2% vs. 1.4%) and very late definite-or-probable stent thrombosis (0.3% for both arms) were low for both Resolute ZES and Xience V EES. These rates were similar to those of RESOLUTE All Comers (2-year definite-or-probable stent thrombosis rate 1.9% vs. 1.0%; very late definite-or-probable stent thrombosis rate 0.3% vs. 0.3%), and also the Xience V EES stent thrombosis rates of SORT OUT IV and COMPARE.(5, 6, 9) In addition, the 2-year definite-or-probable stent thrombosis rates in TWENTE were similar to the pooled 2-year stent thrombosis rates of SPIRIT II and III (1.2%), using Xience V EES in selected patient populations and more stable coronary disease.(22) The 2-year definite stent thrombosis rates in TWENTE were also low, showing a non-significant trend towards a lower rate in Xience V (p=0.12). Nevertheless, it may be difficult to compare stent thrombosis rates of different trials directly, as they could be influenced differences in study populations. In TWENTE, just 1 of the overall 7 definite stent thromboses was lethal, while very late definite-or-probable stent thrombosis was not associated with mortality. Similar findings were observed in other studies evaluating second generation DES.(5, 6, 9) The overall low stent thrombosis rates and low mortality rates associated with stent thrombosis in patients treated with Resolute ZES were similar to Xience V EES, which has shown the lowest stent thrombosis rates in comparison to earlier generation DES.(23, 24) The data of the TWENTE trial underline the safety profile of both second-generation DES.

The low rates of very late stent thrombosis in TWENTE are particularly noteworthy, considering the low rate of DAPT continuation beyond 12 months, which was in accordance with current guidelines.(25, 26) In fact, the rate of DAPT use at 2-year follow-up (6.9%) was much lower than that of several European DES trials in all comer populations, such as LEADERS (23%),(10, 27) RESOLUTE All Comers (18%),(9) and COMPARE (13%),(5) and some US DES trials in patients with somewhat less complex coronary disease,

such as SPIRIT IV (69%)(8, 28) and RESOLUTE US (67%).(29, 30) Hence, TWENTE provides interesting safety information on stringent discontinuation of DAPT at 1 year following PCI in a study population with many complex patients and lesions treated with Resolute ZES and Xience V EES implantation.

Limitations. This prospective, randomized, single-center trial was performed in a high-volume tertiary center by experienced operators, who applied relatively uniform procedural strategies. For that reason, generalization of the study results to other clinical settings may be limited. In addition, conclusions do not apply to STEMI patients requiring primary PCI, as this patient subset was not assessed in the TWENTE trial. The subgroup analysis was not pre-specified. However, to avoid any subjective post hoc selection, we used the same subgroups as RESOLUTE All Comers(31) and the 1-year analysis of the TWENTE trial.(3)

Conclusion. After 2 years of follow-up and stringent discontinuation of DAPT beyond 1 year, Resolute ZES and Xience V EES showed similar results in terms of safety and efficacy for treating real-world patients with a majority of complex lesions and off-label indications for DES.

References

1. 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.
2. 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.
3. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting resolute stents versus everolimus-eluting xience V stents in real-world patients: The TWENTE trial. J Am Coll Cardiol. 2012;59:1350-61.
4. Sen H, Tandjung K, Basalus MW, et al. 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.
5. Smits PC, Kedhi E, Royaards KJ, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: A randomized open label trial). J Am Coll Cardiol. 2011;58:11-8.
6. Jensen LO, Thayssen P, Christiansen EH, et al. 2-year patient-related versus stent-related outcomes: The SORT OUT IV (scandinavian organization for randomized trials with clinical outcome IV) trial. J Am Coll Cardiol. 2012;60:1140-7.
7. Byrne RA, Kastrati A, Massberg S, et al. Biodegradable polymer versus permanent polymer drug-eluting stents and everolimus- versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. J Am Coll Cardiol. 2011;58:1325-31.
8. Stone GW, Rizvi A, Sudhir K, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents. 2-year follow-up from the SPIRIT (clinical evaluation of the XIENCE V everolimus eluting coronary stent system) IV trial. J Am Coll Cardiol. 2011;58:19-25.
9. Silber S, Windecker S, Vranckx P, Serruys PW, RESOLUTE All Comers investigators. 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.
10. Wykrzykowska J, Serruys P, Buszman P, et al. The three year follow-up of the randomised "all-comers" trial of a biodegradable polymer biolimus-eluting stent versus permanent polymer sirolimus-eluting stent (LEADERS). EuroIntervention. 2011;7:789-95.
11. 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;18:360-4.
12. 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.
13. Vranckx P, Cutlip DE, Mehran R, 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;5:871-4.
14. Udipi K, Melder RJ, Chen M, et al. The next generation endeavor resolute stent: Role of the BioLinx polymer system. EuroIntervention. 2007;3:137-9.
15. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol. 2008;52:333-42.
16. 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.
17. 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.
18. 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.
19. 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.
20. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: An autopsy study. Circulation. 2008;118:1138-45.
21. 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;120:391-9.
22. Onuma Y, Serruys PW, Kukreja N, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents: Pooled analysis of the 2-year clinical follow-up from the SPIRIT II and III trials. Eur Heart J. 2010;31:1071-8.
23. 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.
24. Palmerini T, Kirtane AJ, Serruys PW, et al. Stent thrombosis with everolimus-eluting stents: Meta-analysis of comparative randomized controlled trials. Circ Cardiovasc Interv. 2012;5:357-64.
25. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31:2501-55.
26. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the american college of cardiology Foundation/American heart association task force on practice guidelines and the society for cardiovascular angiography and interventions. J Am Coll Cardiol. 2011;58:e44-122.
27. 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.
28. 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.
29. Mauri L, Belardi J, Silber S, et al. Duration of dual antiplatelet therapy after drug-eluting stent treatment by geographic region. J Am Coll Cardiol. 2012;59:E267-E267.
30. 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.
31. 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.

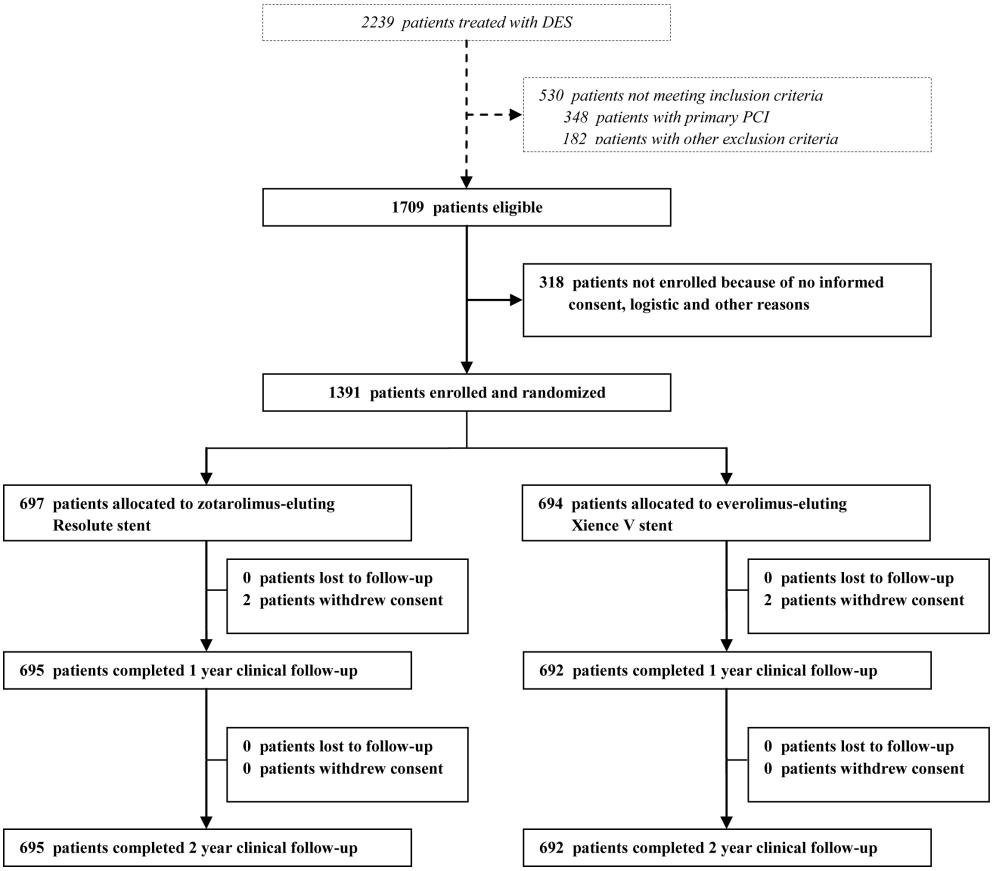
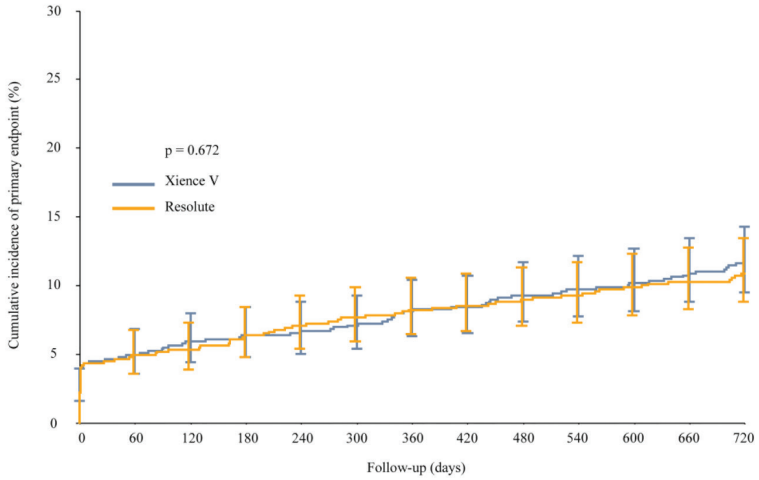


Figure 1. Study flow diagram.

A



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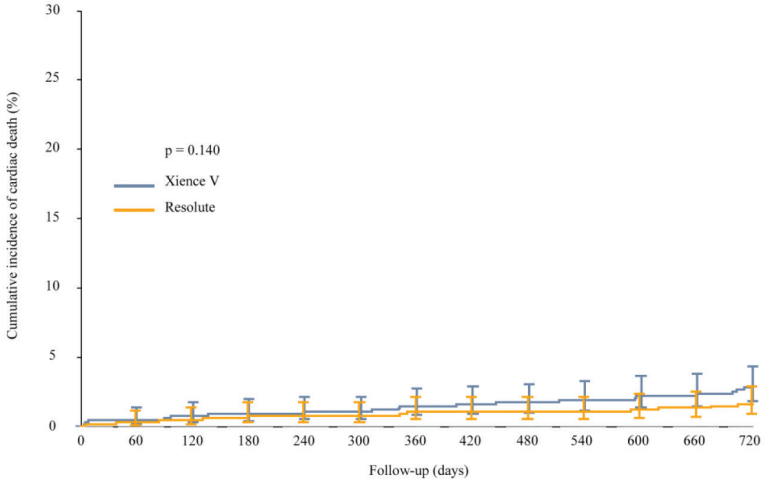
Xience V	694	660	651	646	644	639	632	629	620	616	613	607	582
Resolute	697	661	655	647	642	636	631	629	625	621	613	610	586

B



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Xience V	694	691	687	684	683	681	678	676	672	670	666	664	638
Resolute	697	693	688	685	685	683	680	680	679	677	672	671	649

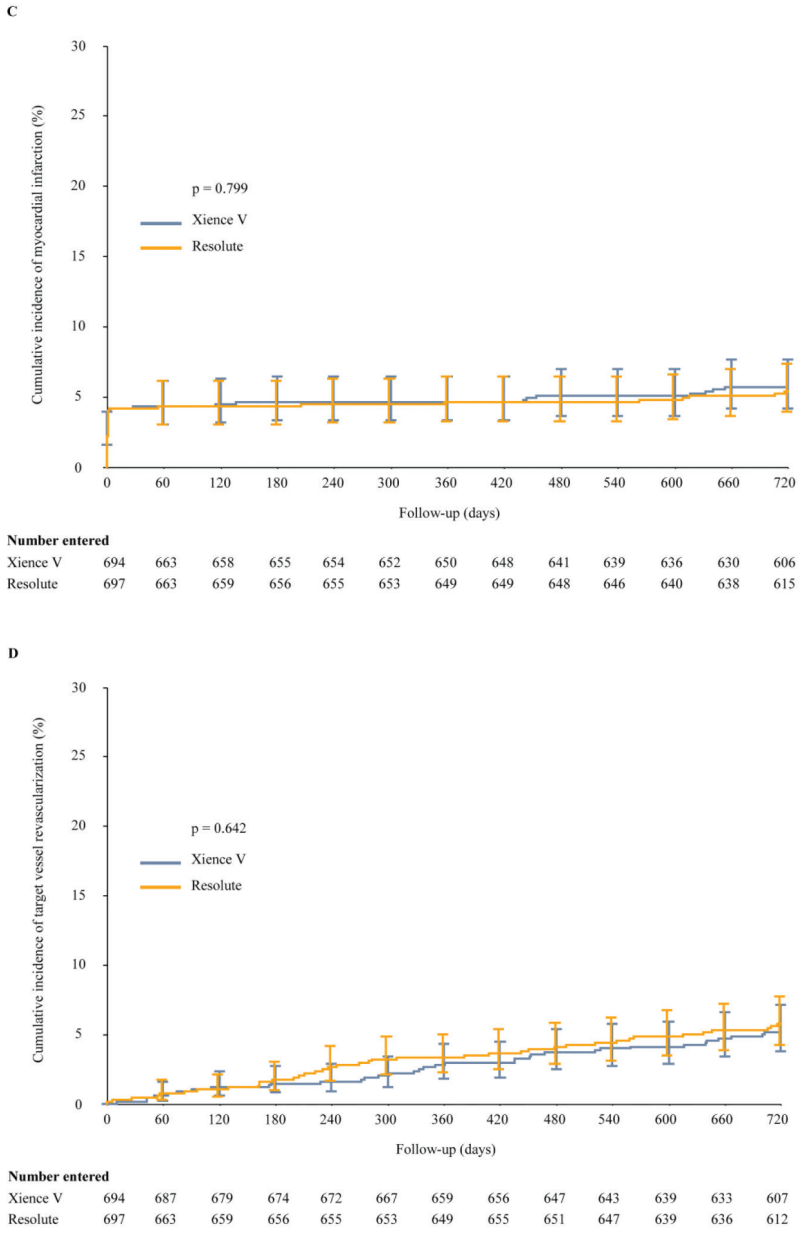

Figure 2. Kaplan-Meier for Primary Endpoint and the Individual Components of the Primary Endpoint.
Kaplan-Meier cumulative incidence curves at 2 year for the primary endpoint, a composite of cardiac death, target-vessel-related myocardial infarction, or target-vessel revascularization (A); cardiac death (B); myocardial infarction (C); and target-vessel revascularization (D) for the zotarolimus-eluting Resolute stent and the everolimus-eluting Xience V stent

	Zotarolimus-Eluting Resolute	Everolimus-Eluting Xience V	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	p Value
All patients (n=1391)	75/697 (10.8)	80/694 (11.5)		0.94 (0.68-1.28)	0.67
Off-label indication (n=1077)	68/547 (12.4)	67/530 (12.6)		0.99 (0.71-1.39)	0.96
Vessel diameter < 2.75 mm (n=874)	54/445 (12.1)	53/429 (12.4)		0.99 (0.68-1.44)	0.94
NSTEMI < 72 hrs. (n=408)	17/202 (8.4)	25/206 (12.1)		0.68 (0.37-1.26)	0.22
Multivessel PCI (n=336)	32/174 (18.4)	22/162 (13.6)		1.40 (0.82-2.42)	0.22
Diabetes (n=301)	25/158 (15.8)	19/143 (13.3)		1.25 (0.69-2.26)	0.47
Overlapping stents (n=503)	35/244 (14.3)	40/259 (15.4)		0.93 (0.59-1.46)	0.74
Bifurcation lesion (n=362)	23/179 (12.8)	21/183 (11.5)		1.13 (0.63-2.04)	0.68
Lesion length > 27 mm (n=293)	28/156 (17.9)	25/137 (18.2)		1.01 (0.59-1.73)	0.98
In-stent restenosis (n=69)	3/36 (8.3)	3/33 (9.1)		0.91 (0.18-4.52)	0.91
Renal insufficiency (n=38)	4/19 (21.1)	2/19 (10.5)		2.03 (0.37-11.12)	0.41
Bypass graft treated (n=41)	6/20 (30.0)	7/21 (33.3)		0.86 (0.29-2.56)	0.78
Left main treated (n=52)	3/26 (11.5)	3/26 (11.5)		1.04 (0.21-5.14)	0.97

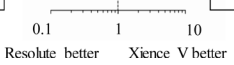

Figure 3. Subgroup analysis: Target-vessel failure at 2 year.
Target-vessel failure is a composite of cardiac death, target-vessel myocardial infarction, or clinically driven target-vessel revascularization. NSTEMI: non–ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention.

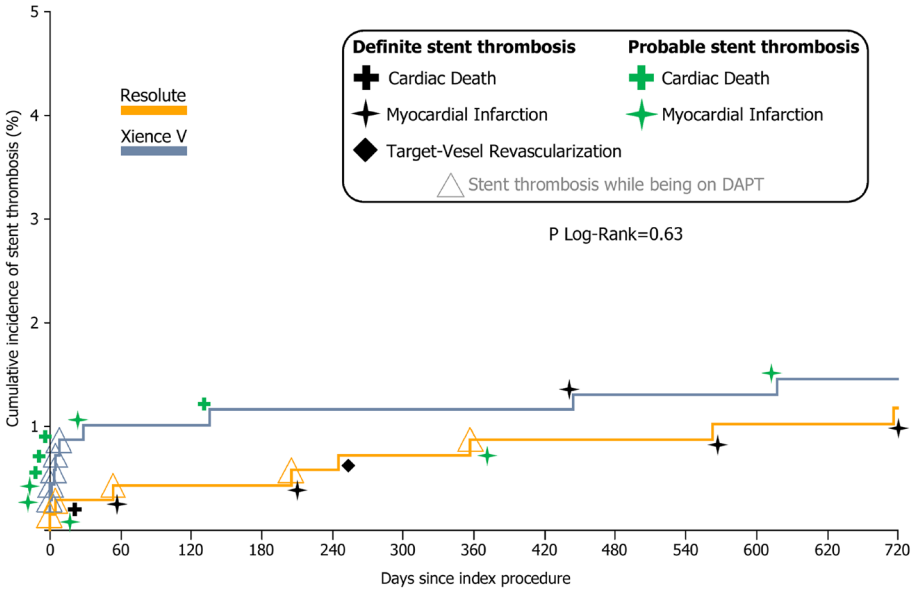

Figure 4. Cumulative Incidence of Definite or Probable Stent Thrombosis in 2 year.

Variable	Total population (N = 1391)	Zotarolimus-eluting stent (N= 697)	Evorolimus-eluting stent (N= 694)	p Value
Age (yrs)	64.2 (10.8)	63.9 (10.9)	64.5 (10.7)	0.32
Men	1009 (72.5)	505 (72.5)	504 (72.6)	0.94
Diabetes mellitus (any)	301 (21.6)	158 (22.7)	143 (20.6)	0.35
Chronic renal failure *	38 (2.7)	19 (2.7)	19 (2.7)	0.99
Arterial hypertension	773 (55.6)	386 (55.4)	387 (55.8)	0.89
Hypercholesterolaemia	803/1357 (59.2)	392/688 (57.0)	411/669 (61.4)	0.10
Current smoker	340 (24.4)	176 (25.3)	164 (23.6)	0.48
Family history of CAD	740/1309 (53.2)	370/660 (53.1)	370/649 (53.3)	0.73
Previous myocardial infarction (any)	450 (32.4)	213 (30.6)	237 (34.1)	0.15
Previous PCI	288 (20.7)	139 (19.9)	149 (21.5)	0.48
Previous CABG	148 (10.6)	68 (9.8)	80 (11.5)	0.28
Stable angina pectoris	674 (48.5)	335 (48.1)	339 (48.8)	0.47
Acute coronary syndrome	717 (51.5)	362 (51.9)	355 (51.2)	0.47
Unstable angina	325 (23.4)	172 (24.7)	153 (22.0)	0.47
Non-ST-elevation MI	392 (28.2)	190 (27.3)	202 (29.1)	0.47
Multivessel treatment	336 (24.2)	174 (25.0)	162 (23.3)	0.48
Total no lesions treated per patient				0.49
One lesion treated	857 (61.6)	422 (60.5)	434 (62.7)	
Two lesions treated	393 (28.3)	198 (28.4)	195 (28.1)	
Three of more lesions treated	141 (10.1)	77 (11.0)	64 (9.2)	
At least one off label indication §	1077 (77.4)	547 (78.5)	530 (76.4)	0.35
Total number of lesions treated	2116	1080	1036	
No• of stents implanted (mean, SD) Per lesion	1.33 (0.62)	1.31 (0.59)	1.35 (0.64)	0.09
Total stent length (mm) Per lesion (mean, SD)	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
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)	
Bifurcated lesion	518 (24.5)	258 (23.9)	260 (25.1)	0.59
Thrombus present†	71 (3.4)	33 (3.1)	38 (3.7)	0.43
Chronic total occlusion	100 (4.7)	53(4.9)	47 (4.5)	0.69

Table 1. Baseline characteristics of patients
Data are number (%) or mean (SD). BMI = body mass index. CAD = coronary artery disease. PCI = percutaneous coronary intervention. CABG = coronary artery bypass grafting. MI = myocardial infarction. CTO = chronic total occlusion. RVD = reference vessel diameter.
* chronic renal failure defined by serum creatinine level ≥ 130 μmol/L
† left ventricular ejection fraction assessed with ultrasound, MRI or LV 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. † thrombus triggering use of trombus aspiration catheters

	Zotarolimus-eluting Resolute stent (N= 695)	Everolimus-eluting Xience V stent (N= 692)	Difference (95% CI)	p Value
Target-vessel failure	75 (10.8)	80 (11.6)	-0.8 (-4.1 to 2.6)	0.65
Death				
Any cause	29 (4.2)	33 (4.8)	-0.6 (-2.8 to 1.6)	0.59
Cardiac cause	11 (1.6)	19 (2.7)	-1.2 (-2.7 to 0.4)	0.14
Target-vessel-related MI				
Any	37 (5.3)	39 (5.6)	-0.3 (-2.7 to 2.1)	0.80
Q-wave	8 (1.2)	9 (1.3)	-0.2 (-1.3 to 1.0)	0.80
Non-Q-wave	29 (4.2)	30 (4.3)	-0.2 (-2.3 to 2.0)	0.88
Clinically indicated TVR				
Any	39 (5.6)	35 (5.1)	0.6 (-1.8 to 2.9)	0.65
Percutaneous	32 (4.6)	28 (4.0)	0.6 (-1.6 to 2.7)	0.61
Surgical	8 (1.2)	8 (1.2)	0.0 (-1.1 to 1.1)	0.99
Target-lesion failure	73 (10.5)	68 (9.8)	0.7 (-2.5 to 3.9)	0.68
Clinically indicated TLR				
Any	34 (4.9)	18 (2.6)	2.3 (0.3 to 4.3)	0.03
Percutaneous	28 (4.0)	13 (1.9)	2.2 (0.4 to 3.9)	0.02
Surgical	7 (1.0)	6 (0.9)	0.1 (-0.9 to 1.2)	0.79
Death from cardiac causes or target-vessel MI	46 (6.6)	53 (7.7)	-1.0 (-3.8 to 1.7)	0.45
Major adverse cardiac events	90 (12.9)	82 (11.8)	1.1 (-2.4 to 4.6)	0.53
Patient-oriented composite end-point	114 (16.4)	118 (17.1)	-0.7 (-4.6 to 3.3)	0.75
Definite ST (0-720 days)	6 (0.9)	1 (0.1)	0.7 (-0.0 to 1.5)	0.12
Definite or probable ST (0-720 days)	8 (1.2)	10 (1.4)	-0.3 (-1.5 to 0.9)	0.63
Definite, probable or possible ST (0-720 days)	14 (2.0)	20 (2.9)	-0.9 (-2.5 to 0.8)	0.29
Very late definite or probable ST (361-720)	2 (0.3)	2 (0.3)	0 (-0.6 to 0.6)	1.00

Table 2. Two-year clinical outcome.
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. Patient-oriented composite end-point is a composite of endpoint of all cause death, any myocardial infarction or any revascularization.

	Zotarolimus-eluting Resolute stent	Everolimus-eluting Xience V stent	Difference (95% CI)	p Value
Target-vessel failure	2.9 (18/631)	3.8 (24/632)	-0.9 (-2.9 to 1.0)	0.35
Death				
Any cause	2.1 (14/680)	2.8 (19/678)	-0.7 (-2.4 to 0.9)	0.37
Cardiac cause	0.6 (4/680)	1.3 (9/678)	-0.7 (-1.8 to 0.3)	0.16
Target-vessel-related MI	0.8 (5/649)	1.1 (7/650)	-0.3 (-1.4 to 0.7)	0.56
Clinically indicated TVR	2.4 (16/657)	2.4 (16/659)	0.00 (-1.7 to 1.7)	0.99
Target-lesion failure	2.8 (18/633)	3.3 (21/641)	-0.4 (-2.3 to 1.5)	0.65
Clinically indicated TLR	2.3 (15/661)	1.2 (8/668)	1.1 (-0.3 to 2.5)	0.13
Major adverse cardiac events	4.5 (28/625)	4.9 (31/630)	-0.4 (-2.8 to 1.9)	0.71
Patient-oriented composite end-point	6.0 (37/617)	7.4 (46/619)	-1.4 (-4.2 to 1.4)	0.31
Very late stent thrombosis (361-720)				
Definite	0.3 (2/677)	0.1 (1/678)	0.2 (-0.4 to 0.7)	0.62
Definite or probable	0.3 (2/677)	0.3 (2/674)	0.00 (-0.6 to 0.6)	1.00
Definite, probable, or possible	0.6 (7/675)	1.5 (10/674)	-0.9 (-2.0 to 0.2)	0.11

Table 3. Outcome differences between 1 and 2 years
Data are presented as percentages (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. Patient-oriented composite end-point is a composite of endpoint of all cause death, any myocardial infarction or any revascularization.

	Zotarolim-us-eluting Resolute stent	Everolim-us-eluting Xience V stent	p Value
At Baseline	**N=697**	**N=694**	
Acetylsalicylic acid *	688 (98.7)	692 (99.7)	0.04
Clopidogrel	697 (100)	694 (100)	1.00
DAPT	688 (98.7)	692 (99.7)	0.04
At 1-Year Follow-up	**N=680**	**N=678**	
Acetylsalicylic acid	635 (93.4)	628 (92.6)	0.59
Clopidogrel Stopped after one year Continued after one year Less than one year	 615 (90.4) 52 (7.7) 13 (1.9)	 633 (93.4) 37 (5.5) 8 (1.2)	0.14
DAPT Stopped after one year Continued after one year Less than one year	 578 (85.0) 45 (6.6) 57 (8.4)	 593 (87.5) 28 (4.1) 57 (8.4)	0.13
At 2-Year Follow-up	**N=662**	**N=650**	
Acetylsalicylic acid	606 (91.5)	599 (92.2)	0.69
Clopidogrel	64 (9.7)	51 (7.8)	0.24
DAPT	51 (7.7)	40 (6.2)	0.27

Table 4. Acetylsalicylic acid, clopidogrel, and dual anti-platelet therapy usage.
Data are number of patients (%). DAPT = Acetylsalicylic acid and clopidogrel
*No Acetylsalicylic acid was used due to allergic reactions or concommitant vitamin K antagonist usage.

	Indication for PCI	Days to ST after PCI	Days after DAPT discontinuation to event	Target Vessel	Clinical event after ST	Anti-platelet therapy use at event
Resolute						
Probable	Stable angina	0	N.A.	RCX, LAD	MI	On DAPT (A+C)
Definite	Unstable angina	5	N.A.	LAD, RCA	Death	On DAPT (A+C)
Definite	Stable angina	54	N.A.	RCA, LAD	MI, TLR	On DAPT (A+C)
Definite	Stable angina	205	N.A.	RCX	MI, TLR	On DAPT (A+C)
Definite	NSTEMI	245	245*	RCA	MI, TLR	Off DAPT (C+VKA)
Probable	Stable angina	357	N.A.	RCX	MI	On DAPT (A+C)
Definite	Unstable angina	563	198	RCA	MI, TLR	Off DAPT (A)
Definite	NSTEMI	715	351	RCA, LAD	MI, TLR	Off DAPT (A)
Xience V						
Probable	NSTEMI	0	N.A.	Vein-graft, RCA	MI	On DAPT (A+C+VKA)
Probable	Unstable angina	0	N.A.	RCA	MI	On DAPT (A+C)
Probable	Stable angina	1	N.A.	RCX, LAD	MI	On DAPT (A+C)
Probable	NSTEMI	3	N.A.	LAD	Death	On DAPT (A+C)
Probable	NSTEMI	5	N.A.	RCA, LAD	Death	On DAPT (A+C)
Probable	Stable angina	8	N.A.	RCX	Death	On DAPT (A+C)
Probable	Unstable angina	28	1	RCA	MI	Off DAPT (C+VKA)
Probable	NSTEMI	136	136†	LAD	MI, Death	Off DAPT (A)
Definite	Stable angina	444	79	RCX, LAD	MI, thrombus aspiration	Off DAPT (A)
Probable	Stable angina	611	246	RCA	TVR, MI	Off DAPT (A)

Table 5. Definite-or-probable stent thrombosis details.
VKA = vitamin K antagonist. DAPT = Acetylsalicylic acid and clopidogrel
*From day 0 on therapy with VKA + clopidogrel due to allergy for acetylsalicylic acid.
† From day 0 only acetylsalicylic acid for unknown reason.

Chapter 6

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.

Introduction

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 37°C. 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).

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).

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.

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.

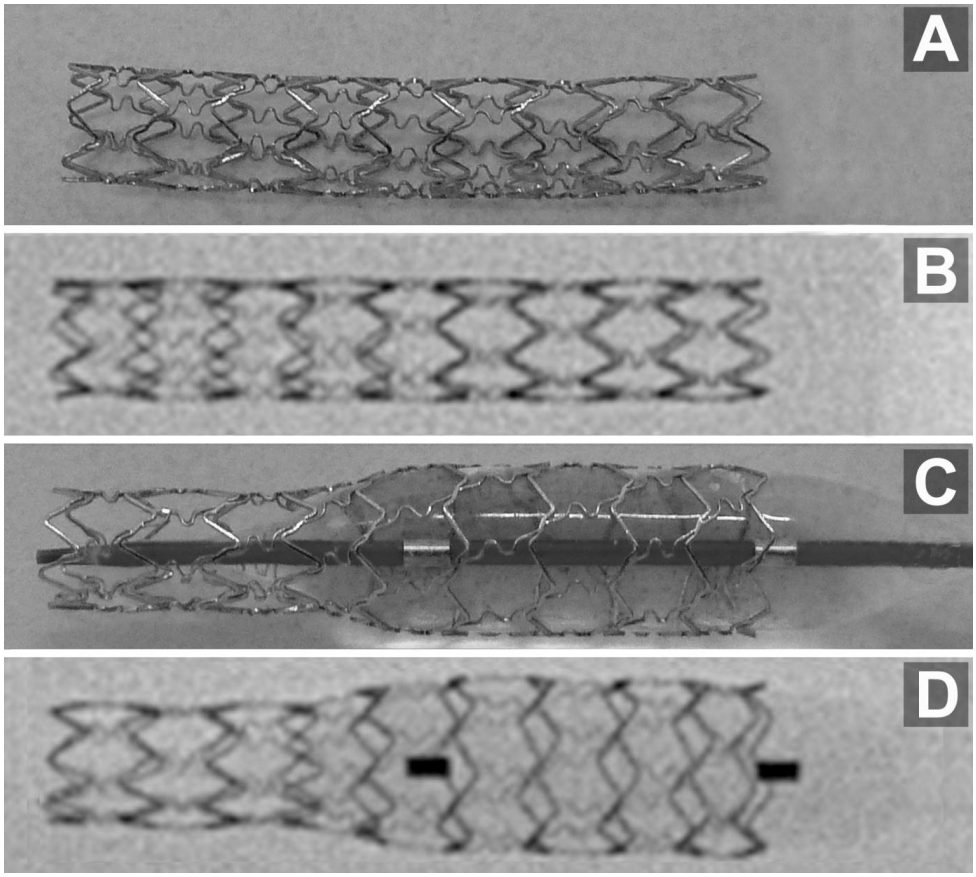

Figure 1. DES postdilatation (example of Cypher Select stent):
A) Photograph of DES after expansion at 14 atm; **B)** high resolution radiographic image of A; **C)** photograph of partial proximal postdilatation with 5 mm non-compliant balloon at 18 atm; **D)** high resolution radiographic image of C.

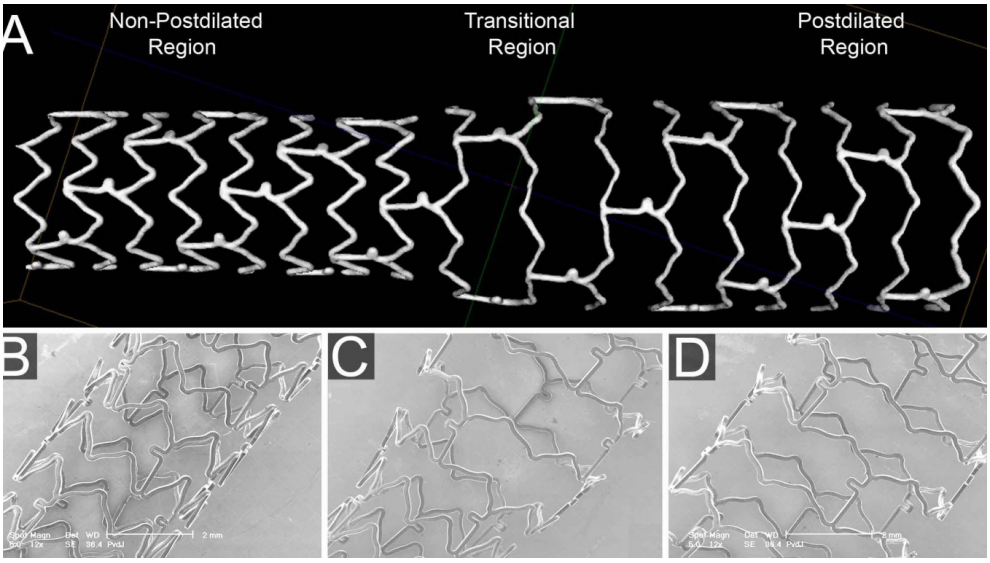

Figure 2. Example of DES configuration after oversized partial postdilatation. Micro-computed tomography image **(A)** indicating (from left to right) the location of the non-postdilated, transitional, and postdilated DES regions. Scanning electron microscopic images of non-postdilated **(B)**, transitional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

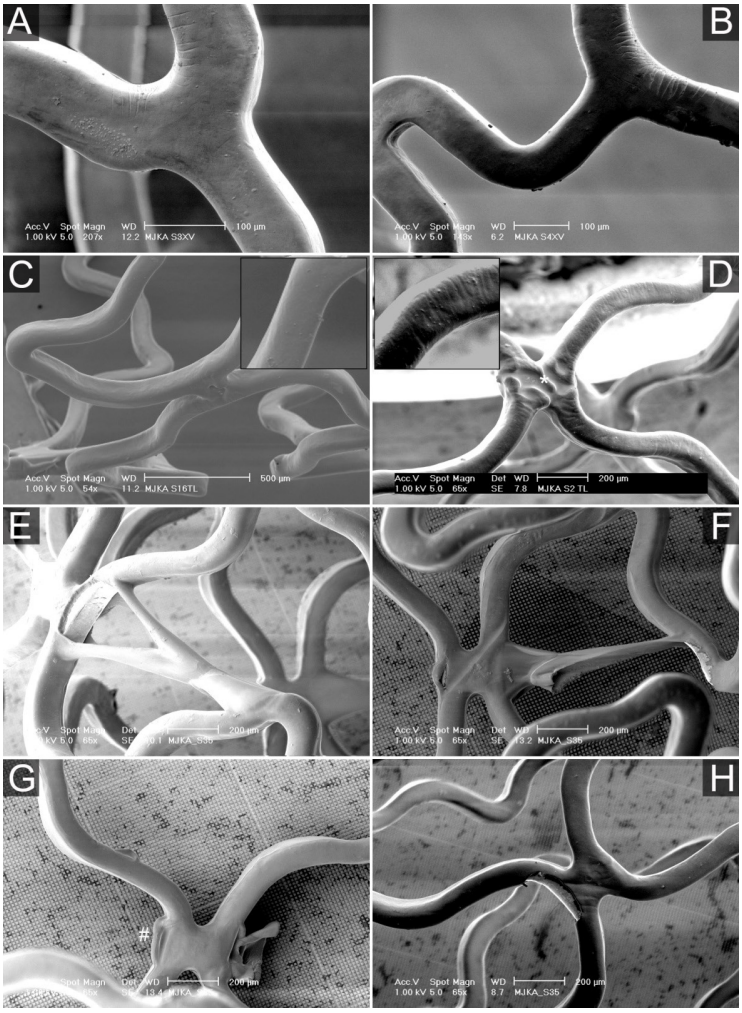

Figure 3. **SEM images of Xience V and Taxus Liberté. A)** Xience V showing wrinkles in non-postdilated region. **B**) Xience V with wrinkles in postdilated region. **C**) Taxus Liberté in non-postdilated region without wrinkles. **D**) Taxus Liberté with wrinkles in non-postdilated region. **D**) Taxus 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.

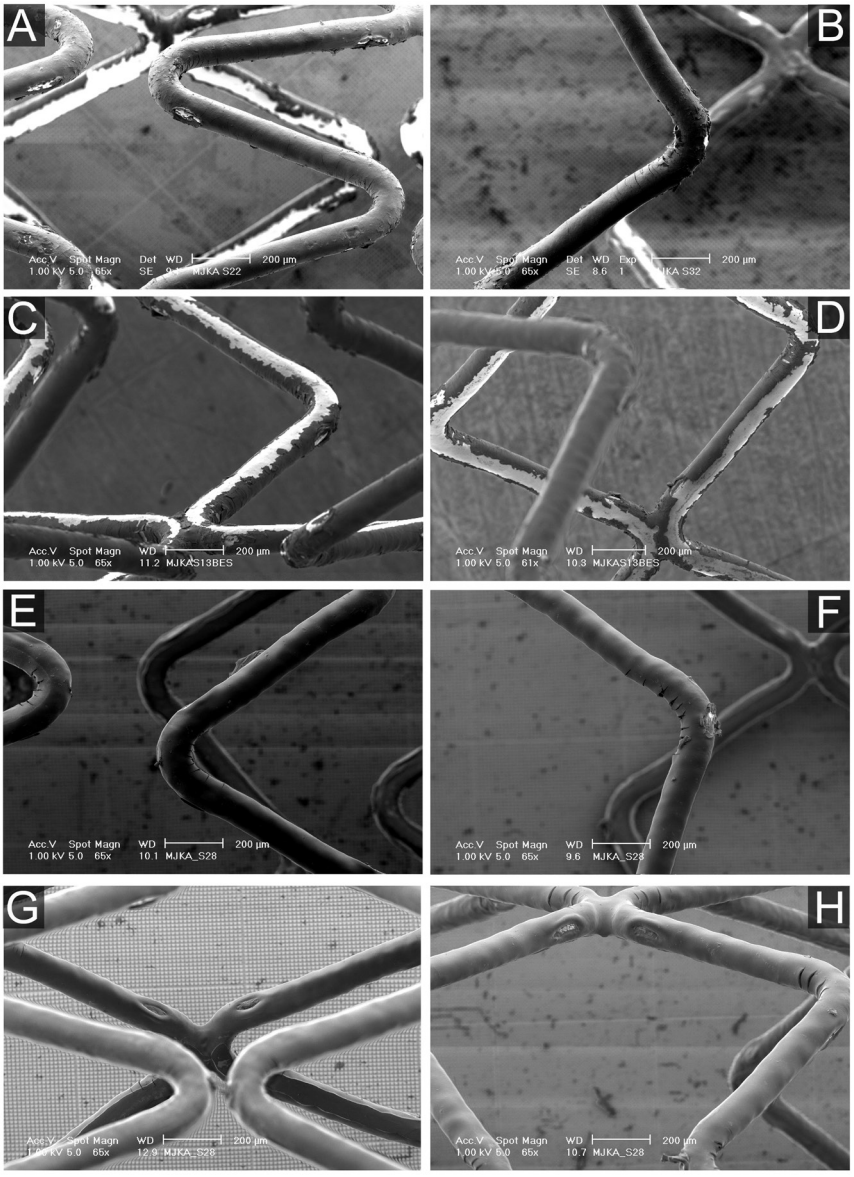

Figure 4. **SEM images of Endeavor Sprint and Resolute. A**) Endeavor Sprint with cracks in non-postdilated region. **B**) Endeavor Sprint with cracks in postdilated region. **C-D**) Very similar incidence of bare metal areas in non-postdilated and postdilated regions of Endeavor Sprint, respectively. **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.

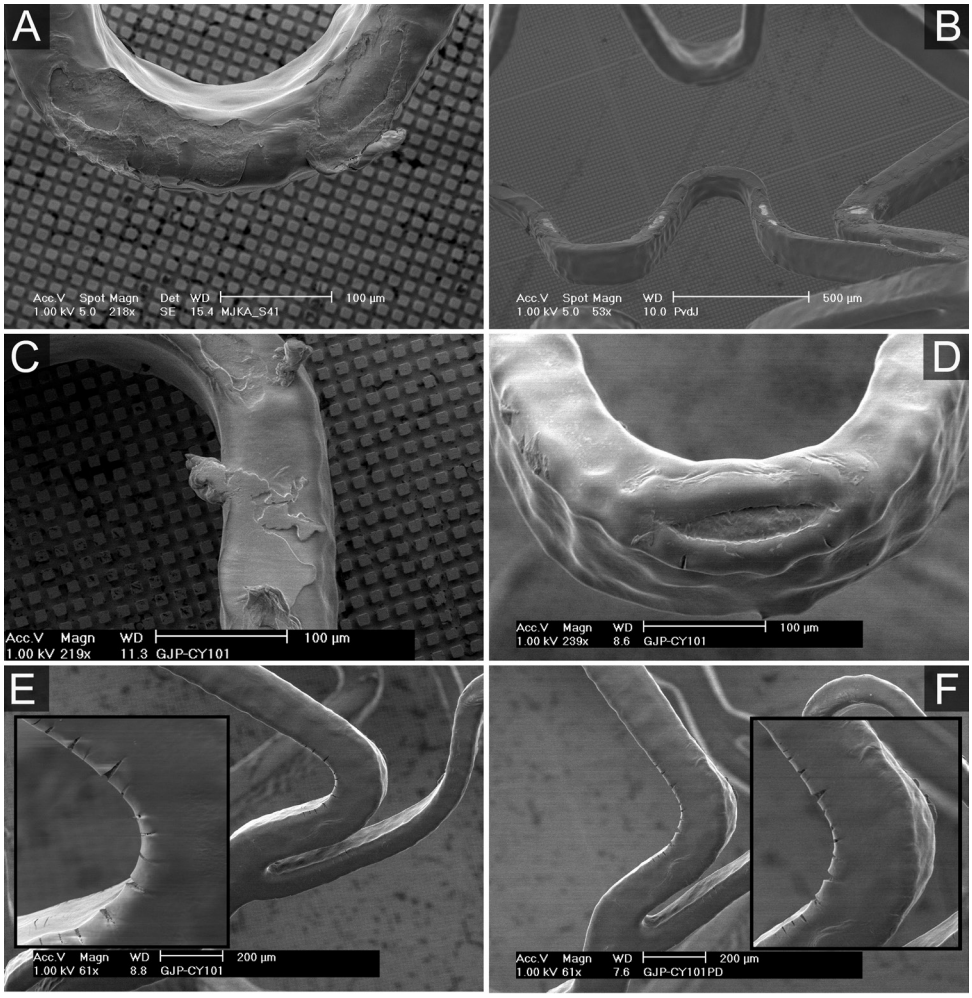

Figure 5. **SEM images of Cypher Select plus. A**) Peeling of polymer without bare metal aspect. **B**) Peeling of polymer with bare metal aspect. **C)** Coarse irregular excess of coating. **D**) Crater lesion. **E**) Cracks in the non-postdilated region of Cypher Select plus. **F)** Cracks in postdilated 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).

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).

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 regionTR: 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		
IVA) Webbing with metal exposure	**Mean frequency /field**	**NPD** 0	**TR** 0	**PR** 0	**NPD** 0.21 ±0.57	**TR** 0.06 ±0.31	**PR** 0.07 ±0.31	**NPD** 0	**TR** 0	**PR** 0	**NPD** 0	**TR** 0	**PR** 0	**NPD** 0	**TR** 0	**PR** 0.01 ±0.1
IVB) Webbingwithout 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

DES and the risk of periprocedural myocardial infarction

Chapter 7

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).

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).

Predictors of PMI

Predictors of PMI based on univariate analyses were: number of stents placed, multivessel PCI, and type C lesions ($p \leq 0.01$), 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.

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.

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
Hypercholesterolemia	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.

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.

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)	<0.01	1.69 (1.34-2.14)	<0.01

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

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 8

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.

Introduction

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.

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).

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.

Conflict of interest: The research department of Thoraxcentrum Enschede has received in the past unrestricted research grants and/or has participated in clinical studies funded by Abbott Vascular, Biosensors International, Biotronik, Boston Scientific, Cordis Corporation, St. Jude medical and Medtronic.

Acknowledgements: For the purpose of bench-side research, free DES samples were provided by Abbott Vascular, Boston Scientific, Cordis and Medtronic; no financial support was obtained for this investigator-initiated study.

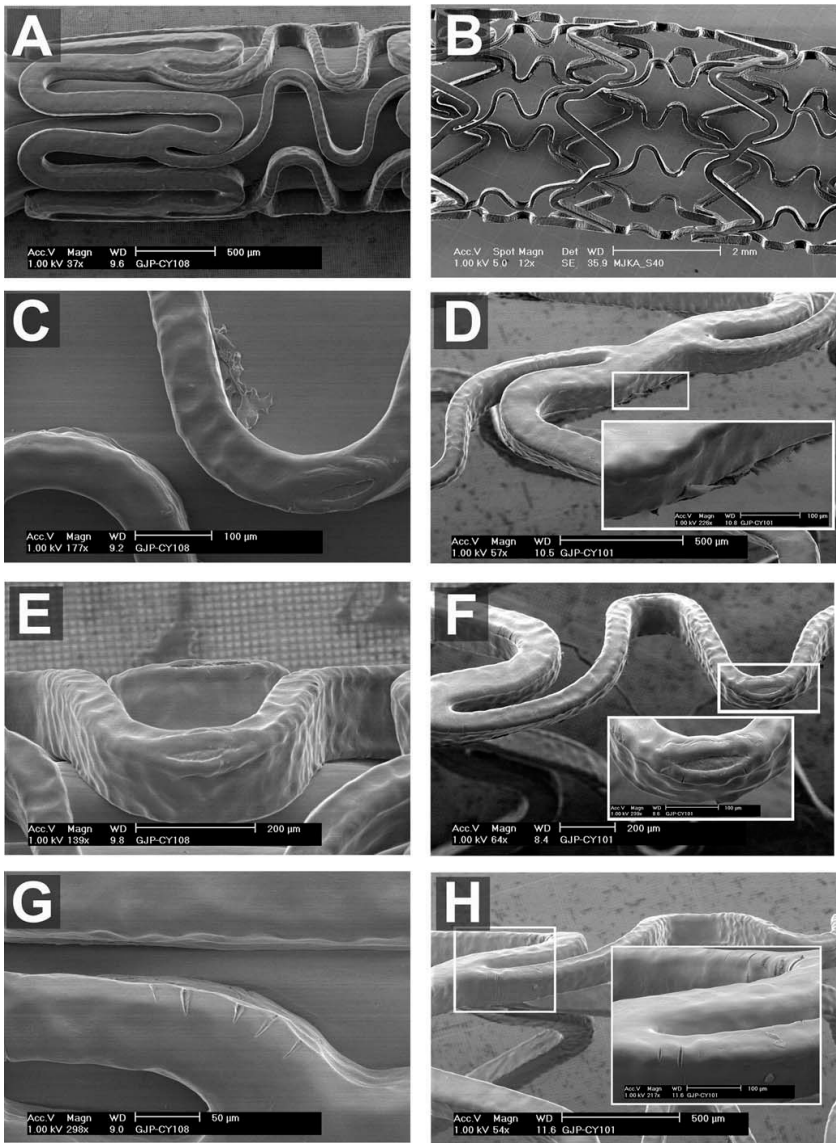

Figure 1. Scanning electron microscopic images of Cypher Select stents.
A)Unexpanded Cypher Select stent. **B**) Expanded Cypher Select stent. **C)** precursor of peeled polymer extending from stent struts to underlying balloon. **D)** Peeled polymer; a high magnification image of peeled polymer is provided 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.

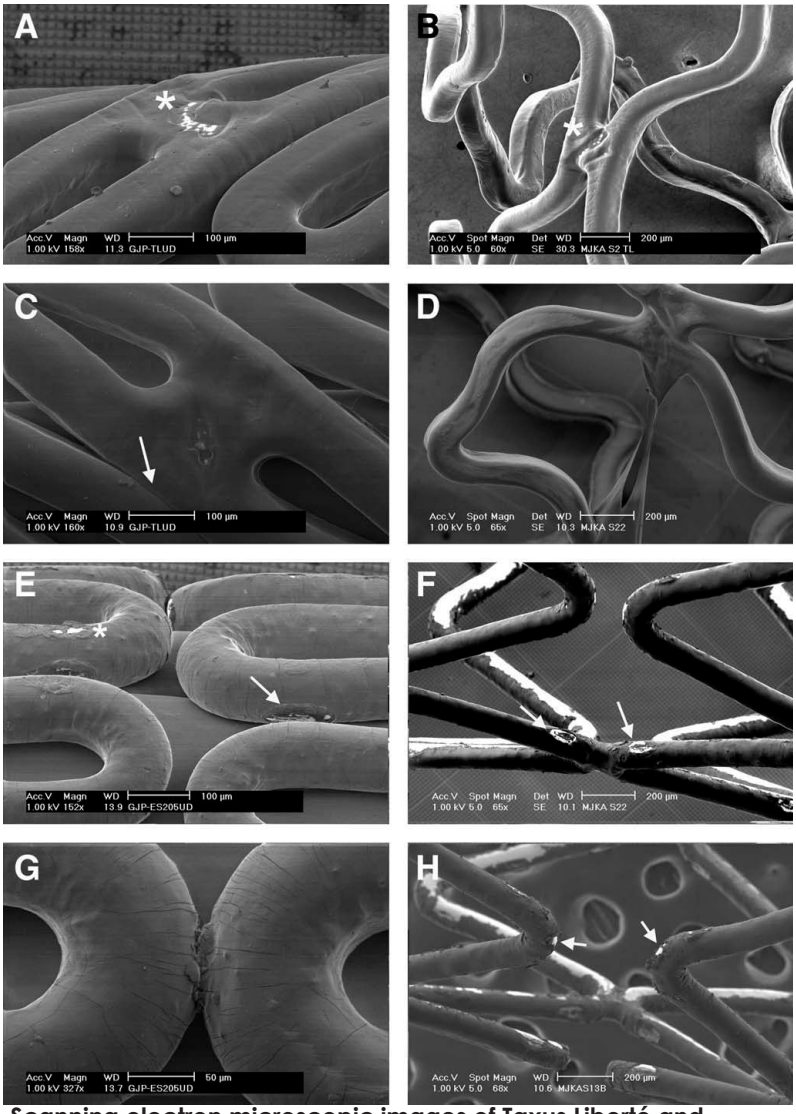

Figure 2. Scanning electron microscopic images of Taxus Liberté and Phosphorylcholine (PC)-based Endeavor stents.

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.

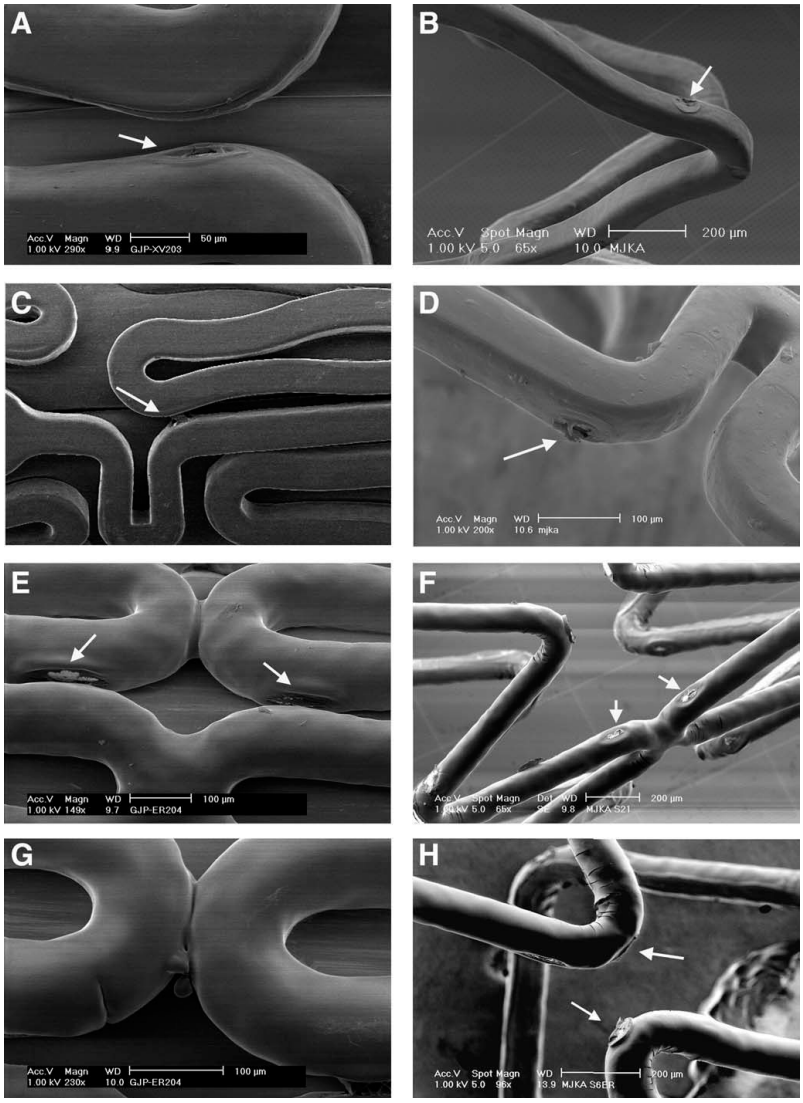

Figure 3. Scanning electron microscopic images of Xience V and Resolute stents. **A)** Crater lesion on unexpanded Xience V stent (arrow). **B)** Crater lesion (arrow) on expanded Xience V stent **C)** A precursor of crater lesion (arrow) on unexpanded Xience V stent. **D)** Crater lesion(arrow) on expanded 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).

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.

	Cypher Select		Taxus Liberté		Endeavor		Xience V		Resolute	
	Unex-panded	Expand-ed	Unexpanded	Expand-ed	Unexpanded	Expanded	Unexpand-ed	Expand-ed	Unex-panded	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	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
IB. Cracks	9.9±4.5	13.0±12.9 p=ns	-	-	Present throughout the stent	Larger, wider and more frequent	-	-	-	17.16±3.01
IC. Reduced thickness of coating at strut crossings	-	-	2.75±0.64	2.64±1.38 p=ns	-	-	-	-	-	-
IIA. 'Auri-cle-shaped' excess of coating	-	-	(precur-sors:5,31±2,69)†	3.69±5.58	-	-	-	-	-	-
IIB. Ridge-shaped ex-cess of coating on strut edge	#	1.0±5.0	-	-	-	-	1.27±1.9	1.41±1.68 p=ns	-	-
IIC. Small rounded struc-ture of excess coating	-	0.05±0.19	-	-	-	-	0.3±0.8	0.52±1.21 p=ns	-	-
IID. Coarse ir-regular excess of coating	0.03±0.18	0.05±0.19 p=ns	-	-	-	-	-	-	-	-

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

	Cypher Select		Taxus Liberté		Endeavor		Xience V		Resolute	
	Unexpand-ed	Expanded	Unexpand-ed	Expanded	Unexpand-ed	Expanded	Unexpand-ed	Expanded	Unexpand-ed	Expanded
IIIA. Crater-shaped with metal exposure	-	-	-	-	12.71±2.86 / (pre-cursors: 6,42±2,77) § p=ns	20.5±6.25	0.27±0.93 / (precur-sors: 0,23± 0,64) | | p=ns	0.07±0.2	10.81±3.46 / (pre-cursors: 6.42±2.77) ¶ p=ns	13.8±9.92
IIIB. Crater-shaped with-out metal exposure	1.06±1.55	0.98±1.64 (p=ns)	-	0.05±0.32		0.3±1.2		0.56±1.27		4.35±5.47
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	-	-	-	0.33±0.72	-	-
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 coat-ing	-	-	-	-	-	-	-	0.06±0.36	-	-
IVD. 'Peeled polymer'	(pre-cursors: 1.40±1.19)*	14.14±20.0 (p= 0.000)	-	-	-	-	-	-	-	-

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

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 ex amination 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.

Chapter 9

Comparison of Frequency of Periprocedural Myocardial Infarction in Patients With and Without Diabetes Mellitus to Those With Previously Unknown but Elevated Glycated Hemoglobin (HbA1c) Levels (From the TWENTE Trial)

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Abstract

In patients without history of diabetes mellitus, elevated levels of glycated hemoglobin (HbA1c) are associated with higher cardiovascular risk. The relation between undetected diabetes and clinical outcome following percutaneous coronary interventions is greatly unknown. To investigate whether these patients may have an increased risk of periprocedural myocardial infarction (PMI), the most frequent adverse event after percutaneous coronary intervention, we assessed patients of the TWENTE trial (a randomized, controlled second-generation drug-eluting stent trial) in whom HbA1c data were available. Patients were classified as known diabetics or patients without history of diabetes, who were subdivided into undetected diabetics (HbA1c ≥6.5%) and non-diabetics (HbA1c <6.5%). Systematic measurement of cardiac biomarkers and electrocardiographic assessment was performed. One-year clinical outcome was also compared. Of 626 patients, 44 (7%) were undetected diabetics, 181 (29%) known diabetics, and 401 (64%) non-diabetics. In undetected diabetics the PMI rate was higher than in non-diabetics (13.6% vs. 6.1%, p=0.01) and known diabetics (13.6% vs. 3.7%, p=0.11). Multivariate analysis, adjusting for covariates, confirmed a significantly higher PMI risk in undetected diabetics compared to non-diabetics (OR 6.13, 95%-CI: 2.07-18.13, p=0.001) and known diabetics (OR 3.73, 95%-CI: 1.17 -11.89, p=0.03). After 1 year, the target vessel MI rate was significantly higher in undetected diabetics (p=0.02) than in non-diabetics, which was mainly related to differences in PMI. Target vessel failure was numerically higher in unknown diabetics than in non-diabetics, but this difference did not reach statistical significance (13.6% vs. 8.0%, p=0.25). In conclusion, undetected diabetics were shown to have an increased risk of PMI.

Introduction

Periprocedural myocardial infarction (PMI) is the most frequent adverse event following percutaneous coronary interventions (PCI) outside the setting of ST-elevation myocardial infarction (STEMI). It has previously been shown that PMI is not necessarily a benign event, and that patients with PMI may have a worse prognosis.[1, 2] Diabetic patients may be particularly prone to PMI because of this disease is associated with dyslipidaemia, hypercoagulability, increased atheroma burden, vessel wall inflammation, and development of vulnerable plaques.[3-5] In patients with undetected diabetes, the metabolic dysregulation and chronic hyperglycaemic state may result in a similar, perhaps even higher, PMI risk. The relation between elevated glycated hemoglobin A1c (HbA1c) and the occurrence of PMI has not yet been examined. We hypothesized that both, undetected diabetes and diabetes mellitus may be related to PMI. In the present study, we therefore assessed this hypothesis in patients of the TWENTE trial – a randomized, controlled trial that compared two second-generation drug-eluting stents (DES) in patients with various clinical presentations with the exception of STEMI.[6]

Methods

The present study was performed in a subpopulation of patients enrolled in the TWENTE trial (ClinicalTrials.gov NCT01066650), in whom HbA1c levels were measured at the time of the index PCI procedure (± one month). Details of the TWENTE study have previously been described.[6] In brief, TWENTE is an investigator-initiated, patient-blinded, randomized non-inferiority study with limited exclusion criteria in a 'real world' patient population treated at the Thoraxcentrum Twente in Enschede, the Netherlands. Between June 2008 and August 2010, a total of 1.391 patients with an indication for PCI with DES implantation were randomized for treatment with the second-generation Resolute (Medtronic Inc., Santa Rosa, CA) or Xience V stent (Abbott Vascular, Santa Clara, CA). There were no angiographic exclusion criteria. The most important exclusion criterion was a recent STEMI.[6] The TWENTE trial was approved by the institutional ethics committee, complied with the Declaration of Helsinki, and all patients provided a written informed consent.

All patients were pre-treated with acetylsalicylic acid and clopidogrel. At discharge we prescribed the combination of 100mg of acetylsalicylic acid once daily indefinitely and clopidogrel 75mg once daily for 1 year. Predilation, direct stenting, stent postdilatation, and/or use of glycoprotein IIb/IIIa antagonists were permitted at the operators' discretion.

The study population was grouped into patients with known history of diabetes mellitus versus patients without a history of diabetes. Patients without a history of diabetes were then subdivided, based on a cut-off HbA1c value of 6.5%: patients with an HbA1c level of ≥6.5% were classified

as undetected diabetics and patients with an HbA1c level of <6.5% as non-diabetic patients. Assessment of HbA1c was performed with a COBAS INTEGRA 800 analysis system (Roche diagnostics, Basel, Switzerland) in the department of Clinical Chemistry of our centre.

In all patients, cardiac biomarkers and electrocardiograms were systematically assessed and analysed before and after PCI to identify PMI.[7] Cardiac biomarker measurements were 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 was established. We used the PMI definition of the Academic Research Consortium: CK >2x the upper limit of normal with elevation of CK-MB and/or troponin. If baseline cardiac biomarkers were above the upper limit of normal or an myocardial infarction (MI) was in progress, PMI was established when 1) there was recurrent chest pain or new ECG changes consistent with MI with a rise of CK > 2x the upper limit of normal or 2) if elevated CK following the index MI has peaked and CK level has returned below the upper limit of normal when there was a rise of CK > 2x the upper limit of normal or 3) if elevated CK following the index MI has peaked and CK level has not returned below the upper limit of normal a rise in CK ≥ 50% above the previous level and > 2x the upper limit of normal confirmed by elevation of CK-MB and/or troponin.[7] Clinical endpoints include Target Vessel Failure (TVF) within 1 year (a composite endpoint consisting cardiac death, target-vessel related myocardial infarction (or not attributable to a non-target vessel), or clinically driven target-vessel revascularization), the individual components of TVF, and a patient-oriented composite endpoint, consisting of all-cause mortality, any myocardial infarction, and any repeat revascularization and stent thrombosis. All clinical endpoints, including stent thrombosis, were defined according to the Academic Research Consortium.[7, 8]

Clinical follow-up data were obtained at visits at outpatient clinics, or, if not feasible, by telephone follow-up and/or medical questionnaire. Follow-up data was available in all patients, 2 patients withdrew informed consent before follow up at 1 year and thus are not included in the follow up analysis. Processing of clinical data and adjudication of all adverse clinical events were performed by an independent external contract research organization (Cardialysis, Rotterdam, the Netherlands).

All statistical analyses were performed with SPSS vers.15.0 (SPSS Inc., Chicago,IL).

When comparing undetected diabetics to non-diabetics and undetected diabetics to known diabetics, differences in categorical variables were assessed with use of $\chi 2$ or Fisher's exact tests, as appropriate, whereas continuous variables were assessed with the Wilcoxon ranksum test or Student's *t* test, as appropriate. Unless otherwise specified, p values and Confidence Intervals (CIs) were two-sided and a p value < 0.05 was considered significant. Univariate and multivariate logistic regression analyses were performed to evaluate diabetic status as independent

predictor of PMI in the subpopulation of undetected diabetics and non-diabetics, and in the subpopulation of undetected diabetics and known diabetics. All variables were evaluated as possible predictors, and only those with a significance at or below p=0.15 for PMI were considered as candidate variables for multivariate logistic regression analysis and were assessed for their relationship with diabetes. If this relationship was also present with a significance at or below p=0.15, they were included in the model. To obtain a parsimonious model, we started with all candidate variables. Subsequently, we eliminated the variables with the highest p-value step by step, until the estimate for diabetes changed by 10% or more or only significant predictors remained.

Results

Of all patients enrolled in the TWENTE trial, 626 had HbA1c measurements within the predefined time frame and formed the *study population* of the present analysis. Patients of the study population had more diabetes mellitus (29% vs 16%, p<0.001), chronic renal failure (3.8% vs 1.8%, p=0.02), hypertension (61% vs 51%, p<0.001), hypercholesterolemia (66% vs 54%, p<0.001), and family history of coronary artery disease (57% vs 50%, p=0.01) than TWENTE trial patients without HbA1c measurements.

Of the study population, 181 (29 %) had a history of diabetes mellitus. In addition, 445 patients of the study population (71 %) had no history of diabetes mellitus; according to the HbA1c levels, 44 patients of the study population were classified as undetected diabetics (7.0%) and 401 as non-diabetic patients (64%).

Baseline characteristics of the study population and the subgroups are presented in Table 1. Compared to the known diabetic patients and non-diabetic patients, undetected diabetics showed many similarities in baseline characteristics but tended to have less often a family history of coronary artery disease (p=0.02 for both groups). As may be expected, the mean HbA1c levels differed across groups, and undetected diabetics had higher HbA1c levels compared tot non-diabetic patients (6.95 vs 5.77, p<0.001).

Angiographic and procedural characteristics are shown in Table 2. Undetected diabetics were less frequently treated for left anterior descending lesions (36% vs 53%, p=0.04), and type B2/C lesions (43.2% vs 60.3%, p=0.03) when compared to non-diabetic patients. Diabetic patients were more frequently treated for long lesions (>27mm) than non-diabetic patients (25% vs 22%, p=0.05). Side branch occlusion was observed in 2.6% of the patients and distal embolization in 0.5% with no significant difference between groups. Medication at discharge did not differ between groups, except for higher rates of ACE-inhibitor and/or AT-blocker prescription in undetected diabetics compared to non-diabetics (p=0.04, Table 3).

PMI occurred in 32 patients (5.1%) of the study population. In undetected diabetics, PMI occurred more frequently than in non-diabetic

patients (13.6% [6 of 44] vs. 3.7% [15 of 401], p=0.01), and known diabetics (13.6% [6 of 44] vs. 6.1% [11 of 181], p=0.11) (Fig. 1).

In a model with only non-diabetic patients and undetected diabetics, variables with a univariate association (p≤0.15) for PMI and diabetic state were: multivessel treatment, number of lesions treated, bifurcations and number of stents placed. Both, diabetic state and number of stents placed turned out to be independent predictors of PMI in a multivariate model. Using non-diabetic patients as the reference group, the adjusted OR of PMI was 6.13 in undetected diabetic patients (95% CI: 2.07-18.13, p=0.001). In addition, number of stents placed was also independently associated with a significantly higher rate of PMI with an OR of 1.80 (95% CI: 1.36-2.38, p<0.001) per additional stent placed. (Fig. 2A)

In a seperate model with only known diabetic patients and undetected diabetics, variables with a univariate association (p≤0.15) for PMI and diabetic state were: treatment of at least one long lesion (>27 mm), and number of stents placed. Both, diabetic state and treatment of at least one long lesion (>27 mm) were significant independent predictors of PMI. Using known diabetic patients as the reference group, the adjusted OR of PMI was 3.73 in undetected diabetic patients (95% CI: 1.17 -11.89, p=0.03). In addition, treatment of at least one long lesion (>27 mm) was also independently associated with a significantly higher rate of PMI with an OR of 5.87 (95% CI: 1.98-17.41, p=0.001). (Fig. 2B)

Clinical follow up at 1 year is described in table 4. The rate of target vessel MI was significantly higher in undetected diabetics (p=0.02) than in non-diabetic patients, caused by increased PMI rates in that group (p=0.01). In addition, the rates of TVF and the patient composite endpoint tended to be lower in non-diabetics compared to undetected diabetics, but this was statistically not significant. When analyzing event rates after discharge from hospital (thus not including PMI), the occurrence of TVF and patient oriented composite endpoint did not differ between groups. Definite-or-probable stent thrombosis rates were relatively low and similar between groups.

Discussion

The main finding of the present study is that undetected diabetics (i.e. patients without a history of diabetes mellitus but with HbA1c levels ≥ 6.5%) had a significantly higher risk of PMI as compared to non-diabetic patients. Undetected diabetes mellitus was associated with a six-fold increased risk of PMI compared to non-diabetic patients, and a risk that was even higher than in known diabetics.

The incidence of PMI, the most common adverse event following stent implantation, ranges from 2 to 20%.[9, 10] Various studies have shown that PMI can be associated with inferior clinical outcome.[1, 2, 10, 11] Risk factors for the occurrence of PMI are factors that are associated with an increase of the general atherosclerotic burden such as the presence

of multivessel disease, lesion eccentricity and calcification, thrombus formation, advanced age, and overt diabetes mellitus.[12, 13] The increased risk of adverse events in diabetic patients undergoing PCI persisted after the introduction of DES and was seen in both, patients treated with first- and second-generation DES.[13-16]

Studies have previously shown that even patients without a history of diabetes mellitus but with elevated HbA1c levels – so-called undetected diabetics – have an increased risk of cardiovascular complications,[17, 18] but the relation between undetected diabetes mellitus and PMI has not been investigated yet. We hypothesized that patients with undetected (and thus untreated) diabetes mellitus may be prone to PMI as their metabolic dysregulation with its chronic hyperglycaemic state leads to dyslipidaemia, increased atheroma burden, hypercoagulability, vessel wall inflammation, and vulnerable plaques.[3-5, 19]

In the present study, undetected diabetics had a significantly increased risk of PMI compared to non-diabetic patients. PMI may result from macro- or microvascular complications but we did not observe any difference in macrovascular complications such as sidebranch occlusion or evident distal embolization. This suggests that the differences in the incidence of PMI between patient groups may reflect differences in microvascular dysfunction or microvascular obstruction, which may be caused by periprocedural microembolization of atherothrombotic debris as suggested by Böse et al.[20]

A recent study by Timmer et al. in non-diabetic STEMI patients as well as our present data suggest that a considerable proportion of patients with coronary artery disease are undetected diabetics.[18] As the global disease burden of diabetes mellitus is increasing,[21] the number of undetected diabetics requiring PCI is likely to also increase. Measurement of HbA1c levels is reproducible and feasible,[22] and it may be a convenient means to assess patients prior to PCI procedures for risk stratification and potential adjustment of treatment. In the present study, undetected diabetics had a higher PMI risk than known diabetics being on anti-diabetic medication. Initiation or optimization of pharmacological treatment for glycaemic control before PCI might reduce the hyperglycaemia-promoted increase in PMI risk.[4] However, it is still unclear which pharmacologic treatment strategy may be most beneficial in patients without history of diabetes but with elevated HbA1c levels. The initiation of glucose lowering treatment may be favourable while very intensive glucose regulation could carry an additional risk.[23, 24] Other measures to reduce PMI risk may be a pre-treatment with drugs that have anti-inflammatory and/or antithrombotic properties such as high-dose statins[25] and/or GPIIb/IIIa antagonists,[26, 27] or treatment with more aggressive antiplatelet regimens as diabetes is also associated with high platelet reactivity.[28]

The identification of undetected diabetics may also be relevant in the context of clinical studies. Most contemporary, randomized DES trials address composite endpoints, of which PMI is an important component.[6, 7,

[29] It might be prudent to routinely assess the diabetic state prior to patient enrollment in randomized studies in order to avoid clustering of these patients in a particular study arm.

The findings of this study should be considered as hypothesis-generating due to the relatively limited number of undetected diabetics. While we found statistically significant differences in PMI rates, the power of comparison was below 80% (post-hoc power analysis revealed that a PMI rate of 15% in the 44 undetected diabetics would have been required to reach 80% power at a significance level of 0.05).

References

1. Bonaca MP, Wiviott SD, Braunwald E, Murphy SA, Ruff CT, Antman EM, Morrow DA. American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation Universal Definition of Myocardial Infarction Classification System and the Risk of Cardiovascular Death: Observations From the TRITON-TIMI 38 Trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38), Circulation 2012;125:577-583.
2. 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;71:318-324.
3. Berry C, Noble S, Gregoire JC, Ibrahim R, Levesquie S, Lavoie MA, L'Allier PL, Tardif JC. Glycaemic status influences the nature and severity of coronary artery disease, Diabetologia 2010;53:652-658.
4. Bansilal S, Farkouh ME, Fuster V. Role of insulin resistance and hyperglycemia in the development of atherosclerosis, Am J Cardiol 2007;99:6B-14B.
5. Jensen LO, Thayssen P, Mintz GS, Egede R, Maeng M, Junker A, Galloee A, Christiansen EH, Pedersen KE, Hansen HS, Hansen KN. Comparison of intravascular ultrasound and angiographic assessment of coronary reference segment size in patients with type 2 diabetes mellitus, Am J Cardiol 2008;101:590-595.
6. 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.
7. 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.
8. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 2007;115:2344-2351.
9. 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.
10. Lindsey JB, Kennedy KF, Stolker JM, Gilchrist IC, Mukherjee D, Marso SP, Pencina MJ, Kleiman NS, Cohen DJ. Prognostic implications of creatine kinase-MB elevation after percutaneous coronary intervention: results from the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry, Circ Cardiovasc Interv 2011;4:474-480.
11. Herrmann J, Von Birgelen C, Haude M, Volbracht L, Malyar N, Eggebrecht H, Konorza TF, Baumgart D, Erbel R. Prognostic implication of cardiac troponin T increase following stent implantation, Heart 2002;87:549-553.
12. Lansky AJ, Stone GW. Periprocedural myocardial infarction: prevalence, prognosis, and prevention, Circ Cardiovasc Interv 2010;3:602-610.
13. 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 2011. In press: doi: 10.1002/ccd.23334.
14. Akin I, Bufe A, Schneider S, Reinecke H, Eckardt L, Richardt G, Burska D, Senges J, Kuck KH, Nienaber CA. Clinical outcomes in diabetic and non-diabetic patients with drug-eluting stents: results from the first phase of the prospective multicenter German DES.DE registry, Clin Res Cardiol 2010;99:393-400.

15. Stone GW, Kedhi E, Kereiakes DJ, Parise H, Fahy M, Serruys PW, Smits PC. Differential clinical responses to everolimus-eluting and Paclitaxel-eluting coronary stents in patients with and without diabetes mellitus, Circulation 2011;124:893-900.
16. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, Gomez-Hospital JA, Alfonso F, Hernandez-Antolin R, Goicolea J, Banuelos C, Escaned J, Moreno R, Fernandez C, Fernandez-Aviles F, Macaya C, DIABETES Investigators. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial, Circulation 2005;112:2175-2183.
17. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults, N Engl J Med 2010;362:800-811.
18. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, Dambrink JH, Bilo HJ, Zijlstra F, van 't Hof AW. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention, Circulation 2011;124:704-711.
19. Zheng M, Choi SY, Tahk SJ, Lim HS, Yang HM, Choi BJ, Yoon MH, Park JS, Hwang GS, Shin JH. The relationship between volumetric plaque components and classical cardiovascular risk factors and the metabolic syndrome a 3-vessel coronary artery virtual histology-intravascular ultrasound analysis, JACC Cardiovasc Interv 2011;4:503-510.
20. Bose D, von Birgelen C, Zhou XY, Schmermund A, Philipp S, Sack S, Konorza T, Mohlenkamp S, Leineweber K, Kleinbongard P, Wijns W, Heusch G, Erbel R. Impact of atherosclerotic plaque composition on coronary microembolization during percutaneous coronary interventions, Basic Res Cardiol 2008;103:587-597.
21. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic, Nature 2001;414:782-787.
22. American Diabetes Association. Diagnosis and classification of diabetes mellitus, Diabetes Care 2012;35 Suppl 1:S64-S71.
23. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC,Jr, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH,Jr, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes, N Engl J Med 2011;364:818-828.
24. Timmer JR, Svilaas T, Ottervanger JP, Henriques JP, Dambrink JH, van den Broek SA, van der Horst IC, Zijlstra F. Glucose-insulin-potassium infusion in patients with acute myocardial infarction without signs of heart failure: the Glucose-Insulin-Potassium Study (GIPS)-II, J Am Coll Cardiol 2006;47:1730-1731.
25. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial, J Am Coll Cardiol 2009;54:558-565.
26. Cohen M, Ferguson JJ. Re-evaluating risk factors for periprocedural complications during percutaneous coronary intervention in patients with unstable angina/non-ST-elevation myocardial infarction: who may benefit from more intensive antiplatelet therapy? Curr Opin Cardiol 2009;24:88-94.
27. Patti G, Pasceri V, D'Antonio L, D'Ambrosio A, Macri M, Dicuonzo G, Colonna G, Montinaro A, Di Sciascio G. Comparison of Safety and Efficacy of Bivalirudin Versus Unfractionated Heparin in High-Risk Patients Undergoing Percutaneous Coronary Intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin Study), Am J Cardiol 2012.
28. Mangiacapra F, Patti G, Peace A, Gatto L, Vizzi V, Ricottini E, D'Ambrosio A, Muller O, Barbato E, Di Sciascio G. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention, Am J Cardiol 2010;106:619-623.

29. 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;163:557-562.

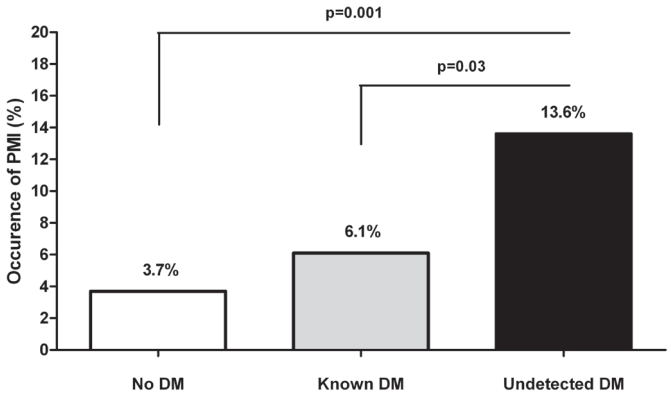

Figure 1. Incidence of periprocedural myocardial infarction stratified for diabetic state according to history of diabetes mellitus and HbA1c. PMI = periprocedural myocardial infarction. No DM = patients without history of diabetes mellitus and HbA1c < 6.5%. Known DM = patients with history of diabetes mellitus. Undetected DM = patients without history of diabetes mellitus and HbA1c ≥ 6.5%. P values were calculated with multivariate logistic regression analysis.

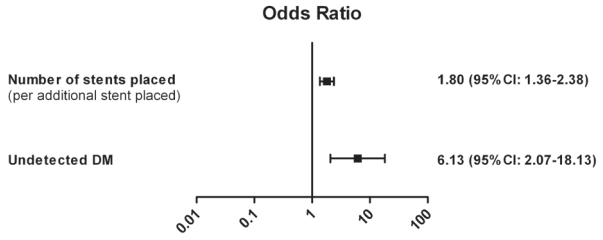

Fig 2A

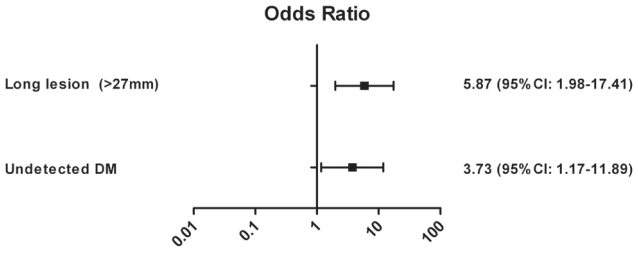

Fig 2B

Figure 2. Multivariate adjusted odds ratios for independent predictors of periprocedural myocardial infarction in undetected diabetics and non-diabetic patients (A), and in undetected diabetics and known diabetic patients (B). CI = confidence interval. Undetected DM = patients without history of diabetes mellitus and HbA1c ≥ 6.5%.

	Study population (N=626)	Undetected DM (N = 44)	No DM (N = 401)	Known DM (N = 181)	p Value Undetected vs No DM	p Value Undetected vs Known DM
Age (years)	64.7 ± 9.9	66.8 ± 9.7	64.1 ± 9.8	65.5 ± 0.3	0.09	0.46
HbA1c (%)	6.25 ± 0.94	6.95 ± 0.74	5.77 ± 0.31	7.13 ± 1.15	<0.001	0.32
Men	450 (72%)	32 (73%)	295 (74%)	123 (68%)	0.91	0.54
Body mass index (kg/m²)	28.0 ± 4.1	27.7 ± 2.8	27.5 ± 3.8	29.2 ± 4.6	0.75	0.10
Insulin treatment	67 (11%)	-	-	67 (37%)		
Insulin treatment and oral glucose lowering medication	43 (7%)	-	-	43 (24%)		
Chronic renal failure *	24 (4%)	2 (5%)	11 (3%)	11 (6%)	0.50	0.70
Arterial hypertension	382 (61%)	30 (68%)	227 (57%)	125 (69%)	0.28	0.91
Hypercholesterolaemia	402/610 (66%)	24/39 (62%)	246/392 (63%)	132/179 (74%)	0.88	0.25
Current smoker	135 (22%)	11 (25%)	90 (22%)	34 (19%)	0.70	0.36
Family history of CAD	358 (57%)	16 (36%)	235 (59%)	107 (59%)	0.02	0.02
Myocardinfarction (any)	186 (30%)	15 (34%)	118 (29%)	53 (29%)	0.52	0.53
Previous PCI	139 (22%)	6 (14%)	84 (21%)	49 (27%)	0.25	0.06
Previous CABG	70 (11%)	4 (9%)	43 (11%)	23 (13%)	0.74	0.51
Clinical indication					0.69	0.51
Stable angina pectoris	426 (68%)	30 (68%)	282 (70%)	114 (63%)		
Unstable angina	120 (19%)	10 (23%)	72 (18%)	38 (21%)		
Non-ST-elevation MI	80 (13%)	4 (9%)	47 (12%)	29 (16%)		
Clinical indication: Acute coronary syndrome	200 (32%)	14 (32%)	119 (30%)	67 (37%)	0.77	0.52
Left ventricular ejection fraction < 30% †	15/473 (3%)	1/35 (3%)	6/294 (2%)	8/144 (6%)	0.75	0.51

Table 1. Baseline characteristics of patients.
Data are number (%) or mean ± SD. CAD = coronary artery disease; DM = diabetes mellitus; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; MI = myocardial infarction.
* Chronic renal failure defined by serum creatinine level ≥ 130 µmol/L.
† Left ventricular ejection fraction assessed with ultrasound, MRI, or LV angiography.

	Study population (N=626)	Undetected DM (N = 44)	No DM (N = 401)	Known DM (N = 181)	p Value Undetected vs no DM	p Value Undetected vs Known DM
Target lesion coronary artery						
Left anterior descending	316 (51%)	16 (36%)	213 (53%)	100 (55%)	0.04	0.16
Left circumflex	216 (35%)	17 (39%)	140 (35%)	59 (33%)	0.62	0.45
Right coronary artery	222 (36%)	15 (34%)	137 (34%)	70 (39%)	0.99	0.57
Left main	24 (96%)	2 (5%)	13 (3%)	9 (5%)	0.65	0.91
Bypass graft	19 (3%)	1 (2%)	12 (3%)	6 (3%)	0.79	0.72
Multivessel treatment	156 (25%)	6 (14%)	106 (26%)	44 (24%)	0.06	0.13
Total lesions treated per patient					0.13	0.21
One lesion treated	384 (61%)	29 (66%)	241 (60%)	114 (63%)		
Two lesions treated	172 (28%)	14 (32%)	110 (27%)	48 (27%)		
Three of more lesions treated	70 (11%)	1 (2%)	50 (13%)	19 (11%)		
No of stents placed	2.08 ± 1.29	1.75 ± 0.99	2.10 ± 1.29	2.11 ± 1.34	0.08	0.10
ACC-AHA lesion class B2 or C lesion treated	361 (58%)	19 (43%)	242 (60%)	100 (55%)	0.03	0.15
De novo coronary lesions only*	582 (93%)	42 (96%)	374 (93%)	166 (92%)	0.58	0.40
At least one CTO	57 (9%)	3 (7%)	41 (10%)	13 (7%)	0.47	0.93
At least one bifurcation	152 (24%)	15 (34%)	92 (23%)	45 (25%)	0.10	0.21
At least one bifurcation with sidebranch treatment	96 (15%)	9 (21%)	59 (15%)	28 (16%)	0.32	0.42
At least one in-stent restenosis	28 (5%)	1 (2%)	17 (4%)	10 (6%)	0.53	0.37
At least one small-vessel (RVD <2.75mm)	419 (67%)	28 (64%)	275 (69%)	116 (64%)	0.50	0.96
At least one lesion length > 27mm	141 (23%)	5 (11%)	90 (22%)	46 (25%)	0.09	0.05
Preprocedural TIMI flow (grade 0-1)	43 (7%)	2 (5%)	29 (7%)	12 (7%)	0.51	0.61
Aggressive stent postdilatation of >18 atm	476 (88%)	30 (81%)	300 (88%)	146 (90%)	0.28	0.12
Sidebranch occlusion	16 (2.6%)	1 (2.3%)	13 (3.2%)	2 (1.1%)	0.73	0.55
Distal embolization	3 (0.5%)	0 (0%)	1 (0.2%)	2 (1.1%)	0.74	0.48

Table 2. Angiographic and procedural characteristics.
Data are number (%) or mean ± SD.
ACC = American College of Cardiology; ACE = Angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blockers; CTO = chronic total occlusion; DM = diabetes mellitus; RVD = reference vessel diameter; TIMI = thrombolysis in myocardial infarction.
* Including chronic total occlusion, but not grafts and in-stent restenosis.

	Study population (N=626)	Undetected DM (N = 44)	No DM (N = 401)	Known DM (N = 181)	p Value Undetected vs no DM	p Value Undetected vs Known DM
Antiplatetelet therapy						
Acetylsalicylic acid	619 (99%)	44 (100%)	397 (99%)	178 (98%)	0.51	0.39
Clopidogrel	625 (100%)	44 (100%)	400 (100%)	181 (100%)	1.00	1.00
Other medication						
Statin	536 (86%)	35 (80%)	345 (86%)	156 (86%)	0.25	0.27
B-blocker	518 (83%)	34 (77%)	331 (83%)	153 (85%)	0.39	0.25
ACE/ARB	321 (51%)	27 (61%)	180 (45%)	114 (63%)	0.04	0.84

Table 3. Medication at discharge.
Data are number (%).
ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blockers; DM = diabetes mellitus.

	Undetected DM (N = 44)	No DM (N = 400)	Known DM (N = 180)	p Value Undetected vs no DM	p Value Undetected vs Known DM
All-cause death	0 (0%)	7 (1.8%)	5 (2.8%)	1.00	0.59
Cardiac death	0 (0%)	5 (1.3%)	4 (2.2%)	1.00	1.00
Target vessel revascularization	1 (2.3%)	13 (3.3%)	10 (5.6%)	1.00	0.70
Target vessel MI	6 (13.6%)	16 (4.0%)	14 (7.8%)	0.02	0.24
Periprocedural MI	6 (13.6%)	15 (3.8%)	11 (6.1%)	0.01	0.11
Spontaneous MI	0 (0%)	1 (0.3%)	3 (1.7%)	1.00	1.00
Target vessel failure	6 (13.6%)	32 (8.0%)	24 (13.3%)	0.25	0.96
Patient-oriented composite endpoint	6 (13.6%)	42 (10.5%)	31 (17.2%)	0.45	0.57
Target vessel failure without PMI	1 (2.3%)	19 (4.8%)	15 (8.3%)	0.71	0.21
Patient-oriented composite endpoint without PMI	1 (2.3%)	28 (7.0%)	19 (10.6%)	0.34	0.14
Definite-or-probable stent thrombosis	0 (0%)	3 (0.8%)	3 (0.8%)	1.00	1.00

Table 4: Clinical outcome at 1 year.
Data are number of patients (%). MI = myocardial infarction. Patient-oriented composite endpoint is a composite of endpoint of all-cause death, any myocardial infarction or any revascularization.

Chapter 10

Predictive Value of the Syntax Score for Periprocedural Myocardial Infarction According to WHO and Third Universal Definition of Myocardial Infarction:

Insights from the TWENTE Trial

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Abstract

The Syntax Score (SxS) is a scoring system to quantify the complexity of coronary artery disease. We investigated the predictive value of the SxS for the occurrence of a periprocedural myocardial infarction (PMI) according to both the definition of the World Health Organization (WHO) and the updated universal definition of MI. The SxS was calculated in 1243 patients enrolled in TWENTE – a prospective randomised trial that assessed second-generation drug-eluting coronary stents. PMI was defined by the historical WHO definition (total CK >2x normal with elevated CK-MB) and the third universal definition of MI (troponin >5x normal or a rise of troponin values >20% if baseline values were elevated, in addition to symptoms, ECG changes, angiographic findings or new regional wall motion abnormalities). Patients were divided in tertiles of SxS: ≤7 (n=430); >7 and <15 (n=390); ≥15 (n=423). PMI according to the historical WHO definition occurred more frequently in patients in the highest tertile group of SxS (7.3% vs. 3.1% vs. 1.6%, p<0.001) compared to the mid and lowest tertile SxS. Similar findings were also seen for universal PMI (9.9% vs. 7.7% vs. 3.7%, p<0.01). After multivariate analysis, SxS was a significant independent predictor of PMI for both definitions: Patients in the highest tertile of SxS had an almost 5 times higher risk for WHO PMI and an almost 3 times higher risk for universal PMI. In conclusion, in a broad patient population treated with second-generation DES, the Syntax Score was able to stratify the risk of PMI.

Introduction

The Syntax Score (SxS) is a scoring system for the assessment of the degree and complexity of atherosclerotic disease burden of coronary arteries. It incorporates several pre-existing scoring systems such as the Leaman classification, American Heart Association/American College of Cardiology, modified BARI classification, and chronic total occlusion and bifurcation scores.[1]
Currently, the SxS is mainly used as a tool to evaluate the suitability of patients with multivessel disease to undergo coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).[2] In addition to this application, the SxS may also be useful to stratify the risk of peri-procedural complications. Myocardial infarction after a percutaneous coronary intervention (PCI) is the most common procedural complication and is an important endpoint in coronary stent trials.[3] There is controversy about the clinical impact of periprocedural myocardial infarction (PMI), however several studies have shown a relation between PMI and an increased mortality.[4-6] So far, there are no established risk models for the prediction of PMI.

We therefore assessed in 1243 real-world PCI patients of the randomised TWENTE trial, treated with second-generation drug-eluting stents (DES), the predictive value of the SxS for the occurrence of PMI, as defined by the extended historical WHO definition as well as the recently updated third universal definition of MI.

Methods

The randomised TWENTE trial (ClinicalTrials.gov NCT01066650) has previously been described and reported.[7, 8] In brief, TWENTE was an investigator-initiated, patient-blinded, randomised, comparative DES trial with limited exclusion criteria in 1391 'real-world' PCI patients 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 randomised for treatment with Resolute (Medtronic Inc., Santa Rosa, CA) or Xience V stents (Abbott Vascular, Santa Clara, CA) in a 1:1 ratio. There were no angiographic exclusion criteria such as a mandatory lesion length, reference vessel size, and number of target lesions or vessels. The main exclusion criterion was a recent ST-elevation myocardial infarction (STEMI). More than 81% of the eligible patients were enrolled in this trial.[9]

In all trial participants, except for 148 patients with a history of CABG, SxS was prospectively assessed by experienced analysts of the angiographic core laboratory at Thoraxcentrum Twente. The study was approved by the institutional ethics committee and complied with the

Declaration of Helsinki. All patients provided written informed consent.

PMI was defined by the extended historical WHO definition (WHO PMI; total CK >2x normal with elevated CKMB) and the third universal definition of MI (troponin >5x normal or a rise of troponin values >20% if the baseline values are elevated, in addition to symptoms, ECG changes, angiographic findings or new regional wall motion abnormalities).

In all patients, cardiac biomarkers and electrocardiograms were systematically assessed before and after PCI in order to identify PMI. Cardiac biomarker measurements were scheduled before PCI and 6 to 18 hours after PCI, with subsequent serial measurements for relevant biomarker increases or complaints, until peak increase was established. Adjudication of WHO PMI was performed by an external clinical event committee (Cardialysis, Rotterdam, Netherlands), and adjudication of PMI according to the universal definition of MI was performed by three experienced cardiologists/research physicians.

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. Means are given with standard deviation (SD) and medians with an interquartile range (IQR). Multivariate logistic regression analyses were performed with the covariates: SxS (according to tertiles or continuous variable), presentation with acute coronary syndrome, diabetes mellitus, age, sex, stent type, history of MI, history of PCI, and chronic renal failure. The variable left ventricular ejection fraction (LVEF) <30% was not included in this model, as data on LVEF were not available in all patients. Unless otherwise specified, p values and CIs were two-sided. A p value <0.05 was considered significant. All statistical analyses were performed with SPSS vers. 15.0 (SPSS Inc., Chicago, IL).

Results

The SxS was assessed in 1243 of the 1391 patients (89.4%) of the TWENTE trial who had not undergone previous CABG. The mean SxS was 12.45 ± 8.36, and the median SxS was 11.00 (IQR 6.00-24.00). Based on tertiles of SxS, the SxS was ≤ 7.0 in 430 patients, >7.0 and <15.0 in 390 patients, and ≥15 in 423 patients.

Baseline characteristics and angiographic and procedural characteristics are described in Tables 1 and 2. Patients with the highest SxS (≥15) were older (p<0.001) and were more likely to have an LVEF <30% (p=0.008), and a previous myocardial infarction (p<0.001). Postdilation with balloon pressures >18 atm and use of glycoprotein IIb/IIIa antagonists were more frequent in patients with higher SxS (p<0.001). Medication at discharge did not differ between groups (Table 3).

The incidence of PMI according to the extended historical WHO definition and universal definition, stratified for SxS, is shown in Table 4. MI according to the extended historical WHO definition occurred more frequently in patients of the highest SxS tertile (7.3% vs 3.1% vs. 1.6%, p<0.001)

as compared to the mid and lowest SxS tertiles. In addition, PMI according to the third universal definition occurred more frequently in patients of the highest SxS tertile (9.9% vs. 7.7% vs. 3.7%, p=0.002).

After multivariate analysis, adjusting for covariates, SxS was a significant independent predictor of PMI according to both definitions. Patients with the highest tertile of the SxS, compared to the lowest tertile, had an almost 5 times higher risk for PMI according to the historical WHO definition (adjusted OR 4.95, 95% CI: 2.13-11.52) and an almost 3 times higher risk according to the updated PMI definition (adjusted OR 2.84, 95% CI: 1.55-5.19) (Figure 1). On a continuous scale, SxS was also a significant independent predictor of PMI according to the extended historical WHO definition (adjusted OR 1.07, 95% CI:1.038-1.098, p<0.001) and third universal definition (adjusted OR 1.04, 95% CI:1.014-1.063, p=0.002).

In a multivariate model with the SxS predicting for PMI, and adjusting for baseline differences, the -2 Log-likelihood was better than the same model with SxS being replaced by the AHA/ACC lesion classification (-2 Log-likelihood of 396.8 versus 407.6). This suggests that the SxS is a better predictor of PMI.

Discussion

The SxS is an independent predictor of PMI according to both the extended historical WHO definition[10] and the recently updated universal definition of MI.[11] According to both definitions, patients in the highest SxS tertile had an almost 3 to 5 times higher chance of developing a PMI than patients in the lowest SxS tertile. Our data demonstrate that PCI patients with complex coronary artery disease have a higher PMI risk, and that the SxS predicted PMI better than the AHA/ACC lesion classification. The present substudy of the TWENTE trial is the first to show that the SxS independently predicts PMI in a patient population with a wide range of complexity of coronary artery disease, including patients with single up to three vessel disease and clinical syndromes ranging from stable angina to non-ST-elevation acute coronary syndromes.

PMI is the most common adverse event after PCI and occurs in 5 to 30% of the procedures, depending on patient population, local practice of post-procedural assessment of cardiac markers, and the diagnostic criteria applied.[12-15] Some studies have shown a relation between PMI and adverse outcome.[4-6] Risk factors of PMI are associated with the burden of atherosclerotic disease (i.e. multivessel disease, calcification) and lesion complexity (i.e. thrombus formation, lesion eccentricity).[16, 17] These risk factors are also included in the SxS, which is a tool to assess the severity and complexity of coronary atherosclerotic disease burden.

In previous studies, the SxS has been shown to be associated with adverse *long-term* clinical outcome [6, 18, 19]; however, there is limited data on the predictive value of the SxS on periprocedural complications in a broad

population of patients undergoing PCI.
Van Gaal et al. previously assessed 100 patients with stable coronary artery disease and suggested, based on their findings in this relatively small population, that the SxS predicts periprocedural necrosis.[20] Farooq et al. recently reported in a post-hoc analysis of the SYNTAX trial that a higher SxS was associated with an increased risk of PMI in 827 patients undergoing PCI with first-generation DES (Taxus; Boston Scientific, Natick, MA) for severe (three-vessel or left main) coronary artery disease.[6]
Our study population differs significantly from both aforementioned studies as 10% of our patients had a history of previous CABG, 58% presented with acute coronary syndromes, and merely 24% underwent multi-vessel PCI.[21] The findings of our present study extend current knowledge by showing that also in a broad population of contemporary PCI patients, treated with second-generation DES, a higher SxS is related to an increased PMI risk.
Various clinical trials have applied different definitions of MI and PMI. In an attempt to standardise definitions, a Joint European Society of Cardiology, American College of Cardiology, American Heart Association, and World Health Foundation Task Force for the development of a Universal Definition of Myocardial Infarction has been established. With the development of even more sensitive assays for markers of myocardial necrosis and new insights from recent studies, the universal definition of MI has recently been updated [11] to make the definition more specific. In contrast to the second universal definition of MI, higher troponin values along with supplemental clinical information are now required in order to diagnose a PMI.

In the present study, we used the extended historical WHO definition as well as the third universal definition of MI to assess a potential relation between SxS and PMI. This relation was shown for both definitions, indicating that the relation between SxS and PMI was not related to use of one particular definition only. Nevertheless, this relation was stronger for the WHO definition of MI, which uses a higher threshold for identifying PMI.
While several previous studies showed a relation between PMI and short-term and long-term clinical outcome[6, 17], there is still an ongoing discussion on this issue as other studies showed no such relation [4, 22, 23]. PMI with limited marker release may have no impact on the clinical course, which recently even triggered the suggestion of a new "clinically relevant" definition of PMI.[24]
Preprocedural assessment of the SxS could help to identify patients at an increased risk of PMI, which might then trigger preventive measures. In patients with particularly high risk of PMI, pre-treatment with drugs that have anti-inflammatory and/or antithrombotic properties might be considered, such as high-dose statin therapy [25], administration of a glycoprotein IIb/IIIa antagonist [26, 27], and perhaps even the initiation of pharmacologic treatment for glycemic control in patients with not previously recognised diabetes mellitus.[28]

In conclusion, in a broad population of patients treated with second-generation DES, the Syntax Score was able to stratify the risk of

periprocedural myocardial infarction according to both WHO and the third universal definition of myocardial infarction. This substudy of the TWENTE trial is limited by its post-hoc nature, and the findings should be considered as hypothesis generating only. Patients undergoing primary PCI were not included in the TWENTE trial. Nevertheless, in STEMI patients the assessment of PMI is challenging, as the discrimination between procedure-related myocardial damage and the natural course of STEMI is difficult.

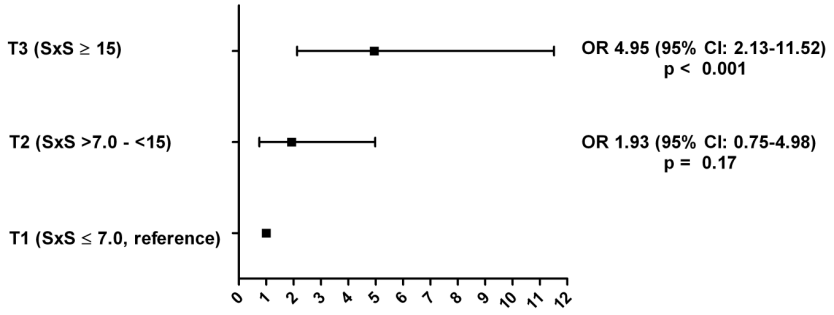

Fig 1A

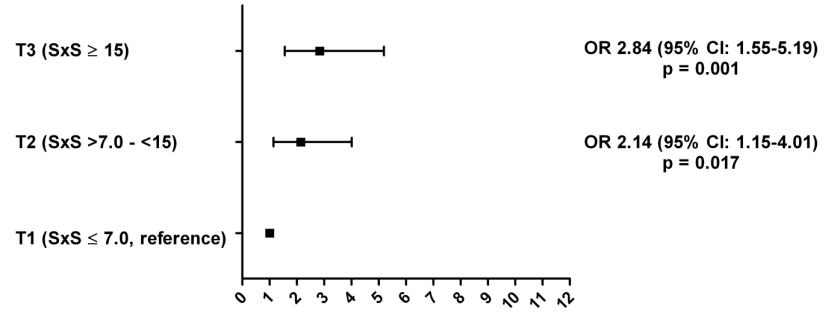

Fig 1B

Figure 1. Multivariate adjusted Odds Ratios (OR) of Syntax Score (SxS) tertiles for periprocedural myocardial infarction according to the WHO definition (A), and third universal defintion of MI (B).

	Study population (N=1243)	SxS <=7,0 (N = 430)	SxS >7,0 and <15 (N = 390)	SxS ≥15 (N = 423)	p Value Across groups
Age (yrs)	63.8 (10.6)	62.2 (10.8)	64.1 (10.6)	65.2 (10.1)	<0.01
Men	890 (71.6)	303 (70.5)	277 (71.0)	310 (73.3)	0.63
Body mass index (kg/ m²)*	27.7 (4.0)	27.9 (4.2)	27.6 (3.9)	27.7 (3.9)	0.56
Diabetes mellitus	262 (21.1)	89 (20.7)	84 (21.5)	89 (21.0)	0.96
Diabetes mellitus receiving insulin	90 (7.2)	34 (7.9)	25 (6.4)	31 (7.3)	0.71
Chronic renal failure †	32 (2.6)	9 (2.1)	7 (1.8)	16 (3.8)	0.15
Arterial hypertension	690 (55.5)	239 (55.6)	208 (5.3)	243 (57.4)	0.50
Hypercholesterolemia	700 (57.8)	248 (58.8)	216 (56.8)	236 (57.6)	0.86
Current smoker	324 (26.1)	119 (27.7)	98 (25.1)	107 (25.3)	0.64
Family history of CAD	651 (52.4)	226 (52.6)	204 (52.3)	221 (52.2)	1.00
Myocardial infarction (any)	392 (31.5)	107 (24.9)	123 (31.5)	162 (38.3)	<0.01
Previous PCI	234 (18.8)	90 (20.9)	77 (19.7)	67 (15.8)	0.14
Clinical indication					0.24
Stable angina pectoris	591 (47.5)	203 (47.2)	182 (46.7)	206 (48.7)	
Unstable angina	285 (22.9)	95 (22.1)	104 926.7)	86 (20.3)	
Non-ST-elevation MI	367 (29.5)	132 (30.7)	104 (26.7)	131 (31.0)	
Clinical indication: Acute coronary syndrome	652 (52.5)	227 (52.8)	208 (53.3)	217 (51.3)	0.83
Left ventricular ejection fraction < 30% ‡	25 (2.6)	5 (1.6)	4 (1.3)	16 (4.9)	<0.01
Multivessel treatment	293 (23.6)	25 (5.8)	99 (25.4)	169 (40.0)	<0.01
Total no lesions treated per patient					<0.01
One lesion treated	762 (61.3)	370 (86.0)	221 (56.7)	171 (40.4)	
Two lesions treated	357 (28.7)	54 (12.6)	142 (36.4)	161 (38.1)	
Three of more lesions treated	124 (10.0)	6 (1.4)	27 (6.9)	91 (21.5)	
***Only de novo* coronary lesions treated §**	60 (4.8)	16 (3.7)	27 (6.9)	17 (4.0)	0.07

At least one CTO treated	83 (6.7)	8 (1.9)	17 (4.4)	58 (13.7)	<0.01
At least one bifurcation treated	337 (27.1)	39 (9.1)	107 (27.4)	191 (45.2)	<0.01
At least one bifurcation with side-branch treated	199 (16.0)	17 (4.0)	69 (17.7)	113 (26.7)	<0.01
At least one in-stent restenosis treated	60 (4.8)	16 (3.7)	27 (6.9)	17 (4.0)	0.07
At least one small-vessel (RVD <2.75mm)	793 (63.8)	231 (53.7)	244 (62.6)	318 (75.2)	<0.01
At least one long lesion (length > 27mm) treated	259 (20.8)	33 (7.7)	87 (22.3)	139 (32.9)	<0.01
Glycoprotein IIb/IIIa antagonist use	176 (14.2)	37 (8.6)	46 (11.8)	93 (22.0)	<0.01

Table 1. Baseline Characteristics of Patients
Data are number (%) or mean (SD). BMI = body mass index. CAD = coronary artery disease. PCI = percutaneous coronary intervention. CABG = coronary artery bypass grafting. MI = myocardial infarction.
CTO = chronic total occlusion. RVD = reference vessel diameter.
* assessed in 1064 patients
† chronic renal failure defined by serum creatinine level ≥ 130 µmol/L
‡ left ventricular ejection fraction assessed with ultrasound, MRI or LV angiography
§ including chronic total occlusion, but not grafts and in-stent restenosis

	Study population (N=1243)	SxS <=7,0 (N = 430)	SxS >7,0 and <15 (N = 390)	SxS ≥15 (N = 423)	p Value
Target lesion coronary artery					
Left anterior descending	695 (55.9)	143 (33.3)	216 (55.4)	336 (79.4)	<0.01
Left circumflex	391 (31.5)	133 (30.9)	119 (30.5)	139 (32.9)	0.74
Right coronary artery	453 (36.4)	181 (42.1)	151 (38.7)	121 (28.6)	<0.01
Left main	23 (1.9)	0	9 (2.3)	14 (3.3)	<0.01
Multivessel treatment	293 (23.6)	25 (5.8)	99 (25.4)	169 (40.0)	<0.01
Total lesions treated per patient					<0.01
One lesion treated	762 (61.3)	370 (86.0)	221 (56.7)	171 (40.4)	
Two lesions treated	357 (28.7)	54 (12.6)	142 (36.4)	161 (38.1)	
Three of more lesions treated	124 (10.0)	6 (1.4)	27 (6.9)	91 (21.5)	
No of stents placed	2.02 (1.18)	1.38 (0.69)	2.00(0.97)	2.68 (1.38)	<0.01
ACC-AHA lesion class B2 or C lesion treated	702 (56.5)	126 (29.3)	241 (61.8)	335 (79.2)	<0.01
At least one ostial lesion treated	113 (9.1)	28 (6.5)	51 (13.1)	34 (8.0)	<0.01
Preprocedural TIMI flow (grade 0-1)	99 (8.0)	24 (5.6)	35 (9.0)	40 (9.5)	0.08
At least 1 lesion directly stented	414 (33.3)	196 (45.6)	124 (31.8)	94 (22.2)	<0.01
At least one stent postdilated >18 atm	954 (76.7)	301 (70.0)	293 (75.1)	630 (85.1)	<0.01

Table 2. Angiographic and procedural characteristics.
Data are number (%) or mean (SD).
ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blockers; CTO = chronic total occlusion; DM = diabetes mellitus; RVD = reference vessel diameter; TIMI = thrombolysis in myocardial infarction.

	Study population (N=1243)	SxS <=7,0 (N = 430)	SxS >7,0 and <15 (N = 390)	SxS ≥15 (N = 423)	p Value
Antiplatetelet therapy					
Acetylsalicylic acid	1233 (99.2)	426 (99.1)	387 (99.2)	420 (99.3)	0.93
Clopidogrel	1243 (100)	430 (100)	390 (100)	423 (100)	1.00
Other medication					
Statin	1061 (85.4)	369 (85.8)	339 (86.9)	353 (83.5)	0.36
Beta-blocker	1026 (82.5)	353 (82.1)	335 (85.9)	338 (79.9)	0.08
ACE/ARB*	581 (46.7)	203 (47.2)	165 (42.3)	213 (50.4)	0.07

Table 3. Medication at discharge.
Data are number (%).
*ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

References

1. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease, EuroIntervention 2005;1:219-227.
2. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR,Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial, Lancet 2013;381:629-638.
3. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 2007;115:2344-2351.
4. 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;44:1210-1214.
5. 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;48:1765-1770.
6. Farooq V, Serruys PW, Vranckx P, Bourantas CV, Girasis C, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, Dawkins KD, Mohr FW, James S, Stahle E. Incidence, correlates, and significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous based revascularisation: A substudy from the Synergy between Percutaneous Coronary Interventions with Taxus and Cardiac Surgery (SYNTAX) Trial, Int J Cardiol 2013;168:5287-5292.
7. 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.
8. 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.
9. Sen H, Tandjung K, Basalus MW, Lowik 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;8:664-671.
10. 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.
11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction, Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD, Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Trials & Registries Subcommittee,

Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction, J Am Coll Cardiol 2012;60:1581-1598.

12. Babu GG, Walker JM, Yellon DM, Hausenloy DJ. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection, Eur Heart J 2011;32:23-31.
13. 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.
14. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention, N Engl J Med 2011;364:453-464.
15. 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;102:369-378.
16. Lansky AJ, Stone GW. Periprocedural myocardial infarction: prevalence, prognosis, and prevention, Circ Cardiovasc Interv 2010;3:602-610.
17. 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;80:524-530.
18. Garg S, Serruys PW, Silber S, Wykrzykowska J, 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, Van Remortel E, Ronden J, Windecker S. The prognostic utility of the SYNTAX score on 1-year outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial, JACC Cardiovasc Interv 2011;4:432-441.
19. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, J Am Coll Cardiol 2010;56:272-277.
20. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, Banning AP. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention, Int J Cardiol 2009;135:60-65.
21. Tandjung K, Sen H, Lam MK, Basalus MW, Louwerenburg JH, Stoel MG, van Houwelingen KG, de Man FH, Linssen GC, Said SA, Nienhuis MB, Lowik 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;61:2406-2416.
22. 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.

23. 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;54:477-486.
24. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization: An Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions (SCAI), J Am Coll Cardiol 2013;62:1563-1570.
25. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial, J Am Coll Cardiol 2009;54:558-565.
26. Cohen M, Ferguson JJ. Re-evaluating risk factors for periprocedural complications during percutaneous coronary intervention in patients with unstable angina/non-ST-elevation myocardial infarction: who may benefit from more intensive antiplatelet therapy? Curr Opin Cardiol 2009;24:88-94.
27. Patti G, Pasceri V, D'Antonio L, D'Ambrosio A, Macri M, Dicuonzo G, Colonna G, Montinaro A, Di Sciascio G. Comparison of safety and efficacy of bivalirudin versus unfractionated heparin in high-risk patients undergoing percutaneous coronary intervention (from the Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin study), Am J Cardiol 2012;110:478-484.
28. Tandjung K, van Houwelingen KG, Jansen H, Basalus MW, Sen H, Lowik 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;110:1561-1567.

Chapter 11

Coronary Artery Dominancy and the Risk of Adverse Clinical Events Following Percutaneous Coronary Intervention:

Insights from the Prospective, Randomised TWENTE Trial

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Abstract

Aim: Investigate the prognostic value of coronary dominancy for various adverse clinical events following the implantation of drug-eluting stents.

Methods and Results:

We assessed two-year follow-up data of 1387 patients from the randomised TWENTE trial. Based on the origin of the posterior descending coronary artery, coronary circulation was categorised into left and non-left dominancy (i.e. right and balanced). Target vessel-related myocardial infarction (MI) was defined according to the updated Academic Research Consortium (ARC)-definition (2xupper reference limit of creatine kinase (CK), confirmed by CK-MB elevation), and peri-procedural MI (PMI) as MI ≤48 hours following PCI. 136(9.8%) patients had left and 1251(90.2%) non-left dominancy. Target lesions were more frequently located in dominant arteries ($p<0.005$). Left dominancy was associated with more severe calcifications ($p=0.006$) and more bifurcation-lesions ($p=0.031$). Non-left dominancy tended to be less frequent in men ($p=0.09$). Left coronary dominancy was associated with more target vessel related MI (14(10.3%) *vs.* 62(5.0%), $p=0.009$). Left dominancy independently predicted PMI (adjusted 2.19 95%CI: 1.15-4.15, $p=0.017$), while no difference in other clinical endpoints was observed between dominancy groups.

Conclusion: In the population of the TWENTE trial, we observed a higher incidence of peri-procedural myocardial infarction in patients, who had left coronary dominancy.

Introduction

Left coronary artery dominancy is a variant of the normal coronary anatomy, in which the left circumflex artery reaches the crux and supplies both posterior descending and posterolateral branches.[1,2] A recent post-mortem analysis showed a decreasing prevalence of left dominancy with the increase of age, suggesting a worse prognosis for subjects with this dominance pattern.[3] The database of a registry of patients undergoing cardiac catheterisation for acute coronary syndromes has demonstrated a higher all-cause mortality in patients with left dominancy.[4] In addition, a non-invasive study with computer tomography coronary angiography screening of the coronary arteries in a heterogeneous group of patients with chest pain (with or without coronary artery disease) showed left dominancy being an independent predictor of non-fatal myocardial infarction (MI) and all-cause mortality.[2]

However, there is limited knowledge about the relation between coronary dominancy patterns and the risk of various adverse clinical events that can occur following percutaneous coronary interventions (PCI) with contemporary drug-eluting stents (DES). The aim of this study was to investigate the prognostic value of left dominancy in relation to post-PCI outcome – in particular the rate of peri-procedural MI (PMI), which in current DES studies has the highest incidence of all adverse clinical events.[5-7] We performed the analyses in patients in the prospective, randomised TWENTE trial[5,8] which assessed a population of PCI patients with broad inclusion and only few exclusion criteria, treated with second-generation DES.[9]

Methods

Study population. The study assessed patients enrolled in the TWENTE trial (ClinicalTrials.gov NCT01066650), which has previously been described in detail.[5,8] In brief, TWENTE is an investigator-initiated, patient-blinded, randomised non-inferiority study with broad inclusion and limited exclusion criteria in a 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 with an indication for PCI with DES, who were capable of providing informed consent, were randomised for treatment with one of two types of second-generation DES – Resolute (Medtronic Inc., Santa Rosa, CA) or Xience V (Abbott Vascular, Santa Clara, CA). There was no limit for lesion length, reference vessel size, and number of target lesions or vessels to be treated. As a consequence, in a high proportion of study patients there was advanced coronary disease requiring treatment of multiple vessels, bifurcation lesions, long lesions, and lesions in small vessels.[5] A total of 52% of patients presented with an acute coronary syndrome, but as a very recent ST-elevation myocardial infarction (STEMI) was the most important exclusion

criterion, patients requiring primary PCI were not enrolled. The TWENTE trial has demonstrated a similar clinical outcome for both DES.[5] The study was approved by the institutional ethics committee and complied with the Declaration of Helsinki. All patients provided written informed consent. The study population of the present analysis consisted of all TWENTE patients except 4 patients who withdrew their consent during follow-up.

Angiographic assessment of coronary artery dominancy. Coronary dominancy was classified in left and non-left by two experienced analysts who inspected the coronary angiography of all TWENTE patients. A coronary artery system was classified as right dominant when the PDA originated from the right coronary artery (RCA), while left dominancy was defined when the PDA originated from the left circumflex artery (LCX). A balanced dominant coronary system was categorised when the PDA rose from the RCA in combination with a large posterolateral branch originating from the LCX reaching near the posterior interventriculair groove.[2] Right and balanced were referred as non-left dominancy. Any potential disagreement between analysts was resolved by jointly inspecting all angiographic runs available in order to achieve consensus.

Quantitative coronary angiography. Quantitative coronary angiographic analyses were performed offline with the use of edge-detection software (QAngio XA version 7.1, Medis, Leiden, the Netherlands) by angiographic analysts from the Thoraxcentrum Twente.[5]

Follow-up and definition of clinical endpoints. Details of the clinical follow-up have been reported previously.[5,8] In brief, in the TWENTE trial follow-up data were obtained during 2-year follow-up after the index procedure. For any events trigger, all relevant clinical information available was gathered. Clinical event adjudication (of all patients, follow-up information was available) was performed by core laboratory and an external independent research organisation (Cardialysis, Rotterdam, the Netherlands). Clinical endpoints were defined according to the Academic Research Consortium (ARC).[10,11] Cardiac death was defined as any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia). 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), based on the updated ARC definition of MI. Peri-procedural MI (PMI) was defined as MI within 48 hours after PCI.[10,11] Further classification of MI and MI location was based on laboratory information, electrocardiogram, and/or clinical data. Laboratory information included determination of creatine kinase before PCI and cardiac markers 6 to 18 h after PCI, with subsequent serial measurements in case of relevant biomarker elevation or complaints (97% of the cases had at least one blood sampling performed between 12 and 18 h after PCI). Stent thrombosis was

defined according to ARC as definite, probable, or possible.

The composite endpoint *target vessel failure* (TVF) was defined as cardiac death, target vessel–related MI, or clinically driven target vessel revascularisation (TVR). *Target lesion failure* (TLF), was defined as composite of cardiac death, target vessel–related MI, and clinically indicated target lesion revascularisation (TLR); *major adverse cardiac events* as composite of all-cause death, any MI, emergent coronary artery bypass surgery, or clinically indicated TLR; and a *patient-oriented composite endpoint* as composite of all-cause mortality, any MI, and any repeat (target and non-target vessel) revascularisation.[5]

Statistical analysis. Categorical data were presented as frequency and percentage whereas continuous variables were expressed as mean ± standard deviation (SD). To assess potential differences in the prevalence of dominancy patterns between younger and older patients, age was categorized with use of the mean of the total population as cut-off value. The baseline characteristics were compared using chi-square test or Fisher's exact test for categorical variables and one-way analyses of variance (ANOVA) for continuous variables including age, BMI, minimum reference diameter and total stent length, as the data were distributed normally. Kruskal-Wallis test (non-parametric data) was used to compare total number of stent placed between dominancy patterns, and presented as median and interquartile range (IQR). Univariate and Cox regression analysis was performed to assess coronary dominancy as an independent predictor in respect to the predefined endpoints. Potential confounding was identified if p-values were < 0.10 at univariate analysis of the relations between tested parameter vs. both dominancy and predefined clinical endpoints. A multivariate Cox regression analysis was then performed to adjust for potential confounders. The time to the MI was assessed according to the Kaplan Meier method, in which the log-rank test was applied to compare the three coronary dominancy patterns. Analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA). Unless otherwise specified, confidence intervals and p-values were two-sided. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics. A total of 1387 patients were analysed, of which 136 (9.8%) had left dominancy and 1251 (90.2%) non-left dominancy, consisting of right 1077 (77.6%) and balanced 174 (12.5%) dominancy. In all 1387 patients, data for follow-up analysis were available. Baseline characteristics are shown in Table 1. Male gender tended to be more frequent in left than in the non-left dominancy group (78.7% *vs.* 71.8%,

respectively; p=0.087). There was no difference in prevalence of dominancy patterns between patients age ≤64 and older (p=0.79). Patients with left dominancy tended to have less often a previous PCI (p=0.11).

Angiographic and procedural characteristics. Angiographic analysis revealed that target lesions were more frequently located in the dominant artery (Table 2): left and non-left dominancy were present in 64.0% *vs.* 50.8% if target lesions were located in the left anterior descending artery (LAD; p=0.004); 50.7% *vs.* 29.4% if target lesions were located in the CX (p<0.001); and 6.6% *vs.* 39.4% if target lesions were located in the RCA (p<0.001).

The ACC/AHA lesion types did not differ in complexity between dominancy groups (p=0.6). Left dominancy was associated with more severe lesion calcification (p=0.006), more bifurcation lesions (p=0.031) and showed a trend towards more de novo lesions (p=0.079). Between dominancy groups, there was no significant difference in minimum reference vessel size, the number of lesions treated, and other procedural details.

Adverse clinical events during 2-year follow-up. Left dominancy was associated with a higher incidence of target vessel MI (p=0.009, Table 3): in particular non-Q-wave MI (p=0.006) and PMI (p=0.014). For all other adverse cardiac events and composite endpoints, there was no significant difference between dominancy groups. Definite or probable stent thrombosis was non-significantly more frequent in patients with left dominancy than in non-left dominancy (2.2% *vs.* 1.3%, respectively).

Multivariate analysis of coronary dominancy and myocardial infarction.

Severe lesion calcification and at least one bifurcated lesions were referred as potential confounders and were therefore included as covariates in a multivariate model. Using the largest group with non-left dominancy as a reference, left coronary dominancy was shown to be a significant independent predictor of target vessel MI (adjusted HR 1.88, 95%CI: 1.05-3.37, p=0.034) – mainly non-Q-wave MI (adjusted HR 2.35, 95%CI: 1.26-4.36, p=0.007) and PMI (adjusted HR 2.19 95%CI: 1.15-4.15, p=0.017). In addition, severe lesion calcification and at least one bifurcated lesion were independent predictors for target vessel MI (adjusted HR 2.16, 95%CI: 1.35-3.46, p=0.001, adjusted HR 1.60, 95%CI: 1.00-2.55, p=0.048, respectively) and for non-Q-wave MI (adjusted HR 1.81, 95%CI: 1.05-3.14, p=0.034, adjusted HR 2.00, 95%CI: 1.19-3.56, p=0.009, respectively). For PMI severe lesion calcification tended to be predicting PMI (adjusted HR 1.75, 95%CI: 0.99-3.07, p=0.051) and at least one bifurcated lesion was an independent predictor (adjusted HR 2.13, 95%CI: 1.26-3.59, p=0.005). Kaplan-Meier MI-free survival analysis stratified for the dominancy groups demonstrated a higher incidence of MI in patients with left dominancy (p=0.009, Figure 1). The MI occurred most frequently as PMI – that is within the first 2 days, after which

all three survival curves showed hardly any change.

Discussion

Within the 1387 patients of the prospective randomised TWENTE trial, left coronary dominancy was an independent predictor of PMI following the implantation of contemporary second-generation DES and associated with a higher MI rate at 2-year follow-up. The relation between left coronary dominancy and both MI and PMI remained after correcting for confounders, including severe lesion calcification and at least one bifurcated lesion. Despite significant differences in PMI and MI rates at 2-year follow-up, no difference in other clinical endpoints was observed between dominancy groups. While the present study adds novel information on the relation between coronary anatomy and clinical outcome following PCI, the limited power of the analysis requires that the findings of this study should be considered as hypothesis generating.

Peri-procedural myocardial infarction. This study demonstrates that left dominancy is associated with a 2.2-times higher risk of PMI. The relation between anatomical features such as the coronary distribution pattern and PMI had not been assessed so far. In DES trials, the MI rate is a component of several combined clinical endpoints; the PMI rate represents the vast majority of the MI rate which is an endpoint in both stent trials and pathophysiological studies.[12-15] The mechanism underlying the increased PMI risk in left coronary dominancy it still unclear. Previous studies have demonstrated that complex plaque morphologies and greater atheroma volumes bear a greater risk of significant plaque (micro)embolisation that can lead to microvascular injury.[16-20] Furthermore, PCI-related (stent-induced) closure of epicardial arteries may lead to blood flow reduction or occlusion in side branches with subsequent myocardial injury.[16] Both microembolisation and stent-induced closure of very small side branches may not be visible on the angiogram but can lead to cardiac marker release and PMI.

Clinical outcome. A few registries and studies showed relations between left dominancy and inferior clinical outcome[2-4], but the patient populations of these studies differed significantly from that of the TWENTE trial.[5] A recently published *post-mortem* angiography study showed that the prevalence of left and balanced dominancy decreased with increasing age[3] while we found no relation between age and dominancy pattern in the population of TWENTE trial patients, who were on average at a younger age (being normally distributed) than the population of the aforementioned *post-mortem* study that also comprised a wider rage of age (with non-Gaussian distribution). In a heterogeneous group of patients with chest pain, computer tomography coronary angiographic screening revealed left dominancy to independently predict non-fatal MI and all-cause mortality.[2] In addition, in a registry of patients with acute coronary syndromes, left dominancy was associated with higher all-cause mortality.[4]

Our present study in a population of PCI patients with broad inclusion and only few exclusion criteria, consisting almost equally of patients with acute coronary syndromes and stable angina[5,9], adds further information on the prognostic impact of left coronary dominancy with regard to various aspects of clinical outcome following PCI. Although we did not observe an inferior outcome in terms of higher mortality, treatment failure, or major adverse cardiac events, we found an independent association between left dominancy and PMI which, in the presence of major cardiac marker release, may be related to increased mortality.[16,21-24] Furthermore, we observed in patients with left dominancy more bifurcated and severely calcified coronary lesions, lesion with characteristics that are known to be associated with inferior clinical outcome.[25] While our data may not have direct clinical implications, findings suggest that further research may be warranted to clarify the role of coronary dominancy. Left coronary dominancy in the presence of left main disease and a proximal LAD stenosis may sometimes lead to surgical revascularization or, if PCI is performed, may trigger a more aggressive pharmacological anti-platelet and/or anticoagulation therapy, as the occlusion of a dominant CX artery may induce serious complications. This impact of a dominant circumflex coronary artery on PCI procedural risk is also reflected in the SYNTAX score.[26,27]

Limitations of the study. The present study is a non-prespecified post-hoc analysis of the TWENTE trial with two-year clinical follow-up. Nevertheless, any prolongation of follow-up would have had no effect on the difference in PMI between dominancy groups (PMI may only occur during the first 48 hours after PCI), which was the main finding of this study. In addition, none of the other clinical outcome parameter (i.e. other than MI and PMI) showed a trend towards significant difference between coronary dominancy groups. While the adjudication of MI was performed according to the ARC definitions, we did not stratify events for different levels of CK-MB elevation (e.g. >5x or >10x the upper reference limit of CK-MB). In future assessments of this issue, it may be valuable to stratify CK-MB value to certain levels in order to better define the severity of MI. In addition, we cannot completely exclude that during follow-up a subclinical MI might have been missed, especially if it did not lead to hospitalization, revascularization by PCI or CABG, and/or if ECG changes were not recognizable. Because of the limited power of the present post-hoc analysis, no definite conclusion can be drawn and findings should be considered hypothesis generating. Nevertheless, the current findings add novel information on the relation between coronary anatomy and clinical outcome following PCI.

Conclusion. In the population of the TWENTE trial, we observed a higher incidence of peri-procedural myocardial infarction in patients, who had left coronary dominancy.

References

1. Higgins CB, Wexler L. Reversal of dominance of the coronary arterial system in isolated aortic stenosis and bicuspid aortic valve. Circulation. 1975;52:292-296.
2. Veltman CE, de Graaf FR, Schuijf JD, van Werkhoven JM, Jukema JW, Kaufmann PA, Pazhenkottil AP, Kroft LJ, Boersma E, Bax JJ, Schalij MJ, van der Wall EE. Prognostic value of coronary vessel dominance in relation to significant coronary artery disease determined with non-invasive computed tomography coronary angiography. Eur Heart J. 2012;33:1367-1377.
3. Knaapen M, Koch AH, Koch C, Koch KT, Li X, van Rooij PC, Tijssen JG, Peters RJ, van der Wal AC, Damman P, de Winter RJ. Prevalence of left and balanced coronary arterial dominance decreases with increasing age of patients at autopsy. A postmortem coronary angiograms study. Cardiovasc Pathol. 2013;22:49-53.
4. Goldberg A, Southern DA, Galbraith PD, Traboulsi M, Knudtson ML, Ghali WA, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Coronary dominance and prognosis of patients with acute coronary syndrome. Am Heart J. 2007;154:1116-1122.
5. 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.
6. Tandjung K, van Houwelingen KG, Jansen H, Basalus MW, Sen H, Lowik 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;110:1561-1567.
7. 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;80:524-530.
8. Tandjung K, Sen H, Lam MK, Basalus MW, Louwerenburg JH, Stoel MG, van Houwelingen KG, de Man FH, Linssen GC, Saïd SA, Nienhuis MB. Clinical outcome following stringent discontinuation of dual anti-platelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting Resolute and everolimus-eluting Xience V stents: Two-year follow-up of the randomized TWENTE trial. J Am Coll Cardiol. 2013; in press.
9. Sen H, Tandjung K, Basalus MW, Lowik 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;8:664-671.
10. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344-2351.
11. 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.
12. Wang TY, Peterson ED, Dai D, Anderson HV, Rao SV, Brindis RG, Roe MT, National Cardiovascular Data Registry. 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;51:2068-2074.
13. Herrmann J, Haude M, Lerman A, Schulz R, Volbracht L, Ge J, Schmermund A, Wieneke H, von Birgelen C, Eggebrecht H, Baumgart D, Heusch G, Erbel R. Abnormal coronary flow velocity reserve after coronary intervention is associated with cardiac marker elevation. Circulation. 2001;103:2339-2345.
14. Herrmann J, Lerman A, Baumgart D, Volbracht L, Schulz R, von Birgelen C, Haude M, Heusch G, Erbel R. Preprocedural statin medication reduces the extent of periprocedural non-Q-wave myocardial infarction. Circulation. 2002;106:2180-2183.
15. Böse D, von Birgelen C, Zhou XY, Schmermund A, Philipp S, Sack S, Konorza T, Mohlenkamp S, Leineweber K, Kleinbongard P, Wijns W, Heusch G, Erbel R. Impact of atherosclerotic plaque composition on coronary microembolization during percutaneous coronary interventions. Basic Res Cardiol. 2008;103:587-597.
16. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. N Engl J Med. 2011;364:453-464.
17. Goldstein JA. Periprocedural myocardial infarction: it's the plaque, not the stent. Catheter Cardiovasc Interv. 2012;80:531-532.
18. Hong YJ, Mintz GS, Kim SW, Lee SY, Okabe T, Pichard AD, Satler LF, Waksman R, Kent KM, Suddath WO, Weissman NJ. Impact of plaque composition on cardiac troponin elevation after percutaneous coronary intervention: an ultrasound analysis. JACC Cardiovasc Imaging. 2009;2:458-468.
19. Uetani T, Amano T, Ando H, Yokoi K, Arai K, Kato M, Marui N, Nanki M, Matsubara T, Ishii H, Izawa H, Murohara T. The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. Eur Heart J. 2008;29:1714-1720.
20. Watabe H, Sato A, Akiyama D, Kakefuda Y, Adachi T, Ojima E, Hoshi T, Murakoshi N, Ishizu T, Seo Y, Aonuma K. Impact of coronary plaque composition on cardiac troponin elevation after percutaneous coronary intervention in stable angina pectoris: a computed tomography analysis. J Am Coll Cardiol. 2012;59:1881-1888.
21. 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;71:318-324.
22. 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;48:1765-1770.
23. 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.
24. 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;106:1205-1210.
25. Ramakrishna G, Miller TD, Breen JF, Araoz PA, Hodge DO, Gibbons RJ. Relationship and prognostic value of coronary artery calcification by electron beam computed tomography to stress-induced ischemia by single photon emission computed tomography. Am Heart J. 2007; 153: 807-814.
26. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation. 1981;63:285-299.
27. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-227.

Figure 1. MI-free survival of patients with left and non-left coronary dominancy (2-year follow-up).

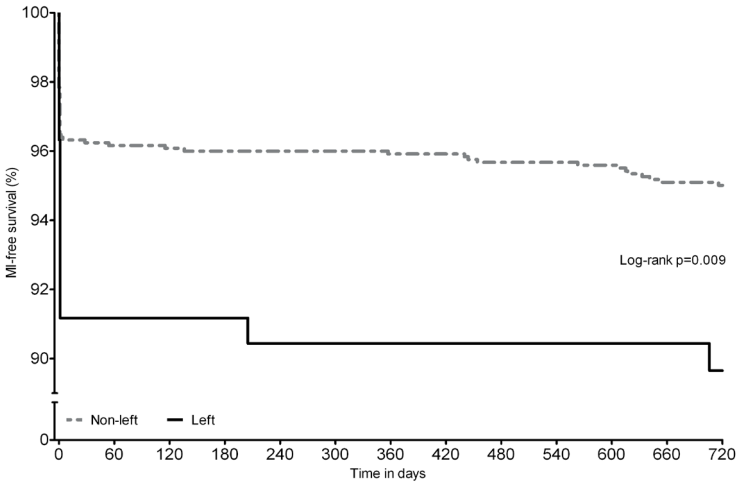

Table based on Kaplan Meier Estimates

Days	0	60	120	180	240	300	360	420	480	540	600	660	720
Number at risk													
Non-left dominancy	1251	1199	1192	1188	1187	1184	1177	1175	1167	1163	1157	1150	1109
Left dominancy	136	124	123	123	122	122	122	122	122	122	119	118	112

Table 1. Patient characteristics in left and non-left coronary dominancy.

	Total population (n=1387)	Left (n=136)	Non-left (n=1251)	p-value
Age (years)	64.3 (10.6)	64.6 (10.7)	64.2 (10.5)	0.69
Equal or younger than 64 years	688 (49.6)	66 (48.5)	622 (49.7)	0.79
Older than 64 years	699 (50.4)	70 (51.5)	629 (50.3)	
Gender (male) (%)	1005 (72.5)	107 (78.7)	898 (71.8)	0.09
Clinical risk factor				
Diabetes mellitus (any)	299 (21,6)	29 (21.3)	270 (21.6)	0.94
Hypercholesterolemia	801/1353 (59.2)	78/132 (59.1) 75 (55.1)	723/1221 (59.2)	0.98
Arterial hypertension	771 (55.6)	65 (47.8)	696 (55.6)	0.91
Family history of CAD	737 (53.1)	33 (24.3)	672 (53.7)	0.19
Current smoking	340 (24.5)	28.1 ± 3.8	307 (24.5)	0.94
Obesity (BMI ≥ 30 kg/m^3)	27.7 ± 4.0 (1186)	(118)	27.7 ± 4.0 (1068)	0.30
Known vascular disease (%)				
Previous myocardial infarction (any)	450 (32,4)	45 (33.1)	405 (32.4)	0.87
Previous PCI	287 (20.7)	21 (15.4)	266 (21.3)	0.11
Previous CABG	148 (10.7)	14 (10.3)	134 (10.7)	0.88
Previous heart valve surgery	4/1368 (0.3)	0/135 (0.0)	4/1233(0.3)	1.00
Previous stroke	43 (3.1)	6 (4.4)	32 (3.0)	0.30
Previous TIA	70 (5.0)	8 (5.9)	62 (5.0)	0.64
Clinical indication				0.44
Stable angina pectoris	672 (48.4)	73 (53.7)	599 (47.9)	
Unstable angina pectoris	324 (23.4)	29 (21.3)	295 (23.6)	
Non-ST-elevation MI	391 (28.2)	34 (25.0)	357 (28.5)	
Medication usage				
Acetylsalicylic acid	1376 (99.2)	135 (99.3)	1067 (99.1)	1.00
Clopidogrel	1387 (100)	136 (100)	1251 (100)	
Statins	1191 (85.9)	111 (81.6)	1080 (86.3)	0.13
Beta blocker	1145 (82.6)	116 (85.3)	1029 (82.3)	0.38
ACE inhibitor	394 (28.4)	39 (28.7)	355 (28.4)	0.94
*Left ventricular ejection fraction <30%**	32/1048(3.1)	5/95 (5.3)	27/953(2.8)	0.20

Patient characteristics in left, right and balanced coronary dominancy.
Values are mean ± SD or n (%). *Left ventricular ejection fraction assessed with ultrasound, magnetic resonance imaging or left ventricular angiography.
BMI = body mass index; CAD coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = Transient Ischemic Attack; MI = myocardial infarction.

Table 2. Baseline lesion and angiograph characteristics in patients with left and non-left coronary dominancy.

	Total (n=1387)	Left (n=136)	Non-left (n=1251)	p-value
Target lesion coronary artery				
Left main stem	52 (3.7)	7 (5.1)	45 (3.6)	0.366
Left anterior descending artery (LAD)	723 (52.1)	87 (64.0)	636 (50.8)	0.004
Left circumflex artery (RCX)	437 (31.5)	69 (50.7)	368 (29.4)	<0.001
Right coronary artery (RCA)	502 (36.2)	9 (6.6)	493 (39.4)	<0.001
Bypass graft	41(3.0)	2 (1.5)	34 (3.2)	0.423
ACC/AHA lesion class				
A	91 (6.6)	12 (8.8)	79 (6.3)	0.591
B1	294 (21.2)	27 (19.9)	267 (21.3)	
B2	428 (30.9)	45 (33.1)	383 (30.6)	
C	574 (41.4)	52 (38.2)	522 (41.7)	
Type of lesions				
De novo lesions only*	1284 (92.6)	131 (96.3)	1153 (92.2)	0.079
At least one chronic total occlusion	95 (6.8)	9 (6.6)	86 (6.9)	0.910
At least one in-stent restenosis	68 (4.9)	3 (2.2)	65 (5.2)	0.125
At least one bifurcation lesion	362 (26.1)	46 (33.8)	316 (25.3)	0.031
At least one aorto-ostial lesion	152 (11.0)	8 (5.9)	144 (11.5)	0.046
At least one severe calcification	274 (19.8)	39 (28.7)	235 (18.8)	0.006
At least one thrombus present #	61 (4.4)	4 (2.9)	57 (4.6)	0.510
At least one total occlusion	184 (13.3)	16 (11.8)	168 (13.4)	0.587
Total number of lesions treated/ patient	856 (61.7)	84 (61.8)	772 (61.7)	0.913
1 lesion treated	391 (28.2)	37 (27.2)	354 (28.3)	
2 lesions treated	140 (10.1)	15 (11.0)	125 (10.0)	
3 or more lesions treaded				
Multivessel treatment	334 (24.1)	34 (25.0)	300 (24.0)	0.792
PCI related characteristics				
Minimum reference diameter (mm)	2.6 ± 0.6	2.5 ± 0.6	2.6 ± 0.6	0.408
Total number of stents	2.0 (1.0-3.0)	2.0(1.0-3.0)	2.0 (1.0-3.0)	0.219
Total stent length (mm)	40.98 ± 26.9	39.2 ± 24.1	41.4 ± 27.1	0.484
At least one direct stenting	662 (47.7)	62 (45.6)	517 (48.0)	0.868
At least one stent post-dilation	1218 (87.8)	121 (89.0)	948 (88.0)	0.610
Maximal inflation pressure (atm)	15.9 ± 2.6	15.9 ± 2.8	15.9 ± 2.6	0.898

Baseline lesion and angiograph characteristics in patients with left, right and balanced coronary dominancy. Values are n (%). *Including chronic total occlusion but not grafts and in-stent re-stenosis. #Thrombus triggering use of thrombus aspiration catheters. ACC = American College of Cardiology; AHA = American Heart Association; TIMI = Thrombolysis in Myocardial Infarction.

Table 3. 2-years clinical outcome in patients with left and non-left coronary dominancy.

	Total (n=1387)	Left (n= 136)	Non-left (n= 1251)	p-value
Death				
Any cause	62 (4.5)	8 (5.9)	54 (4.3)	0.401
Cardiac cause	30 (2,2)	4 (2.9)	26 (2.1)	0.511
Myocardial infarction				
Any	79 (5.7)	14 (10.3)	65 (5.2)	0.015
Target-vessel	76 (5.5)	14 (10.3)	62 (5.0)	0.009
Q-wave	17 (1.2)	1 (0.7)	16 (1.3)	1.000
Non–Q-wave	59 (4.3)	13 (9.6)	46 (3.7)	0.010
Periprocedural MI	57 (4.1)	12 (8.8)	45 (3.6)	0.004
*Major adverse cardiac event**	172 (12.4)	22 (16.2)	150 (12.0)	0.160
Patient-oriented composite endpoint#	232 (16.7)	28 (20.6)	204 (16.3)	0.204
Clinically indicated TVR	74 (5.3)	5 (6.8)	69 (5.5)	0.365
Any	60 (4.3)	3 (2.2)	57 (4.6)	0.201
Percutaneous	16 (1.2)	2 (1.5)	14 (1.1)	0.665
Surgical				
Clinically indicated TLR	52 (3.7)	3 (2.2)	49 (3.9)	0.318
Any	41 (3.0)	2 (1.5)	39 (3.1)	0.423
Percutaneous	13 (0.9)	1 (0.7)		1.000
Surgical			12 (1.0)	
Target lesion failure	141 (10.2)	18 (13.2)	123 (9.8)	0.212
Target vessel failure	155(11.2)	19 (14.0)	136 (10.9)	0.276
Stent thrombosis&	18 (1.3)	3 (2.2)	15 (1.2)	0.410

Clinical outcome in patients with left, right and balanced coronary dominancy. Values are n (%). *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 revascularisation (TLR). #Patient-oriented composite endpoint is a composite of endpoint all-cause death, any MI, or any revascularisation. TVR = target vessel revascularisation; & definite or probable stent thrombosis.

Chapter 12

Usefulness and Safety of the GuideLiner Catheter to Enhance Intubation and Support of Guide Catheters:

Insights from the Twente GuideLiner Registry

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Abstract

Aims: Optimal ostial seating and adequate backup of guide catheters are required for challenging percutaneous coronary interventions (PCI). The GuideLiner (GL) is a guide catheter extension system that provides active backup support by deep coronary intubation. We aimed to assess feasibility and safety of GL-use in routine clinical practice.
Methods and results: We prospectively recorded patient and procedural details, technical success, and in-hospital outcome of 65 consecutive patients, undergoing 5-in-6F GL-facilitated PCI of 70 target vessels. The GL was mainly used for PCI of complex coronary lesions: 97%(68/70) lesion types B2/C; 53%(37/70) distally located and 23%(17/70) heavily calcified. Indications were to increase backup of the guide and facilitate stent delivery (59%, 41/70), achievement of co-axial alignment of the guide catheter (29%, 20/70), and selective contrast injections (13%, 9/70). Device success rate was 93%(65/70). There were no major complications and two minor complications managed without clinical sequelae: one air embolism and one stent dislodgement.
Conclusions: GL-use resulted in increased backup and guide catheter alignment for stent delivery in unfavorable tortuous coronary anatomies and complex, heavily calcified, and often distally located lesions, which otherwise may have been considered unsuitable for PCI. Procedural success rate was high and there were no major complications.

Introduction

Despite the advancements made in percutaneous coronary interventions, the interventional cardiologist nowadays has to deal with an increasing complexity of procedures. A good backup of the guide catheter is essential to advance guidewires and balloons, and to deliver stents. Support of the guide can be increased by use of extra-backup guides and larger guide dimensions. In addition, the stability of the guide can be improved by advancing a buddy wire, and use of stiffer guidewires or anchoring balloons[1,2]. Another way to increase backup support is deep intubation of the guide[3,4]. There is, however, a considerable risk of dissecting the vessel. Introduction of guide catheter extension systems, in which a long guide catheter with a flexible tip is advanced through the mother guide, has further refined this concept[5-7]. Besides the improvement in backup support, the use of guide catheter extensions provides selective visualization of the target vessel, improves the stability of the guide and allows co-axial alignment of the guide.

There are three systems available: the Heartrail II™ catheter, the Proxis™ device and the GuideLiner™ catheter. The Heartrail II™ catheter and Proxis™ device are 120-cm catheters that are introduced into the mother guide by removing the Y-connector[6-9]. The GuideLiner (GL) catheter (**Figure 1**) is a novel rapid-exchange guide catheter extension system that provides active guide support by its 20-cm-long flexible tubular end, which can be deeply advanced into target vessels[10-18]. Its handling is particularly easy, as it is does not require disconnection of the hemostatic valve at the proximal end of the guide catheter and is compatible with standard 180-centimeter-long guidewires. Its soft distal tip promises a low risk of dissecting vessels compared to deep-seating of regular guide catheters.

So far, only a limited number of reports and case series have been published on the GL guide catheter extension[10-18]. Mamas *et al.* reported a case series of 13 complex coronary interventions, performed via the radial artery with the 5-in-6F GL system[10]. Although their success rate was high, the main limitation encountered was stent damage upon advancement of the stent across the metallic collar of the GL (2 out of 32 stents)[10]. Recently, Luna *et al*. published their experience with the GL catheter in a series of 21 patients[15]. In their study, a transfemoral approach and 7F guide catheters were used in the majority of the cases with a procedural success rate of 90%. Pressure dampening was seen in 57% of their patients, contributing to 3 out of 4 unsuccessful cases. There was one major complication in the series reported by Luna *et al.*, which was a flow-limiting dissection in the proximal LAD but they noted no case of stent damage[15]. The purpose of the present Twente GuideLiner Registry was to assess feasibility and safety of use of the 5-in-6F GL guide catheter extension system during routine, clinical PCI procedures as performed at Thoraxcentrum Twente, a high-volume PCI center located in Enschede, the Netherlands.

Methods

Study population. Between November 2010 and July 2011, we prospectively collected data of a consecutive series of 65 patients, in whom the GL was applied to facilitate routine PCI. The patients had a background of stable or unstable angina pectoris, or presented with an acute myocardial infarction.

Interventional procedures. A team of 5 interventional cardiologists performed the PCI procedures; each of them had performed PCI for more than 5 years (250–500 PCI procedures per operator annually; total PCI experience of 4,000 or more per operator). PCI procedures were performed according to standard clinical protocols via de femoral or radial route, using 6F guide catheters as a standard. All patients received a bolus of unfractionated heparin (5,000IE or 70-100IE/kg). Prior to PCI, all patients received adequate loading doses of acetylsalicylic acid (300mg) and clopidogrel (300-600mg), if not pretreated. During the procedure, an intracoronary bolus of nitrates was administered. The choice of interventional approaches, devices, and techniques was left at the operators' discretion, considering current clinical protocols and guidelines. Following PCI, clopidogrel was prescribed for one year (75mg once daily (o.d.) in addition to life-long treatment with acetylsalicylic acid (at least 100mg o.d.).

The GuideLiner catheter and its use. The GL (Vascular Solutions, Minneapolis, MN, USA) consists of a flexible 20cm straight, flexible, soft-tipped extension tube that is connected via a metal collar to a thin 115-cm-long stainless-steel shaft **(Figure 1A&B**). The extension tube has a silicon coating for lubricity. The procedure starts by positioning the mother guide and advancing the guidewire across the target lesion. Then the GL is advanced over the guidewire through the hemostatic valve of the y-adapter (handling comparable to regular balloons) to intubate the target coronary artery or bypass graft (**Figure 1C**). The GL reduces the inner diameter of the mother guide by approximately 1F, but it does not lengthen the guide outside the patient. As the GL is in place, balloons and stents can be delivered over the same initial guidewire. The GL is available in sizes of 6F, 7F, and 8F. In this study, only 6F GL were used (also called 5-in-6 system), which has an internal diameter of 0.056" (1.422mm). Notably, the use in vessels <2.5 mm is dissuaded by the manufacturer. Bifurcation lesions in our study were treated as follows: Two wires were advanced through the guide. Then, the GL was advanced over both wires simultaneously. Provisional stenting was the strategy of choice. In case a kissing balloon technique was demanded, a wire exchange was performed followed by balloon dilation of the side branch through the stent struts. Before the final kissing balloon inflation could be performed, the GL had to be removed.

Study parameters and data acquisition. To assess the usefulness (feasibility and safety) of the GL in clinical practice, we prospectively recorded

various procedural data and clinical details on the in-hospital outcome of a consecutive series of 65 patients, who underwent PCI with the use of the GL. Patient demographics, indication for GL use, angiographic and procedural details including technical success, and all complications were recorded. Quantitative coronary angiography (QCA) was used to determine the intubation depth of the GL catheter. Procedural success was defined as the achievement of <20% diameter stenosis with TIMI 3 flow in the target vessel. 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 creatine kinase (CK) was measured. Peri-PCI myocardial infarction was defined as two times the upper reference limit of CK, confirmed by significant elevation of other specific biomarkers (MB-fraction of CK or troponin).

Statistical analysis. Values are expressed as mean±SD or median with range. Comparison of continuous variables was performed with Student's t-test. Categorical variables are presented as numbers or percentages and were tested with Chi-square test or Fisher exact test. A p value<0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 15.0 for Windows (SPSS Inc.,Chicago,Illinois).

Results

Patient population and lesion characteristics. The demographic characteristics of the study population are presented in **Table 1**. The majority of patients were male (74%), and the mean age was 67±13 years. Target lesions were relatively complex as is shown in **Table 2**. Most lesions (97%) had AHA/ACC (American Heart Association/American College of Cardiology) lesion types B2 or C, with more than half of them being located in distal vessel segments. A total of 90% of lesions was classified as being calcified: 67% mild to moderately and 23% heavily calcified. Mean lesion length was 38±26mm, which is indicative of long lesions.

Indication for GL use and procedural details. All procedures were carried out with the 5-in-6F GL device. As shown in **Table 3**, the primary indications for GL use were to increase backup of the guide catheter, in general to facilitate stent delivery (59%), and to improve alignment of the guide catheter (29%). In a few patients (13%), the GL was used for selective contrast injection, predominantly dominant LCA and/or renal impairment. There were differences between the application in RCA and LCA interventions. In the LCA, the GL catheter was used regularly to improve the alignment of the guide or enhance selective contrast injections, whereas its use in RCA interventions was mainly to increase catheter backup (p=0.024). An example is shown in **Figure 2**.

A 6F guide catheter was used in all subjects while radial access was chosen in one third of cases. Multi-vessel procedures were performed in almost one third of the patients, and there were 17% chronic total

occlusions. Of all 126 stents implanted, 123 (98%) were third-generation DES. In this registry, we noted a single stent that was damaged upon advancement across the metallic collar of the GL; damage to the (secondary) guidewire tip when passing the metallic collar of the GL occurred slightly more often (4/70; 6%).

Device success and device failures. The overall success rate of the GL was 93%. The average depth by which the GL was intubated in the proximal target vessels was 33±22mm (range: 0 to 106mm), however, these generally deep intubations did not cause any coronary dissection. The rate of procedural success of the transradial and transfemoral access routes was 95.5% and 88.4% (p=0.35), but the power of the study was insufficient to draw sound conclusions from this comparison. There were five device failures (5/70; 7%) which are illustrated in **Figure 3**.

Complications. We noted no major complications or coronary dissections. There were 2 minor complications that are outlined below. In the first case, during PCI of a diffusely diseased RCA in a 53-years-old male, the GL was deeply advanced (61mm intubation depth) to increase backup support and to pass a balloon catheter across the heavily calcified distal RCA stenosis. During this maneuver, some air embolism was noted as a result of insufficient venting of the wedged GL, which caused a brief phase of stasis of coronary flow that was rapidly resolved. . The second minor complication occurred during PCI of a long mid lesion in an RCA with "shepherd's crook" anatomy. After predilatation and stenting of the mid RCA, a second stent was attempted to advance through the first one, which turned out to be extremely difficult. To increase support, the GL was advanced over both guidewire and the second stent-balloon system (stent still undeployed), which led to dislodgement of the stent from the balloon. Eventually the dislodged stent was crushed behind a third stent and was postdilated with high balloon pressures, leading to a good final angiographic result with an uneventful clinical course until the 8 months follow-up.

Discussion

Good backup of the guide catheter is crucial for both wiring and equipment delivery. The development of guide catheter extension systems has further expanded the therapeutic arsenal of the interventional cardiologist[5-12]. Intubation of the guide catheter extension system into the target vessel provides enhancement of equipment delivery in challenging coronary lesions, and facilitates engagement in case of difficult takeoff of the coronary ostium. Takahashi *et al.* demonstrated that a guide catheter extension system provides a substantial improvement in backup support[5]. The support was directly related to the depth of intubation. For example, insertion of a 5Fr guide catheter for 15mm into a 6Fr catheter doubled the backup support. The guide catheter extension system may be used as a

tool for deeper intubation of the guide, referred to as "rail-roading", as was described in detail by Farooq *et al*[18]. Its use in graft interventions is well recognized by aiding graft cannulation and enhancing the stability of the guide in the graft ostium. Further backup may be achieved by advancing the extension catheter, thereby allowing the guide to back out and down until it rests on the aortic valve or contralateral aortic wall (Swan-neck maneuver)[18]. And finally, guide catheter extension systems can be used as an aspiration device[18].

The Twente GuideLiner Registry reports on a consecutive series of GL applications in 65 patients, treating 70 target vessels with implantation of 126 stents (98% being third-generation DES). So far, this is the largest registry on the use of the GL in routine daily practice. Demographics and clinical characteristics of the study population are similar to previous all comers stent studies and our general PCI population[19-24]. However, lesion characteristics differed a lot from the general patient population as the majority of target lesions were long and complex: All but 2 target lesions (97%) were classified as lesion type B2 or C with more than half of them being located distally, and the vast majority being at least moderately calcified.

During the first months, the GL was used as a bailout device in challenging cases, when the "old familiar tricks" (e.g. deep-seating maneuvers or use of buddy wires) had failed. However, after getting more familiar with the device, we switched to a more upfront use in difficult anatomical situations. In our present series, the main indication for GL use was to improve guide support to facilitate stent delivery (59%). An illustration is shown in **Figure 2**. However, in one third of the cases the GL was used to improve co-axial alignment of the guide catheter in anatomical situations with an abnormal takeoff of the target vessel (e.g. shepherd's crook-shaped proximal RCA) or a vertical takeoff of either RCA or left main stem. In particular, a vertical offspring of the left main stem, as may be seen in young lean patients or patients with pulmonary emphysema, bears an increased risk of dissecting the left main stem with a guide catheter. Gentle intubation of the GL substantially facilitated the intervention in such patients (**Figure 4**). In a small number of patients, the GL was used to perform selective contrast injections for a better visualization of the vessel of interest with smaller amounts of contrast; this indication for GL use may be considered in patients with large caliber vessels, such as a dominant left coronary artery, and an impaired renal function, or if an adequate visualization cannot be achieved by other means[25].

The GL may also be useful to facilitate demanding diagnostic coronary angiographies, which has not been described so far and was beyond the scope of our registry of GL use in PCI patients. Nevertheless, we would not like to withhold the information that our group also used the GL in several demanding cases of diagnostic angiographic visualization of bypass grafts. **Figure 5** shows an example of a gastroepiploic artery (GEA) graft, visualized both with and without use of a GL. It should be emphasized

that in case of coronary angiography, the operator should refrain from the use of intracoronary wires and devices as much as possible. However, there are circumstances in which a graft cannot be properly visualised. Instead of accepting a poor visualisation, the use of a guide catheter extension system can be considered in order to achieve conclusive angiographic imaging. It should be used by an interventional cardiologist with great care, and maximum effort should be taken to prevent that such manoeuvres give rise to a coronary dissection.

Success rate, shortcomings, and potential procedural risk. The success rate of the GL was 93% in our study, which is in agreement with previously reported smaller case series[10,15,17,18]. Stent damage at the site of the metallic collar of the GL occurred in 1 out of 126 stents implanted, which was a drug-eluting stent with a nominal diameter of 3.5mm. Others reported a higher rate of stent damage (6%) due to the collar of the GL catheter[10]. Therefore, we discourage the use of stents with a nominal diameter of 4mm or more through a 5-in-6 F GL catheter. Murphy et al. recently reported an uncommon case of balloon damage at the site of the metallic collar[16]. In addition, secondary (buddy) guidewires can be damaged upon advancement when the GL is in place, as reported in our present study. The 5-in-6 GL catheter permits the passage of virtually all regular balloon catheters, contemporary OCT catheters, and coronary stents up to a nominal diameter of 3.5mm. However, it does not allow the use of larger devices such as thrombectomy catheters, some IVUS probes, and simultaneous kissing balloon inflations.

Although the GL turned out to be generally beneficial with a relatively low rate of device failure, we identified some scenarios, in which the usefulness of the GL may be questionable. First, a difficult access due to iliacal tortuosity may impede the advancement of the GL through the mother guide, as was seen in one of our patients. And secondly, the proximal part of the target vessel should be suitable for intubation of the GL catheter; therefore, ostial/very proximal lesions or sharp angles of coronary arteries may lead to device failure, as was noted in the majority of our cases with device failure.

In general, use of the GL turned out to be safe. No major complications were noted, but there were two minor complications with favorable outcome and an otherwise uneventful clinical course. There was one case of air embolism due to insufficient venting. In the second case, a stent was dislodged from the balloon by the tip of the GL when advancing the GL over a stent-balloon system. Both complications could have been avoided, if more care had been taken and the instructions of the manufacturer had been followed. Luna *et al*.[15] reported a substantially higher number of cases with pressure dampening (57%) during engagement of the GL catheter; however, dissimilar to our study, they used a 6-in-7F system in the majority of cases.

How to use the Guideliner and to avoid complications. Several considerations can be mentioned in order to choose or refrain from the use of a guide catheter extension. If more backup of the guide catheter is required, the first step can be the use of buddy wires, extra stiff wires, or buddy balloons. However, if these measures fail, a GL catheter may be considered, which allows the mother guide and wires to be left in place. The operator should, however, be convinced that the proximal part of the target vessel is suitable for intubation. If the lesion extends to the proximal segment or if there is sharp angulation, the use of a guide catheter extension system is generally not recommended. Alternatively, the proximal segment may be stented first, followed by gentle intubation of the GL catheter and treatment of the distal segment (so-called proximal-to-distal stenting). However, care should be taken to avoid deformation or longitudinal compression of the proximal stent[26,27]. If there is a problem with co-axial alignment of the available guide catheters, the operator should estimate the risk of performing the procedure with a suboptimal position of the tip of the guide (in case of a simple proximal lesion one may continue). However, if substantial backup is required, it appears wise to use a guide catheter extension. This decreases the risk of guide-induced dissections and improves the backup of the mother guide. If the patient has an impaired renal function and the operator expects to use large amounts of contrast (e.g. in a dominant left system), a guide catheter extension system may be considered as a valuable first choice. And finally, if the operator intends to treat a bifurcation lesion, it should be realized that a 5-in-6 system does not allow the simultaneous use of 2 balloons. So, a choice should be made to use a larger guide catheter extension system (6-in 7 system or Proxis™ device), remove the guide catheter extension system before the kissing procedure, or refrain from its use and stick to the old tricks.

A word of caution: Intubation of the GL bears the risk of causing a dissection in a proximal coronary artery and should be performed carefully. If resistance is encountered when advancing the device, the GL can be retrieved into the mother guide and then re-advanced over a balloon catheter (to improve alignment) into the target vessel[17]. After advancing the GL into the vessel, the operator should check the coronary pressure waves and verify the presence of adequate, preserved antegrade coronary flow. Since use of the GL reduces size of the working lumen, there is an increased risk of air embolism, which can be diminished by slow advancement and withdrawal of the equipment; then time should be taken to carefully vent the system. A limitation of the GL device is the metallic collar located at the entrance of the extension tube. In case of resistance while advancing the stent, the location of the stent in relation to the metallic collar of the GL should be checked and the stent should be inspected for damage. If the collar is located at a bend in the catheter, the GL should be retrieved gently into a straight section of the mother guide in order to allow more co-axial alignment of the collar[17]. The use of more than one guidewire in combination with a relatively large size of the stent delivery

system may render stent passage through the collar of the GL sometimes difficult and occasionally impossible. Factors such as operator awareness, experience, number and type of guidewires, size of the stent, vascular anatomy, the shape of the guide catheter, and indication for GL use may have an effect on the incidence of this problem that differs between case series[17].

Limitations. The present registry in a consecutive series of PCI patients treated with use of the 5-in-6F GL provides some "real-life" insight into efficacy, limitations, and potential risk of this device. Although our patient population is larger than that of all previously reported cases and patient series altogether[10-18] the population is still relatively small. In addition, due to well-known limitations inherent to registries, this single centre registry cannot provide the scientific level of insight that might be obtained from a randomized study. We cannot exclude that in cases with upfront use of the GL, a standard guide catheter or other maneuvers and tricks (e.g. deep intubations or buddy wires) could also have led to procedural success.

Conclusions. Use of the GuideLiner catheter resulted in an increased backup support and guide catheter alignment for stent delivery in the presence of unfavorable tortuous coronary anatomies and in complex, heavily calcified, and often distally located lesions, which otherwise may have been considered unsuitable for PCI. The procedural success rate of the GL was high without major complications.

Disclosure statement
This investigator-initiated study was performed without specific funding. The research department has received educational and/or research grants in the past and has participated in clinical studies funded by Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Cordis, and Medtronic. Dr. von Birgelen is consultant to and has received lecture fees or travel expenses from Abbott, Medtronic, and Boston Scientific; and has received a speaker's honorarium from MSD. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Burzotta F, Trani C, Mazzari MA, Mongiardo R, Rebuzzi AG, Buffon A, Niccoli G, Biondi-Zoccai G, Romagnoli E, Ramazzotti V, Schiavoni G, Crea F. Use of a second buddy wire during percutaneous coronary interventions:A simple solution for some challenging situations. J Invasive Cardiol.2005;17:171-174.
2. Hirokami M, Saito S, Muto H. Anchoring technique to improve guiding catheter support in coronary angioplasty of chronic total occlusions. Catheter Cardiovasc Interv.2006;67:366-371.
3. Peels HO, van Boven AJ, den Heijer P, Tio RA, Lie KI, Crijns HJ. Deep Seating of six French guiding catheters for delivery of new Palmaz-Schatz stents. Catheter Cardiovasc Interv.1996;38:210-213.
4. von Sohsten R, Oz R, Marone G, McCormick DJ. Deep intubation of 6F guiding catheters for transradial coronary interventions. J Invasive Cardiol.1998;10:198-202.
5. Takahashi S, Saito S, Takanak S, Miyashita Y, Shiono T, Arai F, Domae H, Satake S, Itoh T. New method to increase a backup support of a 6 French guiding coronary catheter. Catheter Cardiovasc Interv.2004;63:452-456.
6. Mamas MA, Fath-Ordoubadi F, Fraser D. Successful use of the Heartrail II catheter as a stent delivery catheter following failure of conventional techniques. Catheter Cardiovasc Interv.2008;71:358-363.
7. Mamas MA, Eichhöfer J, Hendry C, El-Omar M, Clarke B, Neyses L, Fath-Ordoubadi F, Fraser D. Use of the Heartrail II catheter as a distal stent delivery device; an extended case series. EuroIntervention.2009;5:265-271.17.
8. Brilakis ES, Banerjee S. Novel uses of the Proxis embolic protection catheter. Catheter Cardiovasc Interv.2009;74:438–445.
9. Banerjee S, Brilakis ES. Use of the Proxis embolic protection device for guide anchoring and stent delivery during complex saphenous vein graft interventions. Cardiovasc Revasc Med.2009;10:183–187.22.
10. Mamas MA, Fath-Ordoubadi F, Fraser DG. Distal stent delivery with GuideLiner catheter: first in man experience. Catheter Cardiovasc Interv.2010;76:102-111.
11. Kumar S, Gorog DA, Secco GG, Di Mario C, Kukreja N. The GuideLiner "child"catheter for percutaneous coronary intervention - early clinical experience. J Invasive Cardiol.2010;22:495-498.
12. Rao U, Gorog D, Syzgula J, Kumar S, Stone C, Kukreja N. The GuideLiner "child" catheter. EuroIntervention.2010;6:277-279.
13. Hanna EB, Dasari TW, Hennebry TA. Use of the GuideLiner catheter for the treatment of a bifurcational total occlusion of the native left anterior descending artery through a tortuous composite venous graft. J Invasive Cardiol.2011;23:E40-2.
14. Wiper A, Mamas M, El-Omar M. Use of the GuideLiner catheter in facilitating coronary and graft intervention. Cardiovasc Revasc Med.2011;12(1):68.e5-7.
15. Luna M, Papayannis A, Holper EM, Banerjee S, Brilakis ES. Transfemoral use of the guideliner catheter in complex coronary and bypass graft interventions. Catheter Cardiovasc Interv.2011(doi: 10.1002/ccd.23232)
16. Murphy JC, Spence MS. Guideliner catheter – friend or foe? Catheter Cardiovasc Interv.2011(doi: 10.1002/ccd.23261)
17. Cola C, Miranda F, Vaquerizo B, Fantuzzi A, Bruguera J. The Guideliner™ catheter for stent delivery in difficult cases: tips and tricks. J Interv Cardiol.2011;24(5):450-61.
18. Farooq V, Mamas MA, Fath-Ordoubadi F, Fraser DG. The use of a guide catheter extension system as an aid during transradial percutaneous coronary intervention of coronary artery bypass grafts. Catheter Cardiovasc Intern.2011;78(6):847-63.
19. Tandjung K, Basalus MWZ, Muurman E, Louwerenburg HW, van Houwelingen KG, Stoel MG, de Man FHAF, Jansen H, Huisman J, Linssen GCM, Droste HT, Nienhuis MB, von Birgelen C. Incidence of periprocedural myocardial infarction following stent deployment: Comparison between first and second generation drug-eluting stents. Catheter Cardiovasc Interv.2011(doi 10.1002/ccd.23334).

20. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, Farhat N, Caputo R, Xenopoulos N, Applegate R, Gordon P, White RM, Sudhir K, Cutlip DE, Petersen JL; SPIRIT III Investigators. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. Circulation2009;119:680-686.
21. Windecker S, Remondino A, Eberli FR, Jüni P, Räber L, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, Roffi M, Corti R, Sütsch G, Maier W, Lüscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med.2005;353:653-62.
22. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbæk 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;363:136-146
23. 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. The Lancet 2010;375:201-209.
24. von Birgelen C, Basalus MW, 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. Expedited online publication: February 15, 2012. doi:10.1016/j.jacc.2012.01.008.
25. Tunuguntla A, Daneault B, Kirtane AJ. Novel use of the guideLiner catheter to minimize contrast use during PCI in a patient with chronic kidney disease. Catheter Cardiovasc Interv.2011(10.1002/ccd.23331).
26. Hanratty CG, Walsh SJ. Longitudinal compression: a "new" complication with modern coronary stent platforms-time to think beyond deliverability? EuroIntervention.2011;7(7):872-7
27. Williams PD, Mamas MA, Morgan KP, El-Omar M, Clarke B, Bainbridge A, Fath-Ordoubadi F, Fraser DG. Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms. EuroIntervention.2011 (pii: 20111018-02).

Table 1. Demographic characteristics of study population.

Age (years)	67±13
Male gender	74%(48/65)
Hypertension	57%(37/61)
Hypercholesterolemia	54%(35/61)
Diabetes	25%(16/65)
Current smoking	22%(14/61)
Family history of CAD	28%(18/61)
Prior myocardial infarction	32%(21/65)
Prior PCI	26%(17/65)
Prior CABG	26%(17/65)
Indication for PCI	
ST elevation MI	12%(8/65)
Non-ST elevation MI	20%(13/65)
Unstable angina	6%(4/65)
Stable angina	62%(40/65)

Table 2. Target vessels and lesion characteristics.

Target vessels	
Left anterior descending artery	17/70(24%)
Left circumflexartery	20/70(29%)
Right coronary artery	23/70(33%)
Vein graft	10/70(14%)
Target lesions	
Type B2/C lesion	68/70(97%)
Distal location	37/70(53%)
Severe calcification	16/70(23%)
Chronic total occlusion	12/70(17%)
Reference vessel diameter(mm)	3.0±0.5
Diameter stenosis(%)	89±13
Lesion length(mm)	38±26

Table 3. Procedural details, success, failures, and complications.

Procedural details	
Radial access	22/65(34%)
Multi vessel procedure	19/65(29%)
Procedural time (min)	79±43
Volume of contrast (ml)	220±118
Total length of stents implanted (mm)	41±29
Number of stents implanted	1.8±1.2
Depth of GuideLiner intubation (mm)	33±21
Primary indication for GuideLiner use	
Improvement of backup and facilitated stent delivery	41/70(59%)
More selective contrast-injection	9/70(13%)
Improvement of alignment of the guide	20/70(29%)
Success, failures, and complications	
Device success	65/70(93%)
Procedural success	64/70(91%)
Major complications	0/70
Minor complications	2/70(3%)
Air embolism	1/70
Stent dislodgment	1/70

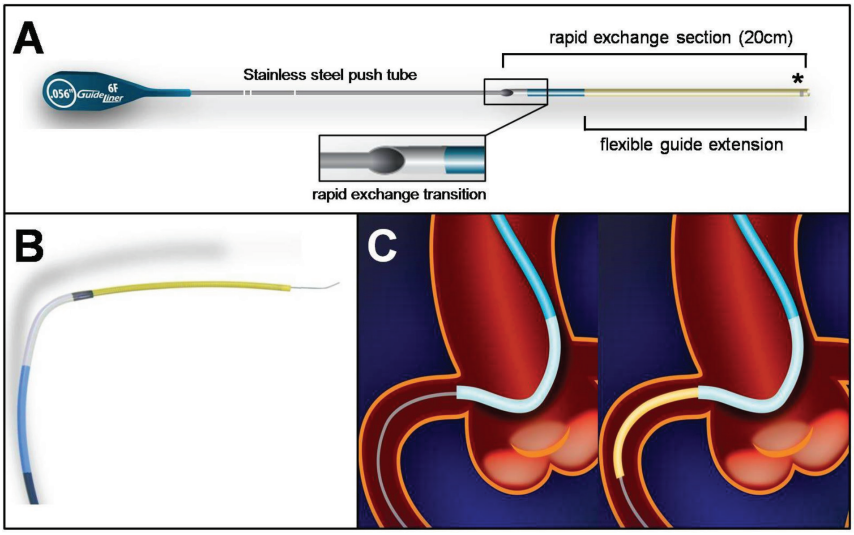

Figure 1. Schematic presentation of the GuideLiner catheter.

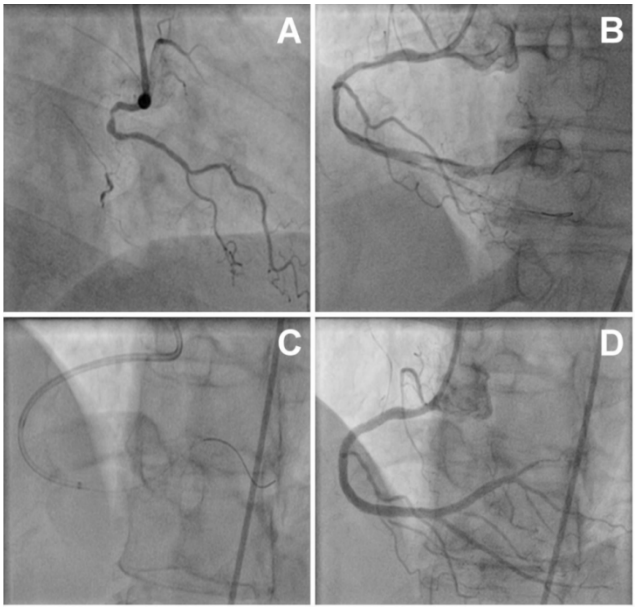

Figure 2. Angiography of a chronically occluded RCA in a 55-year old female patient(**A**). Wire crossing was achieved using a pilot-50 wire. After subsequent passage en dilation with low profile balloons, the flow is partially restored and a long dissection can be noted that extends into the posterolateral branch(**B**). Passage of a stent was unsuccessful due to marked resistance in the distal segment of the vessel. With the help of an anchoring balloon, the GuideLiner catheter was deeply intubated over the guidewire(**C**). Then, several drug-eluting stents were successfully delivered and postdilated, with an excellent final angiographic result(**D**).

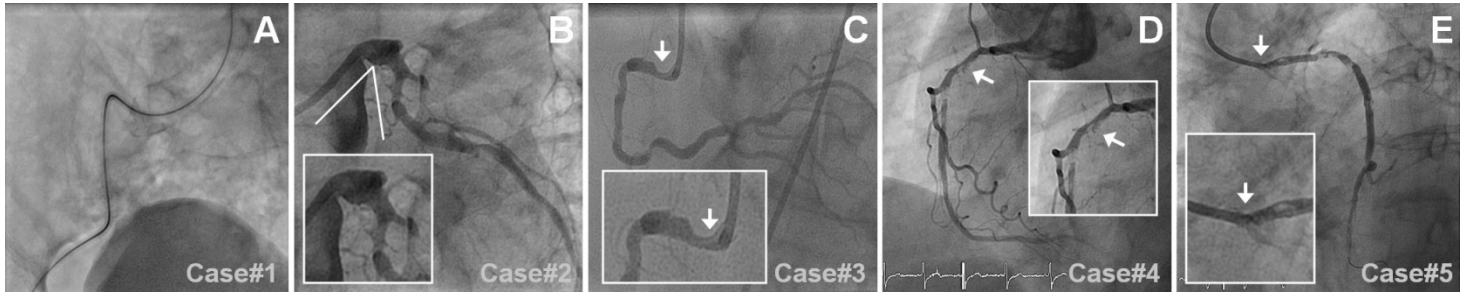

Figure 3. Angiographic overview of the device failures: (*Case #1*) The first case was a 79-year-old male patient with an acute inferior MI. The target lesion was located in a diffusely diseased, heavily calcified RCA. The GL could not be advanced through the guide catheter because of severe iliacal tortuosity (**Figure 3A**), but procedural success was accomplished by use of a 3DRC guide catheter, 2 guidewires, and a distal anchoring balloon. (Case #2) The second case was a long and calcified proximal LCX lesion, being located behind a sharp angle between LM and LCX that prevented GL intubation (**Figure 3B**). (*Case #3*) The third case was 56-years-old subject who underwent an elective PCI of a diffusely diseased RCA. The GL catheter could not be intubated in the vessel due to a proximal lesion (**Figure 3C**). The procedure was finished successfully with a AL1 guide. (*Case #4*) In the fourth patient, the target lesion was a heavily calcified long mid RCA lesion (**Figure 3D**). The proximal RCA segment was diffusely diseased, which prevented deep GL intubation (depth of only 5mm) and resulted in insufficient support; however, this problem was solved by rotablation of the ostium. (*Case #5*) The fifth case was a vital 87-years-old female with stable angina due to a severely calcified proximal lesion in an 18-year-old saphenous vein graft. An AL2 guide catheter was positioned in the ostium and a flexible guidewire with hydrophilic coating was advanced across the lesion. Use of the GL was attempted to increase backup support but the GL could not be advanced into the ostium (**Figure 3E**), and the PCI procedure was terminated as not even a second guidewire passed the ostium. We discussed the patient with our thoracic surgeons, who then performed an elective repeat bypass surgery with an uneventful clinical course.

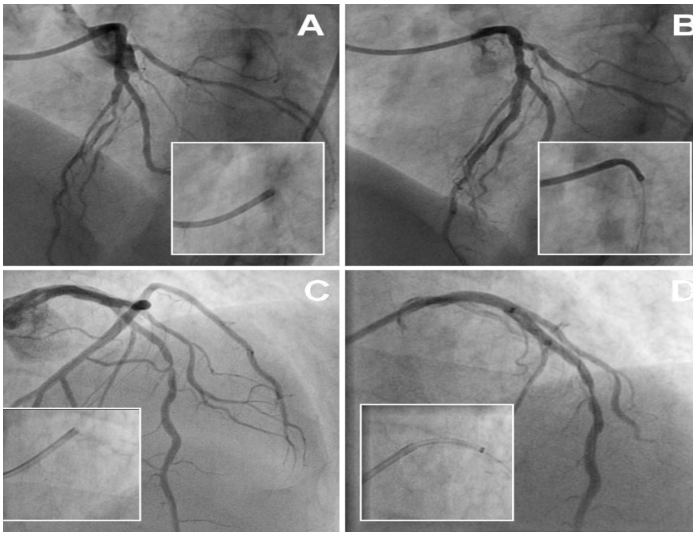

Figure 4. Angiographic overview of a subject with a vertical offspring of the left main (**A&B**)**.** The GuideLiner catheter was used for co-axial alignment of the guiding catheter, providing gentle intubation in the LM and good support to treat the LAD lesion.

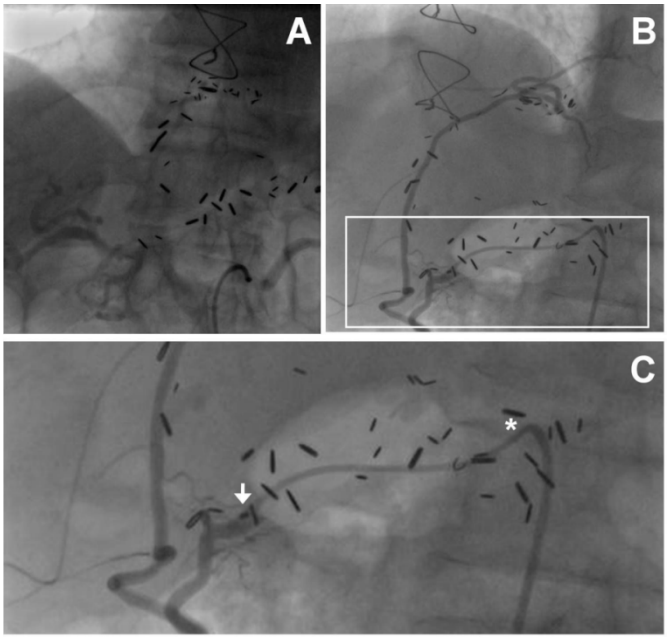

Figure 5. Visualization of a gastroepiploic artery (GEA) graft in a 66-year-old male patient. Panel **A** shows vague images of the GEA graft, obtained during routine angiography 2 years earlier. Panel **B** illustrates the difference in image quality, obtained recently with the use of the GuideLiner (GL) catheter. The arrow in Panel **C** is pointed at the tip of the GL catheter.

Chapter 13

Aspiration of Intact Coronary Bifurcation Thrombus in ST-Elevation Myocardial Infarction

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Letter to the Editor

We report a case of a 74-year-old female patient with acute chest pain was admitted for primary percutaneous coronary angioplasty. The electrocardiogram indicated an acute ST-elevation myocardial infarction of the anterolateral wall. Coronary angiography showed a thrombus-containing lesion in the left anterior descending coronary artery with absence of a major diagonal branch (Figure 1A; arrowhead). Administration of abciximab was not considered as there was some leakage of blood from the punctured, calcified femoral artery. An aspiration catheter was slowly advanced into the lesion, before vacuum-suction was initiated to remove thrombus. After careful retrieval, we found at its tip an intact Y-shaped thrombus (Figure 1D) that resembled the shape of the bifurcation. After thrombus removal, blood flow was fully restored in the diagonal branch (Figure 1B, arrowhead; Figure 1E, 3D reconstruction by dedicated 3D QCA software[1] (Medis, Leiden, The Netherlands)). Following stent implantation of two drug-eluting coronary stents (Figure 1C), the in-hospital course of our patient was uneventful, and the patient was discharged after 5 days. This case with a unique removal of an *intact* coronary bifurcation thrombus nicely illustrates the pathophysiological principle of thrombus propagation from a fissured or ruptured plaque into both subordinate branches of a bifurcation.[2]

References

1. Tu S, Jing J, Holm NR, et al. In vivo assessment of bifurcation optimal viewing angles and bifurcation angles by three-dimensional (3D) quantitative coronary angiography. Int J Cardiovasc Imaging 2012, 28:1617-1625.
2. Rittersma SZ, van der Wal AC, Koch KT, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. Circulation 2005;111:1160-1165.

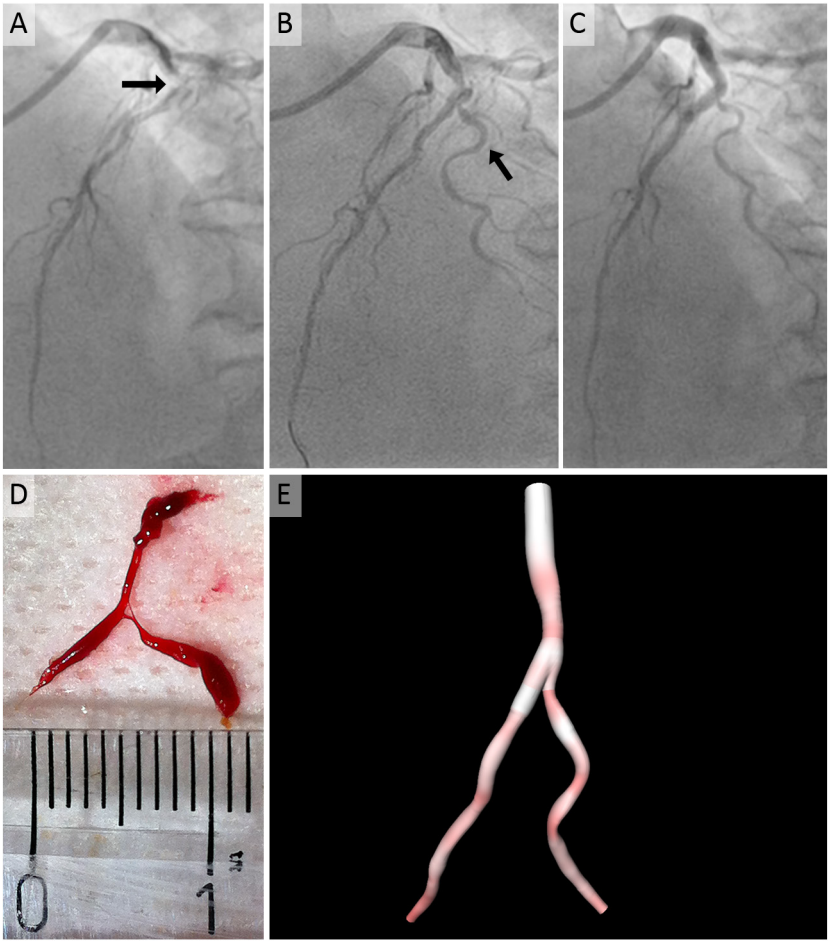

Figure 1. Coronary angiographic images of the interventional procedure (A-C); intact Y-shaped thrombus (D) and 3D reconstruction of the bifurcation anatomy from two-dimensional angiographic projections (E).

Clinical research beyond the TWENTE trial

Chapter 14

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 non-inferiority 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 CE and recently FDA-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 CE-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.

Methods

Study hypothesis/ objective and design

The main objective of the DUTCH PEERS (ClinicalTrials.gov #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. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. Stent manufacturing companies will have no access to the study database and are not involved in the interpretation of data or manuscript preparation.

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 such as non-ST-elevation myocardial infarctions (non-STEMI) and 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.

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.

PCI 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 (QCA).

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) TVF 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 non-cardiac 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 peri-procedural myocardial infarction.(11) Clinically driven repeated target vessel revascularization includes revascularization procedures by means of CABG 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-squared test. We applied a non-inferiority 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 non-inferiority margin 3.6%, Resolute Integrity will be considered non-inferior to Promus Element. Considering the aforementioned parameters, 894 patients per group (total study population: 1788 patients) would allow to demonstrate non-inferiority, 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 Target Vessel Failure (TVF) rate at 12 months will be analyzed by means of Chi-squared 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 endpoint target-lesion failure at 1-year follow-up (a composite of cardiac death, target-vessel myocardial infarction and target-lesion revascularization) occurred 38% less often compared to 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 non-inferior 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 ($p_{non\text{-}inferiority}$ <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. Non-inferiority of Resolute versus Xience V was maintained at 2-year follow-up.(5) The randomized TWENTE trial recently confirmed non-inferiority 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)

While 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 non-inferiority 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 non-inferior 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 neo-intima. (12) As 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.

As 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 one 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 non-inferiority 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.

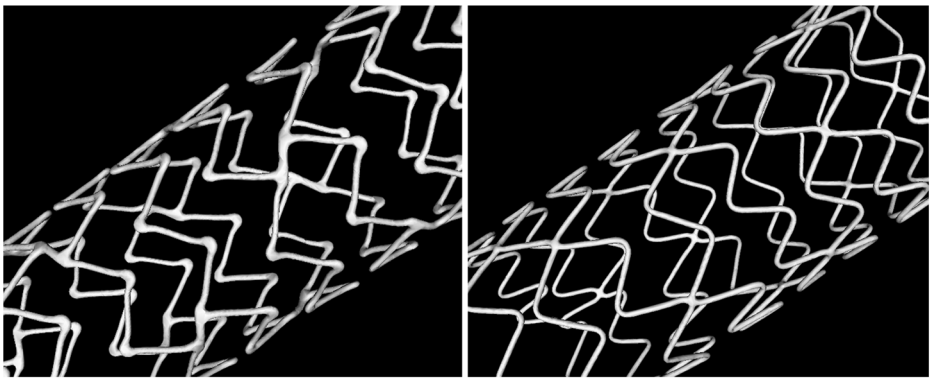

Figure 1. Micro computed-tomography images of DES compared in DUTCH PEERS. Promus Element (left panel) and Resolute Integrity (right panel); images from ongoing bench side studies performed by C. von Birgelen and co-workers, University of Twente, Enschede, the Netherlands.

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.

Table 1. DUTCH PEERS inclusion and exclusion criteria.

Chapter 15

Highly Deliverable Third-Generation Zotarolimus-Eluting and Everolimus-Eluting Stents in All-Comer Patients (DUTCH PEERS): A Randomised Trial

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Summary

Background: Third-generation, permanent-polymer-based drug-eluting stents with novel, flexible designs might be more easily delivered than previous generations of stents in complex coronary lesions, but might be less longitudinally stable. We aimed to assess the safety and efficacy in all-comer patients of two third-generation stents that are often used clinically, but that have not yet been compared, and one of which has not previously been assessed in a randomised trial.

Methods: In this investigator-initiated, single-blind, multicentre, randomised, two-arm, non-inferiority trial, patients aged 18 years and older who required a percutaneous coronary intervention with implantation of a drug-eluting stent were recruited from four study sites in the Netherlands. We randomly assigned patients by independently managed computer-generated allocation sequences in a 1:1 ratio to receive either cobalt-chromium-based zotarolimus-eluting stents (Resolute Integrity, Medtronic, Santa Rosa, CA, USA) or platinum-chromium-based everolimus-eluting stents (Promus Element, Boston Scientific, Natick, MA, USA). Patients and analysts were masked to the allocated stent, but treating clinicians were not. The primary endpoint of target-vessel failure was a composite of safety (cardiac death or target-vessel-related myocardial infarction) and efficacy (target-vessel revascularisation) at 12 months, analysed by intention to treat (with a non-inferiority margin of 3·6%).

Findings: Between Nov 25, 2010, and May 24, 2012, 1811 eligible all-comer patients, with 2371 target lesions, were enrolled in the study. 370 (20%) patients presented with ST-elevation myocardial infarction and 447 (25%) with non-ST-elevation myocardial infarction. 906 patients were assigned to receive zotarolimus-eluting stents and 905 to receive everolimus-eluting stents. Ease of stent delivery was shown by very low numbers of patients requiring treatment other than their assigned study treatment (six [1%] in the zotarolimus-eluting stent group vs five [1%] in the everolimus-eluting stent group; p=0·22). 12-month follow-up results were available for 1810 patients (one patient in the zotarolimus-eluting stent group withdrew consent). The primary endpoint was met by 55 (6%) of 905 patients in the zotarolimus-eluting stent group and 47 (5%) of 905 in the everolimus-eluting stent group. The zotarolimus-eluting stent was non-inferior to the everolimus-eluting stent (absolute risk difference 0·88%, 95% CI –1·24% to 3·01%; upper limit of one-sided 95% CI 2·69%; non-inferiority p=0·006). We noted no significant between-group differences in individual components of the primary endpoint. Definite stent thrombosis occurred in three (0·3%) patients in the zotarolimus-eluting stent group and six (0·7%) patients in the everolimus-eluting stent group (p=0·34). Longitudinal stent deformation was seen only in the everolimus-eluting stent group (nine [1·0%] of 905 vs 0 of 906, p=0·002; nine of 1591 [0·6%] everolimus-eluting stents implanted became deformed), but was not associated with any adverse events.

Interpretation: Both stents were similarly efficacious and safe, and provided excellent clinical outcomes, especially in view of the large number of patients who presented with acute myocardial infarctions.

Introduction

Drug-eluting stents that counteract the development of restenosis by delivering antiproliferative drugs from polymer-based coatings have revolutionised the percutaneous treatment of obstructive coronary artery disease.[1,2] First-generation durable-polymer drug-eluting stents were made from bare-metal stent platforms with little flexibility and fairly plain permanent-polymer coatings, which were associated with an increased risk of late and very late stent thrombosis.[3,4] Second-generation drug-eluting stents with durable coatings that were more biocompatible than those of first-generation stents were then developed. These newer stents showed superior safety profiles in various clinical settings.[5–9]

Most recently, third-generation, durable-polymer-based drug-eluting stents were developed to answer the demand for more flexible and highly deliverable devices that can tackle very challenging coronary lesion and vessel anatomies, as are increasingly encountered in ageing western patient populations. Although the coatings of these stents contain the same established drug and durable polymer combinations as their second-generation counterparts, the design and material of their bare-metal stent platforms have been changed substantially.[10–14] However, such changes might have the trade-off of reducing longitudinal stent stability,[15,16] which would account for the occurrence of longitudinal stent deformation that has been reported after contact between deployed stents and guiding catheters, balloon catheters, or other catheter-based devices.[16–19] Data so far reported about the incidence and clinical significance of longitudinal stent deformation have been conflicting.[16–19]

A cobalt-chromium-based zotarolimus-eluting stent, made from a single sinusoidal-formed wire (Resolute Integrity, Medtronic, Santa Rosa, CA, USA), and a laser-cut platinum-chromium-based everolimus-eluting stent (Promus Element, Boston Scientific, Natick, MA, USA), are two such third-generation drug-eluting stents.[11–14] Although clinical outcome data for the use of the Promus Element stent in patients with mild-to-moderate clinical risk have been,[11] no such data are available for the Resolute Integrity stent. We aimed to compare clinical outcomes from the use of these two third-generation drug-eluting stents in a broad population of all-comer patients.

Methods

Study design and patients

We undertook a randomised trial entitled "*Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity* (DUTCH PEERS): *Randomized Multicenter Trial in All Comers Population Treated Within Eastern Netherlands II* (TWENTE II)" at four Dutch PCI centres (Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Scheper Hospital, Emmen; Medisch Centrum Alkmaar, Alkmaar). This investigator-initiated study, which is registered with ClinicalTrials.gov

(NCT01331707), is a single-blinded, multicentre, randomised, two-arm, non-inferiority trial.[10] All-comer patients ≥18 years, capable of providing informed consent and requiring a percutaneous coronary intervention with DES implantation, were randomised for treatment with one of the study stents. All coronary syndromes, de-novo and restenotic lesions, and coronary artery or bypass stenoses were permitted (no limit for lesion length, reference size, and number of lesions or diseased vessels). There were few exclusion criteria: participation in another randomised drug-or-device study before reaching the primary endpoint of that study; planned surgery within 6 months unless dual anti-platelet therapy was maintained; known intolerance to a P2Y12 receptor antagonist preventing adherence to dual anti-platelet therapy, or intolerance to aspirin, heparin, or DES components; known pregnancy; and life expectancy <1 year. The study complied with the CONSORT 2010 Statement and Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centres. All patients provided written informed consent.

Randomisation

After guide wire passage (or predilation), patients were randomised in blocks of 8 and 4 in random order by a computer program (block stratified randomisation V5·0 by S. Piantadosi). Patients were assigned on a 1:1 basis to one of the DES (patients blinded for assigned DES). The random allocation was implemented by use of sequentially numbered, opaque, sealed envelopes.

Procedures

The third-generation cobalt-chromium-based zotarolimus-eluting stent (Resolute Integrity, Medtronic, Santa Rosa, CA, USA) employs a novel, open-cell stent design for increased flexibility and deliverability.[13,14] The stent platform is made from a single, sinusoidal-formed, helically wrapped, locally laser-fused wire (strut thickness 91 μm).[13] It is covered by a 6 μm layer of coating consisting of zotarolimus and the BioLinx polymer system, which have been efficacious on the second-generation Resolute stent (Medtronic).[7,8,20] Zotarolimus-eluting stents were available with stent diameters of 2·25–4·0 mm and lengths of 8–38 mm. The platinum-chromium alloy-based stent platform (minimum strut thickness 81μm) of the third-generation everolimus-eluting stent (Promus Element, Boston Scientific, Natick, MA, USA) has a novel, laser-cut, open-cell stent design, consisting of short serpentine rings connected by helically distributed links.[11,12] The stent, which was designed for improved deliverability and visibility (i.e. radiopacity), is covered by a 7 μm everolimus-eluting fluoropolymer coating that has been demonstrated to be efficacious on the second-generation cobalt-chromium-based everolimus-eluting Xience V/Promus stent (Xience V, Abbott Vascular Devices, Santa Clara, CA, USA; Promus stent distributed by Boston Scientific).[5,8] Everolimus-eluting stents were available in diameters

of 2·25–4·0 mm with lengths of 8–38 mm.

Interventions were done with standard techniques. Lesion predilation, use of glycoprotein IIb/IIIa receptor antagonists, direct stenting, and stent postdilation were left at the operator's discretion. Staged procedures with allocated stents were permitted within 6 weeks. Concomitant medication did not differ from routine treatment; further medical treatment was performed according to current medical guidelines and the physician's judgment.[10] In general, dual antiplatelet therapy was prescribed for 1 year.

Electrocardiograms were systematically assessed before and after the intervention, prior to discharge, and at suspicion of ischemia, and recommended at 12-month follow-up. Laboratory tests included systematical assessment of cardiac markers following the intervention and subsequent serial measurements in the case of relevant elevations or complaints. In patients with acute coronary syndromes, cardiac markers were also assessed before the intervention.[10] Angiographic analysts, blinded for the stent type used, performed off-line quantitative coronary angiography according to current standards (QAngio XA 7·2, Medis, Leiden, the Netherlands).

Operators were requested to report any evident or suspected longitudinal stent deformation, which was defined as distortion or shortening of an implanted stent in the longitudinal axis following initially successful deployment.[16–18] On angiography, longitudinal stent deformation was identified as a localised change in radiopacity pattern of a stent, which occurred between initial deployment and the end of the procedure, following manipulations with the guiding catheter or the use of further catheter-based devices (e.g. the attempt to re-cross a deployed stent with a balloon catheter, imaging catheter, or another stent). The angiograms of all patients were reviewed for stent deformation by an analyst, blinded for reported longitudinal stent deformation and allocated stent type. Measurement of stent length–both final and immediately after deployment–and calculation of the post-deployment stent length ratio (stent length final/stent length after deployment) was performed in cases in which longitudinal stent deformation was noted by the operator or visually identified by the analyst.[19]

Clinical endpoints were defined according to the Academic Research Consortium (ARC), including the addendum on myocardial infarction.[10,21,22] The pre-specified primary composite endpoint of *target vessel failure* assessed both device efficacy and patient safety at 12 months and was composed of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularisation (components in hierarchical order). Death was considered cardiac, unless an unequivocal non-cardiac cause could be established. Myocardial infarction was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarkers.[22] A target vessel-related myocardial infarction was related to the target vessel or could not be related to another vessel;

further classification was based on laboratory, electrocardiographic, angiographic, and/or clinical data.[10,22] Revascularisation procedures were considered clinically indicated (i.e. there was sufficient objective evidence of lesion significance) if the angiographic percent diameter stenosis of the then treated lesion was ≥50% in the presence of ischaemic signs or symptoms, or if the diameter stenosis was ≥70% irrespective of ischaemic signs or symptoms.[22]

Prespecified secondary endpoints included: components of the primary endpoint; all-cause mortality; any myocardial infarction; clinically indicated target lesion revascularisation; and stent thrombosis.[10,22] Further composite endpoints (components in hierarchical order) were: a composite endpoint of *target lesion failure*, consisting of cardiac death, target vessel-related myocardial infarction, or clinically indicated target lesion revascularisation; a composite endpoint of *major adverse cardiac events*, consisting of all-cause death, any myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularisation; and a more global *patient-oriented composite endpoint,* consisting of all-cause death, any myocardial infarction, or any coronary revascularisation. A final residual diameter stenosis <50% was defined as *device success* if achieved with assigned study stents only; *lesion success* if achieved with any approach; and *procedure success* if achieved without in-hospital major adverse cardiac events. An exploratory subgroup analysis of the primary endpoint was performed in line with previous trials.[7,8,20]

The 12-month clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up and/or a medical questionnaire (staff blinded to assigned study stents). The Contract Research Organisation (CRO) Cardio Research Enschede (Enschede, the Netherlands) coordinated trial and data management, and the regular safety data were reported to the independent Medical Ethics Committee Twente.

Data monitoring was performed by the CRO Diagram (Zwolle, the Netherlands) and comprised: (1) informed consent and DES type and size (100% of patients); (2) all potential clinical events reported by investigators and/or patients (100% of event triggers); and (3) further in-depth monitoring of all demographic, procedural, and clinical outcome data (at random in 10% of patients).

Processing of clinical outcome data and clinical event adjudication were performed by the CRO Cardialysis (Rotterdam, the Netherlands). The clinical event committee in Rotterdam, which was blinded for the assigned treatment, adjudicated all clinical endpoints with the only exception being the secondary endpoint *non-target vessel revascularisation* that was adjudicated by CRO Cardio Research Enschede.

Statistical considerations and analysis

The main outcome was the difference in primary endpoint at 12 months between patients assigned to treatment with zotarolimus-eluting or everolimus-eluting stents, analysed by $\chi 2$ test with at least 80% power to

detect non-inferiority at a one-sided type-I error of 0·05.[23] We applied a non-inferiority margin of 3·6% with the expectation of 10% events (on the basis of results from the RESOLUTE ALL-COMERS trial[7]). With a maximum loss to follow-up of 3%, a minimum of 1788 patients was needed. All analyses were based on the intention-to-treat principle. We also performed a per-protocol analysis of the primary endpoint. Categorical variables were assessed with $\chi 2$ test, whereas continuous variables were assessed with Student's t-test or with the Wilcoxon rank-sum test, as appropriate. The time to primary endpoint and the components thereof were assessed according to Kaplan-Meier analysis;[24] the log-rank test was applied to compare groups. We calculated relative risk using the log-binomial method and hazard ratios (HRs) using Cox proportional hazards regression analysis. To account for intra-patient correlation (due to inter-lesion dependence), we did an additional lesion-based analysis using the generalised estimating equation method. We used logistic regression to test for interaction between subgroups and stent type with respect to the primary endpoint. A p-value <0·05 was regarded as significant. All p-values and CIs were two-sided, except those for non-inferiority testing of the primary endpoint. After non-inferiority was assessed, we calculated regular two-sided 95% CIs and two-sided p values to allow conventional interpretation of results (as for superiority trial design). Since it is unnecessary to compare baseline characteristics statistically in randomised trials,[25] we do not report individual p values for these data. We used SPSS 15.0 (SPSS, Chicago, IL, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA) for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT01331707.

Role of the funding source

The sponsors of this study had no role in the development of the study design, data collection and monitoring, data analysis and interpretation, or writing of the report. They had no access to the clinical trial database. The authors had full access to all study data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Nov 25, 2010, and May 24, 2012, 1811 eligible all-comer patients, aged 21–91 years, with 2371 target lesions, were enrolled and randomly assigned to

treatment with third-generation zotarolimus-eluting Resolute Integrity stents (906 patients, 1205 lesions) or everolimus-eluting Promus Element stents (905 patients, 1166 lesions; figure 1). One patient from the zotarolimus-eluting stent group withdrew consent after 1 day; therefore, baseline data and interventional results are reported for 1811 patients and follow-up results for 1810 patients. We obtained 12-month follow-up data for all 1810 remaining trial participants, which were used for clinical endpoint analysis.

We recorded no significant differences in baseline patient and preprocedural lesion characteristics between the study groups (tables 1, 2). Patients often presented with ST-elevation or non-ST-elevation myocardial

infarction, which contributed to the overall high proportion of acute coronary syndromes at presentation (1062 patients [59%]). Most patients (1068 [59%]) were treated for at least one lesion in a small vessel, and many patients underwent treatment for bifurcation lesions (table 1). Of all coronary lesions, most (1558 [66%]) were complex, with lesion class B2 or C, and many lesions had severe plaque calcification (table 2).

More than 99% of patients were successfully treated with the assigned study stents only, across both groups (table 3); the proportion of patients with deviation from the assigned treatment was low and similar for both groups (six [1%] of 906 patients in the zotarolimus-eluting stent group vs five [1%] of 905 patients in the everolimus-eluting stent group; p=0·76; figure 1). Stenting without predilation (direct stenting) was done in 678 (29%) of the 2371 lesions (table 3). The frequency of stent post-dilation was high and differed between lesions treated with zotarolimus-eluting and everolimus-eluting stents (table 3). We recorded no significant difference between groups for any of the other procedure-related parameters (table 3). An additional lesion-based analysis of procedural details and results (with analyses corrected for intra-patient correlation with generalised estimating equations) did not change the overall fi ndings (appendix I). At coronary intervention, 521 (29%) patients were treated with a glycoprotein IIb/IIIa antagonist (table 1), whereas only two patients (<1%) were treated with bivalirudin. At discharge, most (1790 [99%] of 1810) patients were treated with an antiplatelet therapy that included clopidogrel and aspirin; only three patients (<1%) received ticagrelor and 18 (1%) received prasugrel.

Table 4 shows clinical outcome at 12 months. The primary endpoint of target-vessel failure was met by 55 (6%) of 905 patients in zotarolimus-eluting stent group and 47 (5%) of 905 patients in the everolimus-eluting stent group. The zotarolimus-eluting Resolute Integrity stent was non-inferior to the everolimus-eluting Promus Element stent, with an absolute risk difference of 0·88% (95% CI −1·24 to 3·01) and an upper limit of the one-sided 95% CI of 2·69% (non-inferiority p=0·006). We noted no significant between-group differences in individual components of the primary endpoint (figure 2) or in the secondary clinical endpoints (table 4). HRs (with 95% CIs) and log-rank p values for the clinical outcomes at 1 year are reported in the appendix (appendix II-III). An exploratory subgroup analysis revealed no significant between-group difference in the primary endpoint across the various subgroups (appendix IV).

In both stent groups, frequencies of definite and definite-or-probable stent thrombosis were low (table 4). No definite stent thrombosis occurred beyond 3 months after stenting. Figure 3 shows the time-to-event curve of definite-or-probable stent thrombosis and information bout corresponding clinical events.

Longitudinal stent deformation during the index procedure was seen only in patients assigned to treatment with everolimus-eluting stents (nine [1·0%] of 905 vs 0 of 906 patients; p=0·002). With respect to the number of stents implanted, nine (0·6%) of 1591 everolimus-eluting stents became deformed. However, none of the patients with longitudinal stent

deformation had any adverse clinical events as a result (appendix p 5).

To account for the possibility that deviation from the assigned stent might have affected the primary outcome, we also did a per-protocol analysis of the primary endpoint, which gave a similar result to the intention-to-treat analysis. The primary endpoint of target-vessel failure was met by 53 (6%) of 899 patients treated with zotarolimus-eluting stents and 45 (5%) of 900 patients treated with everolimus-eluting stents. The zotarolimus-eluting stent remained non-inferior, with an absolute risk difference of 0·90% (95% CI −1·20 to 3·00) and an upper limit of the one-sided 95% CI of 2·66% (non-inferiority p=0·006).

Discussion

DUTCH PEERS is the first randomised comparison of these third-generation drug-eluting stents. In addition, it is the first trial ever to investigate the zotarolimus-eluting Resolute Integrity stent. In this all-comer patient population, there was no significant difference between stent groups in the incidence of the primary endpoint target vessel failure at 12-month follow-up. As a result, the zotarolimus-eluting Resolute Integrity stent met the criterion of non-inferiority as compared to the everolimus-eluting Promus Element stent. No significant differences were seen in the individual components of the primary endpoint (cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-vessel revascularisation). Stent thrombosis was rare in both groups, and no definite stent thrombosis occurred beyond 3 months from stenting.

Clinical outcomes were excellent for both stent groups, especially in view of the large proportion of patients with complex lesions and acute myocardial infarction at presentation. Our findings showed favourable event rates in a population in which most patients had advanced cardiovascular disease. Therefore, these data might serve as an important reference for future stent trials. Our study assessed many patients with increased clinical, lesion-related, or procedural risk. The proportions of patients with acute coronary syndrome and, in particular, ST-elevation myocardial infarction, were among the highest of all randomised, multicentre trials of drug-eluting stents in an all-comers population.[7,19,26–28] The proportion of patients with complex type B2/C coronary lesions and bifurcation lesions were also high compared with other trials.[6–8,19,27,28]

Very few patients deviated from their assigned stents in this trial, which suggests excellent deliverability and similar feasibility for both devices. In fact, deviation from the assigned stents was much higher in the permanent polymer-based DES arms of various other randomised stent trials, such as TWENTE, RESOLUTE ALL-COMERS, COMPARE II, and LEADERS, in which treatment of 1·6–5·3% of patients deviated from the assigned stents.[7,8,26,29]

Up to now, the third-generation Promus Element stent *has only been compared with second-generation* DES.[11,19] In the PLATINUM trial, which enrolled low-to-moderate risk patients, the Promus Element stent

demonstrated non-inferiority as compared to the second-generation cobalt-chromium-based everolimus-eluting Xience V/Promus stent showing a low rate of the target vessel-related composite endpoint (4·2%).[11] Our findings show excellent results for the Promus Element stent in an all-comers population with a much higher risk profile than that of the PLATINUM trial. The HOST-ASSURE trial has compared the Promus Element stent with the second-generation zotarolimus-eluting Resolute stent in Korean all-comers (patients with reference vessel diameter <2·5mm or heart failure excluded).[19] The investigators attributed the very low rates of clinical endpoints to the excellent device characteristics and generally lower clinical event rates in East Asian populations.[19] DUTCH PEERS provides the first randomised assessment of Promus Element stents in an all-comer population of European patients. Besides the difference in ethnic background, the patient population of DUTCH PEERS differed from the HOST-ASSURE patients in its much higher proportion of acute ST-elevation myocardial infarctions at presentation (20% vs. 11%), treatment of more complex target lesions (lesion class B2/C: 66% vs. 51%) and treatment of more lesions in small vessels (mean reference diameter: 2·7mm vs. 3·0mm). Moreover, a very small randomised study from Spain also reported favourable outcome data of 150 patients treated with Promus Element stents, but this study did not permit a meaningful between-stent comparison.[30] Compared to the second-generation everolimus-eluting stent in the TWENTE and RESOLUTE ALL-COMERS trials, which involved broad patient populations, the Promus Element stent group of DUTCH PEERS showed lower rates of both target vessel-related (5·2% vs. 8·1– 9·6%) and target lesion-related composite endpoints (4·5% vs. 6·8–8·3%).[7,8]

Only a small-scale first-in-man study reported data on the bare metal stent platform that is employed in the third-generation zotarolimus-eluting Resolute Integrity stent.[14] Our trial is the first clinical study to investigate this particular stent, and has shown it to have a favourable outcome in a broad patient population. The frequencies of target-vessel-related composite endpoint events and the number of definite stent thromboses were much lower than reported for its second-generation counterpartin the randomised TWENTE and RESOLUTE ALL-COMERS trials (6·1% vs. 8·2–9·0%; and 0·3% vs. 0·6–1·2%).[7,8]

A potential trade-off of the novel, flexible stent designs of third-generation DES might be a reduced longitudinal device stability.[15,16] Since the introduction of the Promus Element stent, longitudinal stent deformation has been reported much more frequently.[18] Retrospective analyses have shown longitudinal deformation to occur with an incidence of 0·3–0·9% per stent implanted, although such deformations are associated with a mostly benign clinical course.[16,17] In the HOST-ASSURE trial, longitudinal deformation of the Promus Element stent was noted in seven out of 2938 patients (0·2%) but not associated with future adverse events.[19] In our study, visually assessed longitudinal stent deformation was noted only in the everolimus-eluting Promus Element stents, with a frequency of 0·6% per stent implanted, but without clinical sequelae. Quantitative coronary angiographic

assessment of longitudinal stent deformation was not done systematically, but was restricted to cases with visually determined stent deformation. Investigators of two previous studies[19,31] did systematic, quantitative, coronary angiography-derived measurement of post-deployment stent length compared with the nominal stent length and showed the absence of a systematic shortening of this stent platform. The excellent radiographic visibility of the Promus Element stent might have contributed to the more frequent recognition of longitudinal stent deformation and the slightly higher frequency of stent post-dilation compared with the Resolute Integrity stent.

Although the use of the highly device-oriented composite endpoint target lesion failure has been advocated as primary endpoint,[21] DUTCH PEERS used the of target vessel failure.[10] Target vessel failure is also very appropriate and has been used as primary endpoint by other trials of drug-eluting stents in all-comers.[26-28] Both composite endpoints have advantages and disadvantages. Target-lesion failure includes only target-vessel revascularisations for lesions inside the original target-lesion segment, where as target-vessel failure also includes revascularisation procedures for lesions at other sites of the target-vessel (ie, inside and outside the target-lesion segment). Target-vessel failure, therefore, avoids the sometimes difficult discussion about whether the target lesion segment is touched by a stenosis or restenosis, or not. Additionally, target-vessel failure would cover the progression of lesions that are initially not clinically signifi cant to stenoses that require interventional treatment, which might sometimes be caused by the intracoronary use of a bulky device.

Our trial has some limitations. The lower-than-expected event rates of the primary endpoint affect the robustness of the results–in particular the results of the post-hoc subgroup analysis. When designing the present study, we assumed that the tested devices had an event risk that was in the range of their second-generation counterparts tested in RESOLUTE ALL-COMERS,[7] and that enrolment of more patients with ST-elevation myocardial infarction (who have an inherently increased risk of adverse outcome) would slightly increase the frequency of events. However, although we succeeded in enrolling more patients with ST-elevation myocardial infarction than did the RESOLUTE All Comers trial, event frequencies were lower. Underreporting of events in our study is very unlikely, in view of the systematic post-procedural assessment, the complete 12-month follow-up, and the independent monitoring used. Other randomised trials of stents in all-comers [19,29] have also had low event frequencies, suggesting that our findings are actually more representative of the present outcomes of percutaneous coronary interventions than of those from when the trial was designed. Nevertheless, even with a more conservative non-inferiority margin of 2·7% (to compensate for the lower-than-expected event rate), the primary outcome of non-inferiority of the Resolute Integrity stent compared with the Promus Element stent was unchanged. A one-sided alpha of 0·05–also used by other DES trials in all-comers[7,28,29]–is less conservative in establishing non-inferiority of two therapies, but the use of a one-sided alpha of 0·025

would not have an effect on the outcome of our study (i.e. the upper limit of the 97·5% CI of the difference is 3·01%, which is below our prespecified non-inferiority margin). Two final issues should also be mentioned, relating to our subgroup analysis of the primary endpoint and the definition of third-generation drug-eluting stents used. On the first point, because the subgroup analysis done for the primary endpoint of target-vessel failure was not prespecified, we applied subgroup definitions from previous trials[7,8] to avoid a subjective post-hoc selection.

On the second, although the term third-generation drug-eluting stents is sometimes used for a broader spectrum of novel stents, we have used the term to refer specifically to the more flexible, highly deliverable durable-polymer stents that followed the second-generation durable-polymer stents.

In conclusion, both stents were similarly efficacious and safe, and provided excellent clinical outcomes, especially in view of the large number of patients who presented with acute myocardial infarctions

Panel: Research in context

Systematic Review

In August 2013, we searched PubMed and the most recent EuroPCR, Transcatheter Cardiovascular Therapeutics (TCT), and American College of Cardiology (ACC) conferences for reports on randomised trials comparing the zotarolimus-eluting Resolute Integrity stent or the everolimus-eluting Promus Element stent with another drug-eluting stent (we used as search terms "coronary" and "stent" in combination with one or more of the following: "zotarolimus", "everolimus", "Resolute Integrity", "Promus Element", "platinum", "randomised", and "randomized"). We learned that the third-generation Resolute Integrity stent has not yet been assessed by a randomised trial. The Promus Element stent has been assessed by two randomised clinical trials.[11,19] In the PLATINUM trial, Promus Element demonstrated non-inferiority versus the cobalt-chromium-based Xience V stent in low-to-moderate risk patients.[11] Preliminary data of the HOST-ASSURE trial in Korean all-comers showed very low event rates for both, Promus Element and the second-generation Resolute stent (presented at the ACC conference 2013);[19] but there are marked differences between the study populations of HOST-ASSURE and DUTCH PEERS, which are comprehensively discussed in the manuscript.

Interpretation

Third-generation permanent polymer zotarolimus and everolimus-eluting stents were similarly efficacious and safe with excellent clinical outcome in a real all-comers population. DUTCH PEERS is the first randomised trial to investigate the zotarolimus-eluting Resolute Integrity stent. Consequently, this is also the first randomised comparison between the Resolute Integrity and Promus Element stents. In addition, DUTCH PEERS provides the first randomised assessment of Promus Element stents in predominantly Caucasian all-comers.

Contributors
CvB, KT and MWZB designed the trial. CvB wrote the first draft of the report. KT, MKL and MML participated in drafting the report, and all other authors revised the draft. HS, MKL, MML and KT gathered and analysed data. KT and CJMD performed statistical analyses. CvB, HS, MKL, MML, CJMD and KT interpreted data and had full access to the data. All authors read and approved the final version of the manuscript. CvB, the principal investigator and corresponding author, had final responsibility for the decision to submit for publication.

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Conflicts of interest
CvB is a consultant to Abbott Vascular, Boston Scientific, and Medtronic, and he has received a travel grant from Biotronik and lecture fees from Biotronik and MSD. All other authors declare that they have no conflict of interest. The research department of Thoraxcentrum Twente has received educational and/or research grants funded by Abbott Vascular, Biotronik, Boston Scientific, and Medtronic.

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References

1. 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.
2. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013; 368: 254–65.
3. 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.
4. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: Evidence from a comprehensive network meta-analysis. Lancet 2012; 379: 1393–402.
5. 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.
6. 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.
7. 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.
8. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: The TWENTE trial. J Am Coll Cardiol 2012; 59: 1350–61.
9. 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.
10. 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: 557–62.
11. Stone GW, Teirstein PS, Meredith IT, 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: 1700–8.
12. Meredith IT, Whitbourn R, Scott D, 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: 84–90.
13. Turco MA. The Integrity bare-metal stent made by continuous sinusoid technology. Expert Rev Med Devices 2011; 8: 303–6.
14. Lee SW, Chan MP, Chan KK. Acute and 16-month outcomes of a new stent: the first-in-man evaluation of the Medtronic S9 (Integrity) stent. Catheter Cardiovasc Interv 2011; 78: 898–908.
15. Ormiston JA, Webber B, Webster MW. Stent longitudinal integrity bench insights into a clinical problem. JACC Cardiovasc Interv 2011; 4: 1310–7.
16. Abdel-Wahab M, Sulimov DS, Kassner G, Geist V, Toelg R, Richardt G. Longitudinal deformation of contemporary coronary stents: an integrated analysis of clinical experience and observations from the bench. J Interv Cardiol 2012; 25: 576–85.
17. Williams PD, Mamas MA, Morgan KP, et al. Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms. EuroIntervention 2012; 8: 267–74.
18. Mamas MA, Williams PD. Longitudinal stent deformation: insights on mechanisms, treatments and outcomes from the Food and Drug Administration Manufacturer and User Facility Device Experience database. EuroIntervention 2012; 8: 196–204.
19. Kim HS, Park KW, Kang SH, et al. Randomized comparison of PtCr-EES versus CoCr-ZES in all-comers receiving PCI: The HOST-ASSURE randomized trial. American College of Cardiology Scientific Sessions; San Francisco (CA), USA; March 9, 2013.

20. Tandjung K, Sen H, Lam MK, et al. 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.
21. 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.
22. Vranckx P, Cutlip DE, Mehran R, 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: 871–4.
23. Cohen J. Statistical power analysis for the behavioral sciences. 2nd Edition. Hillsdale, New Jersey: Lawrence Erlbaum; 1988.
24. 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.
25. Senn S. Seven myths of randomisation in clinical trials. Statist Med. 2013; 32: 1439–50.
26. 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.
27. Jensen LO, Thayssen P, Hansen HS, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 2012; 125: 1246–55.
28. Christiansen EH, Jensen LO, Thayssen P, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): A randomised non-inferiority trial. Lancet 2013; 381: 661–9.
29. Smits PC, Hofma S, Togni M, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet 2013; 381: 651–60.
30. De la Torre Hernandez JM, Garcia Camarero T, Lerena P, et al. A real all-comers randomized trial comparing Xience Prime and Promus Element stents. J Invasive Cardiol 2013; 25: 182–5.
31. Kereiakes DJ, Popma JJ, Cannon LA, et al. Longitudinal stent deformation: quantitative coronary angiographic analysis from the PERSEUS and PLATINUM randomised controlled clinical trials. EuroIntervention 2012; 8: 187–95.

Table 1. Baseline characteristics of patients and target lesions

	Zotarolimus-eluting stent (906 patients)	Everolimus-eluting stent (905 patients)
Age (years)	64 (56-72)	65 (57-72)
Men	665 (73·4)	675 (72·6)
Body mass index (kg/m²)*	27·1 (25·0–30·0)	27·2 (24·9–30·5)
Diabetes mellitus (any)	167 (18·4)	157 (17·3)
Insulin-dependent diabetes mellitus	63 (7·0)	50 (5·5)
Chronic renal failure†	35 (3·9)	28 (3·1)
Arterial hypertension	500 (55·2)	484 (53·5)
Hypercholesterolemia	418 (46·1)	430 (47·5)
Current smoker‡	213 (23·6)	231 (25·5)
Family history of coronary artery disease§	452 (50·1)	451 (49·9)
Previous myocardial infarction	207 (22·8)	190 (21·0)
Previous percutaneous coronary intervention	182 (20·1)	167 (18·5)
Previous coronary bypass surgery	84 (9·3)	89 (9·8)
Clinical syndrome at presentation:		
Stable angina pectoris	372 (41·1)	377 (41·7)
Unstable angina pectoris	113 (12·5)	132 (14·6)
Non-ST-elevation myocardial infarction	246 (27.2)	201 (22·2)
ST-elevation myocardial infarction	175 (19·3)	195 (21·5)
Acute coronary syndrome (any)	534 (58·9)	528 (58·3)
Left ventricular ejection fraction <30%¶	15 (1·7)	13 (1·4)
De novo coronary lesions only ‖	817 (90·2)	810 (89·5)
At least one chronic total occlusion	38 (4·2)	38 (4·2)
At least one bifurcation	244 (26·9)	221 (24·4)
At least one bifurcation with only main vessel stenting	186 (20·5)	174 (19·2)
At least one bifurcation with main vessel and side branch stenting	54 (6·0)	36 (4·0)
At least one in-stent restenosis	27 (3·0)	28 (3·1)
At least one small-vessel (RVD <2·75mm)	551 (60·8)	517 (57·1)
At least one lesion length >27mm	161 (17·8)	157 (17·3)
Glycoprotein IIb/IIIa antagonist	262 (28·9)	259 (28·6)
Number of lesions treated per patient:		
One lesion treated	668 (73·7)	688 (76·0)
Two lesions treated	191 (21·1)	182 (20·1)
Three or more lesions treated	47 (5·2)	35 (3·9)
	Zotarolimus-eluting stent (1205 lesions)	**Everolimus-eluting stent (1166 lesions)**
Left main stem	19 (1·6)	21 (1·8)
Left anterior descending artery	493 (40·9)	469 (40·2)
Left circumflex artery	304 (25·2)	280 (24·0)
Right coronary artery	378 (31·4)	379 (32·5)
Bypass graft	30 (2·5)	35 (3·0)
ACC/AHA lesion class:		
A	73 (6·1)	70 (6·0)
B1	339 (28·1)	331 (28·4)

B2	432 (35·9)	412 (35·3)
C	361 (30·0)	353 (30·3)
De novo lesion‖	1147 (95·2)	1103 (94·6)
Chronic total occlusion	38 (3·2)	39 (3·3)
In stent restenosis	28 (2·3)	28 (2·4)
Aorta-ostial lesion	59 (4·9)	65 (5·6)
Severe calcification	221 (18·3)	251 (21·5)
Bifurcated lesion	282 (23·4)	249 (21·4)
Thrombus present **	165 (13·7)	174 (14·9)
Total occlusion	167 (13·9)	153 (13·1)
Lesion length (mm)	13·63 (9·58-20·41)	13·46 (9·56-20·68)
Diameter of reference vessel (mm)	2·64 (2·25-3·06)	2·66 (2·27-3·07)
Minimum lumen diameter (mm)	0·88 (0·63-1·18)	0·88 (0·61-1·23)
Lumen diameter stenosis (%)	65·25 (53·83-75·84)	64·48 (53·92-76·17)
Preprocedural TIMI flow grade:		
0	175 (14·5)	155 (13·3)
1	40 (3·3)	39 (3·3)
2	128 (10·6)	125 (10·7)
3	862 (71·5)	847 (72·6)

Data are number (%) or median (IQR). RVD=reference vessel diameter.
ACC/AHA=American College of Cardiology/American Heart Association.
TIMI=thrombolysis in myocardial infarction.
* Out of 721 patients in the zotarolimus-eluting stent group and 703 patients in the everolimus-eluting stent group.
†Chronic renal failure defined by serum creatinine level ≥130 μmol/L.
‡ Out of 903 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group.
§ Out of 903 patients in the zotarolimus-eluting stent group and 902 patients in the everolimus-eluting stent group.
¶ Left ventricular ejection fraction assessed with ultrasound, MRI, or left ventricular angiography and data out of 900 patients in the zotarolimus-eluting stent group and 903 patients in the everolimus-eluting stent group.
‖ Including chronic total occlusion, but not grafts or in-stent restenosis.
** Thrombus triggering use of thrombus aspiration catheter.
Baseline patient characteristics did not differ significantly between treatment arms. P values were >0·10, except for clinical syndrome at presentation (p=0·07), bifurcation with main and side branch stenting (p=0·052), and severe calcification (p=0·052).

Table 2. Interventional procedure and results

	Zotarolimus-eluting stent (1205 lesions)	Everolimus-eluting stent (1166 lesions)	p value
Implantation of assigned stents only	1195 (99·2)	1161 (99·6)	0·22
Number of stents per patient	1·80 (1·08)	1·76 (1·10)	0·41
Number of stents per lesion	1·35 (0·68)	1·36 (0·70)	0·70
Total stent length per patient (mm) *	30 (18-50)	28 (20-48)	0·64
Total stent length per lesion (mm)	22 (18-36)	24 (16-38)	0·10
Maximum nominal stent diameter per lesion (mm) †	3·00 (2·50-3·50)	3·00 (2·50-3·50)	0·09
Direct stenting	352 (29·2)	326 (28·0)	0·50
Stent postdilation	887 (73·6)	920 (78·9)	0·002
Device success ‡	1194 (99·1)	1158 (99·3)	0·54
Lesion success §	1203 (99·8)	1162 (99·7)	0·39
Procedure success * ¶	884 (97·6)	890 (98·3)	0·25
Post-procedure minimum lumen diameter (mm)†	15·07 (10·58-21·17)	15·73 (10·86-21·63)	0·24
Post-procedure minimum lumen diameter stenosis (%) †	2·22 (1·80-2·64)	2·15 (1·78-2·58)	0·06
Acute lumen gain in segment (mm) †	1·27 (0·85-1·78)	1·24 (0·79-1·77)	0·38

Data are mean (SD), median (IQR) or number (%).
* Data per patient: out of 906 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group.
† Data on 1204 lesions in the zotarolimus-eluting stent group and 1165 lesions in the everolimus-eluting stent group.
‡ 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.

Table 3. One-year clinical outcomes

	Total patients (N=1810)	Zotarolim-us-eluting stent (905 patients)	Everolim-us-eluting stent (905 patients)	Relative Risk (95% CI)	p
Primary endpoint target vessel failure *	102 (5·6)	55 (6·1)	47 (5·2)	1·17 (0·80-1·71)	0·42
Death					
Any cause	34 (1·9)	22 (2·4)	12 (1·3)	1·83 (0·91-3·68)	0·08
Cardiac cause	25 (1·4)	15 (1·7)	10 (1·1)	1·50 (0·67-3·32)	0·31
Non-cardiac cause	9 (0·5)	7 (0·8)	2 (0·2)	3·50 (0·73-16·80)	0.18
Target vessel-related myocardial infarction					
Any	32 (1·8)	20 (2·2)	12 (1·3)	1·67 (0·82-3·39)	0·15
Q-wave	5 (0·3)	3 (0·3)	2 (0·2)	1·50 (0·25-8·96)	0·65
Non-Q-wave	27 (1·5)	17 (1·9)	10 (1·1)	1·70 (0·78-3·69)	0·18
Periprocedural (<48h from index procedure)	30 (1·7)	19 (2·1)	11 (1·2)	1·74 (0·83-3·61)	0·14
Non-periprocedural (>48h from index procedure)	2 (0·1)	1 (0·1)	1 (0·1)	1·00 (0·06-15·96)	1·00
Target vessel revascularisation, any	53 (2·9)	26 (2·9)	27 (3·0)	0·96 (0·57-1·64)	0·89
Target vessel revascularisation, clinically indicated	50 (2·8)	24 (2·7)	26 (2·9)	0·92 (0·53-1·60)	0·77
Target lesion revascularisation, clinically indicated	40 (2·2)	20 (2·2)	20 (2·2)	1·00 (0·54-1·85)	1·00
Death from cardiac cause or target vessel-related myocardial infarction	56 (3·1)	34 (3·8)	22 (2·4)	1·55 (0·91-2·62)	0·10
Target lesion failure †	92 (5·1)	51 (5·6)	41 (4·5)	1·24 (0·83-1·86)	0·29
Major adverse cardiac events ‡	102 (5·6)	58 (6·4)	44 (4·9)	1·32 (0·90-1·93)	0·15
Patient-oriented composite endpoint §	156 (8·6)	84 (9·3)	72 (8·0)	1·17 (0·86-1·58)	0·32
Stent thrombosis (0-360 days)					
Definite, any (0-360 days)	9 (0·5)	3 (0·3)	6 (0·7)	0·50 (0·13-2·00)	0·51
Definite, acute (0-1 day)	3 (0·2)	2 (0·2)	1 (0·1)	2·00 (0·18-22·02)	0·56
Definite, subacute (2-30 days)	3 (0·2)	0	3 (0·3)	<0·001	0·08
Definite, late (31-360 days)	3(0·2)	1 (0·1)	2 (0·2)	0·50 (0·05-5·50)	0·56
Definite or probable, any (0-360 days)	13 (0·7)	5 (0·6)	8 (0·9)	0·63 (0·21-1·90)	0·40
Possible, any (0-360 days)	14 (0·8)	8 (0·9)	6 (0·7)	1·33 (0·50-3·83)	0·59
Definite, probable, or possible, any (0-360 days)	27 (1·5)	13 (1·4)	14 (1·5)	0·93 (0·44-1·96)	0·85

Data are number of patients (%).

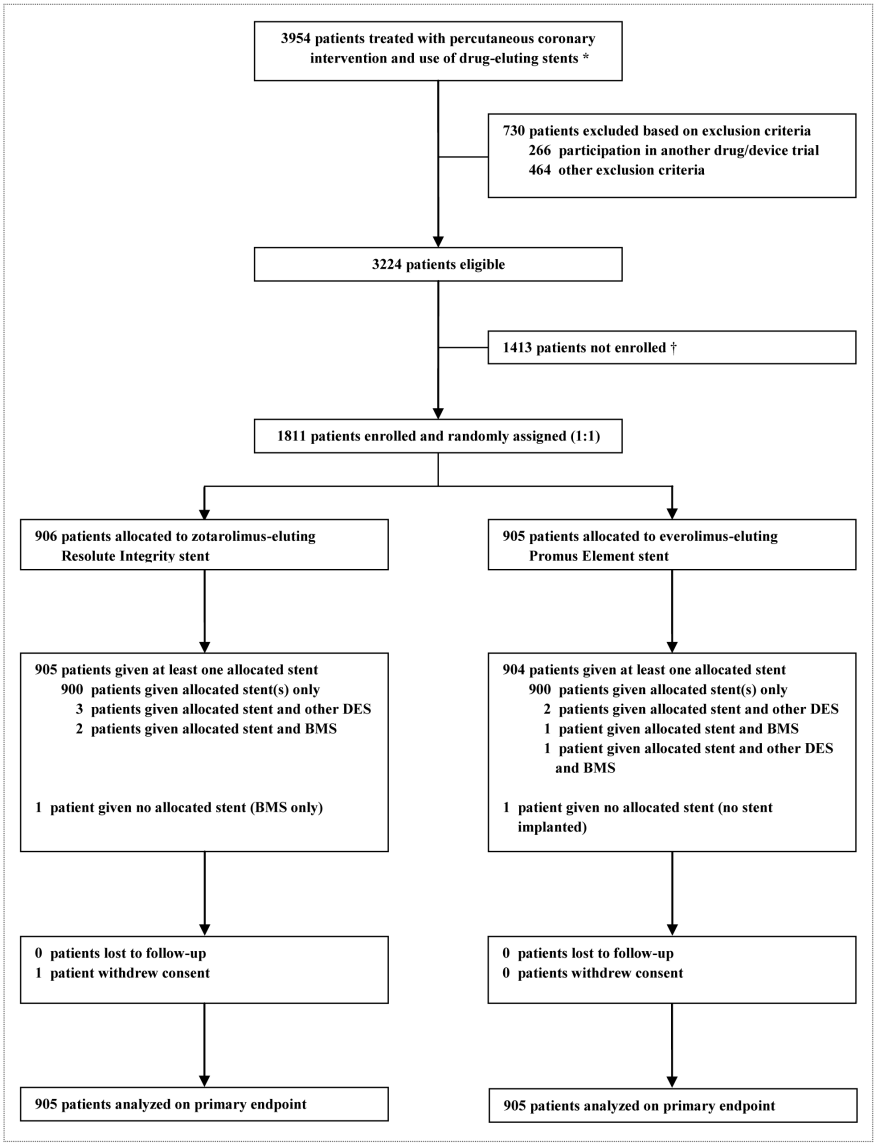
* Primary endpoint target vessel failure is a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularisation.

† Target lesion failure is a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target lesion revascularisation.

‡ Major adverse cardiac events is a composite of all cause death, any myocardial infarction, emergent coronary-artery bypass surgery, or clinically indicated target lesion revascularisation.

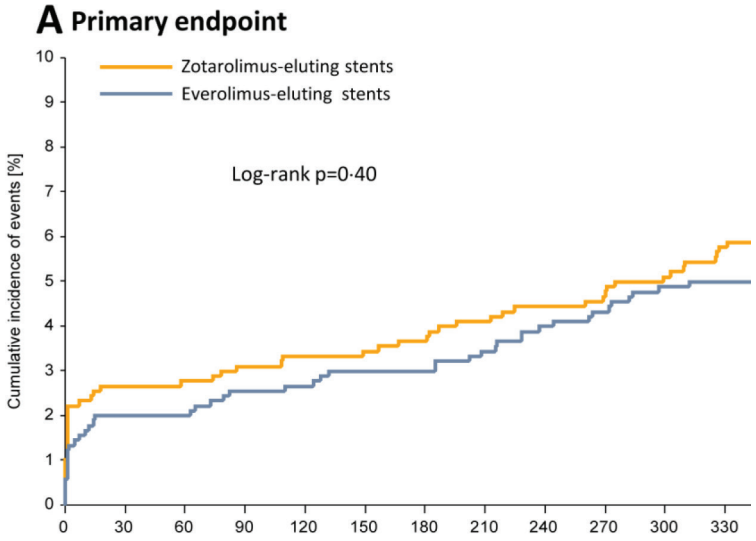
§ Patient-oriented composite end-point is a composite of all cause death, any myocardial infarction, or any revascularisation.

Figure 1. Trial profile



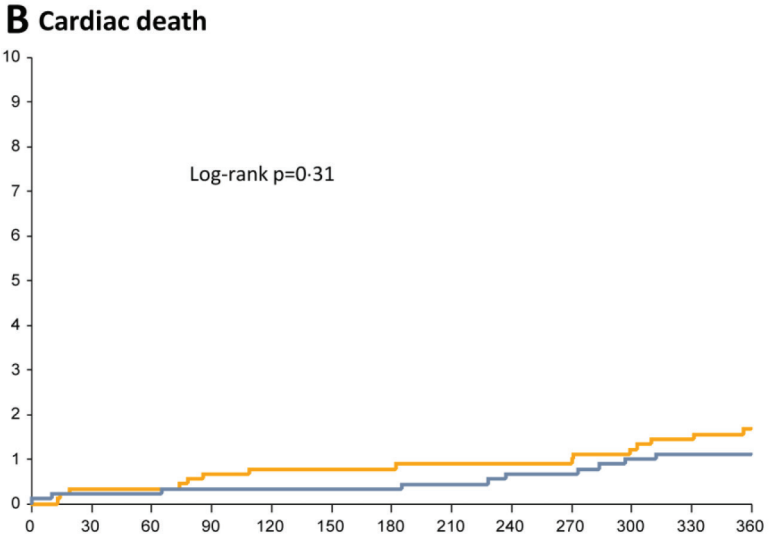
Of the 3224 eligible patients, 1811 patients (56%) were enrolled and randomly assigned to stent types. *Total number of patients who had percutaneous coronary intervention during study period with use of drug-eluting stents, irrespective of inclusion and exclusion criteria. †We have no reliable data on reasons not to enroll eligible patients. BMS=bare metal stent. DES=drug-eluting stent.

Figure 2. Kaplan-Meier cumulative event curves for the primary endpoint target vessel failure and its individual components at 12 months

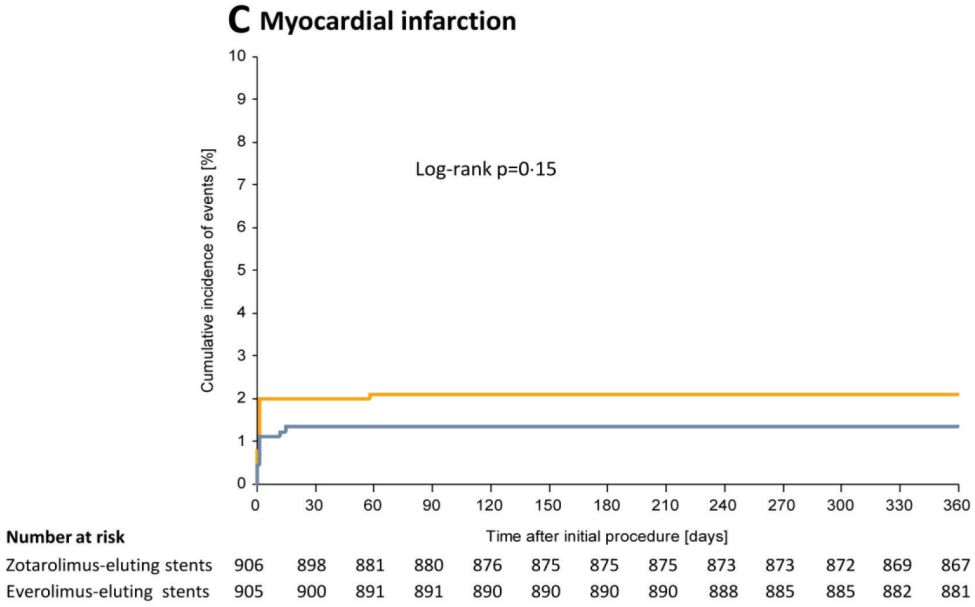


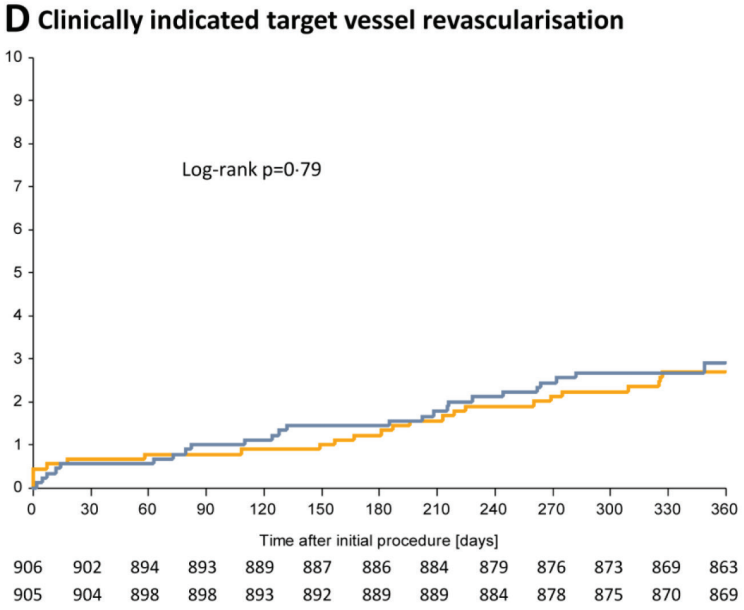
Number at risk

Zotarolimus-eluting stents	906	896	877	876	872	870	869	867	862	859	856	852
Everolimus-eluting stents	905	900	887	887	882	881	878	878	873	867	864	859



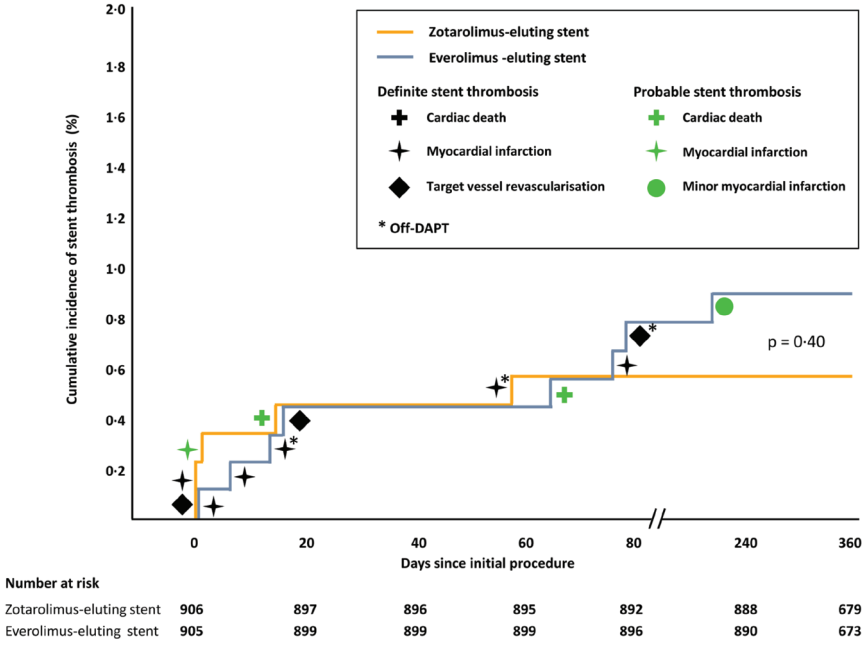
906	906	899	899	895	894	894	894	892	892	891	888	886
905	904	903	903	902	902	902	902	900	897	897	894	893





The primary endpoint target vessel failure(A) is a composite of cardiac death(B), target vessel-related myocardial infarction(C), and clinically indicated target vessel revascularisation(D). Myocardial infarction=target vessel-related myocardial infarction.

Figure 3. Cumulative incidence of definite or probable stent thrombosis



Symbols indicate the hierarchically highest adverse events, associated with stent thromboses.
Black symbols signify definite stent thromboses, of which none was fatal.
Green symbols signify probable stent thromboses.
In patients treated with zotarolimus-eluting Resolute Integrity stents, there was only one single late, definite stent thrombosis in a patient who was not on dual anti-platelet therapy (discussed below). In patients treated with everolimus-eluting Promus Element stents, beyond 3 months there was no definite and only a single probable stent thrombosis based on a minor myocardial infarction (significant elevation of cardiac troponin levels but no significant elevation of creatine kinase levels).
*Off-DAPT indicates stent thromboses in patients not being on dual anti-platelet therapy (DAPT), which consisted of aspirin ≥80mg daily and an adequate dose of a P2Y12 receptor antagonist (generally clopidogrel 75mg daily). Reasons for not being on dual anti-platelet therapy were: clopidogrel was stopped without substitution because of a novel allergic reaction (myocardial infarction on day 12); non-compliance to the prescribed medication (myocardial infarction on day 58); and per-protocol cessation of aspirin after one month of dual anti-platelet therapy because of chronic oral anticoagulation therapy (target vessel revascularisation on day 79).

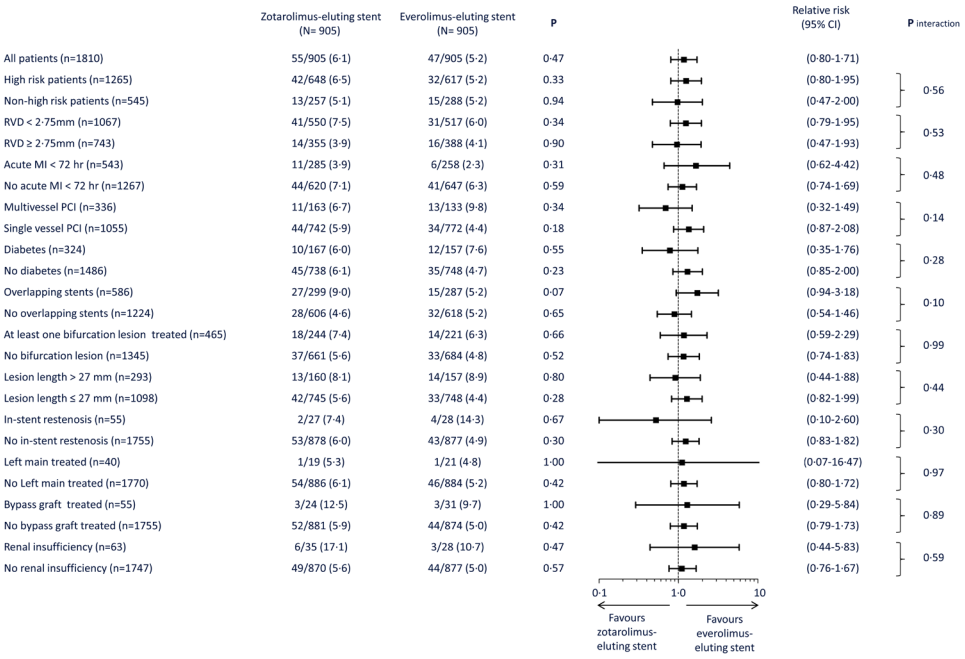
Web Appendix I:
Lesion-based analysis of procedural details and results with analyses corrected for intra-patient correlation with generalised estimating equations

	Zotarolim-us-eluting stent (1205 lesions)	Everolim-us-eluting stent (1166 lesions)	p value
Implantation of assigned stents only	1195 (99·2)	1161 (99·6)	0·36
Number of stents per lesion	1·35 (0·68)	1·36 (0·70)	0·70
Total stent length per lesion (mm)	22 (18-36)	24 (16-38)	0·20
Maximum nominal stent diameter per lesion (mm) *	3·00 (2·50-3·50)	3·00 (2·50-3·50)	0·10
Direct stenting	352 (29·2)	326 (28·0)	0·81
Stent postdilation	887 (73·6)	920 (78·9)	0·01
Device success †	1194 (99·1)	1158 (99·3)	0·79
Lesion success ‡	1203 (99·8)	1162 (99·7)	0·40
Post-procedure minimum lumen diameter (mm)†	2·22 (1·80-2·64)	2·15 (1·78-2·58)	0·11
Post-procedure minimum lumen diameter stenosis (%) *	15·07 (10·58-21·17)	15·73 (10·86-21·63)	0·40
Acute lumen gain in segment (mm) *	1·27 (0·85-1·78)	1·24 (0·79-1·77)	0·41

Data are mean (SD), median (IQR) or number (%). All lesion based analyses were corrected for intrapatient correlation with Generalized Estimating Equations.
* Data on 1204 lesions in the zotarolimus-eluting stent group and 1165 lesions in the everolimus-eluting stent group.
† 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.

Web Appendix II:

Subgroup analysis for the primary endpoint target vessel failure at 12 months



The primary endpoint target vessel failure is a composite of cardiac death, target vessel-related myocardial infarction, and clinically indicated target vessel revascularisation. MI=myocardial infarction. PCI=percutaneous coronary intervention. RVD=reference vessel diameter.

High risk patients comprised: patients with renal failure, heart failure, recent MI, more than 1 lesion per vessel treated, more than 2 vessels treated, long lesions, bifurcation lesions, graft lesions, in-stent restenotic lesions, unprotected left main stem lesions, and total occlusions.

Web Appendix III:
One-year clinical outcomes with HR, 95%CI and log-rank P value

	Zotarolim-us-eluting stent (906 patients)	Everolim-us-eluting stent (905 patients)	Hazard ratio	Log rank P value
Primary endpoint target vessel failure *	55 (6·1)	47 (5·2)	1·18 (0·80-1·74)	0·40
Death				
Any cause	22 (2·5)	12 (1·3)	1·84 (0·91-3·72)	0·08
Cardiac cause	15 (1·7)	10 (1·1)	1·51 (0·68-3·36)	0·31
Non-cardiac cause	7 (0·8)	2 (0·2)	3·52 (0·73-16·93)	0·09
Target vessel-related myocardial infarction				
Any	20 (2·2)	12 (1·3)	1·67 (0·82-3·42)	0·15
Q-wave	3 (0·3)	2 (0·2)	1·50 (0·25-8·98)	0·66
Non-Q-wave	17 (1·9)	10 (1·1)	1·70 (0·78-3·72)	0·18
Periprocedural (<48h from index procedure)	19 (2·1)	11 (1·2)	1·73 (0·82-3·63)	0·15
Non-periprocedural (>48h from index procedure)	1 (0·1)	1 (0·1)	1·01 (0·06-16·15)	0·99
Target vessel revascularisation, any	26 (2·9)	27 (3·0)	0·97 (0·56-1·66)	0·90
Target vessel revascularisation, clinically indicated	24 (2·7)	26 (2·9)	0·93 (0·53-1·62)	0·79
Target lesion revascularisation, clinically indicated	20 (2·2)	20 (2·2)	1·01 (0·54-1·87)	0·99
Death from cardiac cause or target vessel-related myocardial infarction	34 (3·8)	22 (2·4)	1·56 (0·91-2·67)	0·10
Target lesion failure †	51 (5·7)	41 (4·6)	1·26 (0·83-1·89)	0·28
Major adverse cardiac events ‡	58 (6·4)	44 (4·9)	1·33 (0·90-1·97)	0·15
Patient-oriented composite endpoint §	84 (9·3)	72 (8·0)	1·16 (0·85-1·59)	0·35
Stent thrombosis (0-360 days)				
Definite, any (0-360 days)	3 (0·3)	6 (0·7)	0·50 (0·13-2·00)	0·32
Definite, acute (0-1 day)	2 (0·2)	1 (0·1)	2·00 (0·18-22·03)	0·56
Definite, subacute (2-30 days)	0	3 (0·3)	0·02 (<0·01-164·48)	0·08
Definite, late (31-360 days)	1 (0·1)	2 (0·2)	0·50 (0·05-5·55)	0·57
Definite or probable, any (0-360 days)	5 (0·6)	8 (0·9)	0·63 (0·21-1·91)	0·41
Possible, any (0-360 days)	8 (0·9)	6 (0·7)	1·33 (0·47-3·87)	0·58
Definite, probable, or possible, any (0-360 days)	13 (1·4)	14 (1·6)	0·93 (0·44-1·98)	0·85

Data are number of patients (%).
* Primary endpoint target vessel failure is a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularisation.
† Target lesion failure is a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target lesion revascularisation.
‡ Major adverse cardiac events is a composite of all cause death, any myocardial infarction, emergent coronary-artery bypass surgery, or clinically indicated target lesion revascularisation.
§ Patient-oriented composite end-point is a composite of all cause death, any myocardial infarction, or any revascularisation.

Web Appendix IV
Longitudinal stent deformation, classified according to presumed cause

Case	Notified by operator	Notified by analyst	PDSL*	Angiographic projection	Stent size	Vessel and segment	ACC/AHA lesion class	Lesion characteristics	Age	Gender	Post–dilation	Procedural consequences	Consecutive adverse events
Deformation following attempts to re-cross implanted stent													
1	x	x	0·94	RSO	3·0x 38 mm	LAD, mid	C	bifurcation lesion	62	M	x	additional proximal stent	none
2	–	x	0·83	RAO	2·5x 32 mm	RCA, mid	C	severe calcification	77	F	x	additional proximal stent	none
3	x	x	0·74	Caudal	3·5x 24 mm	LAD, prox.	C	bifurcation lesion	48	M	x	additional proximal stent	none
4	x	x	0·79	RSO	2·25x 16 mm	LAD, prox.	C	bifurcation lesion	63	F	–	additional proximal stent	none
Deformation following very oversized stent postdilation													
5	–	x	0·94	RSO	2·25x 22 mm	LAD, prox.	C	severe calcification	74	M	x	additional proximal stent	none
6	x	x	0·87	LIO	3·5x 16 mm	Left main	B2	bifurcation lesion	36	M	x	postdilation of stent	none
Deformation following contact of stent with guiding catheter or balloon catheter													
7	–	x	0·81	LSO	2·5x 32 mm	RCA, distal	C	bifurcation lesion	41	M	x	additional proximal stent	none
8	x	x	0·91	RSO	3·0x12 mm	LAD, prox.	C	moderate calcification	53	M	x	additional proximal stent	none
9	x	x	0·84	LAO	3·0x24 mm	RCA, mid	C	severe calcification	73	M	x	postdilation of stent	none

Longitudinal stent deformation (n=9) as only noted in the everolimus-eluting Promus Element stent group. Deformations were located exclusively in the proximal stent entrance.

ACC/AHA=American College of Cardiology/American Heart Association. F=female. LAD=left anterior descending artery. LAO=left anterior oblique. LIO=left inferior oblique. M=male. PDSL=post-deployment stent length ratio. Prox.=proximal. RAO=Right anterior oblique. RCA=right coronary artery. RSO=right superior oblique. RIO=right inferior oblique. * Post-deployment stent length ratio (PDSL) is defined as final stent length divided by stent length immediately after deployment.

Chapter 16

Safety and Efficacy Outcomes of First and Second-Generation Durable Polymer Drug-Eluting Stents and Biodegradable Polymer Biolimus-Eluting Stents in Clinical Practice:

a Comprehensive Network Meta-Analysis of 60 Randomised Trials Comprising 63,242 Patients

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Abstract

Objectives To investigate the safety and efficacy of durable polymer drug-eluting stents (DES) and biodegradable polymer biolimus-eluting stents (BP-BES).
Design Network meta-analysis of randomised controlled trials (RCTs).
Data sources and study selection MEDLINE, Google Scholar, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) database search for RCTs comparing at least two of the following DES: durable polymer sirolimus and paclitaxel-eluting (sirolimus-ES, paclitaxel-ES), newer durable polymer everolimus-eluting (everolimus-ES), zotarolimus-eluting Endeavor and Resolute (Endeavor zotarolimus-ES, Resolute zotarolimus-ES), and biodegradable polymer biolimus-eluting (biodegradable polymer biolimus-ES) stents.
Primary outcomes Safety (death, myocardial infarction (MI), definite-or-probable stent thrombosis (ST)) and efficacy (target lesion and target vessel revascularisation) assessed at ≤ 1 year and beyond.
Results Sixty RCTs were compared involving 63,242 DES-treated patients with stable coronary artery disease or acute coronary syndrome. At 1 year, no differences in mortality were observed among devices. Resolute zotarolimus-ES, everolimus-ES, Endeavor zotarolimus-ES and sirolimus-ES, but not biodegradable polymer biolimus-ES, significantly reduced the odds of MI by 29-34% compared to paclitaxel-ES. Compared to Everolimus-ES, biodegradable polymer biolimus-ES significantly increased the odds of MI by 29%, while Endeavor zotarolimus-ES and paclitaxel-ES significantly increased the odds of stent thrombosis. All investigated DES were similar with regards to efficacy endpoints, except for Endeavor zotarolimus-ES and paclitaxel-ES which significantly increased the odds of target lesion- and target vessel revascularisations, as compared to other devices. Direction of results beyond 1 year did not diverge from the ≤ 1-year follow-up. Bayesian probability curves showed a gradient in the magnitude of effect, with everolimus-ES and Resolute zotarolimus-ES offering the highest safety profiles.
Conclusions The newer durable polymer Everolimus-ES and Resolute zotarolimus-ES and the biodegradable polymer biolimus-ES maintain the efficacy of Sirolimus-ES; however, for safety endpoints, differences become apparent with Everolimus-ES and Resolute zotarolimus-ES emerging as the safest stents to date.

Introduction

The first-generation of coronary drug-eluting stents (DES) has significantly reduced the need for repeat revascularisation compared to bare metal stents (BMS) and has led to the widespread use of DES worldwide. However, concerns have emerged regarding late and very late thrombotic events, in turn associated with a high rate of death and myocardial infarction (MI)[1, 2]. Such events have been attributed to incomplete re-endothelialisation caused by drug-induced inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis and, importantly, polymer-induced prolonged vessel wall inflammation[3].

To improve the safety of first-generation DES, new devices have been developed, employing either biocompatible durable polymers combined with new metal alloys or biodegradable polymers combined with stainless steel platforms; both have been extensively tested in randomised controlled trials (RCTs). The everolimus-eluting second-generation durable polymer DES (everolimus-ES) has been found safer than BMS and first-generation DES[4-6]. On the other hand, two non-inferiority trials comparing the most investigated biodegradable polymer device, the biolimus-eluting stent (biodegradable polymer biolimus-ES), to the first-generation sirolimus-eluting stent (sirolimus-ES) have provided contradictory results at 1 year[7, 8], with one trial showing non-inferiority and the other failing to do so, while two other trials[9, 10] have shown non-inferiority of biodegradable polymer biolimus-ES compared to everolimus-ES. None of these trials was powered for separate safety and efficacy endpoints.

In light of these findings, the safety and efficacy of the biodegradable polymer devices compared to: 1) first-generation paclitaxel-eluting stents (paclitaxel-ES) and sirolimus-ES, and 2) second-generation durable polymer zotarolimus-eluting Endeavor and Resolute (Endeavor zotarolimus-ES, Resolute zotarolimus-ES) and everolimus-ES, are currently unclear. Therefore we performed a comprehensive network meta-analysis of all relevant DES data published and presented to date in order to gain an evidence-based understanding of the impact of each of these devices, as compared to first-generation DES and among each-other, on major safety and efficacy outcomes.

Methods

Study design and endpoint selection

We compared the safety and efficacy of DES currently approved by the Food and Drug Administration (FDA), i.e., first- and second-generation durable polymer DES, as well as biodegradable polymer biolimus-ES. Biodegradable polymer biolimus-ES were selected among the different types of biodegradable polymer stents for two reasons: 1) they have the most robust trial data, 2) all available biodegradable polymer biolimus-ES prototypes share a stainless steel platform, similar strut thickness and the

same abluminal biodegradable polymer (poly-L-lactic acid), and therefore are generally considered equivalent. In light of the conflicting 1-year outcome results, the primary pre-specified analyses were up to 1-year follow-up; longer follow-ups, however, were also analysed. To provide the most robust evidence, we included RCTs enrolling at least 100 patients and with a minimum follow-up of 6 months.

To appreciate the comparative effect of different DES types within their class, BMS were not included. The following eluting stents were included: first-generation durable polymer sirolimus-ES and paclitaxel-ES, 2) second-generation durable polymer everolimus-ES, Endeavor zotarolimus-ES and Resolute zotarolimus-ES, and 3) biodegradable polymer biolimus-ES. Prespecified safety endpoints comprised overall mortality, MI, and definite-or-probable stent thrombosis (ST) according to the definition criteria of the Academic Research Consortium[11]. Efficacy endpoints were target lesion revascularisation (TLR) and target vessel revascularisation (TVR).

Although the number of trials comparing BP-BES to first- and second-generation DES reporting results beyond 1-year was limited, we additionally performed such an analysis (presented as supplementary material).

Data source and search strategy

Established methods were used in adherence to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses in healthcare interventions[12]. Relevant RCTs were searched until May 15, 2013, through MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar and EMBASE databases and through www.tctmd.com, www.clinicaltrials.gov, www.clinicaltrialresults.org and www.cardiosource.com web sites; documents accessible through the FDA website were scrutinised as well. The following keywords were used: "randomised trials", "drug-eluting stent", "sirolimus stent", "paclitaxel stent", "everolimus stent", "zotarolimus stent", " Endeavor zotarolimus-stent", "Resolute zotarolimus-stent", "biodegradable polymer stent", "bioabsorbable polymer stent", "biolimus stent". No language, date, or publication status restrictions were imposed. For each RCT, the most updated or most inclusive data were used.

Data collection and quality assessment

Identified trials were critically and independently evaluated by 4 investigators (E.P.N., K.T., B.C., M.K.) with regard to patient population, treatment, protocol and endpoint selection. Divergences were resolved by consensus. The RCTs' potential risk of bias was independently appraised by 2 investigators (B.C., K.T.) according to the Cochrane Collaboration guidelines (adequate sequence generation, allocation concealment, blinded adjudication of events)[12]; discrepancies were resolved by discussion with a third investigator (E.P.N.); RCTs with high or unclear risk of bias for any of these components were regarded as trials with a high risk of bias.

Statistical analyses

Network meta-analysis methods on all available treatment comparisons were used to provide the most comprehensive evidence, incorporating direct within-trial comparisons between two treatments (e.g., A vs B) and indirect comparisons from trials having one treatment in common (e.g., A vs C using trials comparing A vs B and B vs C)[13]. Outcome analyses were compared by odds ratios (ORs) and 95% credible intervals (CrIs) using a bayesian hierarchical random-effects model that takes into account multi-arm trials. The random-effects rather than the fixed-effect model was adopted, as the most appropriate and conservative analysis to account for differences among trials. Additional sensitivity analyses were conducted by repeating the main computations using the fixed-effect method and by excluding trials with high risk of bias.

To further corroborate the robustness of the data and make probability inferences, bayesian probability curves were generated for each stent taking sirolimus-ES as reference; rather than focusing on a single probability value, these curves provide a ranking of competing stent treatments with respect to overall safety and efficacy. Median rates of safety and efficacy outcomes, with corresponding CrIs, were also calculated from the original trials in the network meta-analysis.

Heterogeneity was defined as the variability of results across trials over and above chance, with Tau^2 <0.04 indicating low and Tau^2 >0.4 a high level of heterogeneity. Potential inconsistency of the network, defined as the variability of results across the direct and indirect evidence comparisons, was evaluated by the node-split method and the relative bayesian p-value, measuring agreement between direct and indirect evidence for each split node[14]. Inconsistency was additionally evaluated by inspection of the goodness of fit of the model to the data, using residual deviance; the model was considered to provide an adequate fit when the mean of the residual deviance was similar to the number of data points of the model.

For beyond 1-year outcomes, given the quite variable length of follow-up for each of these trials, the rate of outcome per 100 patient*years was used to obtain the log rate ratios (RR) of one stent compared to another. Rates per unit of time, rather than number of events, were deemed the most appropriate outcome measure for long-term analyses as they incorporate the duration of the trials, which was variable. A Poisson regression model was fitted, because this analysis explicitly exploits differences in follow-up among studies, thus maximizing precision[15]. Extent of small study effects/publication bias was assessed by visual inspection of funnel plots. All analyses were based on noninformative prior findings for effect sizes and precision, which yield results that are comparable to those obtained from conventional statistical analyses. Convergence and lack of autocorrelation were checked and confirmed. In the bayesian framework, the results for which the CrI of the OR or RR did not include the unit value were regarded as significant. Data were analyzed according to the intention-to-treat principle. All analyses were conducted using WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and MIX 2.0. Pro for Microsoft Excel, version 2.0.1.2, (BiostatXL, California, USA).

Results

Study selection and patient population

The flow diagram of the analysis, the full electronic MEDLINE database search, and the inclusion/exclusion criteria and risk of bias of the included RCTs are shown in the supplementary material (Figure S1, Table S1 and Table S2). Sixty trials [7-10, 16-88], comprising a total of 63,242 randomised patients, met the inclusion criteria and entered the final analysis; information on stent comparators, follow-up duration and investigated populations is displayed in Table 1. In general, the included populations were high risk groups, with most trials enrolling both stable coronary artery disease (53.7%) and acute coronary syndromes (46.3%). The large majority of included trials were multicenter, with a low risk of bias. The following studies or arms were excluded: i) trials testing 2 stents eluting the same drug but differing in their design[89-91]; ii) trials with different stent metal platforms[92-96]; iii) post-hoc analyses or substudies[97-103]; iv) the BMS arm or polymer free arm of 6 three-arm trials[16, 17, 38, 39, 54, 104]; v) studies not reporting clinical outcomes[105]; vi) arms which did not include treatments in the network. The evidence network of direct comparisons is shown in Figure 1.

One-year outcomes

Safety profile

A total of 46 studies (N = 48,908) contributed to the analysis of 1-year mortality. Second-generation durable polymer DES and biodegradable polymer biolimus-ES were associated with mortality outcomes that did not differ significantly from those of paclitaxel-ES and sirolimus-ES (Figure 2), although median 1-year rates varied almost two-fold, ranging from 1.80% to 3.05% (numerical gradient: Resolute zotarolimus-ES < everolimus-ES < sirolimus-ES < biodegradable polymer biolimus-ES < paclitaxel-ES < Endeavor zotarolimus-ES) (Table 2).

Forty-six studies (N = 51,578) contributed to the analysis of 1-year MI. In comparison to paclitaxel-ES, all DES except biodegradable polymer biolimus-ES significantly reduced the odds of MI, particularly Resolute zotarolimus-ES and everolimus-ES (OR 0.66 [95% CrI 0.46 to 0.91] and 0.67 [0.53 to 0.81], respectively) (Figure 3). Compared to sirolimus-ES, the odds of MI were not significantly reduced by second-generation DES, although everolimus-ES and Resolute zotarolimus-ES, conversely to biodegradable polymer biolimus-ES, showed numerical reductions (Figure 3). When new-generation DES were compared among each other, biodegradable polymer biolimus-ES yielded a significant increase in the odds of MI (OR 1.29 [CrI 1.02 to 1.69]) compared to everolimus-ES. Lowest median MI rates were observed with Resolute zotarolimus-ES and everolimus-ES (Table 2). There was no evidence of high heterogeneity among trials for either death (Tau^2= 0.007) or MI (Tau^2= 0.008) outcomes (supplementary Table 3).

Median stent thrombosis rates were approximately halved with everolimus-ES, Resolute zotarolimus-ES, biodegradable polymer biolimus-ES

and sirolimus-ES compared to paclitaxel-ES and Endeavor zotarolimus-ES (~1% vs ~2.5%) (Table 2). everolimus-ES provided significant reductions of the odds of stent thrombosis at 1 year compared to paclitaxel-ES (OR 0.37 [CrI 0.18 to 0.65]) and a numerical reduction compared to sirolimus-ES (OR 0.63 [CrI 0.33 to 1.06]) (Figure 4); compared with everolimus-ES, Endeavor zotarolimus-ES yielded a significant increase in the odds of stent thrombosis (OR 3.13[CrI 1.15 to 8.89]). There was no evidence of high heterogeneity among trials for ST (Tau^2= 0.21; supplementary Table S3).

Efficacy profile

Forty-four trials including 49,527 patients contributed to the analysis of target lesion revascularisation at 1 year. sirolimus-ES, everolimus-ES, biodegradable polymer biolimus-ES and Resolute zotarolimus-ES significantly reduced the odds of target lesion revascularisation by 46% to 87% in comparison to paclitaxel-ES, and by 59% to 160% in comparison to Endeavor zotarolimus-ES (Figure 5). Compared to sirolimus-ES, the same devices (everolimus-ES, Resolute zotarolimus-ES and biodegradable polymer biolimus-ES) showed a similar degree of efficacy, without significant differences among them (Figure 5). The median target lesion revascularisation rate was ~3% with everolimus-ES, biodegradable polymer biolimus-ES, sirolimus-ES and Resolute zotarolimus-ES vs 5.92% with paclitaxel-ES and 7.52% with Endeavor zotarolimus-ES (Table 2).

Target vessel revascularisation results at 1 year were consistent with target lesion revascularisation outcomes. Compared to sirolimus-ES, everolimus-ES, Resolute zotarolimus-ES and biodegradable polymer biolimus-ES provided similar efficacy profiles, whereas Endeavor zotarolimus-ES and paclitaxel-ES were associated with higher odds of target vessel revascularisation (OR 1.67 [CrI 1.08 to 2.58] and 1.47 [CrI 1.14 to 1.90], respectively) (Figure 6). There was no evidence of high heterogeneity among trials for both target lesion- (Tau^2= 0.13) and target vessel revascularisation (Tau^2= 0.12) outcomes (supplementary Table S3).

Posterior probabilities

Figure 7 shows the posterior probability curves for each DES and for each outcome, with sirolimus-ES as reference treatment. These curves allow probability inferences associated with a specific threshold of risk (odds ratio). Thus, compared with sirolimus-ES, the curves show a probability of 65% for Resolute zotarolimus-ES to reduce the odds of mortality by at least 20% (odds ratio 0.80); a probability of 56% and 49% for Resolute zotarolimus-ES and everolimus-ES, respectively, to reduce the odds of myocardial infarction by at least 10% (0.90); and a probability of 81% with everolimus-ES and 51% with Resolute zotarolimus-ES to reduce the odds of stent thrombosis by at least 20%. Compared with sirolimus-ES, Resolute zotarolimus-ES showed a 30% probability to reduce target vessel revascularisation and a 21% probability to reduce target lesion revascularisation by at least 20% (odds ratio 0.80), which was comparable with the 17% probability seen with everolimus-ES and biodegradable polymer biolimus-ES.

Outcomes beyond one-year

Twenty-four trials (N= 38,097) contributed to the > 1-year analysis (Table 1). Consistently with 1-year mortality results, long-term mortality with first- and second-generation durable polymer DES and with biodegradable polymer biolimus-ES did not differ significantly among the different DES (supplementary Table S4).

Consistently with 1-year outcomes, in comparison to paclitaxel-ES, Endeavor zotarolimus-ES, everolimus-ES and Resolute zotarolimus-ES (similarly to Sirolimus-ES) provided a 31% to 37% significant decrease in MI. Everolimus-ES was associated with a significant 56% reduction of the rate of definite-or-probable stent thrombosis against first-generation sirolimus-ES. Similarly to the 1-year outcomes, as compared to first-generation paclitaxel-ES, newer-generation DES offered significantly lower rates of revascularisation, except for Endeavor zotarolimus-ES which was associated with a 110% increase as compared to everolimus-ES (supplementary Table S4).

Overall fit of the model and additional analyses

Evaluation of the goodness of fit for the various models showed adequate fit for the various analyses. Heterogeneity among the trials was low-to-moderate for all outcomes (supplementary Table 3). Sensitivity analyses based on the fixed-effect model did not significantly change the results of the meta-analysis (supplementary Table S5). Visual inspection of funnel plots did not suggest any small study effects or publication bias (supplementary Figure S2A-D). Exclusion of trials with high risk of bias (supplementary Table S6) yielded results largely consistent with the overall results. Finally, there was no evidence of inconsistency between direct and indirect estimates, with bayesian p-values ranging from 0.06 to 1 (supplementary Table S7).

Discussion

This large meta-analysis, with 63 242 patients, examined the safety and efficacy profile of second generation durable polymer drug eluting stents (DES) and biodegradable polymer biolimus-ES compared with first generation DES and with each other. Second generation durable polymer everolimus-ES and Resolute zotarolimus-ES, the first generation sirolimus-ES, and the biodegradable polymer biolimus-ES were similar to each other with regards to their efficacy and significantly better than Endeavor zotarolimus-ES and paclitaxel-ES with regards to coronary revascularisations. There was a safety gradient, with everolimus-ES and Resolute zotarolimus-ES resulting in lowest rates of death and myocardial infarction and, conversely, biodegradable polymer biolimus-ES, Endeavor zotarolimus-ES, and paclitaxel-ES being associated with significantly increased odds of myocardial infarction or stent thrombosis compared with everolimus-ES.

Possibly, one of the most important findings of this study is the significant increase in the odds of MI with biodegradable polymer biolimus-ES, as compared to durable polymer everolimus-ES. To date

biodegradable polymer biolimus-ES have been perceived to be safer than first-generation sirolimus-ES and non-inferior to second-generation everolimus-ES, mainly based on results from individual trials powered only for composite endpoints of safety and efficacy.[7, 9, 10] We analysed single (instead of composite) endpoints of safety and have provided new insights suggesting that biodegradable polymer biolimus-ES is associated with similar (not higher) safety compared with the first generation sirolimus-ES and with a significantly higher rate of myocardial infarction compared with everolimus-ES. Indeed, the second generation durable polymer everolimus-ES and Resolute zotarolimus-ES were associated with the most favourable safety profile compared with not only the first generation durable polymer paclitaxel-ES but also the second generation Endeavor zotarolimus-ES and biodegradable polymer biolimus-ES. In a wider perspective, this study shows that among all devices compared, the durable polymer second generation everolimus-ES and Resolute zotarolimus-ES are the safest DES to date.

The findings described in this paper are in line with two previous network meta-analyses[4, 5] that compared first- and second-generation DES to BMS. The current meta-analysis, however, substantially differs from the others by incorporating the most recent evidence from head-to-head DES comparison trials and forming the largest DES database ever analysed, with a total of 63 242 patients. We also included biodegradable polymer biolimus-ES, which are used mainly in Europe and Asia, thus providing a comprehensive overview of the most widely used DES in current clinical practice worldwide, not compared so far within their class in such a scale for single safety and efficacy endpoints.

Although our exclusion of BMS might be perceived as a limitation, methodological and conceptual reasons dictated such a choice. For a network meta-analysis to provide the highest degree of precision, robust direct and indirect evidence is required. This would not have been possible if we had included BMS as, to date, the direct comparison between biodegradable polymer biolimus-ES and BMS is limited to a single trial, making indirect comparisons through this "weak" common link imprecise and meaningful conclusions difficult[106]. Moreover, the safety and efficacy of durable polymer limus-eluting stents compared to BMS has already been clarified[4, 5]. Our study differs in

design and in the number of included patients from a previous meta-analysis of three randomised controlled trials comparing biodegradable devices with sirolimus-ES, which found a reduction of stent thrombosis associated with biodegradable stents.[107] The devices pooled in the previous study under the biodegradable group were in fact three distinct types, only one of which is a biodegradable polymer biolimus-ES; all of them represent differences in terms of the biodegradable polymer used, the eluted drug, and stent strut thickness. To provide the most robust conclusions and avoid heterogeneity that might arise by pooling stents with different properties, we decided to include only biodegradable polymer biolimus-ES in this analysis.

Safety

The safety of first-generation DES has been largely debated. The relatively high rates of stent thrombosis observed with these devices, a phenomenon which translates into increased rates of death or MI, raised concerns regarding their widespread use, despite the clear efficacy benefits over BMS[1, 2]. Further studies showed that the mechanisms of stent thrombosis after DES implantation are complex; with device design-related factors being of paramount importance. Indeed, the inflammation induced by the durable polymers of first-generation DES may result in delayed healing and incomplete covering of stent struts by new and functional endothelium, with uncovered stent struts serving as a source for future episodes of stent thrombosis[3]. However, other factors such as stent malapposition and mechanical tissue injury caused by stent struts during implantation may also play a role in stent thrombosis[20]. New-generation DES have addressed the limitations observed with first-generation devices in different ways; biodegradable polymer biolimus-ES use abluminal biodegradable polymers which dissolve within 6-9 months, with the residual metal platform presumably regaining a safety profile similar to a BMS beyond this time frame[108]. Conversely, second-generation durable polymer DES have replaced first-generation polymers with more biocompatible and thinner polymers[109-111]. Interestingly, the design improvements of the new-generation durable polymer DES have run in parallel with a reduction of definite stent thrombosis rates, compared to the first-generation paclitaxel-ES and sirolimus-ES in both early as well as late and very late phases of follow-up[4, 79]. Furthermore late stent thrombosis, with everolimus-ES being the first and most studied prototype, is reduced not only when compared to first-generation DES but also to BMS, suggesting that the durable fluoro-polymer used in these devices may be "thromboresistant" and more biocompatible than BMS[4-6], in turn generating a shift from the contention of an increased risk of stent thrombosis with DES compared to BMS towards the converse relation. In contrast, biodegradable polymer biolimus-ES have failed to provide a significant reduction in 1-year stent thrombosis rates as compared to sirolimus-ES, with both available trials[7, 8] showing rather a numerical advantage of sirolimus-ES. Although the 5-year follow-up of LEADERS - the only available trial with a long follow-up - shows a significant reduction of the 1-5 year stent thrombosis rates as compared to sirolimus-ES, the overall rate at 5 years was not significantly lower than for sirolimus-ES, pointing once more to the impact of the first-year outcomes. In our analysis, the stent thrombosis outcomes continue to favour the newer-generation durable polymer DES, particularly everolimus-ES.

Stent thrombosis, however, remains a surrogate safety endpoint and needs to be interpreted in the context of objective safety endpoints such as death and MI. In the present report, the durable polymer DES yielded lower odds of death and MI compared to biodegradable polymer biolimus-ES, with everolimus-ES reaching a significant MI reduction. Of note, this finding is in line with the results of the NEXT and COMPARE II trials[9, 10], both showing a numerical reduction of MI associated with everolimus-ES as compared

to biodegradable polymer biolimus-ES, becoming statistically significant for Q-wave MI in the latter. The advantage in regards to MI observed with thin-strut devices such as everolimus-ES might be related not only to stent thrombosis but also to lower rates of periprocedural MI resulting from side branch jailing, which in turn for mechanistic reasons might be more frequent with thick strut devices[112]. Higher degrees of re-endothelialisation achievable with these stents compared to the thick strut devices have been shown in preclinical[113] and optical coherence tomography studies[114] and may also play a role. Our findings on safety among different DES should be critically viewed also in the context of the choice of the DES to be implanted in patients who need to undergo non-cardiac surgery; surgery represents one of the most common reasons for premature antiplatelet therapy discontinuation which is associated with a significant increase in mortality and major adverse cardiac events[115].
Indeed, the favourable profile observed with second-generation DES may become clinically relevant in this clinical context also in light of new studies suggesting safety of clinically-indicated transient interruptions (any time beyond 1 month) and shorter overall duration of dual antiplatelet therapy (3-6 months) in patients treated with these devices[116, 117].
In this perspective, newer thin-strut biodegradable polymer DES recently introduced in the market may have the potential to enhance safety and efficacy outcomes post-PCI [(BIO-RESORT) TWENTE III (NCT01674803) and the EVOLVE II QCA (NCT01787799)]. The beyond 1-year analysis, confirmed maintenance of direction of the estimates observed at the 1-year follow-up.

Efficacy
Factors related to design, such as strut thickness, type of antiproliferative agent, drug elution kinetics, and elution time, as well as type of polymer, could all affect efficacy outcomes.[118, 119] We found that the new generation everolimus-ES, biodegradable polymer biolimus-ES, Resolute zotarolimus-ES, and the first generation sirolimus-ES were associated with reduced rates of target lesion and target vessel revascularisation compared with Endeavor zotarolimus-ES and/or first generation paclitaxel-ES. Our findings therefore confirm on a larger scale the comparable efficacy of biodegradable polymer biolimus-ES and second generation DES shown in the recent NEXT trial, powered for target lesion revascularisation as primary endpoint.[10]

Although not a new finding, in this analysis all limus-eluting DES, with the exception of Endeavor zotarolimus-ES, were associated with significantly lower rates of target lesion- and target vessel revascularization than the first-generation paclitaxel-ES. This finding may derive from the differences in the post implantation healing process between paclitaxel and limus-eluting stents. Indeed, the toxicity caused by the long-lasting presence of paclitaxel in the vessel wall may give rise to acellular healing process, with prolonged fibrin deposition and inflammation, as shown in preclinical and post-mortem studies[3, 120]. On the other hand, with Endeavor zotarolimus-ES, short release kinetics may result in insufficient inhibition of neointimal hyperplasia. Indeed, the more recently introduced Resolute zotarolimus-ES, which has a much

longer (up to 180 days) release curve of the same antiproliferative agent, zotarolimus, is associated with a significant reduction in target lesion- and target vessel revascularization compared to Endeavor zotarolimus-ES.

Limitations

As with any meta-analysis, our study shares the limitations of the original studies. Results were analysed on trial level data and therefore we could not assess whether all baseline characteristics were balanced among groups (although for the most part they were balanced within each RCT). Data for follow-ups longer than 1 year are limited but appear to confirm the direction of the estimates at 1-year. The patient inclusion criteria of this meta-analysis are broad, more closely reflecting current practice, comprising both stable and unstable high-risk patients. Potentially heterogeneous definitions of MI used across the trials may represent another limitation. There was no evidence of significant statistical inconsistency among trials; heterogeneity among trials was found to be moderate for stent thrombosis and low to moderate for target lesion and target vessel revascularisation. On the other hand, the stability of the results in the sensitivity analyses performed confirm that the overall outcome effect is robust and justified. Another aspect is the duration of dual antiplatelet therapy i.e., the combination of aspirin and a P2Y12 receptor blocker, that varied among the different trials. The variability of dual antiplatelet therapy may however be less important in the context of the present meta-analysis given that BMS were excluded and most trials employed at least 6-months dual antiplatelet therapy duration (see supplementary file for summary on guideline recommendation[121]). Owing to the limited number of trials assessing Resolute zotarolimus-ES, the findings with this device should be viewed as exploratory but certainly deserve further attention.

Despite these limitations, this network meta-analysis provides the largest-scale comparative information on the efficacy and safety profiles of different DES in current use.

Conclusions

Biodegradable polymer biolimus-ES show a similar efficacy and safety profile compared to first-generation sirolimus-ES. In comparison to second-generation everolimus-ES and Resolute zotarolimus-ES, biodegradable polymer biolimus-ES again provide similar efficacy outcomes. However, safety outcomes favour both everolimus-ES and Resolute zotarolimus-ES, denoting these second-generation durable polymer stents as the safest for current clinical practice.

What is already known on this topic

Coronary stents are widely used to treat patients with coronary artery disease. Drug-eluting stents (DES) are more efficacious than bare metal stents. Among DES, the second-generation durable polymer stents (with

everolimus-eluting being the most studied prototype) are safer than first-generation durable polymer DES and bare metal stents.
The efficacy and safety profile of biodegradable polymer stents (with biolimus-eluting being the most widely used) compared with first- and second-generation durable polymer DES is controversial.

What this study adds

This is the largest network meta-analysis of randomised trials on DES, comparing durable against biodegrable polymer stents and providing a clear visual ranking of the efficacy and safety of all of the most used DES.

The newer durable polymer everolimus- and zotarolimus R-eluting stents, as well as the biodegradable polymer biolimus-eluting stents, provide similar efficacy as first-generation sirolimus-eluting stents. Everolimus- and zotarolimus R-eluting stents emerge as the safest devices to date.

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References

1. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007; Mar 20;115(11):1440,55; discussion 1455.
2. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, 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; Feb 24;369(9562):667-78.
3. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; Jul 4;48(1):193-202.
4. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012; Apr 14;379(9824):1393-402.
5. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012; Jun 12;125(23):2873-91.
6. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet 2012; Oct 27;380(9852):1482-90.
7. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, 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; Sep 27;372(9644):1163-73.
8. Christiansen EH, Jensen LO, Thayssen P, Tilsted HH, Krusell LR, Hansen KN, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. Lancet 2013; Feb 23;381(9867):661-9.
9. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet 2013; Feb 23;381(9867):651-60.
10. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, et al. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. J Am Coll Cardiol 2013; Jul 16;62(3):181-90.
11. 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; May 1;115(17):2344-51.
12. Higgins JPT, Green D. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration [updated March 2011]; 2011. Accessed at www.cochrane-handbook.org on January 10, 2013.
13. Cooper NJ, Peters J, Lai MC, Juni P, Wandel S, Palmer S, et al. How valuable are multiple treatment comparison methods in evidence-based health-care evaluation?. Value Health 2011; Mar-Apr;14(2):371-80.
14. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010; Mar 30;29(7-8):932-44.
15. Spiegelhalter D, Abrams K, Myles J. Bayesian Approaches to Clinical Trials and Health-Care Evaluation (Statistics in Practice). Chichester, England: Wiley; 2004.
16. Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). Lancet 2005; Sep 10-16;366(9489):921-9.

17. Kaiser C, Galatius S, Erne P, Eberli F, Alber H, Rickli H, et al. Drug-eluting versus bare-metal stents in large coronary arteries. N Engl J Med 2010; Dec 9;363(24):2310-9.
18. Park HJ, Kim HY, Lee JM, Choi YS, Park CS, Kim DB, et al. Randomized comparison of the efficacy and safety of zotarolimus-eluting stents vs. sirolimus-eluting stents for percutaneous coronary intervention in chronic total occlusion--CAtholic Total Occlusion Study (CATOS) trial. Circ J 2012;76(4):868-75.
19. Moreno R, Garcia E, Teles R, Rumoroso JR, Carvalho HC, Goicolea FJ, et al. Randomized Comparison of Sirolimus-Eluting and Everolimus-Eluting Coronary Stents in the Treatment of Total Coronary Occlusions: Results From the Chronic Coronary Occlusion Treated by Everolimus-eluting Stent Randomized Trial. Circ Cardiovasc Interv 2013; Feb 1;6(1):21-8.
20. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010; Jan 16;375(9710):201-9.
21. Smits PC, Kedhi E, Royaards KJ, Joesoef KS, Wassing J, Rademaker-Havinga TA, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). J Am Coll Cardiol 2011; Jun 28;58(1):11-8.
22. de Lezo J, Medina A, Pan M, Romero M, Delgado A, Segura J, et al. Drug-eluting stents for complex lesions: randomized rapamycin versus paclitaxel CORPAL study. J Am Coll Cardiol. 2005;45:75A. Abstract.
23. Wang L, Zhang D, Yang X, Ge Y, Wang H, Li W, et al. Comparison of safety and efficacy of Cypher® stent and Endeavor® stent in patients with acute ST elevation myocardial infarction (STEMI) undergoing emergency PCI. J Am Coll Cardiol. 2011;58:B216. Abstract.
24. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus 2-year clinical outcomes of the DES-DIABETES trial. J Am Coll Cardiol 2009; Mar 3;53(9):812-3.
25. Lee SW, Park SW, Kim YH, Yun SC, Park DW, Lee CW, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus: 4-year clinical outcomes of DES-DIABETES (drug-eluting stent in patients with DIABETES mellitus) trial. JACC Cardiovasc Interv 2011; Mar;4(3):310-6.
26. Maeng M, Jensen LO, Galloe AM, Thayssen P, Christiansen EH, Hansen KN, et al. Comparison of the sirolimus-eluting versus paclitaxel-eluting coronary stent in patients with diabetes mellitus: the diabetes and drug-eluting stent (DiabeDES) randomized angiography trial. Am J Cardiol 2009; Feb 1;103(3):345-9.
27. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, 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; Dec 19;48(12):2440-7.
28. Kandzari DE, Mauri L, Popma JJ, Turco MA, Gurbel PA, Fitzgerald PJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A 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). JACC Cardiovasc Interv 2011; May;4(5):543-50.
29. 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; Feb 9;55(6):543-54.
30. Kirtane AJ, Leon MB, Ball MW, Bajwa HS, Sketch MH,Jr, Coleman PS, et al. The "Final" 5-Year Follow-Up From the ENDEAVOR IV Trial Comparing a Zotarolimus-Eluting Stent With a Paclitaxel-Eluting Stent. JACC Cardiovasc Interv 2013; Apr;6(4):325-33.
31. Kim WJ, Lee SW, Park SW, Kim YH, Yun SC, Lee JY, et al. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. Circulation 2011; Aug 23;124(8):886-92.

Table 1. Randomized controlled trials included in the network meta-analysis.

Trial	Year of publication	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)
BASKET [16]	2005	525 (826)	SES vs PES (vs BMS)	Superiority (cost effectiveness) / single-center	6	Stable coronary artery disease/ACS (42/58)
BASKET-PROVE [17]	2010	1549 (2314)	EES vs SES (vs BMS)	Superiority (cost effectiveness) / multicenter	24	Stable coronary artery disease/ACS (35/65)
CATOS [18]	2012	160	ZES-E vs SES	Parallel / multicenter	12	Stable coronary artery disease
CIBELES [19]	2013	207	EES vs SES	Non-inferiority / multicenter	12	Stable coronary artery disease
COMPARE [20, 21]	2010/2011	1800	EES vs PES	Superiority / single-center	24	Stable coronary artery disease/ACS (40/60)
COMPARE II [9]	2013	2707	BP-BES vs EES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (42/58)
CORPAL [22]	2005	515	SES vs PES	Parallel / multicenter	6	Stable coronary artery disease
CREST MI [23]	2011	875	ZES-E vs SES	Parallel / multicenter	6	STEMI
DES-diabetes [24, 25]	2008/2011	400	SES vs PES	Superiority / multicenter	48	Stable coronary artery disease/ACS (42/58)
DiabeDES [26]	2009	153	SES vs PES	Superiority / multicenter	8	Stable coronary artery disease/ACS (67/33)
ENDEAVOR III [27, 28]	2006/2011	436	ZES-E vs SES	Non-inferiority / multicenter	60	Stable coronary artery disease
ENDEAVOR IV [29, 30]	2010/2013	1548	ZES-E vs PES	Non-inferiority / multicenter	60	Stable coronary artery disease/ACS (53/47)
ESSENCE-Diabetes [31]	2011	300	EES vs SES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (58/42)
EXCELLENT [32]	2010	1443	EES vs SES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (48/52)
Hong et al. [33]	2010	169	SES vs PES	Parallel / multicenter	36	Stable coronary artery disease/ACS (39/61)
ISAR-DIABETES [34]	2005	250	SES vs PES	Non-inferiority / multicenter	9	Stable coronary artery disease/ACS (60/40)
ISAR-Left-Main [35]	2009	607	SES vs PES	Non-inferiority / multicenter	24	Stable coronary artery disease
ISAR-Left-Main 2 [36]	2012	650	ZES-R vs EES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (64/36)

Trial	Year of publication	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)
ISAR-SMART 3 [37]	2006	360	SES vs PES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (69/31)
ISAR-TEST-2 [38, 39]	2009/2010	674 (1007)	ZES-E vs SES (vs polymer free dual DES)	Superiority / multicenter	24	Stable coronary artery disease/ACS (58/42)
Juwana et al. [40]	2009	397	SES vs PES	Superiority / single-center	12	STEMI
Kamoi et al. [41]	2011	100	SES vs PES	Parallel / single-center	12	Stable coronary artery disease
Kim et al. [42]	2008	169	SES vs PES	Superiority / multicenter	6	Stable coronary artery disease/ACS (39/61)
KOMER [43]	2011	611	ZES-E vs SES vs PES	Parallel / multicenter	18	STEMI
LEADERS [7, 44]	2008/2013	1707	BP-BES vs SES	Non-inferiority / multicenter	60	Stable coronary artery disease/ACS (45/55)
Long DES II [45]	2006	500	SES vs PES	Superiority / multicenter	9	Stable coronary artery disease/ACS (45/55)
LONG-DES III [46]	2011	450	EES vs SES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (58/42)
LONG-DES IV [47]	2012	500	ZES-R vs SES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (64/36)
Naples diabetes [48]	2010	226	ZES-E vs SES vs PES	Superiority / single-center	36	Stable coronary artery disease/ACS (86/14)
NEXT [10]	2013	3235	BP-BES vs EES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (84/16)
NOBORI 1 - Phase 1 [49]	2007	120	BP-BES vs PES	Non-inferiority / multicenter	9	Stable coronary artery disease/ACS (80/20)
NOBORI 1 - Phase 2 [50]	2009	243	BP-BES vs PES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (72/28)
NOBORI Japan [51, 52]	2012	335	BP-BES vs SES	Non-inferiority / multicenter	36	Stable coronary artery disease/ACS (86/14)
Pan et al. [53]	2007	205	SES vs PES	Superiority / multicenter	24	Stable coronary artery disease/ACS (40/60)

Trial	Year of publication	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)
PASEO [54]	2009	180 (270)	SES vs PES (vs BMS)	Superiority / single-center	48	STEMI
Petronio et al. [55]	2007	100	SES vs PES	Superiority / single-center	9	Stable coronary artery disease/ACS (52/48)
PRISON III [56]	2013	304	SES vs ZES-E + SES vs ZES-R	Superiority / multicenter	12	Stable coronary artery disease
PROSIT [57, 58]	2008/2011	308	SES vs PES	Superiority / multicenter	36	STEMI
PROTECT [59]	2012	8709	ZES-E vs SES	Superiority / multicenter	36	Stable coronary artery disease/ACS (55/45)
R-CHINA RCT [60]	2013	400	ZES-R vs PES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (9/91)
REALITY [61]	2006	1386	SES vs PES	Superiority / multicenter	12	Stable coronary artery disease/ACS (70/30)
RESET [62]	2011	3197	EES vs SES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (82/18)
RESOLUTE All Comers [63, 64]	2010/2011	2292	ZES-R vs EES	Non-inferiority / multicenter	24	Stable coronary artery disease/ACS (35/65)
SEA-SIDE [65]	2011	150	EES vs SES	Superiority / single-center	18	Stable coronary artery disease/ACS (66/34)
Separham et al. [66]	2011	200	BP-BES vs EES	Parallel / single-center	12	Stable coronary artery disease/ACS (29/71)
SIRTAX [67, 68]	2005/2011	1012	SES vs PES	Superiority / multicenter	60	Stable coronary artery disease/ACS (49/51)
SORT OUT II [69]	2008	2098	SES vs PES	Superiority / multicenter	18	Stable coronary artery disease/ACS (45/55)
SORT OUT III [70, 71]	2010/2012	2332	ZES-E vs SES	Superiority / multicenter	36	Stable coronary artery disease/ACS (55/45)
SORT OUT IV [72, 73]	2010/2012	2774	EES vs SES	Non-inferiority / multicenter	24	Stable coronary artery disease/ACS (58/42)
SORT OUT V [8]	2013	2468	BP-BES vs SES	Non-inferiority / multicenter	9	Stable coronary artery disease/ACS (51:49)
SPIRIT II [74, 75]	2006/2012	300	EES vs PES	Non-inferiority / multicenter	60	Stable coronary artery disease/ACS (62/38)

Trial	Year of publication	Total sample size	Stent comparators	Trial design	Maximum follow-up (months)	Clinical setting (%)
SPIRIT III [76, 77]	2008/2011	1001	EES vs PES	Non-inferiority / multicenter	36	Stable coronary artery disease/ACS (80/20)
SPIRIT IV [78, 79]	2010/2011	3717	EES vs PES	Superiority / multicenter	24	Stable coronary artery disease/ACS (72/28)
SPIRIT V [80]	2012	324	EES vs PES	Non-inferiority / multicenter	12	Stable coronary artery disease/ACS (64/36)
TAXI-LATE [81, 82]	2005/2007	202	SES vs PES	Superiority / single-center	36	Stable coronary artery disease/ACS (84/16)
TWENTE [83, 84]	2012/2013	1391	ZES-R vs EES	Non-inferiority / single-center	24	Stable coronary artery disease/ACS (49/51)
XAMI [85]	2012	625	EES vs SES	Non-inferiority / multicenter	12	STEMI
ZEST [86]	2010	2645	ZES-E vs SES vs PES	Superiority (ZES-E vs PES) / Non-inferiority (ZES-E vs SES) / multicenter	12	Stable coronary artery disease/ACS (45/55)
ZEST-AMI [87]	2009	328	ZES-E vs SES vs PES	Superiority / multicenter	12	STEMI
Zhang et al. [88]	2006	673	SES vs PES	Superiority / single-center	12	Stable coronary artery disease/ACS (45/55)

ACS, acute coronary syndrome; BASKET, Basel Stent Kosten Effektivitäts Trial; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; BMS, bare-metal stent; BASKET-PROVE, Basel Stent Kosten- Effektivitäts Trial–Prospective Validation Examination; EES, Everolimus-eluting stent; CATOS, The CAtholic Total Occlusion Study; CIBELES, Randomized comparison of sirolimus-eluting and everolimus-eluting coronary stents in the treatment of total coronary occlusions; COMPARE, Comparison of the Everolimus Eluting XIENCE-V Stent With the Paclitaxel Eluting TAXUS LIBERTE´ Stent in All-Comers; COMPARE II, Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent; BP-BES, biodegradable polymer drug-eluting stent; CORPAL, Drug-eluting stents for complex lesions: Randomized rapamycin versus paclitaxel CORPAL study; CREST MI, Carotid Revascularization Endarterectomy Versus Stenting Trial–Myocardial Infarction; ZES-E, Endeavor zotarolimus -stent; DES-diabetes, Drug-Eluting Stent in Patients With Diabetes Mellitus; DiabeDES, The Diabetes and Drug-Eluting Stent (DiabeDES) Randomized Angiography Trial; ENDEAVOR III, A 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; ENDEAVOR IV, randomized comparison of zotarolimus- and paclitaxel-eluting stents in patients with coronary artery disease; ESSENCE-Diabetes, Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients With Diabetes Mellitus; EXCELLENT, Efficacy of Xience/Promus vs Cypher to rEduce Late Loss after

stENTing; ISAR-DIABETES, The Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents; ISAR-Left-Main, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions; ISAR-Left-Main 2, Zotarolimus- vs. Everolimus-Eluting Stents for Treatment of Unprotected Left Main Coronary Artery Lesions; ISAR-SMART 3, Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels; ISAR-TEST-2, A polymer-free dual drug-eluting stent in patients with coronary artery disease: A randomized trial vs. polymer-based drug-eluting stents; KOMER, Korean multicentre endeavor; LEADERS, Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation; LONG-DES II, Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease; LONG-DES III, Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: A randomized LONG-DES-III (percutaneous treatment of LONG native coronary lesions with drug-eluting stent-III) trial; LONG-DES IV, Comparison of resolute zotarolimus-eluting stents and sirolimus-eluting stents in patients with de novo long coronary artery lesions; ZES-R, Resolute zotarolimus-stent; NAPLES-Diabetes, Novel approaches for preventing or limiting events in diabetic patients (naples-diabetes) trial; NEXT, The NOBORI biolimus-eluting versus XIENCE/PROMUS everolimus-eluting stent trial; NOBORI 1, Randomised comparison of nobori, biolimus A9-eluting coronary stent with a taxus(R), paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries; NOBORI, A randomized comparison of nobori biolimus A9 eluting stent with cypher sirolimus eluting stent for coronary revascularization in Japanese population; PASEO, PaclitAxel or sirolimus-eluting stent vs bare metal stent in primary angiOplasty; PRISON III, Primary Stenting of Totally Occluded Native Coronary Arteries III: a randomised comparison of sirolimus-eluting stent implantation with zotarolimus-eluting stent implantation for the treatment of total coronary occlusions; PROSIT, Prospective Randomized cOmparison of SIrolimus- vs pacliTaxel-eluting stents for the treatment of acute STEMI; PROTECT, Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation; R-CHINA RCT, Resolute Zotarolimus-Eluting Stent Versus the Taxus Liberte Paclitaxel-Eluting Stent for Percutaneous Coronary Intervention in China; REALITY, Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions; RESET, Randomized Evaluation of Sirolimus-eluting stent vs Everolimus-eluting stent Trial; RESOLUTE All Comers, Unrestricted randomised use of two new generation drug-eluting coronary stents; SEA-SIDE, Sirolimus Versus Everolimus-Eluting Stent Randomized Assessment in Bifurcated Lesions and Clinical Significance of Residual Side-Branch Stenosis; SIRTAX, SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization; SORT OUT, Scandinavian Organization for Randomized Trials With Clinical Outcome; STEMI, ST-elevation myocardial infarction; TAXI-LATE, A Prospective Randomized Comparison Between Paclitaxel and Sirolimus Eluting Stents in the Real World of Interventional Cardiology; TWENTE, The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente; XAMI, XienceV Stent vs Cypher Stent in Primary PCI for Acute Myocardial Infarction; ZEST, Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent With Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Lesions and ZEST-AMI; Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent vs Sirolimus-Eluting Stent vs Paclitaxel-Eluting Stent for Acute Myocardial Infarction Patients; NA, not applicable.

Table 2. One-year event rates with different DES types.

	SES	PES	EES	ZES-E	BP-BES	ZES-R
Death Rates (95% CrI)	2.45 (1.86-3.14)	2.68 (1.88-3.75)	2.27 (1.59-3.17)	3.05 (1.96-4.62)	2.48 (1.64-3.67)	1.80 (1.04-3.00)
MI Rates (95% CrI)	2.58 (1.98-3.3)	3.44 (2.53-4.61)	2.32 (1.68-3.16)	2.47 (1.67-3.58)	3.0 (2.07-4.27)	2.28 (1.52-3.39)
ST Rates (95% CrI)	1.42 (0.98-1.96)	2.38 (1.27-4.30)	0.89 (0.44-1.66)	2.74 (1.01-6.91)	1.38 (0.57-3.03)	1.11 (0.33-3.01)
TLR Rates (95% CrI)	3.25 (2.57-4.04)	5.92 (4.3-8.05)	3.03 (2.06-4.40)	7.52 (4.97-11.29)	3.18 (1.95-4.97)	3.25 (1.77-5.71)
TVR Rates (95% CrI)	4.91 (4.07-5.86)	7.05 (5.21-9.41)	4.30 (3.11-5.87)	7.93 (5.11-12.19)	4.93 (3.27-7.43)	4.59 (2.45-8.36)

MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularisation; TVR, target vessel revascularisation. SES, sirolimus eluting stent; PES, paclitaxel eluting stent; EES, everolimus eluting stent; ZES-E, Endeavor zotarolimus-stent; BP-BES, biodegradable polymer biolimus- eluting stent; ZES-R, Resolute zotarolimus-stent.

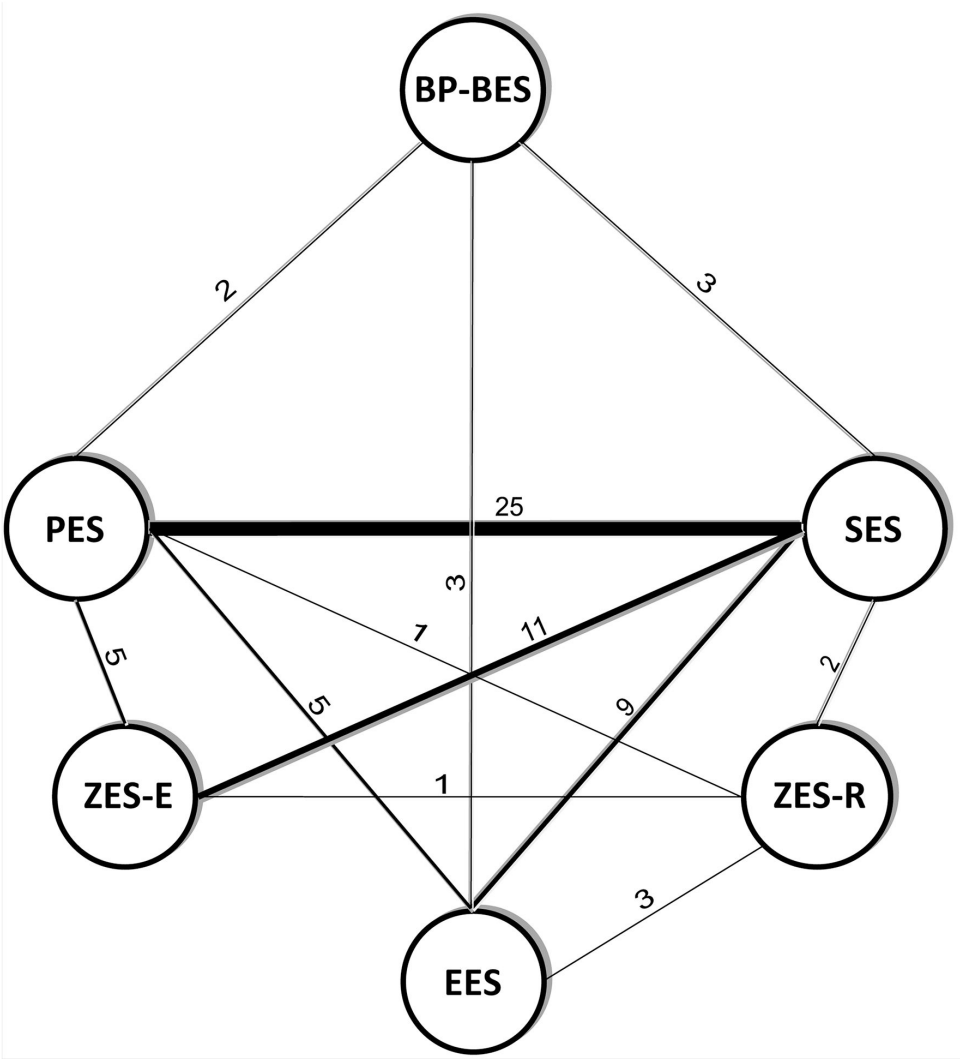

Figure 1. Evidence network among stents included in meta-analysis. Links between stent types represent direct (lines) comparison studies. Nodes denote stent type; thickness of link indicates number of direct comparisons. SES=sirolimus eluting stent; PES=paclitaxel eluting stent; EES=everolimus eluting stent; ZES-E=Endeavor zotarolimus eluting stent;
BP-BES=biodegradable polymer biolimus eluting stent; ZES-R=Resolute zotarolimus eluting stent

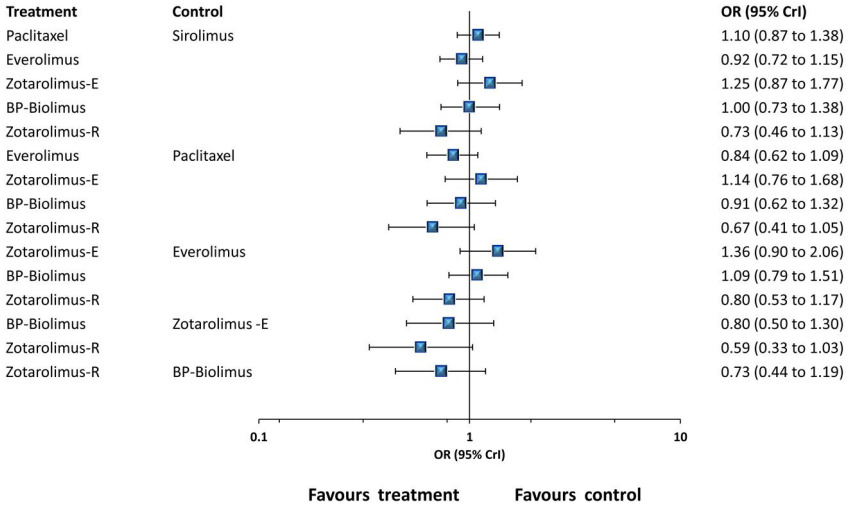

Figure 2. Pooled odds ratio and 95% credible intervals determined by network meta-analysis for mortality. BP=biodegradable polymer; E=Endeavor; R=Resolute

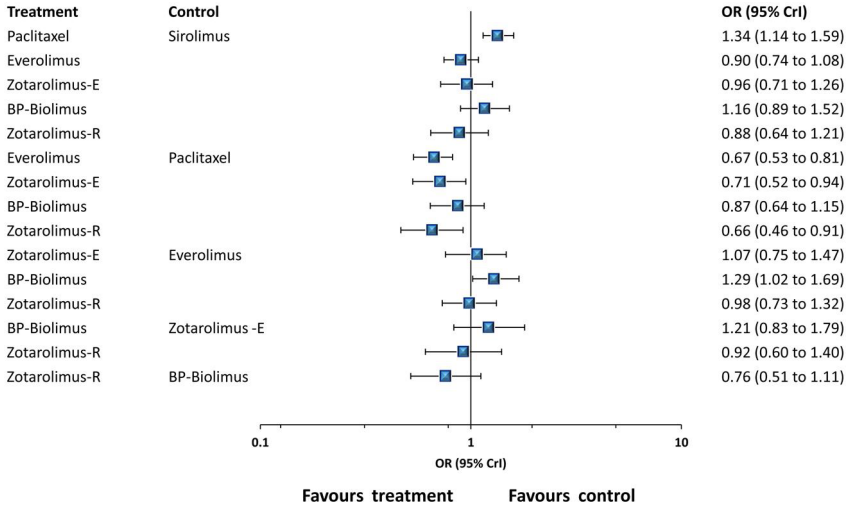

Figure 3. Pooled odds ratio and 95% credible intervals determined by network meta-analysis for myocardial infarction BP=biodegradable polymer; E=Endeavor; R=Resolute

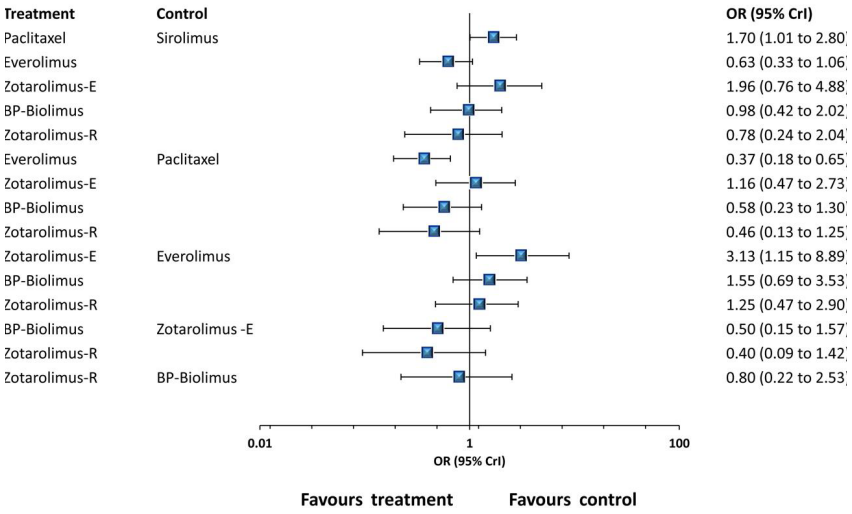

Figure 4. Pooled odds ratio and 95% credible intervals determined by network meta-analysis for definite or probable stent thrombosis. BP=biodegradable polymer; E=Endeavor; R=Resolute

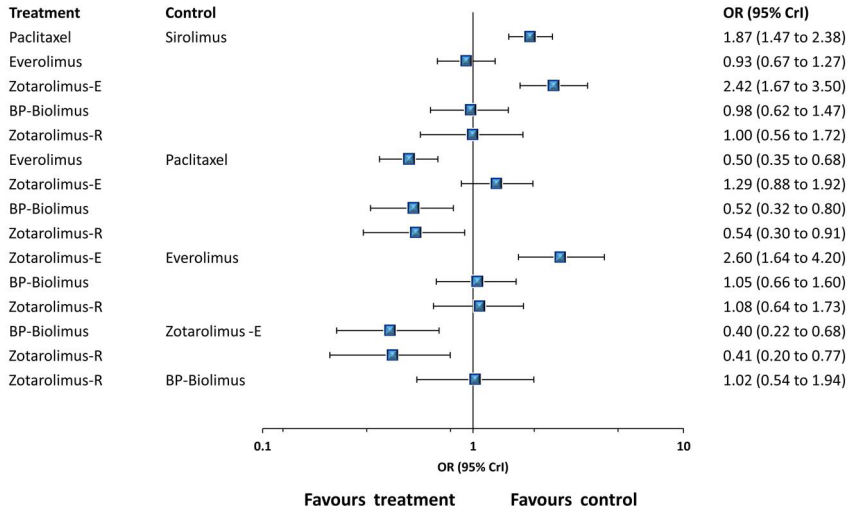

Figure 5. Pooled odds ratio and 95% credible intervals determined by network meta-analysis for target lesion revascularisation. BP=biodegradable polymer; E=Endeavor; R=Resolute

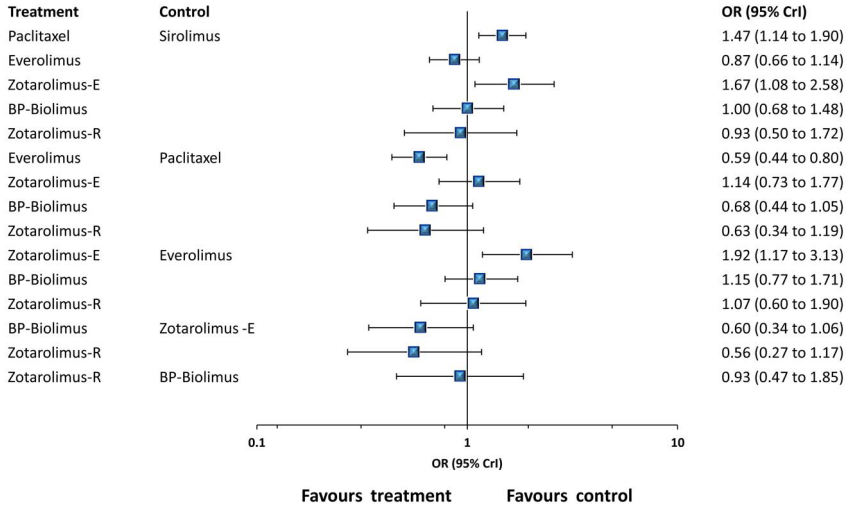

Figure 6. Pooled odds ratio and 95% credible intervals determined by network meta-analysis for definite or probable stent thrombosis. BP=biodegradable polymer; E=Endeavor; R=Resolute

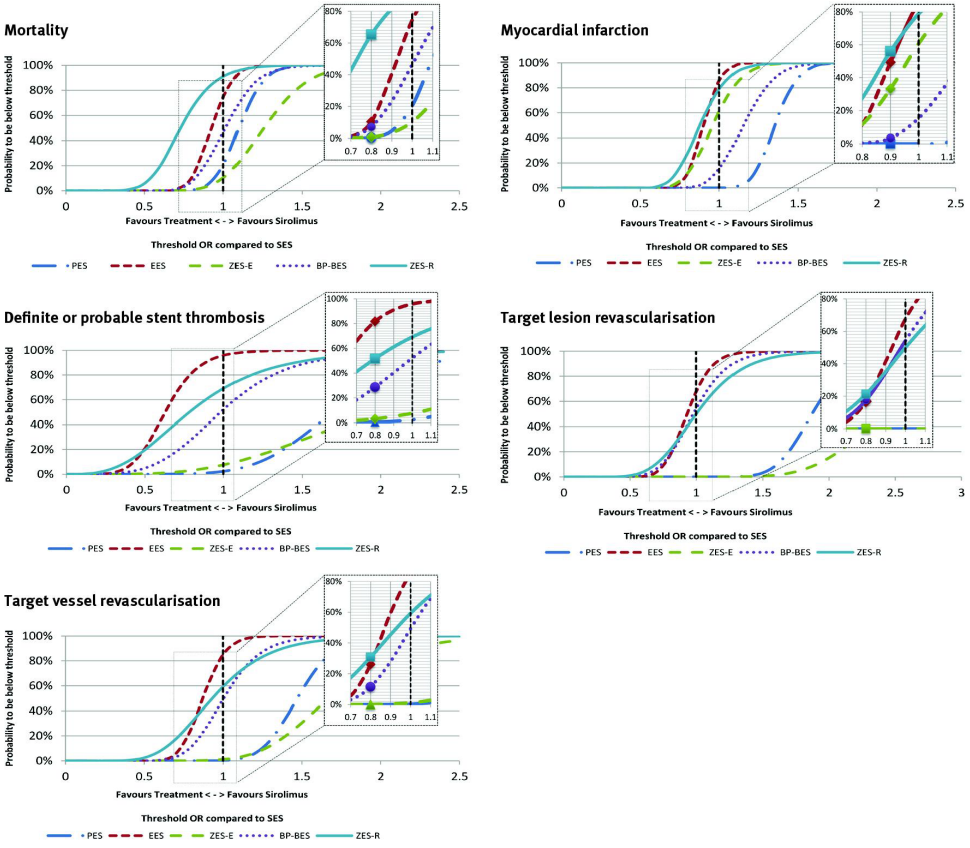

Figure 7. Posterior probabilities of different risk thresholds (odds ratios) for each stent compared with sirolimus eluting stent (reference treatment). Curves can be used to examine overall safety and efficacy profile of specific DES compared with reference treatment sirolimus-ES (SES) (identity line=unit value); improved safety and efficacy profiles indicated by highest leftward shift of curve, as shown with Resolute zotarolimus-ES (ZES-R) and everolimus-ES (EES) with regard to mortality and myocardial infarction; curves allow inferences to extract probabilities of specific risk thresholds corresponding to minimal odds ratio compared with sirolimus-ES as reference treatment. For example, compared with sirolimus-ES, there is probability of 65% that Resolute zotarolimus-ES reduce odds of mortality by at least 20% corresponding to odds ratio of 0.80; conversely, this probability is estimated to be close to 0% with biodegradable polymer biolimus-ES (BP-BES), meaning no additional mortality benefit provided by biodegradable polymer biolimus-ES compared with sirolimus-ES; there is a probability of 56% and 49%, respectively, that Resolute zotarolimus-ES and everolimus-ES reduced odds of myocardial infarction by at least 10% corresponding to odds ratio of 0.90 but this probability is estimated close to 0% with biodegradable polymer biolimus-ES, meaning no additional myocardial infarction benefits provided by biodegradable polymer biolimus-ES compared with sirolimus-ES (reference treatment). PES=paclitaxel eluting stent; ZES-E=Endeavor zotarolimus-ES

Chapter 17

Comparison of three biodegradable polymer and durable polymer-based drug-eluting stents in all-comers (BIO-RESORT): Rationale and study design of the randomized TWENTE III multicenter trial

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Abstract

Aim: To evaluate the safety and efficacy of two novel drug-eluting stents (DES) with biodegradable polymer-based coatings versus a durable coating DES.

Methods and Results: BIO-RESORT is an investigator-initiated, prospective, patient-blinded, randomized multicenter trial in 3,540 Dutch all-comers with various clinical syndromes, requiring percutaneous coronary interventions (PCI) with DES implantation. Randomization (stratified for diabetes mellitus) is being performed in a 1:1:1 ratio between ORSIRO sirolimus-eluting stent with circumferential biodegradable coating, SYNERGY everolimus-eluting stent with abluminal biodegradable coating, and RESOLUTE INTEGRITY zotarolimus-eluting stent with durable coating. The primary endpoint is the incidence of the composite endpoint target vessel failure (TVF) at 1 year, consisting of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization. Power calculation assumes a TVF rate of 8.5% with a 3.5% non□inferiority margin, giving the study a power of 85% (alpha level 0.025 adjusted for multiple testing). The impact of diabetes mellitus on post-PCI outcome will be evaluated. The first patient was enrolled on December 21, 2012.

Conclusions: BIO-RESORT is a large, prospective, randomized, multicenter trial with three arms, comparing two DES with biodegradable coatings versus a reference DES with a durable coating in 3,540 all-comers. The trial will provide novel insights into the clinical outcome of modern DES and will address the impact of known and so far undetected diabetes mellitus on post-PCI outcome.

Background

More than a decade ago, the concept of drug-eluting stents (DES) was developed to minimize the risk of in-stent restenosis by the local delivery of anti-proliferative drugs from stent coatings that also helped control the release kinetics of the drugs. While effectively reducing lesion recurrence, first-generation DES with elementary durable polymer-based coatings did not improve mortality following percutaneous coronary interventions (PCI). This was to a great extent attributed to a higher incidence of late and very late stent thrombosis that was largely related to a limited biocompatibility of early DES.[1] Second-generation DES with more biocompatible durable polymer-based coatings then showed on average a more favorable clinical outcome,[2-7] while contemporary third-generation DES with more refined stent designs showed improved stent deliverability in challenging coronary anatomies.[8-12] The zotarolimus-eluting RESOLUTE INTEGRITY stent (Medtronic Vascular, Santa Rosa, CA, USA) is, such a third-generation durable polymer DES[6,8,9] that utilizes the established combination of zotarolimus elution from a

BioLinx coating, of which previous randomized-controlled trials demonstrated that it is safe, highly efficacious, and non-inferior to that of fluoropolymer-coated everolimus-eluting stents.[4,5,13,14]

In parallel with the refinement of durable coating DES, concerns about durable polymers as a potential trigger of vessel wall inflammation and late adverse events prompted the development of DES with biodegradable polymer-based coatings,[15] which, after degradation, leave only a bare metal stent in the vessel wall that does not induce an excessive or prolonged inflammatory response.[15,16] Such DES recently demonstrated favorable safety and efficacy compared to first generation durable coating DES.[17]

Meanwhile, novel biodegradable coating DES have been introduced, which utilize modern, flexible, thin-strut stent platforms and drugs that are highly efficacious in preventing restenosis.[18,19] These devices employ dissimilar concepts as either the entire stent (i.e. circumferential coating) or only the abluminal stent surface (i.e. external coating) is covered by the biodegradable coating. The ORSIRO stent (Biotronik, Bülach, Switzerland) elutes sirolimus from a thin circumferential biodegradable coating,[20] and the SYNERGY stent (Boston Scientific, Natick, MA, USA) elutes everolimus from a thin abluminal biodegradable coating.[21] While such DES are increasingly used in clinical practice, there is no data from randomized head-to-head comparisons between these stents and established third-generation durable coating DES.

Meanwhile, PCI with DES has become the standard of care. Current randomized comparisons of approved DES therefore address so-called all-comer populations with very limited exclusion criteria, and comprise patients with all clinical syndromes.[8] The findings of such trials are particularly valuable as they reflect the performance of DES in routine clinical practice. Therefore, in the present BIO-RESORT multicenter trial, we assess in an all-comer patient population the safety and efficacy of the ORSIRO and SYNERGY biodegradable coating DES versus the RESOLUTE INTEGRITY durable coating DES as a reference.

Investigational products

ORSIRO

ORSIRO is a Conformité Européenne (CE)-certified hybrid coating DES with a 7.5-µm-thick circumferential coating that consists of a combination of an active (BIOlute) and passive coating (PROBIO). The BIOlute active coating consists of a biodegradable PLLA polymer that elutes sirolimus in which 50% of the drug is released within 30 days and 80% within 3 months (complete degradation of coating within 1–2 years),[22] resulting in promising pre-clinical data.[23] The PROBIO passive coating encapsulates the metal stent and minimizes interaction between metal and surrounding tissue at sites of contact. The configuration of the coating is asymmetrical and thicker on the abluminal side than on the luminal side (7.4µm vs. 3.5µm, respectively), which results in a higher drug dose on the abluminal side of the DES.[23]

The ORSIRO is based on the PRO-Kinetic cobalt-chromium stent platform with a strut thickness of 60µm in stents with a nominal diameter ≤ 3.0mm and 80µm in stents with a nominal diameter >3.0mm. The efficacy of this DES was assessed in the BIOFLOW studies, in which the ORSIRO showed favorable outcome and non-inferiority compared to the durable polymer based Xience Prime (Abbott Vascular, Santa Clara, California).[20,24,25]

SYNERGY

Synergy is a CE-certified DES that elutes everolimus from a 4-µm-thick biodegradable PLGA (poly[lactic-co-glycolic acid]) coating that is completely resorbed within 4 months. To minimize the amount of polymer, the coating is applied on the abluminal side of the stent only. The flexible stent platform is manufactured from 74µm struts of a platinum chromium alloy, a material that is also employed in the durable polymer-based Promus Element DES.[10] To improve stent flexibility, conformability, and longitudinal robustness, the design of SYNERGY stent platform underwent several modifications from the Element platform, including changes in connector angles and peak radius, and the presence of two additional proximal and distal end-connectors.[26] The performance of SYNERGY was assessed in the EVOLVE-I trial, in which SYNERGY achieved long-term angiographic results that were similar to Promus Element.[21]

RESOLUTE INTEGRITY

RESOLUTE INTEGRITY is a CE-certified and Food and Drug Administration (FDA)-approved durable polymer DES. The 5.6-µm-thick BioLinx polymer system, which covers the entire stent platform, elutes zotarolimus as the antiproliferative agent. The polymer system consists of a blend of three different polymers: (1) the hydrophobic C10 polymer, which aids in the control of drug release; (2) the hydrophilic C19 polymer, which supports biocompatibility; and (3) polyvinyl pyrro-lidinone, which increases the initial drug burst and enhances the elution rate. This coating is also used in Resolute, a DES that was shown to be highly effective in reducing restenosis with a favorable safety profile.[4,13] RESOLUTE INTEGRITY is based on a third-generation, cobalt-chromium stent platform (Integrity), which has a strut thickness of 91µm and a stent design that facilitates stent delivery.[11]

Methods

Study hypothesis and design

The main objective of the current investigator-initiated, patient-blinded, randomized, multicenter BIO-RESORT trial (ClinicalTrial.gov no. NCT01674803) is to compare the safety and efficacy of two novel biodegradable coating DES with that of the established RESOLUTE INTEGRITY durable coating DES (the reference device) in an all-comer population with many complex lesions and patients (Figure 1). The study will independently assess whether the safety and efficacy of (1) the ORSIRO stent and (2) the

SYNERGY stent is non-inferior to that of RESOLUTE INTEGRITY. Randomization for DES type is performed in a 1:1:1 ratio after stratification for the prevalence of diabetes mellitus. The investigator-initiated trial was planned and is performed by cardiologists of the participating PCI centers. Biotronik, Boston Scientific, and Medtronic provided equal financial support.

Study population

A total of 3,540 all-comer patients (age ≥18years) with various clinical syndromes, requiring PCI with DES implantation, are studied. All-comers are studied to assess patients and lesions that reflect routine clinical practice. This implies the application of only few exclusion criteria (Table 1).
The study complies with the Declaration of Helsinki and was approved by the Ethical Review Board Twente. All patients provide written informed. Enrollment is currently performed at four study sites in The Netherlands (Thoraxcentrum Twente at Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Albert Schweitzer Hospital, Dordrecht; and Haga Hospital, The Hague). The first patient was enrolled on December 21, 2012. The expected completion of enrollment is by the end of 2014.

Study protocol, patient demographics, and medical data

Patient demographics and clinical data at inclusion are collected online in an electronic database (CRO Diagram, Zwolle, the Netherlands). Cardiac marker assessment is scheduled prior to PCI and 6 to 18 hours after PCI, with subsequent serial measurements in case of relevant biomarker elevation or complaints until the peak elevation has been determined.

PCI will be performed according to routine clinical practice. In accordance with current guidelines, the use of Fractional Flow Reserve (FFR) for the assessment of angiographically intermediate stenoses is recommended. If clinically indicated, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) may be used for guidance of the PCI procedure at the operator's discretion. Operators were requested to report any evident (or suspected) longitudinal stent deformation, which is defined as distortion or shortening of an implanted stent in the longitudinal axis following initially successful deployment.[27] In case of stent thrombosis, the use of OCT or IVUS is encouraged to identify the mechanism of stent thrombosis. If an operator is unable to insert the randomized study stent despite various measures, crossover to a stent of choice is allowed.

Treatment of all target lesions within a single PCI procedure is encouraged, if reasonable and safe; however, staged procedures (defined as procedures planned at the time of the index procedure or shortly thereafter and being performed within 6 weeks with the allocated type DES) are permitted. During follow-up, in patients with potential restenosis and visually determined lumen narrowing ≤80%, the use of FFR is encouraged to evaluate

its hemodynamic significance and indication for reintervention. In case of unplanned revascularization procedures, the use of the allocated type DES is recommended, except for the treatment of a restenosis in a study stent.

Medical therapy during the PCI procedure conforms to routine medical treatment. Dual antiplatelet therapy (DAPT) is recommended for 6-12 months according to current medical guidelines. In patients on oral anticoagulation (e.g. for atrial fibrillation), triple therapy is recommended for at least 1-3 month(s), after which oral anticoagulation in combination with clopidogrel, ticagrelor, or prasugrel is prescribed for 6-12 months.

Follow-up data collection

After 1 month, 12 (±1) months, and 24 (±1) months, follow-up data will be collected at visits at outpatient clinics or, if not feasible, by telephone follow-up and/or a medical questionnaire, carried out by staff that is blinded to the allocated treatment. Follow-up beyond 2 years is intended. During visits and telephone calls, patients will be interviewed regarding repeat hospitalizations, revascularization procedures, and MIs during follow-up. Survival is checked from the municipal population register; in case of death, information will be obtained from the patient's medical chart, general practitioner, and/or cardiologist.

Clinical endpoints and definitions

The primary endpoint is the incidence of target vessel failure (TVF) at 1-year follow-up, a composite endpoint to assess device efficacy as well as patient safety. Components of TVF are in hierarchical order: cardiac death, target vessel MI, and clinically driven target vessel revascularization. *Cardiac death* is defined as any death caused by 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. As in our previous trials,[4,5] *target vessel MI* is defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker,[28] and can be related to a target vessel or cannot be related to another vessel. *Clinically indicated repeated revascularization* includes revascularization procedures by PCI and coronary artery bypass graft surgery.

Secondary endpoints include device and patient-oriented efficacy and safety parameters such as target lesion failure (TLF), major adverse cardiac events (MACE), patient-oriented composite endpoint (POCE) as previously described,[8] and stent thrombosis according to the Academic Research Consortium (ARC)-definitions.[29] Among the secondary endpoints, the impact of diabetes mellitus on post-PCI outcome will be evaluated. In addition, a sub-study will investigate the prevalence of so far undetected diabetes and its potential relevance for clinical outcome. At 24-month follow-up, we will assess TVF as a major secondary endpoint. Moreover, one of the elements of the BIORESORT is the health economic evaluation comprising a Markov decision model constructed to model all three treatment arms.

Information on resource use will be collected during the trial. The EQ-5D, a standardized measure of health status, will be used to estimate quality-adjusted life years in all treatment groups. The incremental cost-effectiveness ratio (ICER) will be calculated for the three stents, and probabilistic sensitivity analysis will be applied to analyze decision uncertainty.

Sample size calculation

The BIO-RESORT trial will assess two non-inferiority hypotheses independently of each other, using RESOLUTE INTEGRITY as the reference to compare the novel biodegradable coating DES ORSIRO and SYNERGY. The main outcome parameter is the difference in TVF between two treatment arms after 12 months, analyzed by Chi-squared test. A total of 3,540 patients is enrolled based on a power calculation that assumes a TVF rate of 8.5% at 1-year follow-up, based on data of the TWENTE and Resolute All Comers trials[4,13], with a 3.5% non□inferiority margin, giving the study a power of at least 85% with a one-sided alpha level of 0.025 (from 0.05 adjusted for multiple testing to 0.025) and allowing for up to 3% loss to follow-up. The sample size calculation was performed with PASS software (NCSS, Kaysville, UA, USA).

Randomization

Patients are randomized by custom-designed computer software (Diagram, Zwolle, the Netherlands) when stent implantation is intended. Randomization is performed in random blocks of 6 and 3 in random order and stratified on the prevalence of medically treated diabetes mellitus.

Statistical considerations

Between-group differences in Target Vessel Failure (TVF) rate at 12 months will be analyzed for the two primary comparisons (SYNERGY versus RESOLUTE INTEGRITY and ORSIRO versus RESOLUTE INTEGRITY). The primary endpoint will be analyzed by the log-rank test by comparing the time to the primary endpoint using the Kaplan-Meier method. Non-inferiority will be achieved if the upper limit of the one-sided 97.5% confidence interval of the absolute risk difference is less than the non-inferiority margin. After non-inferiority has been established, superiority testing will be performed as well as calculation of two-sided 95% confidence intervals. The primary analyses will be performed based on intention-to-treat. In addition, we will perform a more conservative per-protocol analysis (i.e. based on the actual stents implanted) of the primary endpoint. Pre-specified 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. P-values <0.05 will be considered statistically significant, except for the primary analyses, as outlined.

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 will adjudicate all potential clinical endpoints. Moreover, an independent data safety monitoring board will evaluate safety interim analyses of all-cause mortality in the three stent arms performed after inclusion of 33% and 66% of the patient population. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the manuscript, and its final contents. Device-manufacturing companies will have no access to the study database and are not involved in the interpretation of data or manuscript preparation.

Discussion

The prospective BIO-RESORT multicenter trial performs a 1:1:1-randomized head-to-head comparison of two contemporary, flexible biodegradable coating DES (ORSIRO and SYNERGY) versus a third-generation, highly deliverable durable coating DES (RESOLUTE INTEGRITY) in all-comer patients. The trial examines two independent hypotheses, namely that the efficacy and safety of both ORSIRO and SYNERGY is non-inferior to that of RESOLUTE INTEGRITY. In addition, the three-arm study design offers the unique opportunity to compare the clinical performance of two modern biodegradable coating DES as a major secondary research question. The trial does not only compare three devices, but also three different "philosophies" as both biodegradable coating DES differ significantly in the distribution of coating and in the speed by which coatings are resorbed.

The development of DES with biodegradable coatings was prompted by a debate on the role of durable polymers as potential triggers of vascular inflammation and late adverse clinical events.[15,16] While the first biodegradable coating DES had more rigid stent designs with thicker struts, they had a clinical outcome that was generally similar and sometimes even superior to first and some second-generation durable coating DES. For instance, in the LEADERS trial, the BioMatrix stent showed non-inferiority at 5-year follow-up compared to Cypher (Cordis, New Jersey, USA) for a composite primary endpoint that included cardiac death, MI, or clinically-indicated TVR (22.3% vs. 26.1%, respectively; p non-inferiority <0.0001).[17] Similar to LEADERS, in COMPARE II, non-inferiority was shown for the same composite endpoint, comparing the biolimus-eluting, biodegradable coating Nobori stent (Terumo, Tokyo, Japan) with Xience (5.2% vs. 4.8%, respectively; p=0.69).[30] The SORT OUT V study, which compared Nobori and Cypher stents, however, did not find non-inferiority of the biodegradable stent;[31] this may partly be related to the particularly low event rate in SORT OUT V that

was at one year in the biodegradable stent arm lower than that of the BioMatrix stent in LEADERS (5.4% vs. 11%, respectively).[17,31]

Novel biodegradable coating DES, such as ORSIRO and SYNERGY, provide improved stent flexibility due to thin-strut stent designs and more flexible stent materials.[10,21,23] The SYNERGY stent uses a modified Element stent platform, made from a highly radiopaque platinum-chromium alloy with favorable strength and durability;[12,32,33] and the ORSIRO stent is based on a PRO-Kinetic Energy stent platform made from cobalt chromium.[23] While ORSIRO utilizes an asymmetric encompassing coating (abluminal coating >luminal coating) that is degraded within 1-2 years,[23] SYNERGY uses an abluminal coating only[21] that is degraded within 4 months; these dissimilarities in coating might result in differences of vascular inflammatory response to both DES. Differences in strut thickness could be of interest, as flexible thin-strut stent designs have previously been shown to be particularly efficacious in preventing restenosis.[18,19] Data provided by the BIO-RESORT trial may serve as reference to compare the results of upcoming studies with polymer-free DES[34,35] such as the novel BioFreedom stent[36] or the Cre8 stent (CID, Salugia, Italy), which has shown a lower 6-month late lumen loss than the Taxus Liberté stent (Boston Scientific Corporation, Natick, MA).[37]

In parallel with this innovative approach, novel durable coating DES with improved biocompatibility, such as the second-generation RESOLUTE stent, were developed and demonstrated a favorable clinical performance in the randomized Resolute All Comers and TWENTE trials.[4,13] Meanwhile, third-generation durable coating DES, such as RESOLUTE INTEGRITY, combine the proven efficacy and safety profiles of coatings and drugs of second-generation DES with more flexible stent designs. The cobalt chromium Integrity stent design is formed by a continuous sinusoidal technology that has shown to be highly deliverable.[11] The DUTCH PEERS (TWENTE II) trial is the first randomized study that reported safety and efficacy of RESOLUTE INTEGRITY in all-comers.[6]

The comparison of stents in all-comer patient populations is particularly useful, as the results of such studies reflect device performance in routine clinical practice and may be generalized.[2,17,30,31,39,40] A recent analysis of data of the TWENTE trial demonstrated an increased incidence of peri-procedural MI in patients with previously undetected diabetes.[40] Because of the increasing clinical and economic burden of diabetes in aging populations with a western lifestyle, BIO-RESORT pays particular attention to the outcome of diabetic patients. In brief, prior to randomization, all patients are stratified for medically treated diabetes mellitus. In addition, the levels of glycated hemoglobin (HbA1c) and fasting serum glucose are collected to identify previously undetected diabetics and assess the true impact of diabetes on clinical outcome, and to study in diabetic patients the impact of glycemic control on clinical outcome. The collected data will allow evaluation of the added value of testing for undetected diabetes regarding resource utilization.

Thus, BIO-RESORT is a large, prospective, randomized, controlled, mul-

ticenter trial with three arms, comparing in 3,540 all-comers two contemporary biodegradable coating DES versus a third-generation durable polymer coating DES as the reference. The trial will provide novel insights into the clinical outcome of modern DES and will address the impact of known and so far undetected diabetes mellitus on post-PCI outcome.

References

1. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007;50:463-470.
2. 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;375:201-209.
3. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-1674.
4. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350-1361.
5. Tandjung K, Sen H, Lam MK, et al. Clinical Outcome Following Stringent Discontinuation of Dual Anti-Platelet Therapy After 12 Months in Real-World Patients Treated With Second-Generation Zotarolimus- Eluting Resolute and Everolimus-Eluting Xience V Stents: Two-Year Follow-up of the Randomized TWENTE Trial. J Am Coll Cardiol 2013;61:2406-2416.
6. von Birgelen C, Sen H, Lam MK. Highly deliverable third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients (DUTCH PEERS): A randomised trial. Lancet; published online October 31, 2013 (doi:10.1016/S0140-6736(13)62037-1).
7. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393-1402.
8. 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.
9. Foin N, Sen S, Allegria E, et al. Maximal expansion capacity with current DES platforms: a critical factor for stent selection in the treatment of left main bifurcations? EuroIntervention 2013;8:1315-1325.
10. Menown IB, Noad R, Garcia EJ, et al. The platinum chromium element stent platform: from alloy, to design, to clinical practice. Adv Ther 2010;27:129-141.
11. Lee SW, Chan MP, Chan KK. Acute and 16-month outcomes of a new stent: the first-in-man evaluation of the Medtronic S9 (integrity) stent. Catheter Cardiovasc Interv 2011;78:898-908.
12. Stone GW, Teirstein PS, Meredith IT, 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;57:1700-1708.
13. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-146.
14. 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;124:624-632.
15. 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.
16. Waksman R, Maluenda G. Polymer drug-eluting stents: is the future biodegradable? Lancet 2011;378:1900-1902.
17. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease:

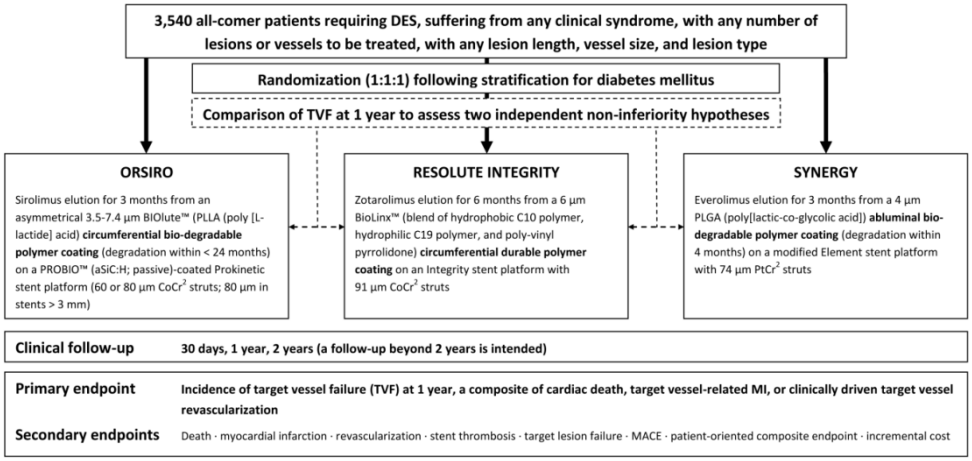
Final 5-year report of the LEADERS randomized, noninferiority trial. JACC Cardiovasc Interv. 2013;6:777-789.
18. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283-1288.
19. Briguori C, Sarais C, Pagnotta P, et al. In-stent restenosis in small coronary arteries: impact of strut thickness. J Am Coll Cardiol 2002;40:403-409
20. Hamon M, Niculescu R, Deleanu D, et al. Clinical and angiographic experience with a third-generation drug-eluting Orsiro stent in the treatment of single de novo coronary artery lesions (BIOFLOW-I): a prospective, first-in-man study. EuroIntervention 2013; 8:1006-1011.
21. Meredith IT, Verheye S, Weissman NJ, et al. Six-month IVUS and two-year clinical outcomes in the EVOLVE FHU trial: a randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent EuroIntervention. 2013; 9: 308-315.
22. Tittelbach M, Diener T. Orsiro - The first hybrid drug-eluting stent, opening up a new class of drug-eluting stents for superior patient outcomes. Interventional Cardiology 2011;6:142-144.
23. Koppara T, Joner M, Bayer G, et al. Histopathological comparison of biodegradable polymer and permanent polymer based sirolimus eluting stents in a porcine model of coronary stent implantation. Thromb Haemost. 2012;107:1161-1171.
24. Windecker S. Safety and clinical performance of the drug-eluting Orsiro stent in the treatment of subjects with single de novo coronary artery lesions-II (BIOFLOW-II). Presented as late breaking trial on May 21th at EuroPCR 2013 in Paris, France.
25. Waltenberger J, Hoffman S, Brachmann J, et al. BIOFLOW-III, an All Comers registry with a sirolimus eluting stent, presentation of one year target lesion failure rate. Presented on May 21th at EuroPCR 2013 in Paris, France.
26. Bennett J, Dubois C. A novel platinum-chromium everolimus-eluting stent for the treatment of coronary artery disease. Biologics 2013;7:149-159.
27. Williams PD, Mamas MA, Morgan KP, et al. Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms EuroIntervention. 2012; 8: 267-274.
28. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. EuroIntervention 2010;5:871-874.
29. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-2351.29.
30. Smits PC, Hofma S, Togni M, et al. 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.
31. Christiansen EH, Jensen LO, Thayssen P, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. Lancet 2013;381:661-669.
32. Wilson GJ, Huibregtse BA, Stejskal EA, et al. Vascular response to a third generation everolimus-eluting stent. EuroIntervention 2010;6:512-519.
33. Wilson GJ, Huibregtse BA, Pennington DE, et al. Comparison of the SYNERGY with the PROMUS (XIENCE V) and bare metal and polymer-only Element control stents in porcine coronary arteries. EuroIntervention 2012;8:250-257.36.
34. Basalus MW, Joner M, von Birgelen C, Byrne RA. Polymer coatings on drug-eluting stents: Samson's hair and Achilles' heel? EuroIntervention. 2013;9:302-305.
35. Waksman R, Pakala R, Baffour R, et al. In vivo comparison of a polymer-free Biolimus A9-eluting stent with a biodegradable polymer-based Biolimus A9 eluting stent and a bare metal stent in balloon denuded and radiated hypercholesterolemic rabbit iliac arteries Catheter Cardiovasc Interv. 2012;80:429-436.
36. Urban P, Abizaid A, Chevalier B, et al. Rationale and design of the LEADERS FREE trial: A randomized double-blind comparison of the BioFreedom drug-coated stent vs the

Gazelle bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy Am Heart J. 2013;165:704-709.
37. Carrie D, Berland J, Verheye S, et al. A multicenter randomized trial comparing amphilimus- with paclitaxel-eluting stents in de novo native coronary artery lesions J Am Coll Cardiol. 2012;59:1371-1376.
38. Silber S, Windecker S, Vranckx P, et al. RESOLUTE All Comers investigators. 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;377:1241-1247.40.
39. Sen H, Tandjung K, Basalus MW, et al. Comparison of eligible non-enrolled patients and the randomised TWENTE trial population treated with Resolute and Xience V drug-eluting stents. EuroIntervention. 2012;8:664-671.
40. Tandjung K, van Houwelingen KG, Jansen H, et al. 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;110:1561-1567.

Table 1. BIO-RESORT inclusion and exclusion criteria.

	Inclusion criteria
1.	Patient ≥ 18 years, capable of providing informed consent and willing and able to cooperate with study procedures and follow-up
2.	Coronary artery or bypass graft lesion(s) requiring PCI with DES implantation according to clinical guidelines and/or the operator's judgment
	Exclusion criteria
1.	Participation in another randomized drug or device trial before reaching its primary endpoint
2.	Known pregnancy
3.	Known intolerance to components of an investigational product, or to antithrombotic or anticoagulant medication, preventing adherence to dual antiplatelet therapy
4.	Planned elective surgical procedure during the first 6 months after randomization, necessitating the interruption of dual antiplatelet therapy
5.	Adherence to scheduled follow-up is uncertain and/or life expectancy assumed to be < 1 year

Figure 1.



Chapter 18

Summary and Conclusions

Summary

Stents have revolutionized the treatment of obstructive coronary disease by improving the safety of percutaneous coronary intervention (PCI) and reducing the need for repeat revascularization. First-generation drug-eluting stents (DES) were highly efficacious, as they further reduced the need for reintervention, but they left room for improvement in safety and stent deliverability. Newer-generation DES were designed for better biocompatibility and deliverability. Nevertheless, only few clinical data on the safety and efficacy of these newer-generation DES are available. This thesis has investigated various aspects of both safety and efficacy of newer-generation DES.

Chapter 1 serves as an introduction to this thesis and provides background information on the history of PCI as well as the development and the components of DES. In addition, this chapter provides a brief outline of the present thesis.

Chapter 2 presents 1-year data on safety and efficacy of second-generation DES, obtained from the TWENTE trial. In this investigator-initiated, patient-blinded, randomized study with limited exclusion criteria and a high proportion of complex patients and lesions, a total of 1391 patients were randomized to treatment with Resolute zotarolimus-eluting stents or Xience V everolimus-eluting stents. The primary composite endpoint target vessel failure (TVF; consisting of cardiac death, target vessel related myocardial infarction (MI), and 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). This large randomized clinical trial demonstrates that Resolute stents are non-inferior to Xience V stents in treating real-world patients with a majority of complex lesions and off-label indications for DES use.

Chapter 3 explores the real-world nature of the TWENTE trial by comparing baseline characteristics and clinical outcome of patients enrolled in the TWENTE trial with eligible patients, who were not enrolled in the randomized trial but treated with the same DES. Baseline characteristics of all eligible patients were analyzed (318 non-enrolled vs. 1.391 randomized patients). Non-enrolled and randomized patients differed in age and cardiovascular history, but 1-year clinical outcome, in particular the primary endpoint TVF (9.8% vs. 8.1%, p=0.34), did not differ significantly. This chapter shows that despite some differences in baseline characteristics, non-enrolled and randomized patients did not differ in one-year clinical outcome, demonstrating that the TWENTE trial enrolled real-world patients and that the favorable outcome may be related to the DES used.

Chapter 4 presents the pre-specified subgroup analysis of the gender-stratified TWENTE trial, which assessed potential differences in procedural and

clinical outcome between women treated with Resolute versus Xience V stents. Women are underrepresented in clinical research, and few data are available from randomized head-to-head comparisons of second-generation DES in female patients. A total of 382 (27.5%) women were randomized to Resolute and Xience V, and were similar in baseline and procedural characteristics, except for smaller vessel and stent diameters in the Resolute group. TVF at 1-year follow-up did not differ significantly between women in both stent arms (8.9 vs. 8.4%, p=0.91). In addition, women in the TWENTE trial were older than men and had more often diabetes mellitus and hypertension; however, there was no significant gender-difference in TVF (adjusted OR: 1.18, p=0.50). This chapter demonstrates no significant difference in safety and efficacy between women treated with Resolute versus Xience V.

In **Chapter 5**, we assess the 2-year outcome of the TWENTE trial in which patients followed a stringent discontinuation policy of dual-antiplatelet therapy (DAPT) after 12 months from PCI. The rate of continuation of DAPT beyond 12 months was very low (5.4%). TVF did not differ between patients treated with Resolute and Xience V (10.8% vs. 11.6%, p=0.65), despite fewer target lesion revascularizations in patients treated with Xience V (2.6% vs. 4.9%, p=0.03). In addition, definite-or-probable stent thrombosis occurred infrequently (1.2% and 1.4%, respectively, p=0.63). Very late definite-or-probable stent thrombosis occurred only in 2 patients per stent group (0.3% vs. 0.3%, p=1.0). This chapter shows that after 2 years of follow-up and stringent discontinuation of DAPT beyond 12 months, Resolute and Xience V show similar results in terms of safety and efficacy for treating patients with a majority of complex lesions and off-label indications for DES use.

Chapter 6 presents the effects of stent postdilatation on the coatings of five durable polymer DES as assessed by scanning electron microscopy (SEM) in a bench-top setting. Between postdilated and non-postdilated stent regions, the incidence and type of coating irregularities differed only mildly. The impact of stent postdilatation was particularly low in newer-generation DES. These findings suggest that even very aggressive stent postdilatation has no more than a modest effect on the coatings of various durable polymer DES.

In **Chapter 7**, we assess the occurrence of periprocedural MI in 800 patients, treated with first (Taxus Liberté or Endeavor) or second-generation DES (Xience V or Resolute). This chapter demonstrates that there is no significant difference in periprocedural MI between first and second-generation DES (5.5% vs. 4.0%, p=0.29) despite more multivessel PCI in patients treated with second-generation DES. Independent predictors of periprocedural MI were the total number of stents implanted and a presentation with an acute coronary syndrome.

Chapter 8 presents findings of our SEM assessment of DES coating irregular-

ities in unexpanded and expanded durable polymer DES in order to gain insight into the origin of coating irregularities. In 15 expanded and 15 unexpanded samples of Cypher Select Plus, Taxus Liberté, Endeavor, Xience V, and Resolute a total of 1.200 SEM images were thoroughly examined. For most coating irregularities, seen on expanded DES, a matching irregularity and/or its precursor was observed in the unexpanded DES. This data show that most coating irregularities are inherent to the unexpanded DES. Determinants of the formation of coating irregularities may be physical properties of the coating or stent geometry, while stent-balloon interaction plays no major role.

In **Chapter 9**, we investigate the relation between previously undetected diabetes mellitus and clinical outcome after PCI with second-generation DES. A total of 626 patients, in whom HbA1c measurements were available, were classified as known diabetics or patients without a history of diabetes, who were then subdivided into previously undetected diabetics (HbA1c >6.5%) and non-diabetics (HbA1c <6.5%). Multivariate analysis confirmed a significantly higher periprocedural MI risk in undetected diabetics compared to non-diabetics (OR 6.13) and known diabetics (OR 3.73). The target vessel MI rate at 1-year was significantly higher in undetected diabetics than in non-diabetics, which was mainly related to differences in periprocedural MI. The composite endpoint TVF was numerically higher in unknown diabetics than in non-diabetics, but this difference did not reach statistical significance. This chapter shows that undetected and thus untreated diabetics are at an increased risk of periprocedural MI, a risk that was even higher than in treated diabetics.

Chapter 10 addresses the predictive value of the Syntax Score (SxS), a scoring system to quantify the complexity of coronary artery disease, for the occurrence of a periprocedural MI according to both, the definition of the World Health Organization (WHO) and the recently updated Universal Definition of MI. The SxS was calculated in 1243 patients enrolled in the TWENTE trial. WHO periprocedural MI occurred more frequently in patients in the highest tertile group of SxS (7.3% vs. 3.1% vs. 1.6%, p<0.001) compared to the mid and lowest tertile groups of SxS. Similar findings were also seen for Universal periprocedural MI (9.9% vs. 7.7% vs. 3.7%, p<0.01). This chapter shows that there is a relation between the angiographic burden, as assessed by the SxS, and the risk of periprocedural MI. Thus, preprocedural assessment of the SxS could help to identify patients at increased risk of periprocedural MI.

Chapter 11 presents the prognostic value of coronary dominance for adverse clinical events following the implantation of second-generation DES. Based on the origin of the posterior descending coronary artery, the coronary circulation can be categorized into left and non-left dominance. Left dominance was associated with more severe calcifications and more bifurcation-lesions. In addition, left coronary dominance was associated

with more target vessel related MI (10.3% vs. 5.0%, p<0.01). Left dominance was independently associated with a periprocedural MI (adjusted OR 2.19, p=0.02), while no difference in other clinical endpoints was observed between coronary dominance groups. While our data may not have direct clinical implications, the findings suggest that further research may be warranted to clarify the role of coronary dominance.

In **Chapter 12**, we provide insight into our center's clinical experience with the use of the GuideLiner (GL) catheter, a guiding catheter extension system that enhances intubation and support of guiding catheters. In 65 consecutive patients, undergoing "5-in-6" Fr GL-facilitated PCI of 70 target vessels, the GL was mainly used for PCI of complex coronary lesions. Indications were to increase back-up of the guiding catheter and facilitate stent delivery (59%), achievement of coaxial alignment of the guiding catheter (29%), and selective contrast injections (13%). Device success rate was 93%. There were only two minor complications managed without clinical sequelae. This chapter shows that GL-use can increase back-up and guiding catheter alignment for stent delivery in unfavorable coronary anatomies that otherwise may have been considered unsuitable for treatment with PCI.

In **Chapter 13,** we present the aspiration of an intact coronary bifurcation thrombus in a patient with ST-elevation MI, who was consecutively treated with Resolute Integrity DES. This is an example of the challenging coronary lesions that interventional cardiologist encounter in their daily clinical practice.

Chapter 14 describes the design of the DUTCH PEERS trial (TWENTE II). This study is the first randomized multicenter trial to investigate the Resolute Integrity stent and the first study to compare the third-generation Resolute Integrity and Promus Element stents in all-comer patients.

Chapter 15 presents the 1-year clinical outcome of the randomized DUTCH PEERS trial to assess the safety and efficacy of these two third-generation DES in all-comer patients. These DES are often used clinically, but had not yet been compared in a randomized trial. In this investigator-initiated, single-blind, multicenter, randomized, non-inferiority trial, 1811 patients were randomized to treatment with Resolute Integrity or Promus Element. The primary endpoint was TVF at 12 months, a composite endpoint reflecting safety and efficacy of the devices. Of all patients, 20% presented with ST-elevation MI and 25% with non- ST-elevation MI. The ease of stent delivery was reflected by a very low number of patients requiring treatment with a stent other than the assigned study stent. TVF was met by 6.1% of patients in the Resolute group and 5.2% in the Promus Element group ($p_{non\text{-}inferiority} = 0.006$). The rate of definite stent thrombosis was low and similar in both DES groups (0.3% and 0.7%, respectively, p=0.34). Longitudinal stent deformation was seen only in Promus Element treated patients (0.6% of all implanted Promus

Element stents), but was not associated with any adverse clinical events. This chapter shows that both third-generation DES were similarly efficacious and safe, and provided excellent clinical outcomes, especially in view of the large number of patients who presented with acute MI.

Chapter 16 describes the results of a network meta-analysis to compare the safety and efficacy of biolimus-eluting biodegradable polymer stents versus first and second-generation durable polymer DES. A total of 60 randomized controlled trials were compared, involving 63242 patients who had all been treated by PCI with DES. At 1-year, there was no difference in mortality among different DES. Resolute zotarolimus-eluting stent, everolimus-eluting stent, Endeavor zotarolimus-eluting stent, and sirolimus-eluting stent, but not biodegradable polymer biolimus-eluting stent, significantly reduced the odds of MI by 29-34% as compared to the paclitaxel-eluting stent. Compared to the everolimus-eluting stent, biodegradable polymer biolimus-eluting stent significantly increased the odds of MI by 29%, while Endeavor zotarolimus-eluting stent and paclitaxel-eluting stent significantly increased the odds of stent thrombosis. All investigated DES were similar with regards to efficacy endpoints, except for zotarolimus-eluting Endeavor stent and paclitaxel-eluting stent, which significantly increased the odds of target lesion and target vessel revascularization. Bayesian probability curves showed a gradient in the magnitude of effect with everolimus-eluting stent and Resolute zotarolimus-eluting stent offering the highest safety profiles. This chapter shows that the durable polymer everolimus-eluting stent and Resolute zotarolimus-eluting stent and the biodegradable polymer biolimus-eluting stent maintain the efficacy of the sirolimus-eluting stent. However, for safety endpoints, everolimus-eluting stent and Resolute zotarolimus-eluting stent emerged as the safest stents to date.

In **Chapter 17,** we describe the design and rationale of the BIO-RESORT (TWENTE III) trial. BIO-RESORT is an investigator-initiated, prospective, patient-blinded, randomized multicenter trial, in which two novel DES with biodegradable polymer coatings are compared with a durable coating-based DES in at least 3540 all-comer patients. The study population is randomized in a 1:1:1 fashion between the Orsiro sirolimus-eluting stent with circumferential biodegradable coating, the Synergy everolimus-eluting stent with abluminal biodegradable coating, and the Resolute Integrity zotarolimus-eluting stent with durable coating. The composite primary endpoint is the incidence of TVF at 1-year. This trial does not only compare three devices, but also three different "philosophies", as both biodegradable coating DES differ significantly in the distribution of coating on the stent struts and in the speed by which the coatings are degraded. The BIO-RESORT trial will undoubtedly provide novel insights into the performance and clinical value of modern DES.

Conclusions

Drug-eluting stents are still subject to a continuous process of refinement in order to optimize stent deliverability and improve clinical outcome. Nowadays, DES are preferably tested in patients who reflect daily clinical practice, rather than in highly selected patient subsets. This thesis shows that PCI with second-generation DES have a favorable clinical outcome in real-world patients without significant differences between the tested stents and regardless of the patient's gender, as demonstrated by the gender-stratified randomized TWENTE trial. The greater biocompatibility of DES coatings and the absence of major coating irregularities, as observed by bench-top research, might have contributed to the favorable results of these DES. Among the overall relatively infrequent adverse events following PCI with second-generation DES, periprocedural MI is most common event, which appears to be related to certain risk factors, such as left coronary dominance and undetected diabetes mellitus. Third-generation durable polymer DES with improved stent designs have an excellent deliverability and clinical outcome, as shown by the randomized DUTCH PEERS (TWENTE II) trial. DES with biodegradable polymer coatings, which were developed to further enhance device biocompatibility, are an alternative to durable polymer DES, as they show similar efficacy without the risk of inducing prolonged vessel wall inflammation. The currently ongoing randomized BIO-RESORT trial (TWENTE III) will answer the question whether modern biodegradable polymer DES are truly non-inferior to third-generation durable polymer DES.

Chapter 19

Nederlandse Samenvatting en Conclusie

Nederlandse Samenvatting

Stents hebben voor een revolutie in de behandeling van coronaire atherosclerose gezorgd door het verbeteren van de veiligheid van percutane coronaire interventies (PCI) en het verminderen van de noodzaak voor een nieuwe revascularisatie na een initiële PCI. Eerste generatie drug-eluting stents (DES) waren zeer doeltreffend, omdat ze de behoefte aan een revascularisatie nog verder verminderden, maar lieten nog ruimte voor verbetering van de veiligheid van de procedure en gemak een stent succesvol te plaatsen. Nieuwere generatie DES werden hierop ontworpen voor een betere biocompatibiliteit en plaatsbaarheid. Niettemin zijn er slechts weinig klinische gegevens beschikbaar over de veiligheid en werkzaamheid van deze nieuwere generatie DES. Dit proefschrift beschrijft de resultaten van ons onderzoek naar verschillende aspecten van zowel de veiligheid en werkzaamheid van nieuwere generatie DES.

Hoofdstuk 1 dient als een inleiding op dit proefschrift en geeft achtergrondinformatie over de geschiedenis van de PCI, alsmede de ontwikkeling en de verschillende componenten van DES.

Hoofdstuk 2 beschrijft de resultaten van 1 jaar follow-up ten aanzien van de veiligheid en werkzaamheid van de tweede generatie DES, verkregen uit de TWENTE trial. In dit onderzoeker geïnitieerde, patiënt geblindeerd, gerandomiseerde onderzoek met een beperkte aantal exclusie criteria en een groot aandeel complexe patiënten en laesies, werden 1391 patiënten gerandomiseerd naar behandeling met Resolute zotarolimus-afgevende stents of Xience V everolimus-afgevende stents. Het samengestelde eindpunt target vessel failure (TVF, bestaande uit overlijden aan een cardiale doodsoorzaak, een niet fataal myocardinfarct (MI), en een revascularisatie) trad op bij 8.2% en 8.1% van Resolute en Xience V behandelde patiënten (p non-inferioriteit = 0.001). Het optreden van definitieve of mogelijke stent trombose kwam relatief weinig voor en was gelijk voor beide DES (0.9% en 1.2%, p = 0.59). Deze grote gerandomiseerde studie toont aan dat Resolute stents niet inferieur zijn aan Xience V stents bij de behandeling van patienten met een meerderheid van complexe coronaire laesies en off-label indicaties voor DES gebruik.

Hoofdstuk 3 laat zien dat patiënten die in de TWENTE trial geïncludeerd zijn, daadwerkelijk een goede afspiegeling zijn van patiënten die gezien worden in de dagelijkse praktijk. Dit werd gedaan door patiënt karakteristieken en de klinische uitkomst van patiënten die geïncludeerd werden in de TWENTE trial te vergelijken met patiënt die in aanmerking kwamen voor de trial, maar niet geïncludeerd zijn en wel met dezelfde DES behandeld zijn. Patiënt karakteristieken van alle patiënten die in aanmerking kwamen voor deelname aan de TWENTE trial werden geanalyseerd (318 niet-geincludeerde versus 1391 gerandomiseerde patiënten). Niet-geincludeerde en gerandomiseerde patiënten verschilden

in leeftijd en cardiovasculaire voorgeschiedenis, echter de klinische resultaten na 1 jaar verschilden niet significant en met name niet op het eindpunt TVF (9.8% versus 8.1%, p = 0.34). Dit hoofdstuk laat zien dat ondanks geringe verschillen in karakteristieken, niet-geincludeerde en gerandomiseerd patiënten niet verschilden in klinische resultaten. Hieruit blijkt dat in de TWENTE trial patiënten werden geïncludeerd die een goede afspiegeling vormen van de dagelijkse praktijk en dat de gunstige uitkomst ook mogelijk gerelateerd kunnen worden aan de gebruikte DES.

Hoofdstuk 4 presenteert de vooraf gespecificeerde subgroepanalyse van de geslachts-gestratificeerde TWENTE trial, om mogelijke verschillen in procedurele en klinische uitkomst te onderzoeken tussen vrouwen die behandeld werden met Resolute of Xience V stents. Vrouwen zijn vaak ondervertegenwoordigd in cardiovasculair onderzoek en daarnaast uit constateringen uit het verleden hadden vrouwen een slechtere uitkomst na een dotter procedure. In totaal werden 382 (27.5%) vrouwen gerandomiseerd voor behandeling met Resolute en Xience V. Zij waren vergelijkbaar in patient karakteristieken en procedurele kenmerken, met uitzondering van gemiddeld kleinere kranslagvaten en stent diameters in de Resolute groep. TVF na 1 jaar follow-up was niet significant verschillend tussen de vrouwen in beide stent groepen (8.9 versus 8.4%, p = 0.91). Verder was er geen significant verschil in TVF tussen vrouwen en mannen (gecorrigeerde odds ratio: 1.18, p = 0.50) ondanks dat zij ouder waren dan mannen en vaker diabetes mellitus en hypertensie hadden. Dit hoofdstuk toont aan dat bij vrouwen Resolute of Xience V stents gelijkwaardig veilig en effectief zijn.

In **hoofdstuk 5** beschrijven we de 2-jaars resultaten van de TWENTE trial. In de TWENTE trial werd een strikt stopzettingbeleid gevolgd ten aanzien van de dubbele anti-trombocyten aggregatie remming (DAPT) 12 maanden na de PCI. Voortzetting van de DAPT na 12 maanden kwam weinig voor (5.4%). TVF verschilde niet tussen patiënten die behandeld waren met Resolute en Xience V stents (10.8% versus 11.6%, p = 0.65), ondanks het minder voorkomen van revascularisaties bij patiënten die behandeld met Xience V stents waren (2.6% versus 4.9%, p = 0.03). In 2 jaar tijd kwam bovendien definitieve of vermoedelijke stent trombose zelden voor (1.2% en 1.4%, respectievelijk, p = 0.63). Definitieve of vermoedelijke stent trombose in het 2e jaar kwam slechts bij 2 patiënten in elke stent groep voor (0.3% versus 0.3%, p = 1.0). Dit hoofdstuk laat zien dat na 2 jaar follow-up en een strikt stopzettingbeleid van DAPT na 12 maanden, Resolute en Xience V stents vergelijkbare resultaten hadden op het gebied van veiligheid en effectiviteit voor de behandeling van patiënten die veelal complexe laesies en off-label indicaties voor DES implantatie hadden.

Hoofdstuk 6 toont de effecten van het postdilateren van een stent op de coatings van vijf permanent polymeer gebaseerde DES, bekeken met scanning electron microscopie (SEM). Tussen gepostdilateerde en niet-gepostdilateerde stent regio's verschilde de incidentie en type coating

onregelmatigheden slechts geringe mate. De impact van de stent postdilatatie was met name beperkt in nieuwere generatie DES. Deze bevindingen suggereren dat zelfs het zeer agressief stent postdilateren slechts een bescheiden effect heeft op de coatings van verschillende permanent polymeer gebaseerde DES.

In **hoofdstuk 7** beoordelen we het optreden van een peri-procedureel MI bij 800 patiënten na implantatie van eerste (Taxus Liberte of Endeavor) of tweede generatie DES (Xience V of Resolute). Dit hoofdstuk toont aan dat er geen significant verschil is in het optreden van een peri-procedureel MI tussen eerste en tweede generatie DES (5.5% versus 4.0%, p = 0.29), ondanks het meer voorkomen van PCI van meerdere vaten tegelijkertijd bij patiënten behandeld met een tweede generatie DES. Onafhankelijke voorspellers voor het optreden van een peri-procedureel MI waren het totaal aantal geïmplanteerde stents en een presentatie met een acuut coronair syndroom.

Hoofdstuk 8 presenteert de bevindingen met SEM ten aanzien van DES coating onregelmatigheden in niet-geëxpandeerde en geëxpandeerde DES om inzicht in het ontstaan van de coating onregelmatigheden te krijgen. In 15 geëxpandeerde en 15 niet-geëxpandeerde samples van Cypher Select Plus, Taxus Liberte, Endeavor, Xience V, en Resolute werden 1200 SEM beelden grondig onderzocht. Voor de meeste coating onregelmatigheden, gezien op geëxpandeerde DES, werd een bijpassende onregelmatigheid en / of zijn voorloper waargenomen in de niet-geëxpandeerde DES. Deze gegevens tonen aan dat coating onregelmatigheden inherent zijn aan de geëxpandeerde DES. Determinanten in de vorming van coating onregelmatigheden kunnen fysieke eigenschappen van de coating of de stent geometrie zijn, terwijl stent-ballon interacties waarschijnlijk geen grote rol spelen.

In **hoofdstuk 9** onderzoeken we de relatie tussen onontdekte diabetes mellitus en de klinische uitkomst na PCI met de tweede generatie DES. 626 patiënten, bij wie HbA1c-metingen beschikbaar waren, werden geclassificeerd als patiënten bekend met diabetes mellitus of patiënten zonder een geschiedenis van diabetes, die vervolgens werden onderverdeeld in onontdekte diabetici (HbA1c> 6.5%) en niet diabetici (HbA1c <6.5%). Multivariate analyse bevestigde een aanzienlijk hoger peri-procedureel MI risico bij onontdekte diabetici vergeleken met niet diabetici (OR 6.13) en bekende diabetici (OR 3.73). MI in een eerder behandeld vat was bij onontdekte diabetici significant hoger dan in niet diabetici, voornamelijk ten gevolge van verschillen in het optreden van een peri-procedureel MI. Het samengestelde eindpunt TVF was numeriek hoger in onontdekte diabeten dan in niet diabetici, maar dit verschil was niet statistisch significant. Dit hoofdstuk laat zien dat onopgemerkt en dus onbehandelde diabetes patiënten een verhoogd risico op het optreden van een peri-procedureel MI hebben, een risico dat zelfs hoger was dan in de bekende diabetici.

Hoofdstuk 10 behandelt de voorspellende waarde van de Syntax Score (SxS , een scoresysteem die de complexiteit van coronaire hartziekte probeert te kwantificeren) voor het optreden van een peri-procedureel MI volgens de definitie van de World Health Organization (WHO) en de onlangs vernieuwde universele definitie van een MI. De SxS werd berekend in 1243 patiënten die deelnamen aan de TWENTE trial. Een WHO peri-procedureel MI kwam vaker voor bij patiënten in het hoogste tertiel van de SxS (7.3% versus 3.1% versus 1.6%, p <0.001) in vergelijking met patiënten uit het middelste en laagste tertiel van de SxS. Soortgelijke bevindingen werden ook gezien voor de peri-procedureel MI volgens de universele definitie (9.9% versus 7.7% versus 3.7%, p <0.01). Dit hoofdstuk laat zien dat er een relatie is tussen de angiografische uitgebreidheid van coronairlijden, zoals beoordeeld met de SxS, en het risico op een peri-procedureel MI. De preprocedurele beoordeling van de SxS zou kunnen helpen om patiënten met een verhoogd risico van op een peri-procedureel MI te identificeren.

Hoofdstuk 11 presenteert de prognostische waarde van coronaire dominantie voor ongunstige klinische gebeurtenissen na de implantatie van tweede generatie DES. Op basis van de oorsprong van de achterste aflopende kransslagader, kan de coronaire circulatie worden onderverdeeld in linker en niet-linker dominantie. Links dominantie werd geassocieerd met meer ernstige verkalkingen en meer bifurcatie stenosen. Bovendien werd linker coronaire dominantie geassocieerd met MI aan een eerdere behandeld vat (10.3% versus 5.0%, p <0.01). Links dominantie werd onafhankelijk geassocieerd met een peri-procedureel MI (aangepaste OR 2.19, p = 0.02), terwijl geen verschil in andere klinische eindpunten werden waargenomen tussen coronaire dominantie groepen. Hoewel onze gegevens niet direct klinische gevolgen zullen hebben, suggereren de bevindingen dat verder onderzoek gerechtvaardigd is om de rol van coronaire dominantie op ongunstige klinische gebeurtenissen te verduidelijken.

In **hoofdstuk 12** geven wij inzicht de klinische ervaring van ons centrum met het gebruik van de GuideLiner (GL) catheter, een catheter extensie systeem die de intubatie en ondersteuning van geleidecatheters verbetert. In 65 opeenvolgende patiënten, waarbij PCI werd verricht van 70 kransslagvaten waarbij een "5-in-6" Fr GL techniek werd gebruikt, werd de GL voornamelijk gebruikt voor PCI van complexe coronaire laesies. Indicaties waren het verbeteren van de ondersteuning van de geleidecatheter om stentplaatsing te bewerkstelligen (59%), verbetering van de coaxiale uitlijning van de geleidecatheter (29%) en voor het vergemakkelijken van electieve contrastinjecties (13%). Het slagingspercentage om een stent te plaatsen was 93%. Er waren slechts twee milde complicaties zonder klinische gevolgen. Dit hoofdstuk laat zien dat GL succesvol gebruikt kan worden om de ondersteuning en uitlijning

van de geleidecatheters te verbeteren in een ongunstige coronaire anatomie die anders niet geschikt geacht waren voor een PCI.

In **hoofdstuk 13** presenteren we de aspiratie van een intacte coronaire bifurcatie trombus bij een patiënt met een ST-elevatie MI, die achtereenvolgens werd behandeld met Resolute Integrity DES. Dit is een uitstekend voorbeeld van uitdagende coronaire laesies die interventiecardiologen tegenkomen in hun dagelijkse klinische praktijk.

Hoofdstuk 14 beschrijft de opzet van de DUTCH PEERS trial (TWENTE II). Deze studie is de eerste gerandomiseerde multicenter trial die onderzoek doet naar de Resolute Integrity stent en de eerste studie die de derde generatie Resolute Integrity en Promus Element stents vergelijkt in een allcomer patiëntenpopulatie.

Hoofdstuk 15 presenteert de 1-jaars resultaten van de gerandomiseerde DUTCH PEERS studie die de veiligheid en werkzaamheid van deze twee derde generatie DES onderzoekt in een allcomer patiëntenpopulatie. Deze DES worden klinisch vaak gebruikt, maar waren nog niet vergeleken in een gerandomiseerde trial. In deze onderzoeker geïnitieerde, patiënt geblindeerd, multicenter, gerandomiseerde, non-inferioriteit studie, werden 1811 patiënten gerandomiseerd naar behandeling met Resolute Integrity of Promus Element. Het primaire eindpunt was het optreden van TVF na 12 maanden (een samengesteld eindpunt die veiligheid en werkzaamheid van stents weergeeft). Van alle patiënten presenteerden 20% met een ST-elevatie MI en 25% met een niet-ST-elevatie MI. Het gemak van stent plaatsing werd weerspiegeld door een bijzonder lage aantal patiënten die met een andere dan de toegewezen studie stent werden behandeld. TVF werd gezien in 6.1% van de patiënten in de Resolute groep en 5.2% in de Promus Element groep (p non-inferioriteit = 0.006). Het percentage definitieve stent trombose was laag en vergelijkbaar in beide groepen DES (0.3% en 0.7%, respectievelijk p = 0.34). Longitudinale stent vervorming werd alleen gezien bij Promus Element behandelde patiënten (0.6% van alle geïmplanteerde Promus Element stents), maar was niet geassocieerd met ongunstige klinische gebeurtenissen. Dit hoofdstuk laat zien dat beide derde generatie DES gelijkwaardig veilig en effectief zijn en uitstekende klinische resultaten hebben, met name gezien het grote aantal patiënten die met een acuut MI werden gepresenteerd.

Hoofdstuk 16 beschrijft de resultaten van een netwerk meta-analyse om de veiligheid en werkzaamheid van biolimus-eluting stents met biologisch afbreekbaar polymeer te vergelijken versus eerste en tweede generatie DES, die een permanent polymeer hebben. In totaal werden 60 gerandomiseerde gecontroleerde studies beoordeeld waarin 63242 patiënten waren behandeld met een PCI met DES plaatsing. Na 1 jaar follow-up was er geen verschil in mortaliteit tussen de verschillende DES. De Resolute zotarolimus-eluting

stent, Endeavor zotarolimus-eluting stent, everolimus-eluting stent, en sirolimus-eluting stent, maar niet de biolimus-eluting stent met biologisch afbreekbaar polymeer, verminderden de kans op het krijgen van een MI met 29-34% ten opzichte van de paclitaxel-eluting stent. Vergeleken met de everolimus-eluting stent, was bij de biologisch afbreekbaar polymeer-biolimus eluting stent de kans op een MI met 29% verhoogd, terwijl de kans op stent trombose verhoogd was bij de Endeavor zotarolimus-eluting stent en paclitaxel-eluting stent. Met betrekking tot overige eindpunten waren de onderzochte DES vergelijkbaar. Bayesiaanse kans curves toonden aan dat de everolimus-eluting stent en de Resolute zotarolimus-eluting stent het beste veiligheidsprofiel hadden. Dit hoofdstuk laat zien dat everolimus-eluting stent, Resolute zotarolimus-eluting stent en biolimus-eluting stent met biologisch afbreekbaar polymeer dezelfde effectiviteit als de sirolimus-eluting stent hebben. Echter, ten aanzien van veiligheidseindpunten komen de everolimus-eluting stent en Resolute zotarolimus-eluting stent naar voren als de veiligste stents tot nu toe.

In **hoofdstuk 17** beschrijven we het ontwerp en rationale van de BIO-RESORT (TWENTE III) trial. De BIO- RESORT trial is een onderzoeker geïnitieerde, prospectieve, patiënt geblindeerde, gerandomiseerde multicenter trial waarin twee nieuwe DES met biologisch afbreekbaar polymeer coating worden vergeleken met een DES met een permanente coating in ten minste 3540 allcomer patiënten. Patiënten worden gerandomiseerd voor behandeling met de Orsiro sirolimus-eluting stent met een circumferentiëel biologisch afbreekbare coating, de Synergy everolimus-eluting stent met een abluminaal biologisch afbreekbare coating en de Resolute Integrity zotarolimus-eluting stent met duurzame polymeer coating. Het primaire eindpunt is optreden van TVF na 1-jaar follow-up. Bij dit onderzoek worden niet alleen drie stents vergeleken, maar ook drie verschillende stent coating "filosofieën": de biologisch afbreekbare coating DES verschillen aanzienlijk in de verdeling van de coating op het stent oppervlak en de snelheid waarmee de coatings worden afgebroken. De BIO-RESORT trial zal nieuwe inzichten verschaffen in de prestaties en klinische waarde van moderne nieuwe DES.

Conclusie

Drug-eluting stents worden continu verfijnd om de stent plaatsing te optimaliseren en klinische uitkomst te verbeteren. Tegenwoordig worden DES bij voorkeur getest in een patiëntenpopulatie die de dagelijkse praktijk weerspiegeld en niet in zeer geselecteerde patiëntengroepen. Dit proefschrift toont aan dat PCI met tweede generatie DES een gunstig resultaat hebben in patiëntenpopulatie die de dagelijkse praktijk weerspiegeld zonder significante verschillen tussen de onderzochte stents, ongeacht het geslacht van de patiënt, zoals blijkt uit de gerandomiseerde TWENTE trial. De biocompatibiliteit van de DES coatings en afwezigheid

van grote coating onregelmatigheden, zoals waargenomen bij bench-top onderzoek, kan hebben bijgedragen aan de gunstige resultaten van deze DES. Van de ongewenste gebeurtenissen na een PCI is een peri-procedureel optredende MI de meest voorkomende. Deze lijkt samen te hangen met bepaalde risicofactoren, zoals links coronaire dominantie en onontdekte diabetes mellitus. Derde generatie DES met een verbeterd stent ontwerp hebben een uitstekende plaatsbaarheid en klinische uitkomst, zoals blijkt uit de gerandomiseerde DUTCH PEERS (TWENTE II) trial. DES met een biologisch afbreekbaar polymeer, die werden ontwikkeld om de biocompatibiliteit te verbeteren, zijn een alternatief voor DES met een permanent polymeer. Deze vertonen een gelijkwaardige werkzaamheid zonder het risico van het induceren van langdurige vaatwand ontsteking. De op dit moment lopende gerandomiseerde BIO-RESORT trial (TWENTE III) zal de vraag beantwoorden of moderne DES met biologisch afbreekbaar polymeer echt gelijkwaardig zijn aan derde generatie DES met een permanent polymeer.

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Portfolio

Curriculum Vitae

Kenneth Tandjung was born on 26 november 1981 in Amstelveen. After his exams at the Hermann Wesselink College at Amstelveen, he studied medicine at the Vrije Universiteit in Amsterdam. After getting his MD degree he pursued a career in cardiology. Before being admitted in the cardiology training program at Thoraxcentrum Twente at Enschede, he worked at the cardiology department of the HagaZiekenhuis at The Hague and the Vrije Universiteit at Amsterdam. In 2010 he commenced his PhD program, which led to this thesis. He was a full-time researcher for 3 years and from 2013 he combined the cardiology training program with his PhD. In 2018 he will complete his cardiology training.

Awards

First prize for oral presentation at the Wetenschapssymposium of Thoraxcentrum Twente. Enschede in 2013.

Publications

1. Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, de Man FH, Louwerenburg JW, 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 Aug;18(7-8):360-4.
2. 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 Apr;24(2):149-61.
3. Basalus MW, Tandjung K, van Westen T, Sen H, van der Jagt PK, Grijpma DW, et al. Scanning electron microscopic assessment of coating irregularities and their precursors in unexpanded durable polymer-based drug-eluting stents. Catheter Cardiovasc Interv. 2012 Mar 1;79(4):644-53.
4. Tandjung K, Basalus MW, Muurman E, Louwerenburg HW, van Houwelingen KG, Stoel MG, et al. Incidence of periprocedural myocardial infarction following stent implantation: Comparison between first- and second-generation drug-eluting stents. Catheter Cardiovasc Interv. 2012 Oct 1;80(4):524-30.
5. von Birgelen C, Basalus MW, Tandjung K, van Houwelingen KG, Stoel MG, Louwerenburg JH, et al. A randomized controlled trial in second-generation zotarolimus-eluting resolute stents versus everolimus-eluting xience V stents in real-world patients: The TWENTE trial. J Am Coll Cardiol. 2012 Apr 10;59(15):1350-61.
6. Tandjung K, Basalus MW, Sen H, Jessurun GA, Danse PW, Stoel M, 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 Apr;163(4):557-62.
7. Sen H, Tandjung K, Basalus MW, Lowik MM, van Houwelingen GK,

Stoel MG, et al. Comparison of eligible non-enrolled patients and the randomised TWENTE trial population treated with resolute and xience V drug-eluting stents. EuroIntervention. 2012 Oct;8(6):664-71.
8. de Man FH, Tandjung K, Hartmann M, van Houwelingen KG, Stoel MG, Louwerenburg HW, et al. Usefulness and safety of the GuideLiner catheter to enhance intubation and support of guide catheters: Insights from the twente GuideLiner registry. EuroIntervention. 2012 Jul 20;8(3):336-44.
9. Sen H, Lam MK, Tandjung K, Lowik MM, Stoel MG, de Man FH, et al. Complex patients treated with zotarolimus-eluting resolute and everolimus-eluting xience V stents in the randomized TWENTE trial: Comparison of 2-year clinical outcome. Catheter Cardiovasc Interv. 2014 Feb 28.
10. Tandjung K, van Houwelingen KG, Jansen H, Basalus MW, Sen H, Lowik MM, et al. 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 Dec 1;110(11):1561-7.
11. Tandjung K, Basalus MW, Sen H, Stoel MG, van Houwelingen KG, Louwerenburg JH, et al. 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 Sep 1;82(3):396-405.
12. Tandjung K, Sen H, Lam MK, Basalus MW, Louwerenburg JH, Stoel MG, et al. 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 Jun 18;61(24):2406-16.
13. von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): A randomised, single-blind, multicentre, non-inferiority trial. Lancet. 2014 Feb 1;383(9915):413-23.
14. Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: Comprehensive network meta-analysis. BMJ. 2013 Nov 6;347:f6530.
15. Lam MK, Tandjung K, Sen H, Basalus MW, van Houwelingen KG, Stoel MG, et al. Coronary artery dominance and the risk of adverse clinical events following percutaneous coronary intervention: Insights from the prospective, randomised TWENTE trial. EuroIntervention. 2014 Feb 28. *In press.*
16. von Birgelen C, Tandjung K, Lam MK. Aspiration of intact coronary bifurcation thrombus in ST-elevation myocardial infarction. Int J Cardiol. 2014 Mar 1;172(1):e245-6.
17. Lam MK, Sen H, Tandjung K, van Houwelingen KG, de Vries AG, Danse PW, et al. Comparison of 3 biodegradable polymer and durable polymer-based drug-eluting stents in all-comers (BIO-RESORT): Rationale and study design of the randomized TWENTE III multicenter trial. Am Heart J. 2014 Apr;167(4):445-51.
18. Lam MK, Sen H, Tandjung K, Lowik MM, Basalus MW, Mewes JC, et al. Clinical outcome of patients with implantation of second-generation drug-eluting stents in the right coronary ostium: Insights from 2-year follow-up of the TWENTE trial. Catheter Cardiovasc Interv. 2014 Apr 18. *In press.*

19. Tandjung K , Lam MK , Sen H, de Man FH, Louwerenburg JW, Stoel MG, van Houwelingen GK, Linssen GC, van der Palen J, Doggen CJ, von Birgelen C. Assessment of the relation between Syntax Score and clinical outcome after percutaneous coronary intervention with second-generation drug-eluting stents in the prospective, randomized TWENTE trial. *Submitted.*