Drug-Eluting Stent Use in Patients With Increased Risk

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COLOFON

Lay-out and printed by: Gildeprint-Enschede
ISBN: 978-94-6108-848-2

Financial support for printing of this thesis was funded by Medical School Twente, Stichting Thoraxcentrum Twente, Stichting Kwaliteitsverbetering Cardiologie, Biotronik, AstraZeneca, MSD, HSS 14-012, department Health Technology and Services Research, University of Twente, Enschede. ISSN 1878-4968 and Lide Jannink Stichting, namens het KNMG district Twente. Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

DRUG-ELUTING STENT USE IN PATIENTS WITH INCREASED RISK

DISSERTATION

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
Prof.dr. H. Brinksma,
on account of the decision of the graduation committee,
to be publicly defended
on Friday December 19, 2014 at 14.45 hrs

by

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Born on 24 October 1986
In Almelo, The Netherlands

This dissertation has been approved by the promotor:
Prof. dr. Clemens von Birgelen

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Chapter 1

Introduction

Coronary artery disease

Cardiovascular disease is common in the general population, affecting the majority of adults beyond the age of 60 years. The majority of patients with cardiovascular disease suffer from coronary artery disease, which can lead to partial obstruction or complete blockage of coronary arteries, and may result in ischemia or infarction of the myocardium.[1] For both genders, the risk of coronary artery disease increases markedly with age; other risk factors are smoking, dyslipidemia, diabetes mellitus, elevated blood pressure, obesity, family history of coronary artery disease, and estrogen replacement therapy.[2]

Atherosclerosis causes coronary heart disease and shows a progressive course with multiple stages.[3] Factors that are associated with greater atherosclerotic plaque burden are an advanced age, vessel wall calcification (more common in patients with renal failure), diabetes mellitus, multivessel coronary arterial disease, and the presence of lesions with coronary thrombus formation.[4] The formation of thrombus, which occurs most often in acute coronary syndromes (ACS), is related to a loss of integrity of the protective endothelial covering of atherosclerotic plaques. That loss and fissures or ruptures of fibrous atheroma caps allow blood to get in contact with highly thrombogenic plaque contents, such as collagen and/or necrotic core material that trigger intraluminal thrombus formation. Compared to patients without diabetes, diabetic patients have more lipid-rich atherosclerotic plaques that are more prone to rupture.[5] Moreover, they often have diffuse coronary artery disease, and lesions are more often located in small coronary vessels.[6] The location and morphology of coronary lesions determine their complexity, which is generally higher in the presence of advanced coronary artery disease. Lesion location and morphology can be best evaluated during coronary angiography, a percutaneous, catheter-based, minimal invasive technique that displays a silhouette of the coronary lumen with x-ray during an intra-coronary dye injection that is performed to opacify the lumen. An aorta-ostial lesion is an example of a complex lesion because of the rigid nature of the vessel wall at the transition between aorta and coronary artery, and as this generally indicates the presence of extensive coronary disease. Lesions located in degenerated vein grafts are often more diffuse and concentric, less often calcified, and often have poorly developed or absent fibrous caps.[7, 8] As a consequence of the higher friability of these lesions, percutaneous interventions in vein grafts are associated with a higher risk of distal plaque embolization, no-reflow during the intervention, and repeat revascularization, as compared to percutaneous coronary intervention (PCI) for lesions in native coronary arteries.[9, 10]

Treatment options for obstructive coronary artery disease

The goal of treatment of hemodynamically significant coronary artery lesions is to abolish myocardial ischemia and chest pain, thereby often improving patient survival. This can be achieved through risk-factor modification, medical therapy, and/or coronary revascularization procedures. A major risk reduction can already be achieved by cessation of smoking, improving the lipid status, lowering elevated arterial blood pressure, weight loss in case of obesity, and

glycemic control in patients with diabetes mellitus.[11] Further options to treat severe coronary artery obstructions are PCI and coronary artery bypass grafting (CABG).

Percutaneous transluminal balloon angioplasty

The introduction of the percutaneous transluminal coronary angioplasty (PTCA) by Andrea Grüntzig in 1977, currently more often called "plain old balloon angioplasty" (POBA), represented an impressive progress in therapy of obstructive coronary artery disease.[12] With this PCI technique, the narrowed arteriosclerotic coronary vessel is dilated by the inflation of a small inflatable balloon catheter, thereby introducing a new field of medicine: interventional cardiology.[13]

However, an important disadvantage of POBA is the fact that it was associated with a significant rate of acute vessel closure from major dissections and stenosis recurrence during follow-up (i.e. restenosis) as a result of early elastic recoil, proliferative growth of the intimal layer, and procedure-induced late constrictive remodeling of the coronary vessel wall.[14-16] These limitations, in particular the risk of acute coronary occlusion during or shortly after POBA, triggered the development of coronary stents.[17]

Bare metal stents

Stents, later called bare metal stents (BMS), are thin, implantable tubes of metallic mesh; they were developed to scaffold the dilated coronary segment for treatment and prevention of acute vessel closure following balloon angioplasty and were first implanted in coronary arteries in 1986.[17] Then, BMS were shown to significantly reduce the risk of lesion recurrence (i.e. restenosis) that occurred after POBA in 30-40% of patients.[18] Nevertheless, after BMS implantation, repeat revascularization procedures for the treatment of restenosis were still required in 20-30% of all patients following PCI with balloon-expandable or self-expandable BMS.[19, 20]

First-generation drug-eluting stents

In order to resolve the problem of restenosis that caused repeat revascularizations in a significant proportion of patients treated with BMS, drug-eluting stents (DES) were developed. These DES were composed of a metallic stent platform and a coating, which covered the entire metallic stent and consisted of a mixture of an anti-proliferative drug and a durable polymer. The coating released the drug locally to act upon the vessel wall, leading to a reduction in neointimal proliferation in response to the PCI-induced trauma to the vessel wall. As a side effect of all DES, vessel healing and endothelial coverage of the stent struts is delayed.[21]

The first-generation DES that entered the clinical arena was a sirolimus-eluting stent, which demonstrated its efficacy by reducing neointimal proliferation.[22] Another DES, the paclitaxel-eluting stent was developed almost simultaneously with the sirolimus-eluting stent.[23] Both stents are associated with significantly lower rates of binary angiographic restenosis and target

vessel revascularization as compared to BMS, [22, 23] resulting in a rapid increase in the clinical use of DES. In 2005, 80-90% of all PCIs in the United States were performed with the use of DES.[24] However, concerns about the safety of first-generation DES during long-time follow-up soon arose.[25] Compared to BMS, first-generation DES appeared to be more frequently associated with the occurrence of myocardial infarction due to late (i.e. after the first 30 days of DES implantation) and very late (i.e. after 12 months) stent thrombosis.[26] Various clinical, procedural, and stent-related factors were identified that might increase the risk of stent thrombosis. Examples were: early cessation of dual anti-platelet therapy,[27, 28] treatment of ACS, [29] bifurcation treatment with side branch stenting, and suboptimal stent deployment with malapposition of the stent struts.[30] Stent-related factors that may have promoted the occurrence of stent thrombosis were the durable polymer coating and the anti-proliferative drug of the DES. The polymer coating was shown to be associated with hypersensitivity reaction and inflammation of the vascular wall, and the anti-proliferative drug is known to delay vessel wall healing and stent strut endothelialization, which prolongs the prothrombotic state of the surface of both treated vessel wall and DES.[25]

Second-generation drug-eluting stents

Second-generation DES were then developed to counteract the undesirable effects of first-generation DES. These second-generation DES had novel coatings that were chosen because of their greater biocompatibility, which reduced their potential of inducing an inflammatory response of the vessel wall and ultimately reduced the risk of (late and very late) stent thrombosis. Two of these second-generation DES are the zotarolimus-eluting RESOLUTE stent (Medtronic, Minneapolis, MN, USA) and the everolimus-eluting XIENCE V stent (Abbott Vascular, Santa Clara, CA, USA). Both DES have thin-strut, open-cell, cobalt-chromium-based stent platforms and thin, durable polymer-based coatings.[31, 32] They showed favorable clinical results that led to widespread use in clinical practice.[33-35] One of the first randomized studies that compared the RESOLUTE and XIENCE V stents in a broad patient population is the TWENTE trial, which evaluated the clinical outcome of 1391 patients with stable angina or non-ST-elevation acute coronary syndrome (Non-ST-ACS).[36]

Third-generation drug-eluting stents

In an all-comers population, operators are confronted with challenging coronary anatomies due to advanced coronary disease and the age of patients with increased risk factors. The tortuous coronary vessels and complex lesion anatomies led to the development of more flexible, highly deliverable DES.[37, 38] The cobalt-chromium-based RESOLUTE INTEGRITY zotarolimus-eluting stent (Medtronic, Santa Rosa, CA, USA) and the platinum-chromium-based PROMUS ELEMENT everolimus-eluting stent (Boston Scientific, Natick, MA, USA) are examples of such highly flexible DES that have been called *third-generation* DES.[39] The term *new-generation (or novel-generation)* DES is also often used to classify these novel stents; and some research groups

even classify second-generation and biodegradable coating DES (outlined below) also as new-generation *(or novel-generation)* DES.

Biodegradable coating drug-eluting stents

Because of the concerns about durable polymers as a potential trigger of vessel wall inflammation and late stent thrombosis, DES with biodegradable polymer-based coatings were developed.[40, 41] After degradation and resorption of the polymer, the DES continues as a BMS that does not induce an inflammatory response of the vessel wall.[41, 42] Favorable safety and efficacy of such DES as compared to first-generation DES (with less biocompatible durable coatings) have been shown.[43] In the meantime, a new generation DES with biodegradable coatings has been introduced that has highly flexible stent platforms to answer to the demand for devices for treatment of the most challenging lesions and very complex coronary anatomies.[44, 45] The SYNERGY (Boston Scientific, Natick, MA, USA) and ORSIRO (Biotronik, Bülach, Switzerland) stents are such novel biodegradable coating DES that differ significantly in distribution of coating (on the metallic stent struts) and speed of coating resorption. The SYNERGY stent elutes everolimus from an abluminal biodegradable coating that is rapidly resorbed,[46] while the ORSIRO stent elutes sirolimus from a circumferential biodegradable coating that is slowly resorbed.[47]

Coronary artery bypass grafting

CABG is a cardio-thoracic surgical procedure that connects left or right internal mammary arteries, radial artery grafts, and/or saphenous vein grafts to native coronary arteries just distal to a significant coronary obstruction or a total coronary occlusion, in order to bypass the obstructed coronary arterial segments and ultimately improve oxygen supply to the myocardium. Depending on the number and location of vessels to be treated, anatomic lesion complexity, and several clinical aspects, CABG may be the preferred choice for the treatment of patients with severe, hemodynamically significant obstructions of the major coronary arteries. After a thorough heart team discussion, CABG is most often preferred in the presence of unprotected left main and/or diffuse three-vessel disease, and – in particular – in patients with diabetes mellitus.[11]

In patients with previous CABG, progression of atherosclerosis in the native coronary arteries and degeneration of bypass grafts may lead to a need for a secondary revascularization, which in the majority of patients is performed by PCI.[48, 49] Some factors contributing to the increased need for secondary revascularization procedures have been observed. The aging of populations with a Western lifestyle, for instance, has increased the likelihood of developing very advanced stages of coronary artery disease as well as graft failure.[48] Angiographic studies have shown that 10 years after CABG, approximately 75% of all vein grafts are occluded or severely diseased.[50, 51] The attrition of vein grafts with the formation of intimal hyperplasia is promoted by the exposure of the thin-walled conduit to the higher and pulsatile pressure in the systemic circulation [52] and the compliance mismatch between vein graft and native coronary arteries.

PCI are less frequently required in arterial grafts than in vein grafts, and PCI of obstructed arterial grafts are generally performed within a shorter time interval from CABG. The reason for this difference is the fact that arterial graft lesions are often the result of neo-intimal hyperplasia secondary to a vascular trauma that occurred during the preparation of the graft or the anastomosis; vein graft lesions, on the other hand, result most often from the more gradual degeneration process that is caused by the exposure of the relatively thin-walled venous conduit to the high pressures of the systemic circulation.[53] In addition, the proximal segments of grafted native coronary arteries often show a rapid disease progression as a result of the reduction in blood flow through these native coronary segments proximal to the anastomosis with the graft.[54, 55]

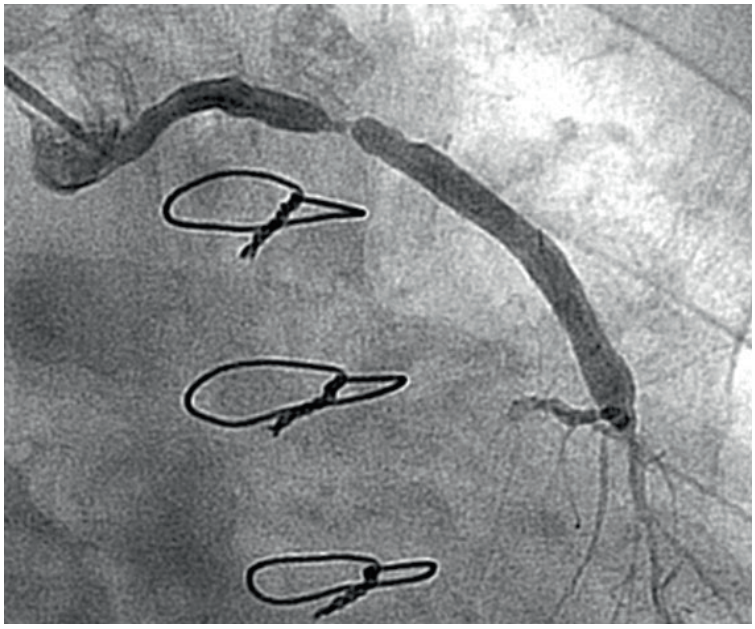

Figure 1. Significant lesion in the saphenous vein graft (arrow) to the left anterior descending artery (asterisk, anastomosis)

Complex patients

After the approval of first-generation DES for clinical use by the U.S. Food and Drug Administration, based on favorable data from the initial randomized trials, first-generation DES were rapidly adopted in routine clinical practice.[56, 57] Initially, DES were supposed to be implanted in easily accessible lesions of low-risk patients. This is still noted on a label on the DES packages. For that reason, these low-risk indications for DES use are generally called "on-label" indications.[58] However, the low-risk patients that meet these indications do not reflect the average patient population as seen in daily clinical practice, as the majority of patients undergo PCI for at least one off-label indication.[59]

Shortly after the approval of DES, complex patients, who were characterized by a higher clinical event risk and more challenging lesion anatomies, were increasingly enrolled in all-comer trials.[60, 61] However, in routine clinical procedures, complex patients who underwent PCI for off-label indications had a higher risk of death, myocardial infarction (MI), and stent thrombosis than patients in initial pivotal trials.[59, 62, 63] The randomized TWENTE trial assessed the outcome of 1391 patients at Thoraxcentrum Twente (treatment between June 2008 and August 2010 at Thoraxcentrum Twente) and compared the second-generation RESOLUTE and XIENCE V stents in these patients of whom 1033 (74.5%) were complex with at least one off-label indication for DES use.[36] Off-label indications for DES use were defined as: renal insufficiency (creatine ≥140 μmol/l); ejection fraction <30%; occurrence of acute MI within the previous 72 hours; more than one lesion/vessel; more than two vessels treated; lesion length >27 mm; bifurcation; saphenous vein graft lesion; arterial bypass graft lesion; in-stent restenosis; unprotected left main lesion; lesion with thrombus; and/or lesion with total occlusion.[64] At that time, data on clinical outcome following PCI with second-generation DES in complex patients were extremely scarce.[62, 65, 66]

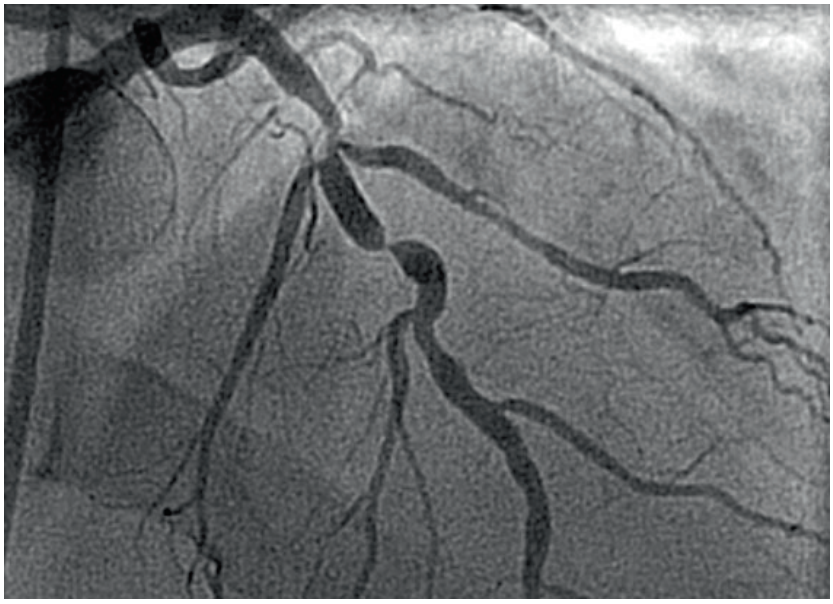

Figure 2. Bifurcation lesion of the left anterior descending artery (arrow), with an additional significant lesion distal from the bifurcation (asterisk)

Outline of this thesis

Much effort has recently been put into the refinement of DES, aiming at improved safety as compared to first-generation DES, while maintaining a high efficacy in suppressing neointima formation to prevent in-stent restenosis. New devices have been developed and introduced in

clinical practice, while often only limited data were available on the clinical outcome of patients with increased risk (i.e. complex patients). This thesis provides insight into the performance of several DES in complex patients undergoing PCI.

In **Chapter 2**, we evaluate whether eligible, non-enrolled patients, who were treated with the same DES (Non-Enrolled TWENTE study), differed from the randomized TWENTE trial population in baseline characteristics and clinical outcome.

In **Chapter 3**, we evaluate the impact of previous coronary artery bypass surgery on clinical outcome after PCI with second-generation DES in a pooled population from the TWENTE trial and Non-Enrolled TWENTE study.

In **Chapter 4**, we assess the two-year outcome of patients from the TWENTE trial, who were treated with the second-generation RESOLUTE or XIENCE V stent and followed a stringent strategy of discontinuation of dual anti-platelet therapy at 12 months from stenting.

In **Chapter 5**, we describe the two-year clinical outcome of TWENTE trial patients who underwent PCI with DES implantation for off-label indications versus on-label indications.

In **Chapter 6**, we evaluate the clinical outcome of complex patients from the TWENTE trial, who were treated for off-label indications with second-generation RESOLUTE or XIENCE V stents.

In **Chapter 7**, we evaluate the impact of right coronary artery aorto-ostial coverage with second-generation DES on two-year clinical outcome of the TWENTE trial.

In **Chapter 8**, we compare the three-year clinical outcome of TWENTE trial patients treated for chronic total occlusion lesions versus patients treated for non-chronic total occlusion lesions only.

In **Chapter 9**, we investigate the long-term safety and efficacy of treating bifurcation lesions with second-generation DES in patients of the TWENTE trial.

In **Chapter 10**, we assess the safety and efficacy of the third-generation RESOLUTE INTEGRITY and PROMUS ELEMENT stents at one year in all-comer patients in the randomized DUTCH PEERS trial.

In **Chapter 11**, we assess the two-year adverse clinical event rates and patient-reported chest pain in patients who were treated with RESOLUTE INTEGRITY and PROMUS ELEMENT stents in the randomized DUTCH PEERS trial.

In **Chapter 12**, we describe the design and rationale of the BIO-RESORT trial, a prospective, randomized, multicenter trial with three arms, comparing the safety and efficacy of the ORSIRO and SYNERGY bioresorbable coating DES with the RESOLUTE INTEGRITY durable polymer DES in 3540 all-comer patients.

In **Chapter 13**, we present a general discussion of the findings of this thesis, which includes the future perspectives.

In **Chapter 14**, we provide the summary and conclusions of this thesis.

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Safety and efficacy of second generation DES in complex patients

Chapter 2

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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EuroIntervention. 2012 Oct;8(6):664-71.

ABSTRACT

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

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

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

INTRODUCTION

Drug-eluting stents (DES) have been rapidly adapted for routine percutaneous coronary interventions (PCI), as they reduced the need for reinterventions.[1,2] As first-generation DES did not improve mortality,[3-6] novel stents with different coatings were developed, aimed at improved clinical outcome.[7,8] Two of these so-called second-generation DES are the zotarolimus-eluting Resolute stent (Medtronic CardioVascular) and the everolimus-eluting Xience V stent (Abbott Vascular Devices). Both DES have thin-strut, open-cell, cobalt-chromium-based stent platforms and thin, durable polymer-based coatings,[9,10] and they have shown favorable clinical results that have led to widespread use in clinical practice.[11-16] For these stents, non-inferiority with regard to safety and efficacy was recently demonstrated by TWENTE, a randomized, controlled study in a patient population with advanced coronary disease and complex lesions,[17] which confirmed with relatively low event rates the results of the RESOLUTE All Comers trial.[18] In addition, TWENTE is one of the relatively few randomized comparative DES trials that have been performed in a study population with very limited exclusion criteria to reflect routine clinical practice.[18-21]
The enrollment in the randomized TWENTE trial was high, comprising more than 80% of all eligible patients. [17] However, it is unknown whether the non-enrolled patients, who were all likewise treated with Resolute and Xience V stents, differ from the randomized TWENTE trial population in terms of baseline characteristics or – perhaps even more relevant – in clinical outcome. To answer this question, we prospectively recorded comprehensive data sets on clinical, procedural, and angiographic characteristics of all eligible but non-enrolled patients in the *Non-Enrolled TWENTE study*. To assure high-quality clinical outcome data and to facilitate meaningful comparisons with findings of the randomized TWENTE trial, an external clinical research organization performed the independent adjudication of all clinical events together in both the *Non-Enrolled TWENTE study* and randomized TWENTE trial.

METHODS

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

of target lesions or vessels. The only exclusion criteria were: ST-elevation myocardial infarction (STEMI) or STEMI-equivalent requiring primary or rescue PCI during the past 48 hours; planned staged revascularization; renal failure requiring hemodialysis; serious conditions that could limit the patient's ability to participate in study procedures, in particular life expectancy <1 year; participation in investigational drug or device study; if the choice of stent type was dictated by logistic reasons (e.g. a stent with required dimensions only available as one type).[17]
During the course of the randomized TWENTE trial, patients who were not enrolled were also treated with one of both, Resolute or Xience V stents, and their clinical course was prospectively registered as part of the *Non-Enrolled TWENTE study*. Operators were asked to report reasons for non-enrollment in PCI reports but incomplete documentation of this detail was not infrequent. We therefore used PCI reports, all clinical records, and interviews with the operators and other medical staff involved to obtain the most reliable estimate of the reasons for non-enrollment. The *Non-Enrolled TWENTE study* and the previously reported randomized TWENTE trial complied with the Declaration of Helsinki for investigation in human beings, and were performed after approval and supervision of our institutional ethics committee.

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

DEFINITIONS OF CLINICAL ENDPOINTS. Definitions of clinical endpoints have been fully described in the main report on the randomized TWENTE trial.[17] The same endpoint definitions were used in the present study. In general, the definitions of the Academic Research Consortium (ARC) were applied.[22,23] In brief, the primary endpoint *Target-Vessel Failure* (TVF) was defined as (in hierarchical order) cardiac death, target-vessel-related myocardial infarction, or clinically driven target-vessel revascularization (TVR) by re-PCI or surgery. Cardiac death was defined as any death due to proximate cardiac cause, un-witnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Classification and location of myocardial infarction was performed based on laboratory testing, electrocardiographic parameters, angiographic information, and clinical data.[17] Laboratory parameters for definition of myocardial infarction was any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker.[23] TVR was defined as any repeat coronary revascularization of the target vessel. Target-vessel (or target-lesion) revascularization was considered clinically indicated if the angiographic percent diameter stenosis of the then treated lesion was ≥50% in the presence of ischemic signs or symptoms, or if the diameter stenosis was ≥70% irrespective of ischemic signs or symptoms.[22]

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

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

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

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

RESULTS

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

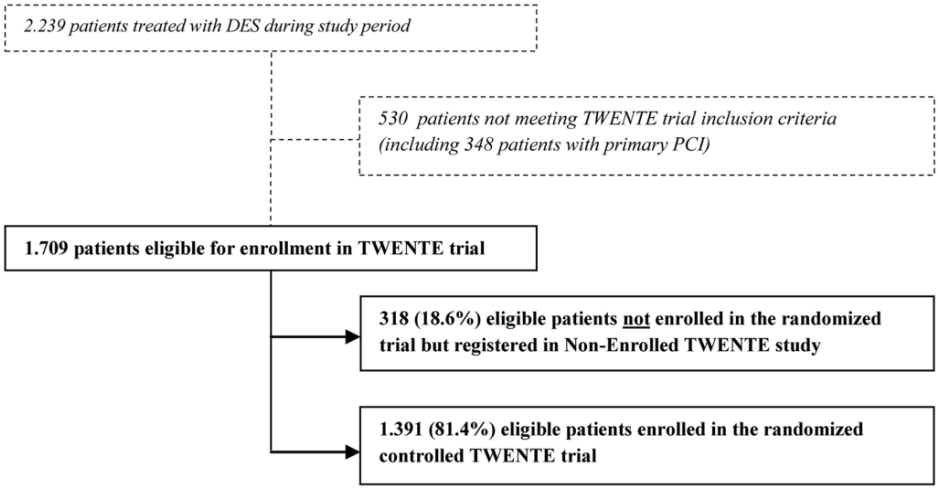

Figure 1. Flow chart of patients treated with DES during the course of the randomized TWENTE trial. Patients of the *Non-Enrolled TWENTE* study and the randomized TWENTE trial were compared.
* Data of the randomized TWENTE trial have previously been reported.[17]

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

PATIENTS, TARGET LESIONS, AND PCI PROCEDURES. Table 1 compares demographics and the procedural characteristics of both the *Non-Enrolled TWENTE study* population versus the randomized TWENTE trial population. Both study populations did not differ in the proportion of genders, diabetes mellitus, and clinical presentation (acute coronary syndromes in 52.5% vs. 51.5%, respectively; p=0.48). Non-enrolled patients were somewhat older (66.0±10.9 vs. 64.2±10.8 years; p=0.01). There was a trend towards less multivessel treatment in the non-enrolled patients (19.2% vs. 24.2%; p=0.06), matching with a more severely impaired left ventricular (6.5% vs. 3.0%; p=0.015) and renal function (6.6% vs. 2.7%; p=0.001) in this group. In addition, non-enrolled patients had more often a history of previous MI (43.1% vs. 32.4%; p<0.001), previous PCI (28.9% vs. 20.7%; p=0.001), and previous CABG (17.0% vs. 10.6%; p=0.002; Table 1). A total of 466 and 2116 lesions were treated in the *Non-Enrolled TWENTE study* and the randomized TWENTE trial, respectively (Table 2). Target lesions of non-enrolled patients showed more often complex B2 or C lesion types (76.1% vs. 70.1%; p=0.047). In parallel with the higher incidence of a history of PCI and/or CABG in the *Non-Enrolled TWENTE* population, more target lesions were restenoses and bypass graft lesions (p<0.001 for both; Table 2).

Table 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=2116 lesions)	p Value
Target lesion coronary artery			
Left main	17 (3.6)	54 (2.6)	0.19
Left anterior descendens	179 (38.4)	878 (41.5)	0.22
Left circumflex	107 (23.0)	483 (22.8)	0.95
Right coronary artery	135 (29.0)	653 (30.9)	0.42
Bypass graft	28 (6.0)	48 (2.3)	<0.001
ACC-AHA lesion class			0.047
A	24 (5.2)	154 (7.3)	
B1	87 (18.7)	478 (22.6)	
B2	153 (32.8)	678 (32.0)	
C	202 (43.3)	806 (38.1)	
De novo lesions	409 (87.8)	1999 (94.5)	<0.001
Chronic total occlusion	30 (6.4)	100 (4.7)	0.13
In stent restenosis	37 (7.9)	75 (3.5)	<0.001
Bifurcated lesion	101 (21.7)	518 (24.5)	0.20

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

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

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

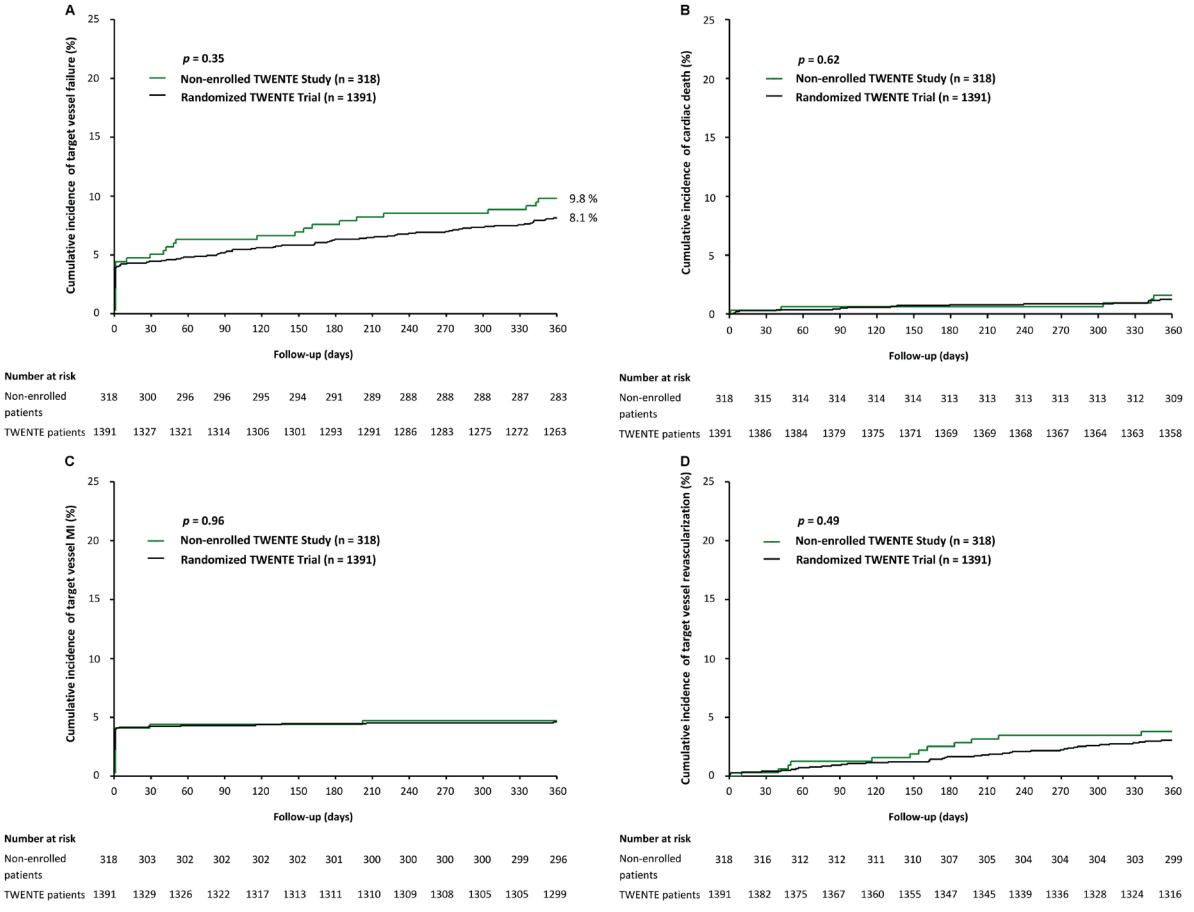

Figure 2. Kaplan-Meier for the primary endpoint and the individual components of the primary endpoint. Kaplan-Meier cumulative incidence curves at one year for the primary endpoint target-vessel failure, a composite of cardiac death, target-vessel related myocardial infarction, or target-vessel revascularization (**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 3. Clinical outcome after one year.

	Non-enrolled patients (N=316)	Randomized patients (N=1387)	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.

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 148/1386 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.

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Chapter 3

Impact of previous coronary artery bypass surgery on clinical outcome after percutaneous interventions with second generation drug-eluting stents in TWENTE trial and Non-Enrolled TWENTE registry

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International Journal of Cardiology. in press, epublished ahead of print 13 August 2014. doi: 10.4244/EIJV8I6A104.

ABSTRACT

Background: Patients with previous coronary artery bypass grafting (CABG) who underwent percutaneous coronary intervention (PCI) have an increased repeat revascularization rate, but data on contemporary second-generation drug-eluting stents (DES) are scarce.

Methods: We evaluated 1-year clinical outcome following secondary revascularization by PCI in patients of the TWENTE trial and Non-Enrolled TWENTE Registry, and compared patients with previous CABG *versus* patients without previous CABG.

Results: Of all 1709 consecutive patients, 202 (11.8%) had previously undergone CABG (on average 11.2±8.5 years ago). CABG patients were older (68.5±9.4 years vs. 64.1±10.7 years, p<0.001) and more often had diabetes (28.7% vs. 20.9%, p=0.01) and previous PCI (40.1% vs. 19.8%, p<0.001) compared to patients without previous CABG. Nevertheless, a higher target vessel revascularization (TVR) rate following PCI in the CABG patients (9.4% vs. 2.3%, p<0.001) was the only significant difference in clinical outcome at 1-year follow-up (available for 99.6%). Among CABG patients, the TVR rate was significantly higher in patients treated for graft lesions (n=65; 95.4% in vein grafts) than in patients treated for native coronary lesions only (n=137) (18.5% vs. 5.1%, p=0.002). Among 1638 patients with PCI of native coronary lesions only, there was only a non-significant difference in TVR between patients with previous CABG versus patients without previous CABG (5.1% vs. 2.3%, p=0.08).

Conclusions: Patients with previous CABG showed a favorable safety profile after PCI with second-generation DES. Nevertheless, their TVR rate was still much higher, driven by more repeat revascularizations after PCI of degenerated vein grafts. In native coronary lesions, there was no such difference.

INTRODUCTION

In patients with previous coronary artery bypass graft surgery (CABG), progression of atherosclerosis and degeneration of bypass grafts may lead to secondary revascularizations – in the majority of patients by means of percutaneous coronary intervention (PCI) [1,2]. So far, most PCI studies with comprehensive assessment of patients with a history of CABG were performed in the era of bare metal and early generation drug-eluting stents (DES) [3-5], while only limited data are available from second-generation DES.

Second-generation DES with more bio-compatible coatings have been shown to be safe and efficacious in several randomized clinical trials with limited exclusion criteria. An example of such a trial is the randomized TWENTE trial, which studied a broad population of patients undergoing PCI with second-generation DES [6]. In parallel with the randomized TWENTE trial, we performed a registry which assessed patients who also underwent PCI with second-generation DES and were eligible for enrollment in the randomized trial but were not enrolled for various reasons [7]. The pooled population of the randomized trial and the non-enrolled registry represent a consecutive series of patients with stable angina or non-ST-elevation myocardial infarction (MI) who underwent a PCI at Thoraxcentrum Twente during a period of 26 months. A total of 11% of patients of the TWENTE trial and 17% of the Non-Enrolled TWENTE Registry had a history of CABG.

In the present study, we analyzed the pooled population of the TWENTE trial and Non-Enrolled TWENTE Registry to assess the impact of previous CABG on individual clinical endpoints following PCI with second-generation DES. In addition, we investigated the potential impact of lesion location (i.e. in bypass graft versus native coronary artery) on clinical outcome.

METHODS

1.1. Study design and patient population.

We performed a pooled analysis of the prospective TWENTE Trial and TWENTE Non-Enrolled Registry. We analyzed 1709 consecutive patients, undergoing PCI with second-generation DES for stable angina or non-ST-elevation acute coronary syndromes (Non-ST-ACS) at Thoraxcentrum Twente in Enschede, the Netherlands. Patients were treated between June 2008 and August 2010. To compare baseline characteristics and clinical outcome between patients with previous CABG versus patients without previous CABG, the patient population was sub-divided, based on history of CABG. Details of the randomized TWENTE trial have previously been reported [6]. In brief, TWENTE (ClinicalTrials.gov NCT01066650) is a randomized, prospective, controlled, patient-blinded DES trial, comparing Resolute ZES and Xience V EES stents after 1:1 randomization in 1391 patients. Patients with stable angina or Non-ST-ACS were eligible,

and few exclusion criteria were applied [6]. The non-enrolled TWENTE Registry has also been reported in detail; it included 318 eligible patients who were not enrolled during the course of the randomized TWENTE trial [7].

1.2. Intervention, medication, electrocardiography, and laboratory testing.

Five experienced interventional cardiologists, of whom each had individual experience of at least 4000 PCI procedures as a first operator, performed all PCI procedures by the use of standard techniques. Pharmacological therapy before, during, and after PCI as well as systematic laboratory testing and ECG assessment have previously been described and did not differ between the TWENTE trial and TWENTE Non-Enrolled Registry [6]. Angiographic analyses were performed offline at Thoraxcentrum Twente.

1.3. Definitions of clinical endpoints.

Definitions of clinical endpoints have been fully described in the main report on the randomized TWENTE trial [6]. In general, the definitions of the Academic Research Consortium (ARC) were applied [8,9]. Cardiac death was defined as any death due to proximate cardiac cause, unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment.

Myocardial infarction (MI) was defined by any creatine kinase concentration of more than twice the upper limit of normal with elevated confirmatory cardiac biomarkers [9]. Further classification and location of MI have been previously described [6]. Target vessel-related MI was related to the target vessel or could not be related to another vessel. Target vessel and target lesion revascularization (TVR and TLR) were defined as any repeat coronary revascularization of the target vessel or target lesion by re-PCI or surgery. Stent thrombosis was defined according to ARC [8].

1.4. Data acquisition and follow-up.

In-hospital adverse events were recorded prior to discharge. One-year follow-up data after PCI of all patients were obtained at visits in outpatient clinics or, if not feasible, by telephone follow-up and questionnaire. For any event trigger, all clinical information available from the referring cardiologist, general practitioner, and hospital involved was gathered. The adjudication of adverse clinical events was performed by an independent CRO (Cardialysis, Rotterdam, the Netherlands).

1.5. 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 continuous variables. The chi-square test and the Fisher's exact test were used to compare frequencies as appropriate. The student's

t-test was used to compare normally distributed continuous variables. 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. A two-sided P value < 0.05 was considered statistically significant.

RESULTS

3.1. Characteristics of patients, lesion, and PCI procedures.

Of all 1709 patients, 202 (11.8%) had a history of CABG (Table 1). These patients were older (68.5±9.4 vs. 64.1±10.7 years), more often males (79.7% vs. 71.1%), and suffered more often from diabetes (28.7% vs. 20.9%), chronic renal failure (6.4% vs. 3.1%), and heart failure (6.9% vs. 3.2%) than patients without a history of CABG. In addition, patients with previous CABG had more often a history of MI (40.6% vs. 33.5%) and PCI (40.1% vs. 19.8%). Despite the – on average – higher cardiovascular risk profile, patients with previous CABG were more often treated for stable angina, rather than for acute coronary syndromes (55.0% vs. 47.4%; Table 1). At discharge, patients with previous CABG did not differ from patients without previous CABG in use of statins (90% vs. 86%, p=0.18), ACE inhibitors (31% vs. 29%, p=0.42), beta blockers (82% vs. 82%, p=0.85), acetylsalicylic acid (99% vs. 99%, p=0.76), and thienopyridine (99% vs. 99.5%, p=0.13) (Table 1).

Patients with previous CABG versus patients without history of previous CABG differed in several lesion characteristics and procedural details (Table 1), including more index PCI for in-stent restenosis (11.4% vs. 5.9%) and type C lesions (62.4% vs. 48.7%) – a difference that was mainly related to bypass graft lesions. Patients with previous CABG less often underwent PCI of lesions in left anterior descending coronary arteries (17.3% vs. 55.4%).

Of the 202 patients with previous CABG, 65 (32.2%) patients were treated for at least one lesion in a bypass graft, of which 62 (95.4%) were located in saphenous vein grafts and 3 (4.6%) in arterial grafts. PCI was performed on average 11.2±8.5 years after CABG. Time between CABG and PCI differed significantly between patients treated for bypass lesions versus native coronary lesions only (9.6±8.6 vs. 14.3±7.5 months, p<0.001). Fig. 1 shows the distribution of patients in time intervals from CABG to index PCI for 65 patients with PCI in graft lesions versus 132 patients with PCI in native coronary lesions only.

Table 1. Baseline characteristics of patients and procedures of patients with versus without previous CABG.

	Patients with CABG in history (N=202)	Patients without CABG in history (N=1507)	p value
Age (yrs)	68.5 ±9.4	64.1±10.7	<0.001
Men	161 (79.7)	1072 (71.1)	0.011
Diabetes mellitus (any)	58 (28.7)	315 (20.9)	0.012
Chronic renal failure*	13 (6.4)	46 (3.1)	0.013
Arterial hypertension	113 (55.9)	845 (56.1)	0.972
Hypercholesterolemia	143/199 (71.9)	853/1476 (57.8)	<0.001
Current smoker	22 (10.9)	388 (25.7)	<0.001
Family history of CAD	108/181 (59.7)	734/1403 (52.3)	0.062
Myocardial infarction (any)	82 (40.6)	505 (33.5)	0.046
Previous PCI	81 (40.1)	299 (19.8)	<0.001
Clinical characteristic			0.023
Stable angina pectoris	111 (55.0)	714 (47.4)	
Acute coronary syndrome	91 (45.0)	793 (52.6)	
Unstable angina	51 (25.2)	358 (23.8)	
Non-ST-elevation MI	40 (19.8)	435 (28.9)	
Left ventricular ejection fraction < 30%†	10/144 (6.9)	35/1106 (3.2)	0.022
Multivessel treatment	52 (25.7)	345 (22.9)	0.368
Total no lesions treated per patient			0.381
One lesion treated	133 (65.8)	927 (61.5)	
Two lesions treated	49 (24.3)	436 (28.9)	
Three of more lesions treated	20 (9.9)	144 (9.6)	
At least one CTO	12 (5.9)	111 (7.4)	0.462
At least one bifurcation	36 (17.8)	409 (27.1)	0.005
At least one in-stent restenosis	23 (11.4)	89 (5.9)	0.003
Postdilatation	177 (87.6)	1323 (87.8)	0.946
Target coronary artery			
Left main‡	35 (17.3)	34 (2.3)	<0.001
Left anterior descending	35 (17.3)	835 (55.4)	<0.001
Left circumflex	60 (29.7)	461 (30.6)	0.797
Right coronary artery	66 (32.7)	550 (36.5)	0.288
Bypass graft	65 (32.2)	-	<0.001
ACC-AHA lesion class			0.003
A	5 (2.5)	70 (4.6)	
B1	22 (10.9)	240 (15.9)	
B2	49 (24.3)	463 (30.7)	
C	126 (62.4)	734 (48.7)	
Medication at discharge			
Statin	180/201(89.6)	1279/1485(86.1)	0.182
Ace-inhibitor	63/201 (31.3)	425/1486 (28.6)	0.421
Beta-blocker	164/201 (81.6)	1219/1484 (82.1)	0.848
Acetylsalicylic acid	199 (98.5)	1486 (98.6)	0.757

Thienopyridine	199 (98.5)	1497/1505 (99.5)	0.132
DAPT	196 (97.0)	1479 (98.1)	0.281
Medication at 1-year§	N=142	N=1216	
Acetylsalicylic acid	130 (91.5)	1133 (93.2)	0.473
Thienopyridine			<0.001
Stopped after 1 year	118 (83.1)	1130 (92.9)	
Less than 1 year	4 (2.8)	17 (1.4)	
Continued after 1 year	20 (14.1)	69 (5.7)	
Dual anti-platelet therapy			<0.001
Stopped after 1 year	109 (76.8)	1062 (87.3)	
Less than 1 year	15 (10.6)	99 (8.1)	
Continued after 1 year	18 (12.7)	55 (4.5)	

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.
‡ 2/35 PCI in left main stems were performed for unprotected left main disease.
§ Based on data from the randomized TWENTE Trial. No data are available for patients from the Non-Enrolled TWENTE registry.

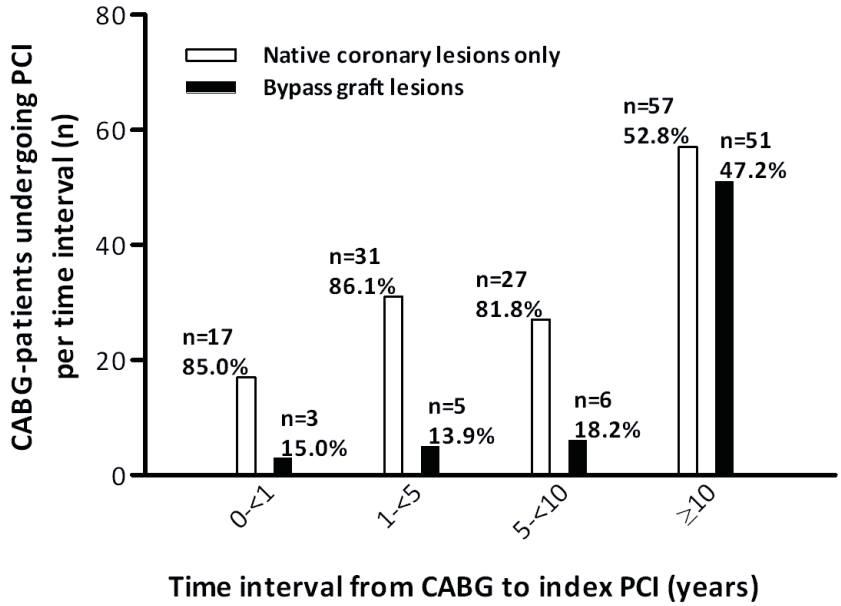

Figure 1. PCI per time interval from CABG to index PCI in patients with previous CABG. The distribution of patients in time intervals from CABG to index PCI for the two patient groups (65 patients with PCI in graft lesions vs. 132 patients with PCI in native coronary lesions only). Analysis based on 197/202 patients with knowledge of exact time interval. Among 17 pts. who underwent PCI in native coronary vessels during 0-1 year from previous CABG, 9 were treated in grafted and 8 in ungrafted coronary arteries.

3.2. Clinical outcome

One-year follow-up was available in 1703 (99.6%) patients. Table 2 shows the clinical outcome of patients with previous CABG versus patients without previous CABG. The only difference was a higher TVR rate in patients with previous CABG (9.4% vs. 2.3%, p<0.001) (Fig. 2A) and explains the significantly higher rate of dual anti-platelet therapy continuation beyond 12 months (12.7% vs. 4.5%, p<0.001) in these patients.

Table 3 presents the outcome of the 202 patients with previous CABG; it shows that *the TVR rate was much higher in 65 patients who were treated for bypass graft lesions* than in the 137 patients who were treated for native coronary lesions only (18.5% vs. 5.1%, p=0.002) (Fig. 2B).

As shown in Table 4, among 1638 patients who underwent PCI for the treatment of native coronary lesions only (irrespective of a history of CABG), there was a non-significant difference in TVR between patients with previous CABG versus patients without previous CABG (5.1% vs. 2.3%, p=0.08).

Table 2. Clinical endpoints at 1-year follow-up of patients with versus without previous CABG.

	Patients with CABG in history (N=202)	Patients without CABG in history (N=1501)	p value
Death			
Any cause	7 (3.5)	29 (1.9)	0.185
Cardiac cause	5 (2.5)	17 (1.1)	0.171
Target vessel-related MI			
Any	13 (6.4)	66 (4.4)	0.196
Clinically indicated TVR			
Any	19 (9.4)	35 (2.3)	<0.001
Percutaneous	18 (8.9)	27 (1.8)	<0.001
Surgical	1 (0.5)	8(0.5)	1.0
Clinically indicated TLR			
Any	13 (6.4)	25 (1.7)	<0.001
Percutaneous	13 (6.4)	18 (1.2)	<0.001
Surgical	0	7 (0.5	1.0
Definite ST (0-360 days)	0	4 (0.3)	1.0
Probable ST (0-360 days)	3 (1.5)	8 (0.5)	0.133
ST (0-360 days)			
Possible	3 (1.5)	6 (0.4)	0.080
Definite or probable	3 (1.5)	12 (0.8)	0.408
Definite, probable or possible	6 (3.0)	18 (1.2)	0.056

Data are number of patients (%). MI=myocardial infarction. TVR=target vessel revascularization. TLR=target lesion revascularization. ST=stent thrombosis.

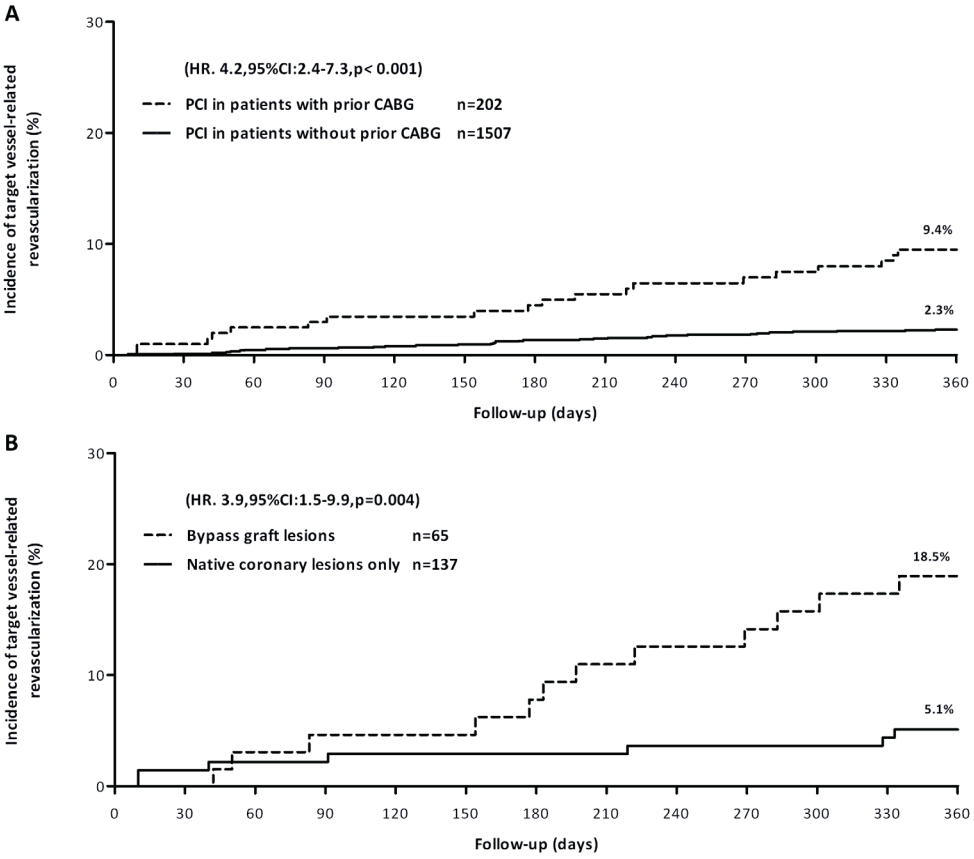

Figure 2. Target vessel revascularization during follow-up of 1 year. A: Kaplan-Meier cumulative incidence curves at 1-year for target vessel revascularization for patients with versus without prior CABG. B: Kaplan-Meier cumulative incidence curves at 1-year for target vessel revascularization for patients with prior CABG treated for graft lesions versus lesions in native coronary vessels only.

Table 3. Clinical outcome at 1-year of CABGpatients treated for graft lesions versus native coronary lesions only.

	Graft lesions (N=65)	Native vessels only (N=137)	p Value
Death			
Any cause	3 (4.6)	4 (2.9)	0.538
Cardiac cause	1 (1.5)	4 (2.9)	0.555
Target vessel-related MI			
Any	6 (9.2)	7 (5.1)	0.265
Clinically indicated TVR			
Any	12 (18.5)	7 (5.1)	0.002
Percutaneous	12 (18.5)	6 (4.4)	0.001
Surgical	0	1 (0.7)	0.490
Clinically indicated TLR			
Any	10 (15.4)	3 (2.2)	<0.001
Percutaneous	10 (15.4)	3 (2.2)	<0.001
Surgical	-	-	-
Probable ST (0-360 days)	1 (1.5)	2 (1.5)	0.966
ST (0-360 days)			
Possible	-	3 (2.2)	0.229
Definite, probable or possible	1 (1.5)	5 (3.6)	0.409

Data are number of patients (%). MI=myocardial infarction. TVR=target vessel revascularization. TLR=target lesion revascularization. ST=stent thrombosis.

Table 4. Clinical outome after 1 year of patients treated for lesions in native coronary vessels only, comparing patients witch versus without previous CABG.

	Native vessels CABG (N=137)	Native vessels non-CABG (N=1501)	p Value
Death			
Any cause	4 (2.9)	29 (1.9)	0.350
Cardiac cause	4 (2.9)	17 (1.1)	0.092
Target vessel-related MI			
Any	7 (5.1)	66 (4.4)	0.665
Clinically indicated TVR			
Any	7 (5.1)	35 (2.3)	0.080
Percutaneous	6 (4.4)	27 (1.8)	0.052
Surgical	1(0.7)	8 (0.5)	0.545
Clinically indicated TLR			
Any	3 (2.2)	25 (1.7)	0.504
Percutaneous	3(2.2)	18 (1.2)	0.412
Surgical	-	7 (0.5)	1.000
Probable ST (0-360 days)	2 (2.2)	8 (0.5)	0.201
ST (0-360 days)			
Possible	3(2.2)	6 (0.4)	0.033
Definite, probable or possible	5(3.6)	18 (1.2)	0.037

Data are number of patients (%). MI=myocardial infarction. TVR=target vessel revascularization. TLR=target lesion revascularization. ST=stent thrombosis.

DISCUSSION

4.1. Major findings

In this pooled analysis of 1709 consecutive patients of the prospective TWENTE Trial and the TWENTE Non-Enrolled Registry, patients with previous CABG had a 4-fold higher 1-year risk of TVR after PCI than patients without previous CABG. Differences in the incidence of cardiac death, target vessel-related MI, and stent thrombosis showed the same trend, but were non-significant. Within patients who underwent PCI for native coronary lesions only, there also appeared to be a difference in TVR rate between patients with previous CABG versus patients without previous CABG, which was almost significant. Among patients with previous CABG, the TVR rate was 3.5-fold higher in patients treated for target lesions in bypass grafts. Thus, the increased TVR risk of patients with prior CABG is mainly related to PCI performed in vein grafts.

4.2. Comparison with previous studies

In the present study, 11.8% of patients had a previous CABG (on average 11.2 years before PCI), which is similar to or higher than several randomized DES trials where 7% to 11.5% had prior CABG procedures [10-14]. During the last decades, there has been an increase in patients with previous CABG, who ultimately required additional coronary revascularization procedures. Some factors may have contributed to this development. For instance, the aging of populations with a western lifestyle has increased the likelihood of developing very advanced stages of coronary disease and graft failure [1]. In addition, coronary revascularization techniques have been spread over time, leading to a substantial increase in the accessibility of coronary revascularization procedures [15].

Angiographic studies have shown that 10 years from CABG approximately 75% of vein grafts are occluded or severely diseased [16,17]. The attrition of vein grafts with the formation of intimal hyperplasia is promoted by the exposure of the thin-walled conduit to the higher and pulsatile pressure in the systemic circulation [18], the compliance mismatch between vein graft and native coronary arteries, and early endothelial damage along suture lines or due to intraoperative handling of vein graft material. Migration of vascular smooth muscle cells, sustained collagen proliferation, and lipid deposition result in the accelerated formation of more friable atherosclerotic plaques [19]. While there are several similarities in the predisposing factors and the general process of atheroma formation between vein graft and native coronary atheromas, vein graft atheromas are more diffuse and concentric, less calcified, and often have poorly developed or absent fibrous caps [19,20]. As a consequence of the higher friability of the lesions, PCI in vein grafts are associated with a higher risk of plaque embolization, no-reflow during PCI, and TVR, as compared to PCI in native coronary arteries [21,22].

PCIs of arterial grafts are more rare and are generally required after a shorter time interval from CABG, as arterial graft lesions are often the result of neo-intimal hyperplasia secondary to a vascular trauma during the preparation of a graft or anastomosis [15]. In addition, the proximal segments of grafted native coronary arteries (i.e. proximal to the anastomosis) often show an increased disease progression as a result of the reduced flow through these segments [23,24]. On the other hand, as a result of a general progression of atherosclerosis in the native coronary vasculature, native vessels may develop significant lesions distal to the anastomosis of a graft [15]. In our present study, patients with STEMI were not assessed, as this subset of PCI patients was not considered for enrollment in the TWENTE trial [6]. However, the rate of STEMI patients with previous CABG is relatively low [25]. In a large US registry, for instance, only 6% of STEMI patients had a previous CABG; and in the randomized APEX-AMI trial 2.2% of all 5,745 STEMI patients had a history of CABG. STEMI patients with previous CABG were older and had more comorbidities (e.g. more diabetes), which may have contributed to a higher mortality (12% vs. 5%, $p<0.001$; in APEX-AMI trial [26]. The mortality of STEMI patients with CABG was particularly high if the culprit vessel was a bypass graft rather than a native coronary artery (19% vs. 6%, $p=0.03$) [26].

The majority of our patients with previous CABG underwent PCI for target lesions in native coronary arteries (68%) rather than bypass grafts (32%). This relation is quite similar to that of other studies, in which patients with previous CABG underwent PCI in 56% to 63% for treatment of lesions in native coronary arteries [3,4,27,28]. In a study among 91 consecutive patients with previous CABG who were treated by PCI with BMS or first-generation DES, a repeat revascularization rate of 10.9% was found [3]. Despite the use of second-generation DES in our present study, we still found a TVR rate of 9.4%.

In another study, 161 patients with previous CABG who were treated between September 2005 and April 2008 with PCI using BMS or DES were analyzed. In that study, a higher incidence of TVR was the only difference in individual clinical endpoints between patients treated for graft versus native coronary lesions (15.0% vs. 4.9%, after mean follow-up of 13 months)[4]. In addition, previous studies have demonstrated a clinical benefit of PCI with DES versus BMS in vein grafts [21]. Our data show that, despite the use of contemporary second-generation DES with biocompatible durable coatings, the discrepancy in TVR between patients treated for graft lesions versus native coronary lesions remained similar (19% vs. 5%, at 1-year follow-up). Data from the large National Cardiovascular Data Registry CathPCI Registry have shown that the in-hospital mortality was higher in patients with previous CABG if they were treated for graft lesions (OR: 1.22, 95% CI: 1.12-1.32, $p<0.001$) [27]. However, CABG with arterial grafting was associated with lower rates of major adverse cardiac events [29].

4.3. Clinical implications

If a secondary revascularization is required in patients with previous CABG, many patients prefer to undergo a PCI rather than a redo-CABG [30], as the redo-CABG is associated with a higher mortality than the initial CABG [31]. Our data confirm that PCI with contemporary DES is feasible and safe in patients with previous CABG. But despite the use of modern DES, PCI of bypass graft lesions is still associated with a much higher TVR rate. Therefore, if PCI of both native coronary and corresponding graft lesions is feasible with a similar resource utilization and chance of lesion success, a thorough heart team discussion on clinical risk may help to choose the most appropriate therapeutic strategy.

STUDY LIMITATIONS

Because of its post hoc nature, the results of the present study should be considered hypothesis generating. The TWENTE trial as well as the Non-Enrolled TWENTE Registry assessed patients with limited exclusion criteria but no acute STEMI; therefore, our results may not be extrapolated to the setting of STEMI [6,7]. In addition, follow-up of this pooled patient population is limited to 1 year. A longer-term follow-up may be of interest to assess potential differences in long-term mortality and morbidity between patients with previous CABG versus patients without previous CABG.

CONCLUSIONS

Patients with previous CABG were older and had a higher prevalence of diabetes, but the safety profile of PCI with contemporary second-generation DES was favorable in this group of patients. Nevertheless, their overall TVR rate was still higher than that of patients without a history of CABG, and it was driven by a higher TVR rate in degenerated vein grafts. Following PCI of native coronary arteries, there was no significant difference between patients with previous CABG versus patients without previous CABG.

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Chapter 4

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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J Am Coll Cardiol. 2013 Jun 18;61(24):2406-16.

ABSTRACT

Objectives: The aim of this study was to assess the safety and efficacy of the implantation of Resolute zotarolimus-eluting stents (ZES) (Medtronic Inc., Santa Rosa, California) and Xience V everolimus-eluting stents (EES) (Abbott Vascular,Santa Clara, California) 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.

Methods: The randomized TWENTE (The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente) trial is an investigator-initiated study performed in a population with many complex patients and lesions and only limited exclusion criteria. Patients were randomly assigned 1:1 to ZES (n=697) or EES (n=694).

Results: Two-year follow-up information was available on all patients. The rate of continuation of DAPT beyond 12 months was very low (5.4%). The primary endpoint of target vessel failure, 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 patients with 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 rates of definite or probable stent thrombosis were 1.2% and 1.4% (p=0.63), respectively. Very late definite or probable stent thrombosis occurred only in 2 patients in 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 drug-eluting stents.

INTRODUCTION

Second-generation drug-eluting stents (DES) such as the Xience V everolimus-eluting stent (EES) (Abbott Vascular,Santa Clara, California) and the Resolute zotarolimus-eluting stent (ZES) (Medtronic Inc., Santa Rosa, California) 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 designed to compare the safety and efficacy of Resolute ZES with that of Xience V EES in a large patient population with complex coronary artery disease (3). This patient population reflects routine clinical practice, as has recently been demonstrated by the findings of a study of eligible nonenrolled patients (4). In the TWENTE trial, the rates of the primary endpoint of target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction (MI), and clinically indicated target vessel revascularization (TVR), at 1 year 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 a patient-oriented composite endpoint.

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

METHODS

Study design and patient population. The TWENTE trial has previously been described in detail (3,11). In brief, TWENTE trial is an investigator initiated, patient-blinded, randomized, comparative trial of DES with limited exclusion criteria in a real-world study population with a majority of complex lesions and off-label indications for DES. Study enrollment was performed between June 2008 and August 2010 at Thoraxcentrum Twente in Enschede, the Netherlands. Patients capable of providing informed consent with an indication for percutaneous coronary intervention (PCI) with DES were randomized to treatment with Resolute or Xience V stents 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-segment-elevation MI. 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 acetylsalicylic acid 100 mgonce daily indefinitely and clopidogrel 75 mg once daily for 12 months was prescribed. Use of DAPT was determined by patient questionnaire and/or information from each patients' general practitioner or pharmacy. Lesion pre-dilation, direct stenting, stent post-dilation, and/or use of glycoprotein IIb/IIIa antagonists were permitted at the operators' discretion. Liberal use of post-dilation was encouraged. Cardiac biomarkers and electrocardiograms were systematically assessed in all patients before and after PCI to identify periprocedural MI.

Definitions of clinical endpoints. Definitions of all clinical endpoints have previously been described in detail (3). The primary clinical endpoint was the incidence of TVF at 1 year, a composite endpoint that was defined as cardiac death, target vessel-related myocardial infarction (or not attributable to a nontarget vessel), and clinically driven 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, and a patient-oriented composite endpoint, 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, including the addendum to the definition of MI (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 patients in the Resolute ZES group and 2 patients in the Xience V EES group). 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 on the basis of the principle of intention-to-treat.

Statistical analysis. Statistical analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, Illinois). Categorical variables were assessed with the chi-square test or Fisher exact test as appropriate, whereas continuous variables were assessed with the Wilcoxon rank sum test or Student *t* test, as appropriate. The times to the primary endpoint and to the components thereof were assessed according to the Kaplan-Meier method, and the log-rank test was applied to compare the 2 groups. A landmark analysis was performed at 1 year for various events. For each type of event, patients were excluded from the landmark analysis if the specific event or death occurred in the first year. Unless otherwise specified, p values and confidence intervals were 2 sided. A p value < 0.05 was considered significant.

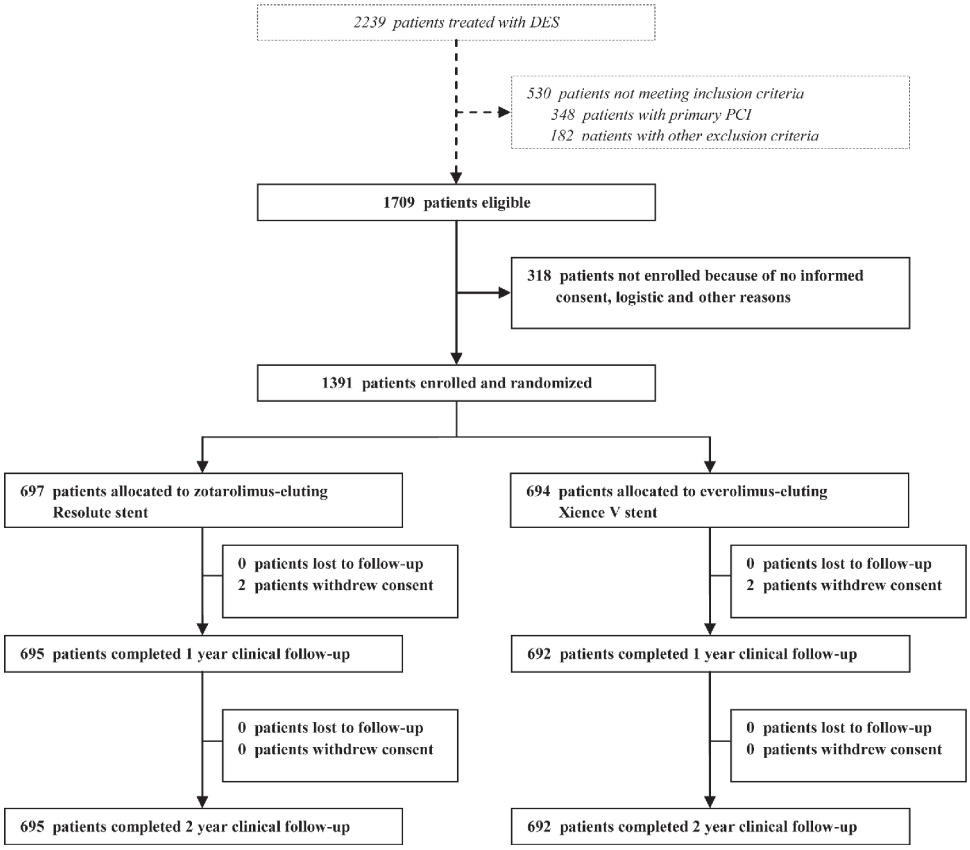


Figure 1. Study flow diagram. A total of 1,391 patients were enrolled in the TWENTE trial. These were randomized to zotarolimus-eluting Resolute stents (n=697) or everolimus-eluting Xience V stents (n=694). DES=drug-eluting stent(s); PCI=percutaneous coronary intervention.

RESULTS

A total of 1,391 patients were randomized to 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 (Fig. 1). Baseline clinical, angiographic, and procedural characteristics of all study patients are summarized in Table 1.

Table 1. Baseline characteristics of patients

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

Values are n (%) or mean ± SD.
* 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

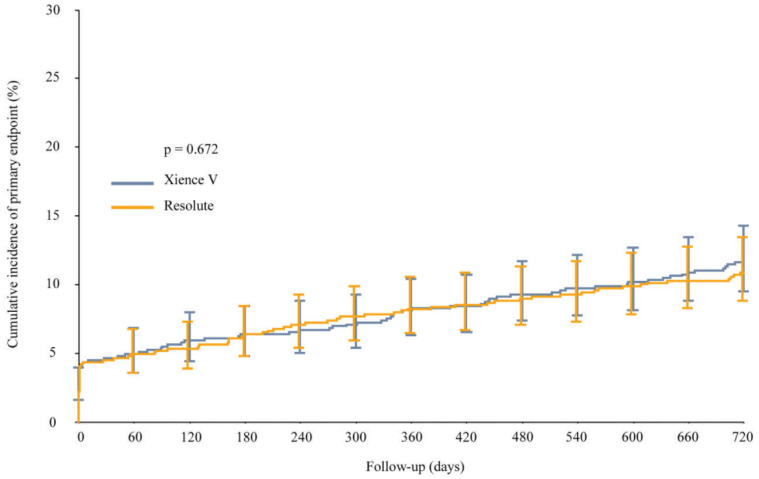
At 2-year follow-up, the composite primary endpoint of TVF occurred in 75 patients (10.8%) in the Resolute ZES and in 80 patients (11.6%) in the Xience V EES group, and did not differ significantly between groups (absolute difference -0.8 [-4.1 to 2.6], p=0.65, Table 2, Fig. 2). The patient-oriented composite endpoint rates were also similar for patients treated with ZES and EES; this endpoint occurred in 114 patients (16.4%) versus 118 patients (17.1%), respectively. For the individual components of the composite primary endpoint of 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.

Table 2. Two-year clinical outcome

	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

Values are n (%).
*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.

A



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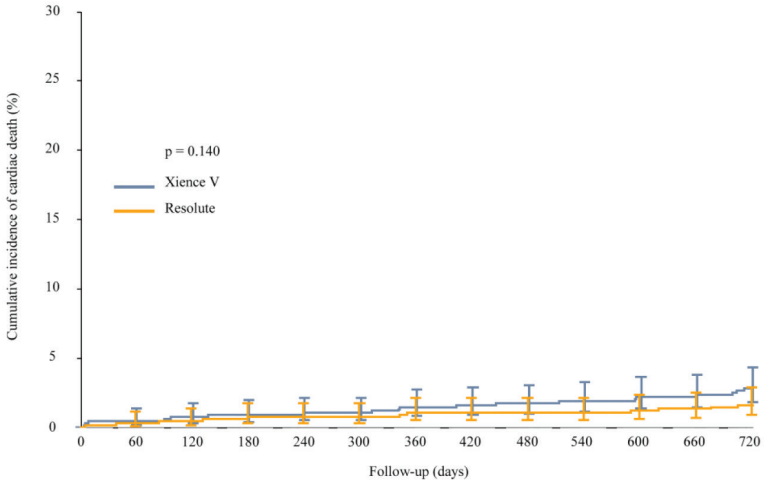
Xience V	694	660	651	646	644	639	632	629	620	616	613	607	582
Resolute	697	661	655	647	642	636	631	629	625	621	613	610	586

B



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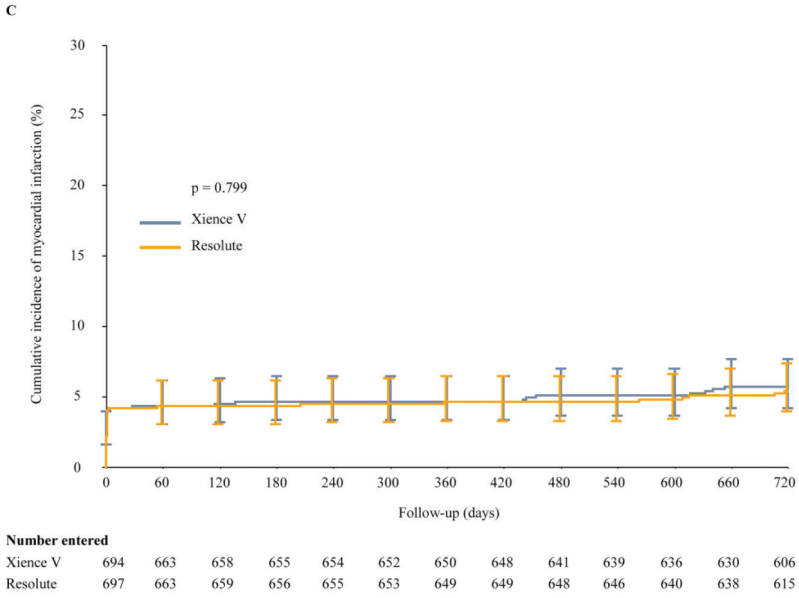
Xience V	694	691	687	684	683	681	678	676	672	670	666	664	638
Resolute	697	693	688	685	685	683	680	680	679	677	672	671	649



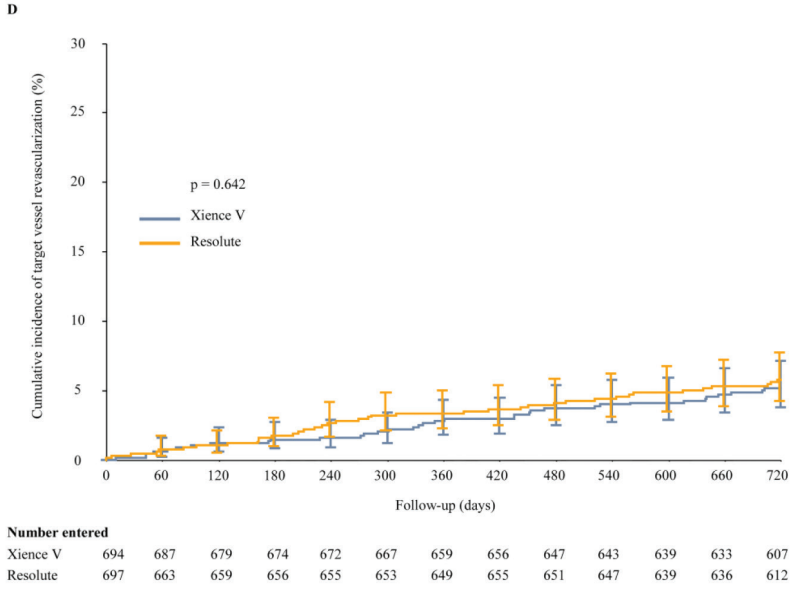


Figure 2. Kaplan-Meier for Primary Endpoint and the Individual Components of the Primary Endpoint. Kaplan-Meier cumulative incidence curves at 2 year for the primary endpoint, a composite of cardiac death, target-vessel-related myocardial infarction, or target-vessel revascularization (A); cardiac death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

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 with Resolute ZES, the use of Xience V EES was associated with a lower rate of 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 of TLF (10.5% vs. 9.8%, p=0.68).

	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

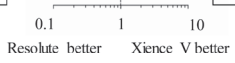


Figure 3. Subgroup analysis: Target-vessel failure at 2 year.
Target-vessel failure is a composite of cardiac death, target-vessel myocardial infarction, or clinically driven target-vessel revascularization. NSTEMI: non–ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention.

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

Table 3. Outcome differences between 1 and 2 years

	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

Values are % (n/N) *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.

In accordance with national and European guidelines, the per-protocol duration of DAPT was 1 year after PCI. Table 4 presents data on the actual use of DAPT. DAPT was discontinued after 1 year or less in 635 patients (93.4%) in the Resolute ZES arm and 650 patients (95.9%) in the Xience V EES group. Of all patients, 73 (5.4%) continued DAPT beyond 12 months. At 2-year follow-up, 51 patients (7.7%) in the Resolute ZES group and 40 patients (6.2%) in the Xience V EES group were still on DAPT.

Table 4. Acetylsalicylic acid, clopidogrel, and dual anti-platelet therapy usage.

	Zotarolimus-eluting Resolute stent	Everolimus-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			0.14
Stopped after one year	615 (90.4)	633 (93.4)	
Continued after one year	52 (7.7)	37 (5.5)	
Less than one year	13 (1.9)	8 (1.2)	
DAPT			0.13
Stopped after one year	578 (85.0)	593 (87.5)	
Continued after one year	45 (6.6)	28 (4.1)	
Less than one year	57 (8.4)	57 (8.4)	
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

Values are n (%). *No Acetylsalicylic acid was used due to allergic reactions or concommitant vitamin K antagonist usage. DAPT = Acetylsalicylic acid and clopidogrel

The rates of ARC-defined stent thrombosis (0.9% vs. 0.1%, p=0.12) and definite or probable stent thrombosis (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 (Fig. 4). Very late definite or probable stent thrombosis was seen in 2 patients in 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.

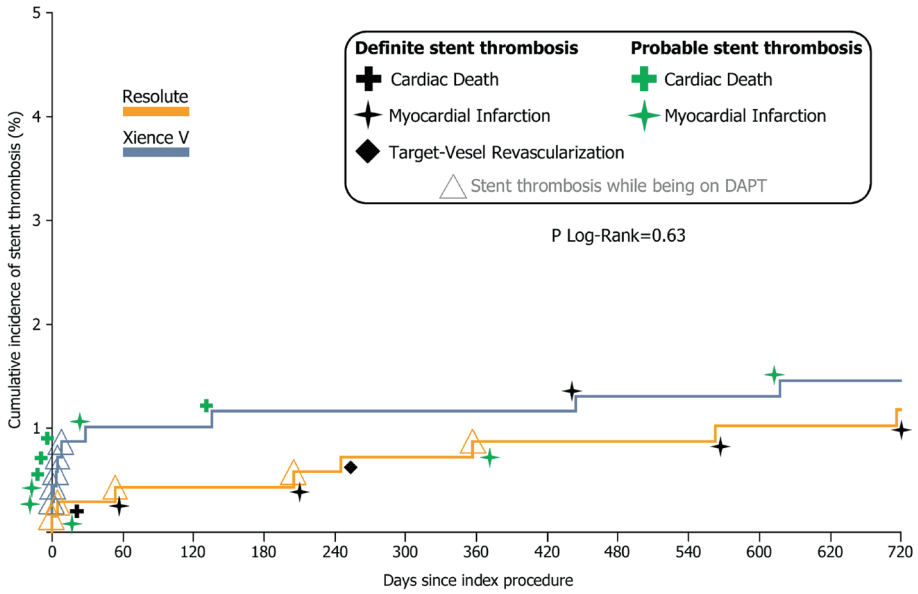


Figure 4. Cumulative Incidence of Definite or Probable Stent Thrombosis over 2 year. The cumulative incidence of definite or probable stent thrombosis in 2 years, according to the Academic Research Consortium definition. DAPT= dual antiplatelet therapy (acetylsaliclic acid and clopidogrel).

Table 5. Definite-or-probable stent thrombosis details.

	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.	Veingraft, 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)

*From day 0 on therapy with VKA+clopidogrel due to allergy for acetylsalicylic acid. † From day 0 only acetylsalicylic acid for an unknown reason. A= acetylsalicylic acid; C= clopidogrel; DAPT= dual antiplatelet therapy (acetylsalicylic acid and clopidogrel); LAD= left anterior descending coronary artery; MI= myocardial infarction; NA= not available; NSTEMI= non–ST-segment elevation myocardial infarction; PCI= percutaneous coronary intervention; RCA= right coronary artery; RCX= ramus circumflex artery; TLR= target lesion revascularization; TVR= target vessel revascularization; VKA= vitamin K antagonist.

DISCUSSION

At the 2-year follow-up of the TWENTE trial, which followed a stringent approach of discontinuation of DAPT after 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 who underwent PCI with a vast majority of complex lesions and off-label indications for use of DES. 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 rate of clinically indicated TLR in the Xience V EES group, there was no significant difference between groups in the device-oriented composite endpoint of TLF and the more patient-oriented composite clinical endpoints (major adverse cardiac events and patient-oriented composite endpoint).

Resolute ZES and Xience V EES are both DES that use 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 because 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 have demonstrated proven sustained safety and efficacy beyond 1 year, which has led 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 rate of TLF after 2 years (6.9% vs. 9.9%, p = 0.003) compared with the paclitaxel-eluting Taxus stent (Boston Scientific, Natick, Massachusetts) (8). The superiority of Xience V EES over theTaxus stent 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% versus 11.3%, p=0.004 (5). The results of SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) demonstrated that Xience V EES had similar and low rates of TLF at 2-year follow-up but showed noninferiority 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 Resolute ZES. After 2 years, Resolute ZES were equivalent to Xience V EES with regard to both TVF (12.6% vs. 12.2%, p=0.85) and the patient-oriented composite endpoint (20.6% vs. 20.5%, p=0.96) (9).

The current 2-year data of the TWENTE trial generally support the findings of the RESOLUTE All Comers trial and show that Resolute ZES have a long-term safety profile that is similar to that of Xience V EES, which was previously shown to be superior to the Taxus stent in SPIRIT IV and COMPARE (5, 8). Although the rates of TLR for Resolute ZES and Xience V EES were similar in the RESOLUTE All Comers trial (5.7% and 5.1%, respectively), in the TWENTE

trial the rate of TLR for Xience V EES 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 of TLF because of a numerically higher cardiac death rate in the Xience V EES group (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 nonsignificant difference in cardiac death during the second year of follow-up (0.6% vs.1.3%, p=0.16). Nevertheless, these data suggest that assessment of this parameter beyond the present 2-year follow-up may be of interest.

At 2-year follow-up in the TWENTE trial, 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 data are reassuring for Resolute ZES, considering that optical coherence tomography data had shown more uncovered stent struts with Resolute ZES than with Endeavor stents (22). The rates of stent thrombosis were similar to those in the RESOLUTE All Comers trial (2-year rate of definite or probable stent thrombosis, 1.9% vs. 1.0%; 2-year rate of very late definite or probable stent thrombosis, 0.3% vs. 0.3%) as well as the rates os stent thrombosis for Xience V EES in SORT OUT IV and COMPARE (5, 6, 9). In addition, the 2-year rates of definite or probable stent thrombosis in the TWENTE trial were similar to the pooled 2-year rates of stent thrombosis in SPIRIT II and III (1.2%), using Xience V EES in selected patient populations with more stable coronary disease (23). The 2-year rates of definite stent thrombosis in the TWENTE trial were also low, showing a nonsignificant trend toward a lower rate in the Xience V EES group (p=0.12). Nevertheless, it may be difficult to directly compare rates of stent thrombosis from different trials, because they could be influenced by differences in study populations. In the TWENTE trial, just one 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 rates of stent thrombosis and low rates of mortality associated with stent thrombosis in patients in the Resolute ZES group were similar to those in patients in the Xience V EES group, which has shown the lowest rates of stent thrombosis in comparison to earlier- generation DES (24, 25). The data of the TWENTE trial underline the safety profile of both second-generation DES.

The low rates of very late stent thrombosis in the TWENTE trial are particularly noteworthy considering the low rate of continuation of DAPT beyond 12 months, which was in accordance with current guidelines (26, 27). 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 allcomer populations, such as LEADERS (23%) (10, 28), RESOLUTE All Comers (18%) (9), and COMPARE (13%) (5), and some U.S. trials of DES in patients with somewhat less complex coronary disease, such as SPIRIT IV (69%) (8, 28) and RESOLUTE US (67%) (30, 31). In addition, in the second year of follow-up after discontinuation of DAPT, rate of definite or probable stent thrombosis was lower compared with

that with first-generation DES, which showed a definite and continuous risk of very late stent thrombosis (32).

Hence, the TWENTE trial provides interesting safety information on stringent discontinuation of DAPT at 1 year after PCI in a study population with many complex patients and lesions treated with Resolute ZES and Xience V EES.

Study limitations. This prospective, randomized, singlecenter trial was performed in a high-volume tertiary care center by experienced operators who applied relatively uniform procedural strategies. For that reason, generalizability of the study results to other clinical settings may be limited. In addition, conclusions do not apply to patients with ST segment elevation MI requiring primary PCI because 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 the RESOLUTE All Comers trial (33) 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.

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Chapter 5

Clinical outcome following second-generation drug-eluting stent use for off-label versus on-label indications: insights from 2-year outcome of the TWENTE Trial

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EuroIntervention.2014 Oct 22; 10(6):664-671.

ABSTRACT

Aim: Drug-eluting stents (DES) were first used on-label – in simple patients with low clinical risk and easily accessible lesions. Currently, DES are increasingly used off-label – in complex patients undergoing percutaneous coronary interventions (PCI) with historically higher event risk. Therefore, our aim was to investigate whether patients with off-label indications for DES use had similar outcomes compared to patients who were treated for on-label indications only

Methods and results: We analyzed two-year follow-up data of 1387 TWENTE trial patients, treated with second-generation everolimus-eluting Xience V or zotarolimus-eluting Resolute stents, and compared off-label vs. on-label DES use with regard to the following clinical endpoints: cardiac death, myocardial infarction (MI), periprocedural MI (≤48h), and target-vessel revascularisation (TVR). Patients with off-label DES use (n=1,033; 74.5%) had more diabetes (22.9% vs. 17.5%; p=0.032), previous MI (35.9% vs. 22.3%; p<0.001), type B2/C lesions (84.7% vs. 62.7%; p<0.001), and acute coronary syndromes (57.8% vs. 33.3%; p<0.001). Nevertheless, cardiac death and TVR rates were similar to those of patients with on-label DES use (p>0.8). Following off-label DES use, there was a higher incidence of periprocedural MI (5.0% vs. 1.4%; p=0.003), of which only 1.1% reached creatine kinase levels >5x the upper limit of normal (ULN).

Conclusions: Despite differences in risk profile, patients with off-label DES use did not differ from patients with on-label DES use in clinical endpoints other than periprocedural MI. These largely positive findings underline the favourable safety profile of second-generation DES.

INTRODUCTION

Initially, drug-eluting stents (DES) were intended to be implanted on-label during percutaneous coronary interventions (PCI) in easily accessible lesions of low-risk patients[1]. Shortly thereafter, DES were increasingly used *off-label* in patients who were characterised by a higher clinical event risk and more challenging lesion anatomies[2]. Nevertheless, in routine clinical procedures with more off-label use of first-generation DES, event rates were higher than in the initial pivotal trials[3]. Patients with off-label use of *first-generation* DES had a higher risk of death, myocardial infarction (MI), stent thrombosis (ST), and repeat revascularisation procedures than patients with on-label DES use[3,4].

Second-generation DES with more biocompatible coatings[5] were developed to improve outcome and counteract the drawbacks of the early-generation DES. The Resolute zotarolimus-eluting (ZES) (Medtronic Cardiovascular, Santa Rosa, CA, USA) and the Xience V everolimus-eluting (EES) (Abbott Vascular, Santa Clara, CA, USA) are two widely used second-generation DES, for which similar safety and efficacy have been demonstrated *in the randomised RESOLUTE All-Comers and TWENTE trials, which enrolled patients with off-label DES use in two thirds and three quarters of their study populations, respectively*[6,7]. So far, most data on clinical outcome following the use of second-generation DES for off-label indications have been derived from registries[8-10]. In particular, outcome data beyond one year were scarce[11]. In a substudy of the prospective TWENTE trial[7,12] we investigated whether patients with off-label indications for DES use had a similar two-year clinical outcome as compared to patients who were treated for on-label indications only.

METHODS

STUDY DESIGN AND PATIENT POPULATION

Details of the randomised TWENTE trial, which was performed between June 18, 2008, and August 26, 2010, at Thoraxcentrum Twente in Enschede, The Netherlands, have previously been reported[7]. In brief, TWENTE (ClinicalTrials.gov NCT01066650) was a randomised, controlled, patient-blinded DES trial, comparing Resolute ZES and Xience V EES stents after 1:1 randomsation in 1,391 patients. Patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) or stable angina were eligible, and few exclusion criteria were applied[7]. In TWENTE, a total of 81.4% of all eligible patients were enrolled, of whom more than 52% presented with ACS. The real-world character of the randomised TWENTE trial was underlined by the findings of the non-enrolled TWENTE study, which demonstrated similar and excellent outcomes of the eligible but non-enrolled patients[13]. The present study population consisted of all 1,387 patients (four patients withdrew consent)[7].

Off-label indications for DES use were defined as: renal insufficiency (serum creatine ≥ 140 µmol/l); ejection fraction <30%; occurrence of acute MI within the previous 72 hours; more than one lesion/vessel; more than two vessels treated; lesion length >27 mm; bifurcation; saphenous vein graft lesion; arterial bypass graft lesion; in-stent restenosis; unprotected left main lesion; lesion with thrombus; and/or lesion with total occlusion.

INTERVENTION, ELECTROCARDIOGRAPHY, LABORATORY TESTING, AND ANGIOGRAPHIC ANALYSIS

Five experienced interventional cardiologists, each of whom had individual experience of at least 4,000 PCI procedures, performed all the PCI procedures of the TWENTE trial using standard techniques. Periprocedural pharmacological as well as systematic laboratory testing and ECG assessment have previously been described[7]. Quantitative coronary angiography analyses were performed offline with QAngio XA version 7.1 (Medis medical imaging systems bv, Leiden, The Netherlands).

CLINICAL ENDPOINTS

Definitions of clinical endpoints were reported on a patient level, was previously described in detail[7], and generally followed the suggestions of the Academic Research Consortium (ARC)[14,15]. Death was considered cardiac unless an unequivocal non-cardiac cause could be established. MI was defined by any creatine kinase concentration of more than twice the upper limit of normal (ULN) with elevated confirmatory cardiac biomarkers[14]. Further classification and location of MI was based on laboratory testing, electrocardiographic parameters, angiographic information, and clinical data[7]. MI was classified as target vessel-related if related to the target vessel or if it could not be related to another vessel. Target vessel revascularization (TVR) and target lesion revascularisation (TLR) by re-PCI or surgery were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischaemic signs or symptoms[15]. Stent thrombosis was defined according to ARC[15].

DATA ACQUISITION, FOLLOW-UP, AND CLINICAL EVENT ADJUDICATION

Two-year follow-up data were available in 100% of patients. For any event trigger, clinical information was gathered from the referring cardiologist, general practitioner, and/or hospital involved. This was facilitated by a close network of cooperation between the care-providers in the Twente region. The processing of clinical data and adjudication of adverse clinical events were performed by an independent, external contract research organisation and core laboratory (Cardialysis, Rotterdam, The Netherlands), which also performed an on-site audit to assess key study data.

STATISTICAL ANALYSIS

Data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 17 (SPSS Inc., Chicago, IL, USA). Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean±SD for continuous variables. Chi-square and Fisher's exact tests 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. Possible predictors of periprocedural myocardial infarction (PMI) were identified if p-values were <0.15 at univariate analysis of the relation between the variables of the definition of off-label versus PMI. A multivariate Cox regression analysis was then performed to evaluate the independent predictors of PMI. Two-sided p-values <0.05 were considered significant.

RESULTS

CHARACTERISTICS OF PATIENTS, LESIONS, AND PCI PROCEDURES

Of the entire population of the TWENTE trial, 1,033 (74.5%) patients were treated with DES for at least one off-label indication and 354 (25.5%) were treated for on-label indications only (Table 1).

Patients with off-label DES use had a slightly higher prevalence of diabetes mellitus (22.9% vs.17.5%; p=0.032) and chronic renal failure (3.3% vs. 1.1%; p=0.032), and significantly more often a history of MI (35.9% vs. 22.3%; p<0.001), NSTE-ACS at presentation (57.8% vs. 33.3%; p<0.001), and more B2/C lesion types (84.7% vs. 62.7%; p<0.001). Between patients with off-label versus on-label DES use, there were significant differences in various angiographic and procedural details which were mainly related to the definition of the groups. In addition, in patients with off-label DES use there were more ostial (12.2% vs. 7.3%; p=0.012) and severely calcified lesions (21.0% vs. 16.1%; p=0.045), and stent post-dilation was more often performed (90.4% vs. 80.2%; p<0.001).

CLINICAL OUTCOME

Two-year follow-up data were available in 1,387 patients. The rates of death from any cause (4.5% vs. 4.2%; p=0.806), cardiac death (2.1% vs. 2.3%; p=0.884), TVR (5.4% vs. 5.1%; p=0.808), and definite-or-probable stent thrombosis (1.4% vs. 1.1%; p=1.0) were similar for patients with off-label and on-label DES use (Table 2).

Table 1. Characteristics of patients and procedures.

	Off-label (n=1,033)	On-label (n=354)	*p*
Age (yrs)	64.4±10.7	64.0±10.2	0.507
Men	752 (72.8)	253 (71.5)	0.629
BMI (kg/m^2)	27.7±3.9	27.9±4.2	0.360
Diabetes mellitus (any)	237 (22.9)	62 (17.5)	0.032
Chronic renal failure*	34 (3.3)	4 (1.1)	0.032
Arterial hypertension	558 (54.0)	213 (60.2)	0.044
Hypercholesterolaemia	577/1004 (57.5)	224/349 (64.2)	0.028
Current smoker	265 (25.7)	75 (21.2)	0.092
Family history of CAD	537 (52.0)	200 (56.5)	0.142
Myocardinfarction (any)	371 (35.9)	79 (22.3)	<0.001
Previous PCI	217 (21.0)	70 (19.8)	0.621
Previous CABG	116 (11.2)	32 (9.0)	0.249
Clinical characteristic			<0.001
Stable angina pectoris	436 (42.2)	236 (66.7)	
Acute coronary syndrome	597 (57.8)	118 (33.3)	
Unstable angina	214 (20.7)	111 (31.4)	
Non-ST-elevation MI	383 (37.1)	7 (2.0)	
Left ventricular ejection fraction <30%¶	32/792 (4.0)	0	0.001
Multivessel treatment	281 (27.2)	53 (15.0)	<0.001
Total no lesions treated per patient			<0.001
1 lesion treated	549 (53.1)	307 (86.7)	
2 lesions treated	344 (33.3)	47 (13.3)	
3 of more lesions treated	140 (13.6)	0	
De novo coronary lesions only	930 (90.0)	354 (100.0)	<0.001
At least 1 CTO	95 (9.2)	0	<0.001
Severe calcification	217 (21.0)	57 (16.1)	0.045
Aorta ostial lesion	126 (12.2)	26 (7.3)	0.012
At least 1 bifurcation	362 (35.0)	0	<0.001
At least 1 bifurcation with SB treatment	213 (20.6)	0	<0.001
At least 1 in-stent restenosis	68 (6.6)	0	<0.001
At least 1 small-vessel (RVD<2.75mm)	657 (63.6)	215 (60.7)	0.335
At least 1 lesion length >27mm	293 (28.4)	0	<0.001
Glycoprotein IIb/IIIa antagonist	175 (16.9)	18 (5.1)	<0.001
Target coronary artery			
Left main	43 (4.2)	9 (2.5)	0.166
Left anterior descending	551 (53.3)	172 (48.6)	0.122
Left circumflex	326 (31.6)	111 (31.4)	0.944
Right coronary artery	387 (37.5)	115 (32.5)	0.093
Bypass graft	41 (4.0)	0	<0.001
ACC-AHA lesion class§			<0.001
A	25 (2.4)	39 (11.0)	
B1	133 (12.9)	93 (26.3)	
B2	280 (27.1)	129 (36.4)	
C	595 (57.6)	93 (26.3)	
Post-dilation	934 (90.4)	284 (80.2)	<0.001

Data are number (%) or mean (SD). *Chronic renal failure was defined by serum creatinine level ≥130µmol/L.
¶ Left ventricular ejection fraction was assessed with ultrasound, MRI or LV angiography.
§Highest lesion classification. SB: side branch; ACC-AHA: American College of Cardiology/American Heart Association; BMI: body mass index; CABG:coronary artery bypass grafting; CAD:coronary artery disease; CTO:chronic total occlusion; MI:myocardial infarction; PCI: percutaneous coronary intervention; RVD: reference vessel diameter

Table 2. Clinical outcome after 2 years

	Off-label (n=1,033)	On-label (n=354)	*p*
Death, any cause	47 (4.5)	15 (4.2)	0.806
Death, cardiac cause	22 (2.1)	8 (2.3)	0.884
Target vessel-related MI	66 (6.4)	10 (2.8)	0.011
CK > 2 ULN*	66 (6.4)	10 (2.8)	0.011
CK > 3 ULN	22 (2.1)	3 (0.8)	0.118
CK > 5 ULN	11 (1.1)	-	0.076
PMI (MI≤48h)	52 (5.0)	5 (1.4)	0.003
2 <CK≤5 ULN	41 (4.0)	5 (1.4)	0.024
CK>5 ULN	11 (1.1)	0	0.076
Non-PMI (MI>48 h) (MI > 48 h)	14 (1.4)	5 (1.4)	1.0
Revascularization, any	99 (9.6)	28 (7.9)	0.346
Target Lesion Revascularization¶	43 (4.2)	9 (2.5)	0.166
Target Vessel Revascularization¶	56 (5.4)	18 (5.1)	0.808
Definite ST (0-720 days)			
All patients	5 (0.5)	2 (0.6)	1.0
Probable ST (0-720 days)			
All patients	9 (0.9)	2 (0.6)	0.739
ST (0-720 days)			
Possible	11 (1.1)	5 (1.4)	0.571
Definite or probable	14 (1.4)	4 (1.1)	1.0
Very late definite or probable ST	2 (0.2)	2 (0.6)	0.270

Data are number of patients (%).*In our study, MI was defined by any creatine kinase (CK) concentration of more than double the upper limit of normal (ULN) with elevated values of a confirmatory cardiac biomarker. ¶ TVR and TLR were clinically indicated. MI: myocardial infarction; PMI: periprocedural MI; ST: stent thrombosis

There was a difference in the incidence of target vessel-related MI (6.4% vs. 2.8%; p= 0.011). While the rate of target vessel-related MI >48 hours was similar for both groups (1.4% vs.1.4%; p=1.0), the rate of target vessel-related MI ≤48 hours (i.e. PMI) was significantly higher in patients with off-label DES use (5.0% vs. 1.4%; p=0.003), of which 1.1% developed a maximum creatine kinase level >5x ULN (Table 2).

Figure 1 shows the Kaplan-Meier cumulative incidence of three major clinical endpoints: cardiac death, target vessel-related MI, and TVR. Of these three endpoints, only target vessel-related MI showed a significantly higher rate in patients with off-label DES use (p -log rank= 0.011). Figure 2 displays the cumulative incidence of target vessel-related MI within ≤48 hours (i.e. periprocedural MI) as well as after >48 hours (i.e. non-PMI), showing that only MI after ≤48 hours occurred significantly more often in patients with off-label DES use (p-log-rank=0.003).

IDENTIFICATION OF POSSIBLE PREDICTORS

The chi-square test was applied to identify independent predictors of PMI. The following variables of the definition of off-label showed a univariate association ($p < 0.15$) with PMI, and were further evaluated: treatment of more than one lesion/vessel; more than two vessels; lesion length >27 mm; bifurcation lesion; and lesion with thrombus.

MULTIVARIATE COX REGRESSION ANALYSIS

Lesion length >27 mm (adjusted HR 2.84, 95%CI: 1.68-4.80, $p<0.001$), more than one lesion/vessel (adjusted HR 2.55, 95%CI: 1.51-4.32, $p<0.001$), and bifurcation lesion (adjusted HR 2.03, 95%CI: 1.20-3.45, $p=0.008$) were the only significant independent predictors of PMI which were related to the definition of off-label DES use.

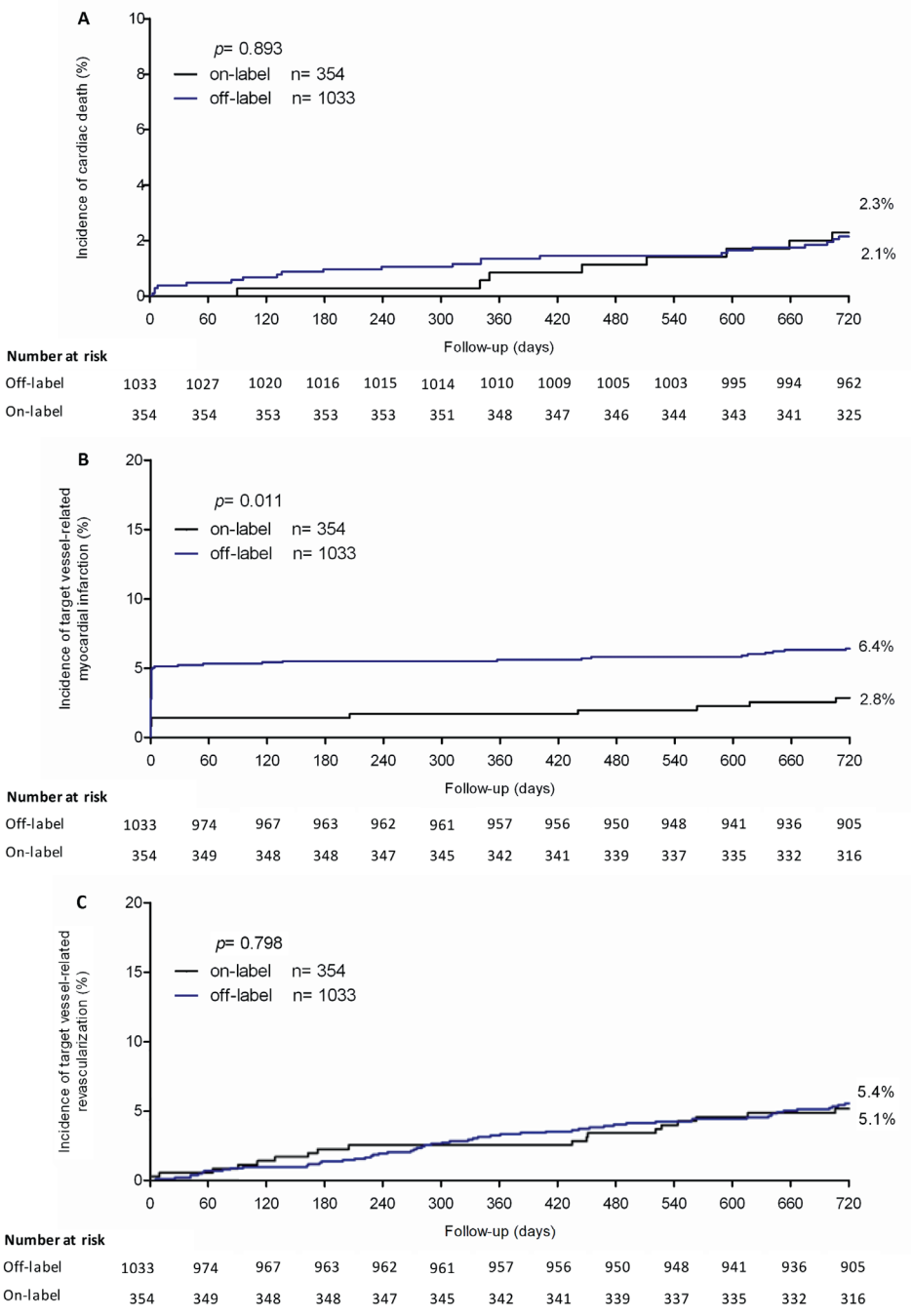

Figure 1. Kaplan-Meier cumulative incidence curves at two years for: A) cardiac death; B) target vessel-related MI and C) target vessel revascularisation for patients treated with off-label and on-label DES use.

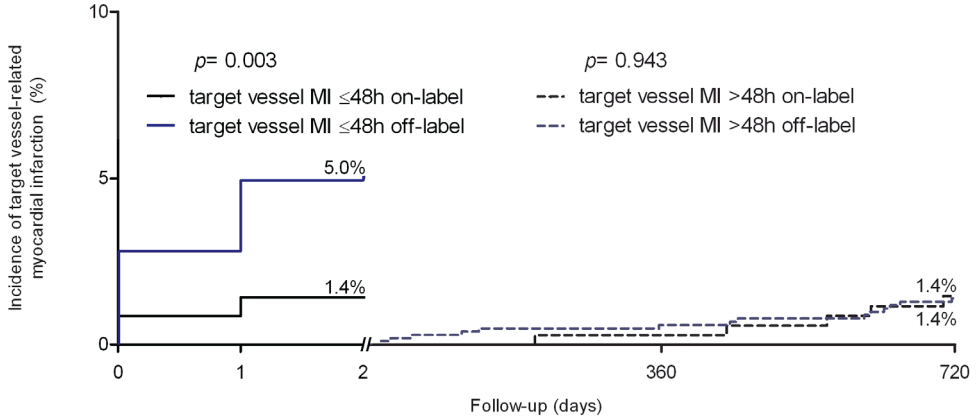

Figure 2. Target vessel-related MI ≤ 48 Hours (periprocedural) and > 48 Hours. Kaplan-Meier cumulative incidence curves at two years for (left) target vessel-related MI ≤48 hours and (right) target vessel-related MI >48 hours for patients treated with off-label and on-label DES use.

DISCUSSION

In the TWENTE trial, off-label DES use was associated with more clinical, lesion, and procedure-related characteristics of increased risk, as might have been expected from the definition of off-label profile, both patient groups showed low and similar two-year rates of various clinical endpoints such as death from any cause, cardiac death, target vessel revascularisation, and definite or probable stent thrombosis. The only exception was a *higher incidence of PMI* (i.e. MI ≤ 48 hours following PCI) in patients with off-label DES use, of whom only a minority developed a myocardial necrosis with a maximum CK level of more than five times the upper limit of normal. These findings underline the favourable safety profile of second-generation DES.

In this analysis, there was *no difference in target vessel-related MI after more than 48 hours* between patients with off-label and on-label DES use (1.4% vs. 1.4%); there was a higher rate of (periprocedural) target vessel-related MI in patients with off-label DES use (5.0% vs. 1.4%) only within the first 48 hours after PCI. Such PMI typically results from microembolisation of plaque material, or stent-induced closure of small side branches, which occurs more frequently in patients with ACS and in extensive coronary disease[16,17]. In the present analysis, the higher incidence of PMI following off-label DES use led to a higher rate of target vessel-related MI during two years of follow-up (6.4% vs. 2.8%, respectively).

COMPARISON WITH PREVIOUS STUDIES

Off-label use of *first-generation DES* was previously shown to be associated with a higher risk of death, MI, and/or repeat revascularisation procedures[3,4,17,18]. Detailed analyses of clinical outcome

following off-label use of *second-generation DES* were performed in a few studies only[8-11]. Latib et al reported a retrospective analysis of patients treated with Xience V EES (248 (72%) off-label) and a median follow-up of 12 months[8]. Galasso et al. and Romagnoli et al. published two registries of patients treated with Resolute ZES (311 (84%) and 504 (61%) off-label) and an average follow-up duration of 17 and 12 months, respectively[9,10]. Stefanini et al reported data from the only randomised study – the RESOLUTE All Comers trial – which compared 12-month clinical outcome of patients treated with Resolute ZES and Xience V EES in 1,520 (66.3%) complex patients (with off-label DES use) versus (33.7%) simple patients[11]. Our present analysis of the randomized TWENTE trial, which included 1033 (74.5%) patients with off-label DES use, is the first comprehensive analysis of 24-month follow-up data to compare the clinical outcome of patients treated for off-label and on-label indications with either Resolute ZES or Xience V EES. In the RISICO registry, Romagnoli et al found no significant difference in the incidence of in-hospital MI between off-label and on-label treatment with Resolute ZES (3.8 vs. 2.5%, respectively; p=0.4)[10]. While the RISICO registry defined MI by the elevation of creatine kinase or creatine kinase-MB levels to ≥3 times the upper limit of normal[10], in the TWENTE trial MI was defined by CK levels ≥2 times the upper limit of normal with elevated confirmatory cardiac biomarkers[7]. This may partly explain the slightly higher incidence of PMI (5.0%) in TWENTE patients with off-label DES use. The TWENTE trial compared the same DES types as RESOLUTE ALL COMERS, and also evaluated DES use in daily clinical practice within a slightly different population which did not include acute STEMI. Using the same criteria of off-label DES use, the proportion of complex patients was somewhat higher in the TWENTE trial (74.5% vs. 66.3%; p<0.001). Nevertheless, it is difficult to compare the outcome results of both trials as the corresponding subgroup analysis of RESOLUTE All Comers focused on stent level comparisons[11]. While all-comer DES trials generally comprise relatively low rates of PCI for unprotected left main lesions, which is one of the off-label criteria, the ISAR-LEFT MAIN 2 study recently reported in 650 patients treated with Resolute and Xience V stents for unprotected left main lesions a favourable outcome at one-year follow-up[19].

In the four-year follow-up data of the LEADERS study, a subgroup analysis of the primary composite endpoint TVF favours the biolimus-eluting Biomatrix stent with biodegradable polymer coating (Biosensors Inc., Newport Beach, CA, USA) over the first-generation sirolimus-eluting Cypher stent with biodurable coating (Cordis, Johnson & Johnson, Warren, NJ, USA) in patients treated for off-label indications[20]. Nevertheless, only limited individual outcome data of patients treated with DES with biodegradable coatings for off-label versus on-label indications have been reported. In the NOBORI 2 study, which comprised 2,242 patients treated with the biolimus-eluting Nobori stent with biodegradable coating (Terumo Medical Corp., Tokyo, Japan) for at least one off-label indication, off-label stent use was associated with higher rates of cardiac death (1.9% vs. 0.7%, p=0.02), TVR (5.1% vs. 2.3%, p<0.01), and MI (2.7% vs. 1.5%, p=0.04)[21]. In addition, in that study there was no significant difference in the rate of definite or probable stent thrombosis between patients with off-label versus on-label DES use[21].

In the present study, we also found a higer rate of MI in off-label patients, and there was no significant difference in stent thrombosis between patients with off-label versus on-label indications. Our findings differ from NOBORI 2 with regard to cardiac death and TVR, which were similar for our off-label and on-label patients. Due to differences in patient population and limitations inherent to the study design, it may be difficult to compare the findings of registries and randomised trials. In addition, we post-dilated stents in 90.4% and 80.2% of the off-label and on-label patients, respectively ($p<0.001$), while in the NOBORI 2 study postdilation was only performed in 34.9% and 31.5%, respectively ($p=0.07$), of both patient groups[21]. Substantial differences in material (stainless steel vs. cobalt-chromium) and strut thickness (relatively thick struts vs. thinner struts) of the stent platforms might also have contributed to differences in certain outcome parameters between both studies.

PERIPROCEDURAL MYOCARDIAL INFARCTION

In our analysis, target vessel-related MI ≤ 48 hours following PCI was the only clinical endpoint which was significantly higher in patients with off-label DES use. In fact, many criteria of off-label DES use characterise patients with an advanced stage of coronary disease with greater atherosclerotic burden and more complex lesions[8]. Such patients often require stenting of multiple lesions with more aggressive interventional treatment which often includes stent post-dilation with high balloon pressures[7]. In addition, greater atheroma volumes and complex lesion morphologies bear a greater risk of significant microembolisation of plaque or thrombi, which can lead to myocardial injury and PMI[16]. PMI is frequently a marker of atherosclerotic burden and of the complexity of the interventional procedure[16]. It has previously been related to an increased mortality during short-term and long-term follow-up after PCI[22-25], while other studies showed no significant relation between PMI and clinical outcome[26,27]. In fact, the extent of cardiac marker release may be relevant, as an impact on prognosis may be more likely in the presence of large PMI[16]. In the present analysis the vast majority of patients with PMI had no more than moderate PMI with maximum CK levels between 2x the ULN and 5x the ULN.

In our study, off-label patients had relatively low cardiovascular event rates. Several factors might have contributed to this phenomenon. First, the improved flexibillity of the cobalt-chromium based stents, the more biocompatible coatings of second-generation DES, and improvement of other procedural devices (e.g. balloon catheters, guidewires) may have played a role. Secondly, the high post-dilatation rate of 88% may have improved DES apposition which might have contributed to the overall favourable findings. Thirdly, the modification of adjunctive medication and the increased awareness of the importance of dual antiplatelet therapy continuation by various healthcare providers may also have played a role in improving clinical outcome of DES in our present study as well as in other recent DES studies – an improvement that may be most pronounced in the subset of complex patients.

Study limitations. Because of the post hoc nature of this analysis, the results should be considered as hypothesis-generating. Off-label criteria of DES are 'moving targets' and may differ between DES types. For that reason, for the entire study population we applied a definition that was recently used by another research group[11]. In the present study patients with on-label DES use showed a higher prevalence of arterial hypertension and hypercholesterolaemia, for which we do not have an explanation. The TWENTE trial enrolled patients with limited exclusion criteria but no acute STEMI; therefore, our results may not be extrapolated to the setting of STEMI[7]. Nevertheless, the vast majority of patients were complex and the rate of NSTE-ACS was high. All patients were treated in a high-volume tertiary PCI centre by five experienced interventional cardiologists who applied stent post-dilation in the vast majority of cases; therefore, generalisation of the findings may be limited in other settings.

Conclusion. Despite differences in risk profile, patients with off-label DES use did not differ significantly from patients with on-label DES use in clinical endpoints other than PMI. These largely positive findings underline the favourable safety profile of second-generation DES.

Impact on daily practice. Off-label patients of the TWENTE trial had two-year event rates for cardiac death, target vessel revascularisation and stent thrombosis that were comparable to those of patients with on-label indications for drug-eluting stent (DES) use. Off-label use of contemporary DES was associated with a higher rate of periprocedural myocardial infarction, but only a minority of these patients developed maximum creatine kinase levels of more than 5 times the upper limit of normal. Overall, our findings show that PCI with these DES is feasible and safe in patients with off-label DES use. Therefore, in clinical practice with implantation of second-generation DES, distinction between patients with off-label and on-label indication for DES use may be of limited value.

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Chapter 6

Complex patients treated with zotarolimus-eluting Resolute and everolimus-eluting Xience V stents in the randomized TWENTE trial: comparison of 2-year clinical outcome

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Catheter Cardiovasc Interv. in press, epublished ahead of print 14 February 2014.
DOI: 10.1002/ccd.25464

ABSTRACT

Objective: To assess the differences in clinical outcome between complex patients treated with Resolute zotarolimus-eluting stents (ZES) versus Xience V everolimus-eluting stents (EES).

Background: Nowadays, many complex patients with coronary disease are treated with percutaneous coronary interventions, using drug-eluting stents (DES).

Methods: We analyzed 2-year outcome data of 1,033 complex patients of the TWENTE trial, treated with second-generation Resolute ZES or Xience V EES. Complex patients had at least one of the following characteristics: renal insufficiency (creatinine ≥140 µmol/l); ejection fraction <30%; acute myocardial infarction (MI) within previous 72 hrs; >1 lesion/vessel; >2 vessels treated; lesion length >27 mm; bifurcation; saphenous vein graft lesion; arterial bypass graft lesion; in-stent restenosis; unprotected left main lesion; lesion with thrombus; or lesion with total occlusion. Target vessel failure (TVF), the primary composite endpoint of the trial, was defined as cardiac death, target vessel-related MI, or target vessel revascularization.

Results: Among the 1,033 complex patients, 529 (51%) were treated with Resolute ZES and 504 (49%) with Xience V EES. Patient and procedure-related characteristics were similar between DES groups. After 2-year follow-up, outcome was also similar between DES groups. TVF occurred in 12.1% of patients treated with Resolute ZES and 12.3% of patients treated with Xience V EES. In addition, DES groups did not differ significantly in cardiac death, MI, or target vessel revascularization – the individual components of TVF.

Conclusion: Complex patients treated with Resolute ZES and Xience V EES showed similar safety and efficacy during 2-year follow-up.

INTRODUCTION

Drug-eluting stents (DES) are increasingly used in complex patients with a high clinical or lesion-related risk of adverse events [1]. Although first-generation DES were already used in a large proportion of complex patients undergoing percutaneous coronary intervention (PCI) [2-6], the advent of second-generation DES, such as the Resolute zotarolimus-eluting stent (ZES) and the Xience V everolimus-eluting stent (EES), resulted in further use of DES in complex patients [7-9]. Even in randomized studies of second-generation DES such as the RESOLUTE All-Comers and TWENTE trials, which compared Resolute ZES and Xience V EES in populations with very few exclusion criteria, large proportions of trial participants were complex (66.3% and 74.5%, respectively) [10, 11].

Most information on the outcome of PCI with one of these DES in complex patients was derived from registries with a mean follow-up of less than 2 years [7-9]. To date, only one randomized trial reported outcome data of complex patients treated with Resolute ZES and Xience V EES [12]. In the present study, we therefore compared the efficacy and safety of both DES within the complex patients of the TWENTE trial, using 2-year clinical outcome data [13].

METHODS

Study Population and Design

The present study was performed in 1,033 complex patients of TWENTE trial, which represent 74.5% of the total trial population. The TWENTE trial has studied 1,391 PCI patients treated with second-generation DES at Thoraxcentrum Twente in Enschede, the Netherlands. Comprehensive details of the randomized TWENTE trial have previously been reported [11,13]. In brief, TWENTE (ClinicalTrials.gov NCT01066650) is a randomized, controlled, patient-blinded DES trial, comparing Resolute ZES and Xience V EES stents after 1:1 randomization [11]. In the TWENTE trial, PCI procedures were performed according to standard clinical techniques [11].

Patients were considered *complex* if they had at least one of the following characteristics: renal insufficiency (creatinine ≥140 μmol/l); ejection fraction <30%; occurrence of acute myocardial infarction (MI) within the previous 72 hrs; more than one lesion/vessel; more than two vessels treated; lesion length >27 mm; bifurcation; saphenous vein graft lesion; arterial bypass graft lesion; in-stent restenosis; unprotected left main lesion; lesion with thrombus; and/or lesion with total occlusion. These features have also been called off-label characteristics by others [12].

Analysts of the core laboratory in Enschede, who were blinded to the assigned DES, performed quantitative coronary angiographic analyses by use of edge-detection software (Qangio XA version 7.1, Medis, Leiden, the Netherlands). They also assessed angiographies for the presence of

lesion calcification and determined for each lesion the American college of Cardiology – American Heart Association lesion class.

Clinical Endpoints

The definitions of clinical endpoints, which have previously been described in detail [11], followed in general the suggestions of the Academic Research Consortium [14,15]. In brief, death was considered cardiac, unless an unequivocal noncardiac cause could be established [11]. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarkers [14]. A target vessel-related MI was related to the target vessel or could not be related to another vessel. Target vessel revascularization (TVR) and target lesion revascularization by re-PCI or surgery were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms [15]. Stent thrombosis was defined according to Academic Research Consortium [15]. Target vessel failure (TVF), the primary endpoint of the TWENTE trial, was defined as cardiac death, target vessel-related MI, or clinically indicated TVR. In addition, we assessed the following composite secondary endpoints (components in hierarchical order): *patient-oriented composite endpoint* (all-cause mortality, any MI, or any revascularization); *major adverse cardiac events* (all-cause death, any MI, emergent coronary bypass surgery, or clinically-indicated target lesion revascularization); and *target lesion failure* (cardiac death, target vessel-related MI, or clinically indicated TVR).

Clinical event adjudication

The processing of clinical data and adjudication of adverse clinical events were performed by an independent, external contract research organization and core laboratory (Cardialysis), which also performed an on-site audit to assess key study data. Regular safety data were reported to the Medical Ethics Committee Twente.

Statistical Analysis

Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean ±SD for continuous variables. Chi-square and Fisher's exact tests were used to compare dichotomous and categorical variables. Student's t-test was used to compare continuous variables. The Kaplan-Meier method was used to calculate the time to clinical endpoints and the log-rank test to compare between-group differences. Two-sided P-values <0.05 were considered significant. Data analysis was performed with SPSS (version 17, SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Patients, Lesions, and Interventional Procedures

Among the total number of 1,033 complex patients of the present study, 529 (51%) were treated with Resolute ZES and 504 (49%) with Xience V EES. In both DES groups, 58% of patients presented with an acute coronary syndrome. At least one complex lesion (type B2 or C) was treated in 75% of patients with Resolute ZES and 78% of patients with Xience V EES. Further patient and procedure-related baseline characteristics (Table I) also did not differ significantly between stent groups. In the Resolute ZES arm, there was a trend toward fewer patients with side branch treatment of bifurcations (19% vs. 29%, p=0.09).

Clinical Outcome

Follow-up was available in all patients. At 30-days and 1-year follow up, the two DES groups showed no significant differences in TVF, the primary endpoint of the TWENTE trial (Table II). At 2-year follow-up, the two DES groups also showed no significant difference in TVF (Fig. IA). In addition, there was no significant difference between Resolute ZES and Xience V EES in the individual components of TVF: cardiac death (1.9% vs. 2.4%, p=0.59); target vessel-related MI (6.0% vs. 6.7%, p=0.65); and clinically indicated TVR (5.7% vs. 5.2%, respectively, p=0.69) (Fig. IB–D). Other composite endpoints such as target lesion failure (11.7% vs. 10.9%, p=0.68) and the patient-oriented composite endpoint (18.3% vs. 17.7%, p=0.77) were also similar for the two DES groups (Table II).

Table I: Characteristics of Patients and Procedures

	ZES Resolute (N=529)	EES Xience V (N=504)	*P*-value
Age (yrs)	64.0 ± 10.8	64.8 ± 10.5	0.28
Men	392 (74.1)	360 (71.4)	0.33
BMI (kg/m2)	27.8 ± 4.00	27.6 ± 3.83	0.52
Diabetes mellitus (any)	124 (23.4)	113 (22.4)	0.70
Chronic renal failure[a]	17 (3.2)	17 (3.4)	0.89
Arterial hypertension	283 (53.5)	275 (54.6)	0.73
Hypercholesterolaemia	290/521 (55.7)	287/483(59.4)	0.23
Current smoker	139 (26.3)	126 (25.0)	0.64
Family history of coronary artery disease	277 (52.4)	260 (51.6)	0.80
Any MI	181 (34.2)	190 (37.7)	0.24
Previous PCI	110 (20.8)	107 (21.2)	0.86
Previous coronary artery bypass grafting	56 (10.6)	60 (11.9)	0.50
Clinical characteristic			0.28
Stable angina pectoris	223 (42.2)	213 (42.3)	
Acute coronary syndrome	306 (57.8)	306 (57.7)	
Unstable angina	119 (22.5)	95 (18.8)	
Non-ST-elevation MI	187 (35.3)	196 (38.9)	
Left ventricular ejection fraction < 30%[b]	19/407 (4.7)	13/385 (3.4)	0.36
Multivessel treatment	148 (28.0)	133 (26.4)	0.57
Total no lesions treated per patient			0.63
One lesion treated	278 (52.6)	271 (53.8)	
Two lesions treated	174 (32.9)	170 (33.7)	
Three of more lesions treated	77 (14.6)	63 (12.5)	
Only de novo coronary lesions treated	477 (90.2)	453 (89.9)	0.88
At least one chronic total occlusion treated	51 (9.6)	44 (8.7)	0.61
Severe calcification treated	114 (21.6)	103 (20.4)	0.66
Aorta ostial lesion treated	66 (12.5)	60 (11.9)	0.78
At least one bifurcation treated	179 (33.8)	183 (36.3)	0.41
At least one bifurcation with side branch treatment	98 (18.5)	115 (22.8)	0.09
At least one in-stent restenosis treated	35 (6.6)	33 (6.5)	0.97
At least one small-vessel(RVD< 2.75 mm) treated	336 (63.5)	321 (63.7)	0.95
At least one lesion length > 27mm treated	156 (29.5)	137 (27.2)	0.41
Glycoprotein IIb/IIIa antagonist use	83 (15.7)	92 (18.3)	0.28
Target coronary artery			
Left main	23 (4.3)	20 (4.0)	0.76
Left anterior descendens	280 (52.9)	271 (53.8)	0.79
Left circumflex	167 (31.6)	159 (31.5)	0.99
Right coronary artery	199 (37.6)	188 (37.3)	0.92
Bypass graft	20 (3.8)	21 (4.2)	0.75
Highest ACC-AHA lesion class treated			0.79
A	25 (4.7)	23 (4.6)	
B1	107 (20.2)	91 (18.1)	
B2	154 (29.1)	145 (28.8)	
C	243 (45.9)	245 (48.6)	
Post-dilation	474 (89.6)	460 (91.3)	0.36

Data are number (%) or mean (standard deviation).

[a] Chronic renal failure was defined by serum creatinine level ≥ 130 µmol/L.

[b] Left ventricular ejection fraction was assessed with ultrasound, MRI or LV angiography.

BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; RVD, reference vessel diameter; ACC–AHA, American College of Cardiology–American Heart Association.

Table II: Clinical Outcome

	Resolute ZES (N=529)	Xience V EES (N=504)	*P*-Value
At 30 days			
Target vessel failure (TVF)[a]	29 (5.5)	28 (5.6)	0.96
Cardiac death	1 (0.2)	3 (0.6)	0.36
All target vessel-related myocardial infarction (MI)	27 (5.1)	27 (5.4)	0.86
Target vessel revascularization (TVR)	2 (0.4)	-	0.50
At one-year			
Death			
Any cause	13 (2.5)	10 (2.0)	0.61
Cardiac cause	6 (1.1)	8 (1.6)	0.53
All target vessel-related MI	29 (5.5)	29 (5.8)	0.85
Periprocedural MI (MI ≤ 48 h)	27 (5.1)	25 (5.0)	0.92
Clinically indicated TVR	19 (3.6)	14 (2.8)	0.46
TVF	51 (9.6)	46 (9.1)	0.78
Target lesion failure	49 (9.3)	41 (8.1)	0.52
Death from cardiac causes or target-vessel MI	31 (5.9)	28 (5.6)	0.83
Major adverse cardiac events	62 (11.7)	50 (9.9)	0.35
Patient-oriented composite end-point	68 (12.9)	58 (11.5)	0.51
Definite or probable stent thrombosis	5 (0.9)	7 (1.4)	0.51
At two-year			
Death			
Any cause	26 (4.9)	21 (4.2)	0.56
Cardiac cause	10 (1.9)	12 (2.4)	0.59
All target vessel related MI	32 (6.0)	34 (6.7)	0.65
Periprocedural MI (MI ≤ 48 h)	27 (5.1)	25 (5.0)	0.92
Non-PMI target vessel MI (MI > 48 h)	5 (0.9)	9 (1.8)	0.24
(MI > 48 h)			
Clinically indicated TVR	30 (5.7)	26 (5.2)	0.72
Any revascularization	48 (9.1)	51 (10.1)	0.57
TVF	64 (12.1)	62 (12.3)	0.92
Target lesion failure	62 (11.7)	55 (10.9)	0.68
Death from cardiac causes or target-vessel MI	40 (7.6)	42 (8.3)	0.65
Major adverse cardiac events	77 (14.6)	64 (12.7)	0.39
Patient-oriented composite endpoint	97 (18.3)	89 (17.7)	0.78
Stent thrombosis (0-720 days) 72			
Definite	4 (0.8)	1 (0.2)	0.38
Probable	2 (0.4)	7 (1.4)	0.10
Possible	5 (0.9)	6 (1.2)	0.70
Definite or probable	6 (1.1)	8 (1.6)	0.53
Very late definite or probable stent thrombosis (360-720 days)	1 (0.2)	1 (0.2)	1.00

Data are number of patients (%).
[a]TVF is a composite of cardiac death, target vessel-related MI, or TVR.
TVF, target vessel failure; MI, myocardial infarction; PMI, periprocedural myocardial infarction; TVR, target vessel revascularization.

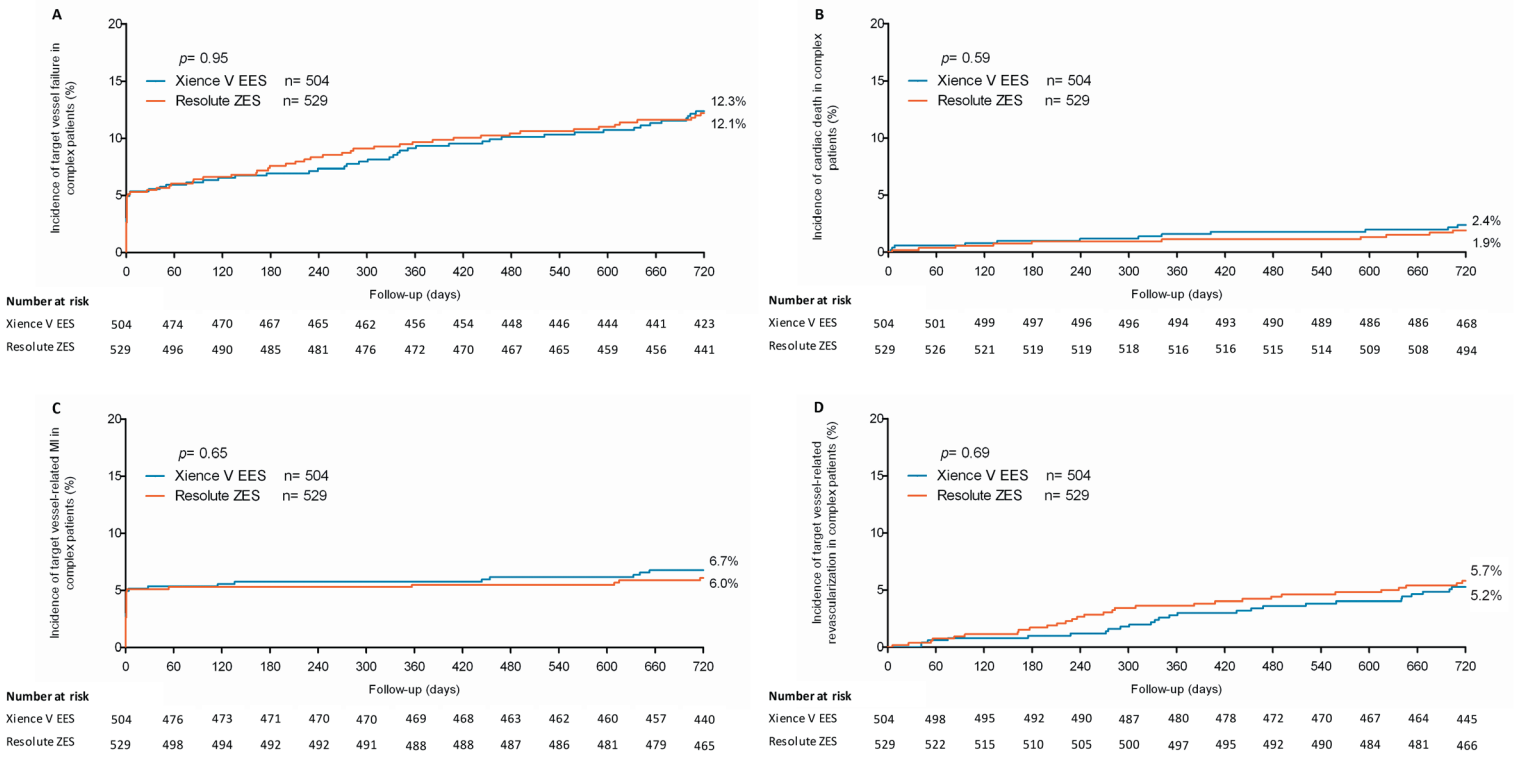

Figure. 1. Kaplan–Meier curves at 2-years for the composite primaryendpoint and its individual components in patients treated with Resolute ZES and Xience V EES. (A) Kaplan–Meier cumulative incidence curves at 2-years for TVF, a composite of cardiac death, target vessel-related MI, or TVR for patients treated with Resolute ZES and Xience V EES. (B)Kaplan–Meier cumulative incidence curves at 2-years for cardiac death. (C) Kaplan–Meier cumulative incidence curves at 2-years for target vessel-related MI. (D) Kaplan–Meier cumulative incidence curves at 2-years for TVR.

Stent Thrombosis and Duration of Dual Antiplatelet Therapy

The incidence of definite-or-probable stent thrombosis was low in both DES groups; stent thrombosis occurred in 6 (1.1%) patients of the Resolute ZES group and 8 (1.6%) of the Xience V EES group (Table II). The duration of dual antiplatelet therapy was 12 months after PCI (in accordance with applicable European guidelines). Dual antiplatelet therapy was continued beyond 12 months only in 6.8% in Resolute ZES group and 4.3% in Xience V EES group (Table III). The rate of very late definite-or-probable stent thrombosis was low for both DES groups (0.2%) and did not differ between stents.

Table III: Dual antiplatelet therapy usage.

	Resolute ZES(N=529)	Xience V EES (N=504)	*P*-Value
At 1 year follow-up	**N=516**	**N=494**	
Dual antiplatelet therapy			0.20
Stopped after 12 months	439 (85.1)	435 (88.1)	
Less than 12 months	42 (8.1)	38 (7.7)	
Continued after 12 months	35 (6.8)	21 (4.3)	
At 2-Year Follow-up	**N= 500**	**N=478**	
On dual antiplatelet therapy	38 (7.6)	30 (6.3)	0.42

Data are number of patients (%).

DISCUSSION

Within 1,033 complex patients of the TWENTE trial, treated with Resolute ZES and Xience V EES, the 2-year outcome data showed no significant difference between DES groups in primary and secondary endpoints. The rates of definite-or-probable stent thrombosis, in particular the incidence of very late stent thrombosis, were low and similar for both DES groups. The latter is particularly remarkable, as a strict policy of dual antiplatelet therapy discontinuation beyond 12 months was applied. This resulted in a very low rate of dual antiplatelet therapy after 12 months (5.5%) that was similar to the dual antiplatelet rate of the entire population of the TWENTE trial (5.4%) [13]. Besides that, other factors might have contributed to the relatively low event rates in our complex patients. First, the improved flexibility of the cobalt-chromium based stent platforms and the more biocompatible coatings of both second-generation DES (compared with the first-generation DES) might have played a role. Second, the high postdilation rate of 88% might have improved DES apposition. Third, the improvement of other procedural devices (e.g. balloon catheters, guide wires, etc.) might have contributed to the overall favorable findings.

Previous registries and randomized trials

Most information on the outcome of PCI with one of both second-generation DES in complex patients was derived from non-randomized registries that reported a median follow-up of less than 2 years.

Latib et al. [7] reported data of a retrospective registry with a median follow-up of 12 months, showing a major adverse cardiac events rate of 12.2% in 248 complex patients treated with Xience V EES, which matches well with the 12.7% major adverse cardiac events rate of our 504 complex, Xience V EES-treated patients. Despite the high complexity of patients, definite stent thrombosis rarely occurred in either: the registry of Latib et al. [7] (0.8%) and our Xience V EES treated patients (0.2%). Resolute ZES was examined in two Italian registries, comprising 311 and 504 complex patients with an average follow-up duration of 17 and 12 months [8,9]. Galasso et al. [8] reported cardiac death (3.3%), MI (3.3%), and TVR (5.5%) rates. Ramagnoli et al. [9] observed cardiac death (3.4%), MI (7.2%; including 3.8% in-hospital MI), and TVR (6.7%) [9]. The comparison of our data with these registries might be limited by differences in MI definition, follow-up duration, and study design (e.g. systematic sampling of cardiac markers and electrocardiogram). Nevertheless, the rates of cardiac death, MI, and TVR in complex patients of the TWENTE trial, treated with Resolute ZES, matched quite well with the results of these two registries (1.9%, 6.0%, and 5.7%, respectively). As recently reported in a pooled analysis of all patients of the TWENTE trial, complex patients (i.e., patients with "off-label" indications for DES use) had significantly more diabetes (23% vs. 18%), previous MI (36% vs. 22%), type B2/C lesions (85% vs. 63%), and acute coronary syndromes at presentation (58% vs. 33%) compared with the non-complex patients. At 2-year follow-up, the rate of target vessel-related MI was significantly higher in the complex patients (6.4% vs. 2.8%; p=0.01 [16]. Our present study adds to those findings by showing that complex patients treated with ZES versus EES do not differ in target vessel-related MI (6.0% vs. 6.7%; p=0.65) [16].

To date, there is only one randomized study, the RESOLUTE All Comers trial that compared *1-year* clinical outcomes of Resolute ZES and Xience V EES-treated complex patients [12]. Using the same criteria for the definition of complex patients as in the TWENTE trial, 66% of the RESOLUTE All Comers patients were complex [10], whereas this proportion was 74% in the TWENTE trial. In complex RESOLUTE All Comers patients, the 1-year clinical outcome of the Resolute ZES and Xience V EES groups was similar for cardiac death (1.3% vs. 2.2%), MI (4.3% vs. 4.4%), and TVR (5.6% vs. 5.5%) [12]. In our present analysis of 2-year outcome in complex TWENTE patients, we also found no significant difference between the two DES groups for these adverse clinical endpoints.

Between complex RESOLUTE All Comers patients treated with Resolute ZES versus Xience V EES, there was no significant difference in target lesion failure and patient-oriented composite endpoint at 2-year follow-up (12.1% vs. 12.6%, p=0.81, and 21.5% vs. 22.5%, p=0.66, respectively) [17]. In our present analysis, we found similar or slightly lower target lesion failure

and patient-oriented composite endpoint rates for the two DES groups in the complex TWENTE patient population (11.7% vs. 10.9%, p=0.68, and 18.3% vs. 17.7%, p=0.78, respectively). The ISAR-LEFT MAIN 2 study recently also reported comparable clinical outcome at 1-year follow-up of 650 patients treated with Resolute ZES and Xience V EES stents for unprotected left main lesions – one of the criteria that define complex patients. The combined primary endpoint of death, MI, and target lesion revascularization occurred in 17.5% vs. 14.3% of patients, respectively [18]. Efficacy and safety of these second-generation DES have also been demonstrated in a network meta-analysis by Navarese et al [19].

Limitations

The findings of the present post-hoc analysis, which was based on the 2-year clinical outcome data of complex TWENTE patients, should be considered as hypothesis-generating. The TWENTE trial enrolled patients with limited exclusion criteria, but no patients with acute ST segment elevation MI; nevertheless, the vast majority of enrolled patients were complex and the rate of acute coronary syndromes at presentation (52%) was similar to many other randomized DES trials with limited exclusion criteria [10,20, 21]. As our patients were treated in a high-volume tertiary PCI center by five interventional cardiologists who all had an individual experience of at least 4,000 PCI procedures and applied stent postdilation in the vast majority of complex patients (91% of lesions), generalization of our findings to other settings may be limited.

Conclusions

Complex patients treated with Resolute ZES and Xience V EES showed similar safety and efficacy during 2-year follow-up. Despite a strict policy of dual antiplatelet therapy discontinuation beyond 12 months, the rates of stent thrombosis were similar and low for both DES arms in this complex patient population.

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Chapter 7

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*

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Catheter Cardiovasc Interv. in press, epublished ahead of print 18 April 2014. DOI: 10.1002/ccd.25518.

ABSTRACT

Objectives: The aim of the present study was to assess the impact on clinical outcome of right coronary artery (RCA) ostial coverage with second-generation drug-eluting stents (DES).

Background: Treatment of the aorta-ostial (AO) region of the RCA with bare metal stents and first-generation DES has been associated with a higher risk of target-lesion revascularisation (TLR).

Methods: Of the 1,391 patients of the prospective TWENTE trial, we identified 321 (23%) with single-vessel RCA treatment, who were categorized into stenting *with* AO stent coverage (AOC) versus stenting *without* AOC. The AO region was defined as 3 mm from the aortic orifice.

Results: The 67 (20.9%) patients with AOC showed more severe lesion calcifications than the 254 patients *without* AOC (31.3% vs. 12.6%; p<0.01). In the AOC group, there was a higher prevalence of hypercholesterolemia and family history of coronary disease (75.4% vs. 61.6%, and 68.7% vs. 53.5%, respectively; p=0.03). During 2-year follow-up, patients in the AOC group had a higher incidence of TLR (7.5% vs. 1.6%; p=0.02). Following adjustment for confounders, AOC independently predicted TLR with an adjusted hazzard ratio of 4.1 (95%CI: 1.17-14.39; p=0.03).

Conclusion: AO treatment of the RCA with second-generation DES is feasible, but our data suggest that stent coverage of the right AO segment remains a predictor of TLR.

INTRODUCTION

Percutaneous coronary interventions (PCI) of the aorto-ostial (AO) region are known to be technically challenging as interventional location and guiding catheter engagement share the same space [1]. While balloon angioplasty often led to suboptimal results in ostial lesions[2,3], use of bare metal stents [4,5] and first-generation drug-eluting stents (DES)[6] increased both early procedural success and safety of PCI in the AO region. However, stenting was associated with a higher incidence of in-stent restenosis in the most proximal coronary segments [6,7], which has been attributed to stent recoil due to the rigid nature of the vessel wall [2]. To date, most DES studies that have addressed AO disease have been performed with bare metal stents and first-generation DES[6,8-11].

Implantation of bare metal stents and predominantly early generation DES in AO lesions of the right coronary artery (RCA) has been associated with a 10 times higher risk of repeat revascularization procedures than treatment of left main ostial lesions [8]. For that reason, a focused evaluation of PCI procedures that involve the RCA ostium is of interest. Meanwhile, second-generation DES with more biocompatible durable polymer-based coatings have been developed, such as the zotarolimus-eluting Resolute stent (Medtronic, Santa Rosa, CA) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA), which showed favorable clinical results [12-14].

Currently, there is only limited knowledge about the outcome of PCI with second-generation DES involving the AO region of the RCA. We therefore assessed patients with RCA single-vessel treatment with second-generation DES in the prospective TWENTE trial [12,13,15], and compared the 2-year clinical outcome of patients *with* versus *without* ostial stent coverage.

METHODS

Study Population

We assessed patients with single-vessel RCA treatment within the randomized TWENTE trial (*Clinical-Trials.gov NCT01066650*), which was performed between June 2008 and August 2010 at Thoraxcentrum Twente, Enschede, the Netherlands, and has previously been described in detail [12,13]. In brief, in a broad and heterogeneous patient population with many complex lesions [15], patients with an indication for PCI with DES, who were capable of providing informed consent, were randomized for treatment with either the Resolute or Xience V stent. The study was approved by the institutional ethics committee and complied with the Declaration of Helsinki, and all patients provided written informed consent.

Angiographic Assessment

Angiographic data were categorized into stenting *with* AO stent coverage (AOC) versus stenting *without* AO stent coverage (No AOC). A patient was allocated to the AOC group if any part of the stent covers the AO region, the area arising within 3 mm of the aortic orifice (Fig. 1). Classification was performed by two experienced angiographic analysts; in the case of disagreement, two interventional cardiologists were consulted to achieve consensus. Quantitative coronary angiographic analyses were performed offline with the use of edge-detection software (QAngio XA version 7.1, Medis, Leiden, the Netherlands)[12].

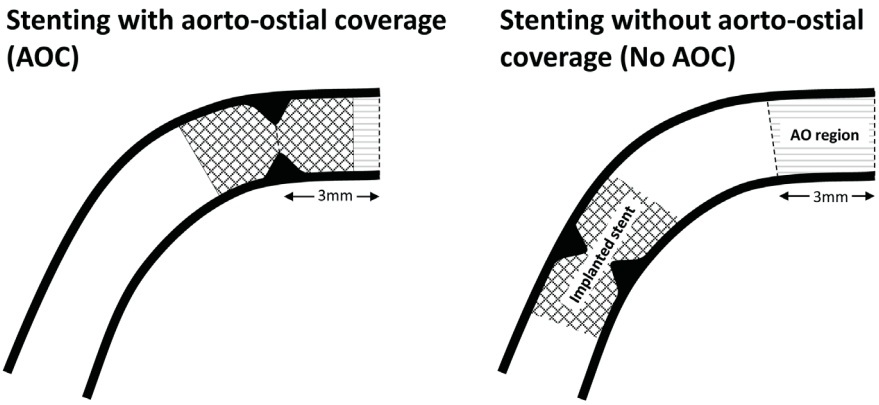

Figure 1. Scheme explaining the definition of the compared patient groups. Patients with AOC were compared with patients without AOC (no AOC).

Follow-up and Definition of Clinical Endpoints

Details of the 2-year clinical follow-up have been reported previously [13] and were used to assess clinical outcome of stenting *with* and *without* AOC. In addition, we compared the outcome of patients of the AOC group treated with Resolute versus Xience V. Clinical event adjudication (follow-up data were available in all patients of this study) was performed by the independent, external research organization Cardialysis (Rotterdam, the Netherlands). Clinical endpoints were defined according to the Academic Research Consortium (ARC) [16,17]. *Cardiac death* was defined as any death due to proximate cardiac cause (e.g., myocardial infarction (MI), low-output failure, and 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 and *periprocedural MI* was defined as MI within 48 hrs after PCI [16,17]. Cardiac markers were systematically assessed with subsequent serial measurements in the case of relevant biomarker elevation or complaints (97% of the cases had at least one blood sampling performed between 12 and 18 hr after PCI). *Stent thrombosis* was defined according to ARC as definite or probable.

The composite endpoint *target-vessel failure* (TVF) was defined as cardiac death, target-vessel-related MI, or clinically driven target-vessel revascularization (TVR). *Target-lesion failure* (TLF) was defined as composite of cardiac death, target-vessel-related MI, and clinically indicated target lesion revascularization (TLR); and a *patient-oriented composite endpoint* (POCE) as a composite of all-cause mortality, any MI, and any repeat (target-vessel and non-target vessel) revascularization [12].

Statistical Analysis

Categorical data were presented as numbers and percentages whereas continuous variables were expressed as mean ± standard deviation (SD). Baseline characteristics were compared using chi-square test or Fisher's exact test for categorical variables and using one-way analyses of variance for continuous variables including age, body-mass index, minimum reference diameter and maximal stenosis as data were normally distributed. Kruskal-Wallis rank-sum test (nonparametric data) was used to compare total number of stents and stent length between AOC, and presented as median and interquartile range. The time to the individual endpoint was assessed according to the Kaplan-Meier method, and the log-rank test was applied to compare stenting with versus without AOC. Univariate and Cox regression analyses were performed to assess the event risk for stenting *with* versus *without* AOC. A potential confounder was identified if P-values were <0.10 at univariate analysis. A multivariate Cox regression analysis was then performed to adjust for potential confounders. Confidence intervals and P-values were two-sided and a P-value <0.05 was considered statistically significant. Analyses were performed using SPSS 15.0 (SPSS., Chicago, Illinois).

RESULTS

Patient and Lesion Characteristics

A total of 321 patients with single-vessel RCA treatment were analyzed, of whom 67 (20.9%) underwent stenting *with* AOC and 254 (79.9%) stenting *without* AOC. Patients with AOC had a higher prevalence of hypercholesterolemia compared to patients without AOC (75.4% *vs.* 61.1%; p=0.03) and more frequently a family history of coronary artery disease (68.7% *vs.* 53.5%; p=0.02; Table I). The prevalence of diabetes mellitus tended to be higher in patients of the AOC group (35.8% *vs.* 24.4%; p=0.06).

In patients of the AOC group, lesions were more often severely calcified (31.3% *vs.* 12.6%; p<0.01) and restenotic (13.4% *vs.* 5.1%; p=0.03). As may be expected, based on the definitions of both groups, patients with AOC had a larger vessel diameter (minimum reference 3.3±0.7mm *vs.* 2.8±0.6mm; p<0.01), and a higher number (2.0 (1.0-3.0) *vs.* 1.0 (1.0-2.0); p<0.01) and total length of stents implanted (53 (18.0-74.0)mm *vs.* 30 (18.0-48.0)mm; p<0.01). In addition,

lesions in the AOC group were more frequently postdilated (97.0% *vs.* 85.8%; p=0.01) and stents were more often overlapping (52.2% *vs.* 33.9%; p<0.01). Residual stenosis and minimal lumen diameter (MLD) were substantially improved after stent implantation for both the groups. Nevertheless difference (pre PCI and post PCI) in MLD and maximal diameter stensosis did not differ between the AOC and No AOC group (MLD: -1.6±0.8mm vs. -1.6±0.6mm; p<0.63 and 52.2±16.6% *vs.* 56.0±16.8%; p=0.10, respectively).

Clinical Follow-Up

Patients with AOC had a higher incidence of TVF (16.4% *vs.* 7.5%; p=0.03) and TLF (14.9% *vs.* 6.7%; p=0.03) as compared to patients without AOC (Table II). The composite endpoint POCE was also significantly higher in patients of the AOC group (26.9% *vs.* 12.2%; p<0.01), which was mainly attributed to a higher rate of TLR (7.5% *vs.* 1.6%; p=0.02). Of the AOC group, 5/67 patients required TLR, which was in two patients related to the ostial stent (and in three related to a stent other than the ostial stent). Definite stent thrombosis was noted in none of the patients with AOC and in two (0.8%) of the patients without AOC.

Table I. Characteristics of study patients undergoing single-vessel PCI of the RCA.

	AOC (n=67)	No AOC (n=254)	*P*-value
Age (years)	63.2 ± 9.6	64.4 ± 10.6	0.42
Gender (male)	40 (59.7)	177 (69.7)	0.12
Clinical risk factor			
Diabetes mellitus	24 (35.8)	62 (24.4)	0.06
Hypercholesterolemia	49/65 (75.4)	151/247 (61.1)	0.03
Arterial hypertension	35 (52.2)	150 (59.1)	0.32
Family history of CAD	46 (68.7)	136 (53.5)	0.03
Current smoking	13 (19.4)	65 (25.6)	0.29
Obesity (BMI ≥ 30 kg/m^3)	28.2 ± 4.4	28.0 ± 4.1	0.82
Cardiovascular history			
Previous myocardial infarction (any)	24 (35.8)	88 (34.6)	0.86
Previous PCI	15 (22.4)	67 (26.4)	0.51
Previous CABG	10 (14.9)	30 (11.8)	0.49
Clinical syndrome at presentation			
Stable angina pectoris	35 (52.2)	118 (46.5)	
Unstable angina pectoris	21 (31.3)	52 (20.5)	0.02
Non-ST-elevation MI	11 (16.4)	84 (33.1)	
Lesion characteristics			
De novo lesions only	58 (86.6)	241 (94.9)	0.03
Aorta-ostial lesion[a]	36 (53.7)		
At least one chronic total occlusion	9 (13.4)	20 (7.9)	0.16
At least one in-stent restenosis	9 (13.4)	13 (5.1)	0.03
At least one bifurcation lesion	0 (0.0)	7 (2.8)	0.35
At least one severe calcification	21 (31.3)	32 (12.6)	<0.01
At least one thrombus present	2 (3.0)	16 (6.3)	0.38
At least one total occlusion	55 (82.1)	210 (82.7)	0.91
Number of lesions treated			
One lesion treated	44 (65.7)	194 (76.4)	
Two lesions treated	19 (28.4)	55 (21.7)	0.07
Three or more lesions treated	4 (6.0)	5 (2.0)	
Procedure-related characteristics			
Reference diameter (mm)	3.3 ± 0.7	2.8 ± 0.6	<0.01
MLD pre (mm)[b]	1.2 ± 0.6	0.9 ± 0.5	<0.01
MLD post (mm)[b]	2.8 ± 0.6	2.5 ± 0.6	<0.01
Δ Pre-post MLD (mm)	-1.6 ± 0.8	-1.6 ± 0.6	0.63
Lumen diameter stenosis pre (%)[b]	63.5 ± 17.3	68,9 ± 14.7	0.11
Lumen diameter stenosis post (%)[b]	11,4 ± 6.2	12.9 ± 8.4	0.15
Δ Pre-post stenosis (%)	52.2 ± 16.6	56.0 ± 16.8	0.10
Total number of stents	2.0 (1.0-3.0)	1.0 (1.0-2.0)	<0.01
Total stent length (mm)	53 (18.0-74.0)	30 (18.0-48.0)	<0.01
At least one direct stenting	25 (37.3)	103 (40.6)	0.63
At least one stent post-dilation	65 (97.0)	218 (85.8)	0.01
Overlapping stents	35 (52.2)	86 (33.9)	<0.01

Data are n (%), mean±SD or median (IQR); CAD, coronary artery disease; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; MLD, Minimum lumen diameter post.

[a]An AO lesion was defined as any lesion with a luminal stenosis of ≥ 50% by visual estimation, arising within 3 mm of the aortic orifice.

[b]In case of more than one lesion, data of the most sever lesion (i.e., lesion with the highest diameter stenosis pre PCI) are presented.

Table II. Two-year clinical outcome in patients with single-vessel PCI of the RCA.

	AOC (n=67)	No AOC (n=254)	p-value	AOC population (n=67)		
				Resolute (n=29)	*Xience V (n=38)*	*p-value*
Death						
All-cause mortality	5 (7.5)	6 (2.4)	0.06	2 (6.9)	3 (7.9)	1.00
Cardiac death	3 (4.5)	3 (1.2)	0.11	1 (3.4)	2 (5.3)	1.00
Myocardial infarction						
Target vessel MI	2 (3.0)	12 (4.7)	0.74	1 (3.4)	1 (2.6)	1.00
Revascularization						
Target vessel revascularization	6 (9.0)	9 (3.5)	0.10	3 (10.3)	3 (7.9)	1.00
Target lesion revascularization[a]	5 (7.5)	4 (1.6)	0.02	3 (10.3)	2 (5.3)	0.65
Stent thrombosis						
Definite or probable stent thrombosis	1 (1.5)	4 (1.6)	1.00	0 (0.0)	1 (2.6)	1.00
Composite endpoints						
Target vessel failure	11 (16.4)	19 (7.5)	0.03	5 (17.2)	6 (15.8)	1.00
Target lesion failure	10 (14.9)	17 (6.7)	0.03	5 (17.2)	5 (13.2)	0.74
Major adverse cardiac events	12 (17.9)	20 (7.9)	0.02	6 (20.7)	6 (15.8)	0.60
Patient-oriented composite endpoint	18 (26.9)	31 (12.2)	<0.01	8 (27.6)	10 (26.3)	0.90

Data are n (%).
[a]2 of the 5 TLR were related to the ostial stent and 3 to a stent other than the ostial stent.

The TVF rates of all patients treated with Resolute versus Xience V stent showed no significant difference (13/162(8.0%) vs. 17/159(10.7%); p=0.41). Within patients of the AOC group, there was no statistically significant difference in clinical outcome between both stents groups (Table II).

Figure 2 presents the Kaplan-Meier curves for TLF (and the components thereof) for patients with versus without AOC, showing a diverging course of TLF (p=0.03) after 2 months, which was mainly based on a significant difference in TLR (p<0.01), while the time-to-event curves of target-vessel MI were very similar. A Cox regression analysis revealed that AOC was associated with the composite endpoint TLF (hazard ratio 2.32, 95% confidence interval: 1.10-5.10; p=0.04). After adjustment for potential confounders (only adjustment for overlapping stents was required), AOC was independently associated with TLR (adjusted hazard ratio 4.07 95% confidence interval: 1.07-15.48; p=0.04).

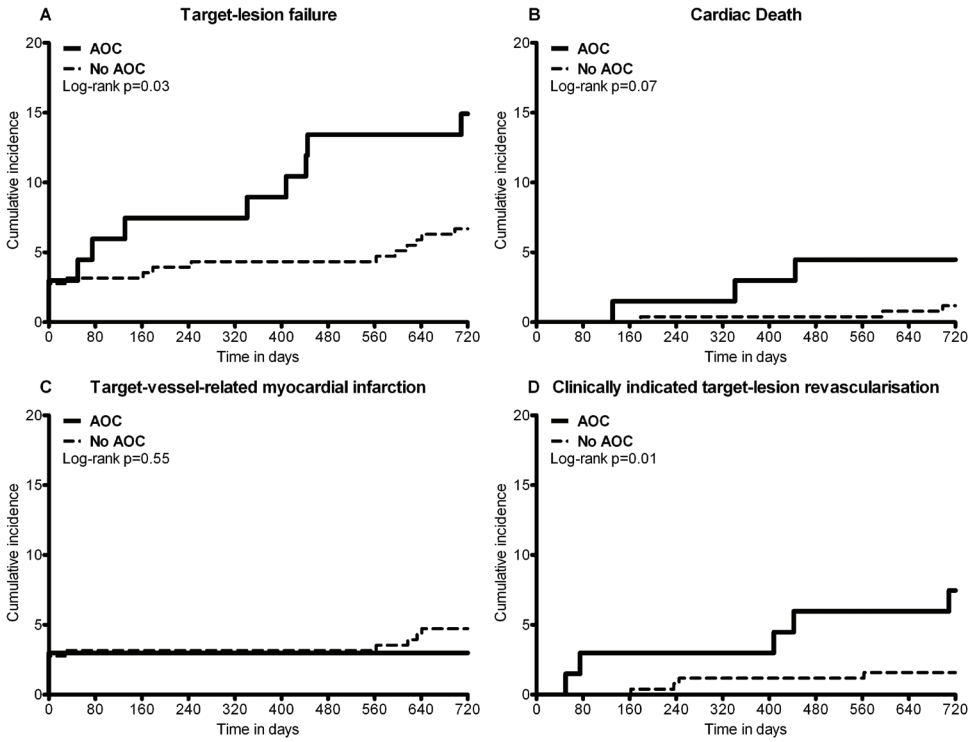

Figure 2. Two-year clinical outcome in patients with versus without RCA AOC. Kaplan–Meier curves of AOC (n=67) versus No AOC (n=254) of the composite endpoint target-lesion failure (A) and its components: cardiac death (B), target-vessel-related MI (C), and clinical indicated target-lesion revascularization (D).

DISCUSSION

The present substudy of the TWENTE trial in patients with single-vessel treatment of the RCA demonstrates that treatment of the AO region with second-generation DES is feasible but associated with a higher risk of repeat revascularization procedures. This may be partly attributed to the rigid nature of the vessel wall in the coronary ostium [2]. In addition, we found that only two of the five TLR events were related to the ostial stent. This suggests that the need for stenting of the RCA ostium may indicate the presence of extensive and advanced coronary atherosclerosis that is associated with a higher risk of repeat revascularizations within the various stented coronary segments.

An increased risk of TLR following AO stenting has also been observed by a French group in a retrospective analysis of 181 patients, treated for AO coronary disease in the RCA and left main stem [8]. They found that in RCA AO lesions, the risk of TLR was 10 times higher than in AO lesions of the left main stem [8]. Therefore, a focused assessment of RCA ostial treatment, as

performed in our present study, is of interest. In addition, we report data on the use of second-generation DES in AO disease, which is currently scarce. Only a single retrospective study by a Japanese group focused on the treatment of RCA lesions in a study population of 135 patients and compared the implantation of first-generation sirolimus-eluting Cypher stents (Cordis/Johnson & Johnson, New Brunswick, NJ) and bare metal stents in ostial (n=73) and proximal RCA lesions (n=62).[6] In this study, the TLR rate of ostial RCA lesions was 13.5% after 8 months in the Cypher stent group and 36.1% months after 6.5 months in the bare metal stent group ($p<0.05$) [6]. Despite the longer follow-up of 24 months, we found in our present study a lower TLR rate of 8.3% in RCA AO lesions, which suggests a rather favorable performance of the second-generation DES in this setting.

Thus far, more attention has been paid to stenting of AO left main lesions [7], but many studies have not reported outcome separately for ostial and other target-lesion locations. The introduction of DES for the treatment of left main disease has reduced the need for repeat revascularization (from 15-30% in bare metal stents) to 10-19%, making PCI of the left main stem a reasonable alternative to bypass surgery [18]. Mehilli et al. recently compared second-generation zotarolimus-eluting Resolute stents and everolimus-eluting Xience V stents in a randomized study of unprotected left main PCI with routine follow-up and reported 1 year after stenting similar TLR rates of 11.7% and 9.4% ($p=0.35$) [19]. The SYNTAX Score regards the AO lesion location as an adverse feature since percutaneous treatment is technically more challenging, but the score adds the extra point for the AO lesion location irrespective of whether this lesion is located in the RCA or in the left main stem [20].

A high radial strength in combination with a high visibility and longitudinal stability of the device may be characteristics of an "ideal" stent for the treatment of AO lesions. The radial strengh of the implanted devices can sometimes be increased by the so-called double stenting technique (i.e. stent in stent implantation), which has improved angiographic outcome in selected cases with acute stent recoil [21]. Most recently, third-generation DES (also called novel generation DES) have been introduced to meet the demand for more flexible and highly deliverable devices, which has been achieved by novel designs and/or materials of bare-metal stent platforms [22]. To date, no comprehensive data are available on the outcome of PCI with such DES in the subgroup of AO lesions. However, as the high flexibility and thin-strut design of third-generation DES may be associated with reduced longitudinal device stability [23,24], it is uncertain whether these novel devices may improve the outcome of PCI in AO lesions.

In the present study, the rate of definite–or–probable stent thrombosis following DES implantation in the AO region (1.5%) was not higher than in patients without ostial stent coverage (1.6%; i.e., No AOC group). Thrombotic occlusion of a stent in the most proximal coronary segment may result in a particularly large myocardial necrosis with a high clinical risk [25]. Besides a delayed endothelial coverage of DES struts, both vessel wall inflammation and premature occurrence of neoatherosclerosis have been identified as triggers of stent-thrombosis in durable-polymer based

DES [26-30]. The two latter factors may be greatly avoided by the use of DES with biodegradable coatings [31,32], of which–after degradation of the coating material–only a bare metal stent remains in the coronary artery [29,33].

Implications

The findings of the present study show that treatment of the right coronary ostium with second-generation DES is feasible and associated with relatively favorable clinical outcome in a study population that resembles routine clinical practice. The higher risk of repeat revascularizton procedures in patients with AO stent coverage (i.e. AOC group) did not result from an excess in ostial instent restenosis but may most likely be related to the greater extent of atherosclerotic disease burden in patients who require stenting of the most proximal segment of the RCA. Our data suggest that the need to cover the ostium of the RCA with a stent may be considered as an indicator of a generally increased risk of repeat revascularization that should be taken into account when planning the initial revascularization therapy in a heart team discussion.

Limitations

This study was limited by its posthoc nature and should be considered as hypothesis generating. The low number of AO-lesion within the AOC group (36/67) did not permit further meaningful subanalyses. Nevertheless, our data suggest that the increased risk of TLR in the AOC group is not related to problems that occur in the AO segment, but that the need for stenting the RCA ostium is an indicator of extended atherosclerotic disease burden with an inherent risk of more TLR events. Our study adds novel information on the performance of second-generation DES in the AO segment of the RCA. Nevertheless, the regular use of intravascular ultrasound (IVUS) could have further improved our understanding of true ostial involvement in the lesion and the presence and extent of calcium [34]. Although patients with very recent ST-segment elevation MI were not studied in the TWENTE trial, a total of 52% of the patient population presented with acute coronary syndromes, and the vast majority of patients had complex lesions and met the criteria of so-called off-label DES use.

Conclusion

Treatment of the AO region of the RCA with second-generation DES is feasible, but our data suggest that stent coverage of the right AO segment remains a predictor of TLR in the RCA.

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Chapter 8

Three-year clinical outcome after treatment of chronic total occlusions with second-generation drug-eluting stents in the TWENTE trial

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Catheter Cardiovasc Interv. in press, epublished ahead of print 23 October 2014.
DOI: 10.1002/ccd.25713

ABSTRACT

Objective: To compare long-term outcome of patients treated for chronic total occlusion (CTO) lesions versus patients treated for non-CTO lesions only.

Background: Percutaneous coronary interventions (PCI) for CTO lesions generally have a higher adverse event risk than PCI for non-CTO lesions. However, long-term outcome data from prospective studies with second-generation drug-eluting stent (DES) use in CTO lesions is scarce.

Methods: We analyzed in this sub-study of the TWENTE trial the data of 674 patients, who had stable angina and were electively treated with second-generation DES (Resolute zotarolimus-eluting or Xience V everolimus-eluting stents). Main outcome parameter was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction, or target lesion revascularization (TLR).

Results: Patients with CTO lesions (n=59, 8.8%) were more often treated for lesions in small vessels (94.9% vs. 63.1%, p<0.001), long lesions (52.5% vs. 17.7%, p<0.001) and multiple vessels (42.4% vs. 22.4%, p<0.001), and were less often males (62.7% vs. 74.6%, p<0.05) than patients with non-CTO lesions (n=615, 91.2%). J-CTO scores ≥2 were present in 56% of CTO lesions. Despite significant differences in characteristics of patients, lesions, and interventional procedures, the TLF rate at 3-year follow-up was similar for both groups (13.6% vs. 12.9%, p=0.89). In addition, a patient-oriented composite endpoint (any death, MI or revascularization) did not differ between groups (18.6% vs. 18.8%, p=0.97).

Conclusion: Patients treated with second-generation DES for CTO lesions showed at 3-year follow-up an incidence of adverse clinical events that was low and similar to patients with non-CTO lesions only.

INTRODUCTION

As much as 6 to10% of all patients who undergo percutaneous coronary interventions (PCI) require treatment of chronic total occlusion (CTO) lesions [1-3]. Following successful recanalization and treatment with bare metal stents, CTO lesions previously showed an increased risk of adverse clinical events as compared to non-CTO lesions [2]. First-generation drug-eluting stents (DES) that had been developed to reduce the need for repeat revascularization [4,5], lowered the rate of adverse clinical events in CTO lesions [6-8]. More recently, second-generation DES with more biocompatible, durable coatings have been developed [9-11] to reduce the risk of (very) late stent thrombosis, which was increased in first-generation DES [12-15]. The zotarolimus-eluting Resolute stent (Medtronic, Minneapolis, MN, USA) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA, USA) are two such second-generation DES that have shown favorable results in the broad patient population of the prospective, randomized TWENTE trial [16].

Data to compare long-term outcome of patients treated with second-generation DES for CTO lesions versus non-CTO lesions are scarce. Available data are generally derived from registries that comprise mostly first-generation DES [17,18]. As treatment of a CTO lesion was traditionally a criterion for off-label DES use, only limited data on CTO treatment are available from prospective randomized studies. More recently, several investigator-initiated, randomized DES studies in broad patient populations and in all-comers liberally enrolled patients with various lesion types, including CTO lesions. Nevertheless, up to now, long-term data from prospective studies with second-generation DES use in CTO lesions are scarce.

We therefore analyzed in the present sub-study of the TWENTE trial the data of 674 patients with stable angina, who underwent elective PCI with implantation of second-generation DES, and compared post-hoc the 3-year clinical outcome of patients with treatment of at least one CTO lesion versus patients with treatment of non-CTO lesions only.

METHODS

Study population, design, and procedures. We analyzed all 674 patients in the TWENTE trial (investigator-initiated, patient-blinded, randomized TWENTE trial (ClinicalTrial.gov NCT01066650), who (1) had stable angina and (2) underwent the PCI procedure in an elective setting. In this study population, target lesions were classified as CTO lesions in the presence of a total luminal obstruction with TIMI flow grade 0 within the occluded segment and a duration of the occlusion >3 months [19]. Details of the randomized TWENTE trial, which enrolled patients between June 18, 2008 and August 26, 2010 at Thoraxcentrum Twente in Enschede, the Netherlands, have previously been reported [16]. Interventional procedures with implantation

of second-generation DES (Resolute zotarolimus-eluting or Xience V everolimus-eluting stents) were performed according to routine clinical protocols and current guidelines [16]. Dual anti-platelet therapy was prescribed for 12 months following PCI. The TWENTE trial complied with the Declaration of Helsinki for investigation in human beings and was approved by the institutional ethics committee. All patients provided written, informed consent for participation in the trial.

Monitoring, processing of adverse clinical event data, and the adjudication of adverse clinical events were independently performed by two Dutch contract research organizations (CRO Cardialysis, Rotterdam, and CRO Diagram, Zwolle). Angiographic analyses were performed offline at Thoraxcentrum Twente. An experienced interventional cardiologist and a clinical researcher (KGvH, HS) determined the J-CTO score, as previously described [20]. The J-CTO score predicts successful crossing of a guide wire within 30 minutes through a CTO lesion in a native coronary artery and classifies lesions into four groups with increasing difficulty of treatment: 0 = easy; 1 = intermediate; 2 = difficult; ≥3 = very difficult.

Definition of clinical endpoints. The definitions of clinical endpoints, which have previously been described [16], followed suggestions of the Academic Research Consortium (ARC)[21,22]. In brief, the main outcome parameter *target lesion failure* (TLF) was defined as a composite of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target lesion revascularization (TLR). Death was considered cardiac, unless an unequivocal non-cardiac cause could be established. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarker [22]. A target vessel-related MI was related to the target vessel or could not be related to another vessel. Target vessel revascularization (TVR) and target lesion revascularization were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms [21]. Stent thrombosis was classified according to the ARC definitions [21]. In addition, we assessed these composite clinical endpoints: *target vessel failure* (TVF: cardiac death, target vessel-related MI, or clinically indicated TVR); *major adverse cardiac events* (MACE: all-cause death, any MI, emergent coronary bypass surgery, or clinically indicated target lesion revascularization); *patient-oriented composite endpoint* (POCE: all-cause mortality, any MI, or any revascularization).

Statistical Analysis. Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean ± SD for continuous variables. Chi-square and Fisher's exact tests were used to compare dichotomous and categorical variables. Student's t-test was used to compare continuous variables. The Kaplan-Meier method was used to calculate the time to clinical endpoints and the Log-rank test to compare between-group differences. Two-sided p-values <0.05 were considered significant. Data analysis was performed with SPSS (version 17, SPSS Inc., Chicago, IL)

RESULTS

Characteristics of patients, lesions, and PCI procedures. Among the study population of 674 patients, 59(8.8%) patients were treated for at least one CTO lesion (mean length 31.3 ±20.3 mm) of which the majority had J-CTO scores ≥2 (56%) (Figure I), indicating that most CTO lesions were classified as difficult to cross. All CTO interventions were performed with antegrade wire crossing technique only, of which 14 patients were treated with complex antegrade wire techniques (with use of sliding and/or aggressive wires (6 times), kissing balloons (2 times), rotablation (2 times), over-the-wire balloon dilatation, Culotte stenting, or aspiration catheters, as well as treatment of an in-stent CTO).

The remaining 615(91.2%) patients were treated for non-CTO lesions only (Table I). Patients with CTO lesions were more often treated for lesions in small vessels (94.9% vs. 63.1%, p<0.001) and long lesions (52.5% vs. 17.7%, p<0.001), and were less often male (62.7% vs. 74.6%, p<0.05). In addition, patients of the CTO group underwent significantly more often multivessel treatment (42.4% vs. 22.4%, p<0.001). The target lesion location differed significantly between groups, as patients in the CTO lesion group showed more involvement of the right (55.9% vs. 34.0%, p<=0.001) and left circumflex (49.2% vs. 31.1%, p<0.01) coronary arteries than patients with non-CTO lesions only. Moreover, there was a trend towards more stent postdilatation in patients with treatment of CTO lesions (96.6 % vs. 88.7%, p=0.06). In patients in the CTO group, significantly more stents were implanted (2.97 vs. 1.98, p<0.001) and subsequently the total stent length (66.3mm vs. 39.6mm, p<0.001) per patient was longer than patients with non-CTO lesions.

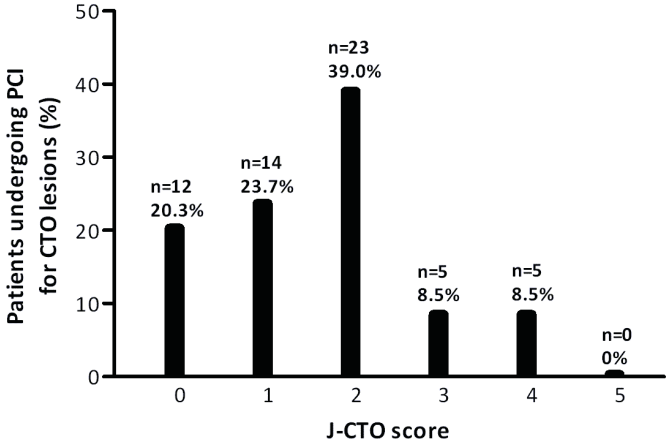

Figure I. J-CTO score of patients treated for CTO lesions. The J-CTO score predicts successful crossing of a guide wire within 30 minutes through a CTO lesion in a native coronary artery; lesions are classified into four groups with increasing difficulty of treatment (0 = easy; 1 = intermediate; 2 = difficult; ≥3 = very difficult) [20].

Table I. Characteristics of patients, lesions, and interventional procedures.

	Patients treated for CTO lesions	Patients treated for non-CTO lesions only	P
	N=59	*N=615*	
Age (yrs), mean (SD)	63.3±9.9	64.5±9.7	0.37
Men	37 (62.7%)	459 (74.6%)	<0.05
BMI (kg/m²)	27.9±3.7	27.9±4.1	0.97
Diabetes mellitus (any)	10 (16.9%)	133 (21.6%)	0.40
Chronic renal failure*	2 (3.4%)	18 (2.9%)	0.69
Arterial hypertension	32 (54.2%)	378 (61.5%)	0.28
Hypercholesterolemia	33/57 (57.9%)	390/605 (64.5%)	0.32
Current smoker	12 (20.3%)	126 (20.5%)	0.98
Family history of CAD	29 (49.2%)	360 (58.5%)	0.16
Previous MI	14 (23.7%)	146 (23.7%)	1.00
Previous PCI	13 (22.0%)	128 (20.8%)	0.83
Previous CABG	7 (11.9%)	76 (12.4%)	0.91
Left ventricular ejection fraction < 30%†	1/44 (2.3%)	17/452 (3.8%)	1.000
Multivessel treatment	25 (42.4%)	138 (22.4%)	<0.001
Total no. of lesions treated per patient			0.02
One lesion treated	27 (45.8%)	394 (64.1%)	
Two lesions treated	23 (39.0%)	156 (25.4%)	
Three of more lesions treated	9 (15.3%)	65 (10.6%)	
Severe calcification	13 (22.0%)	129 (21.0%)	0.85
Aorta-ostial lesion	10 (16.9%)	69 (11.2%)	0.19
At least one bifurcation	17 (28.8%)	154 (25.0%)	0.53
At least one bifurcation with side branch treatment	10 (16.9%)	94 (15.3%)	0.74
At least one small-vessel (RVD< 2.75 mm)	56 (94.9%)	388 (63.1%)	<0.001
At least one lesion length > 27mm	31 (52.5%)	109 (17.7%)	<0.001
Target vessel			
Left main stem	1 (1.7%)	35 (5.7%)	0.36
Left anterior descending artery	24 (40.7%)	316 (51.4%)	0.12
Left circumflex coronary artery	29 (49.2%)	191 (31.1%)	<0.01
Right coronary artery	33 (55.9%)	209 (34.0%)	0.001
ACC-AHA lesion class§			-
A	-	35 (5.7%)	
B1	-	112 (18.2%)	
B2	-	181 (29.4%)	
C	59 (100%)	287 (46.7%)	
Postdilatation	57 (96.6%)	546 (88.8%)	0.06
No. of stents implanted per patient, mean (SD)	2.97±1.43	1.98±1.18	<0.001
Total stent length (mm) per patient, mean (SD)	66.3±34.9	39.6±26.4	<0.001

Data are number (%) or mean (SD). CTO=chronic total occlusion. BMI= body mass index. CAD=coronary artery disease. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. RVD=reference vessel diameter. ACC = American College of Cardiology. AHA = American Heart Association.

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

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

§ ACC-AHA lesion class = highest morphology type.

Three-year clinical outcome. Three-year follow-up was available in 670 out of 674 (99.7%) patients. The incidence of the main outcome parameter TLF was similar for patients with treatment of CTO lesions and patients with non-CTO lesions only (13.6% vs. 12.9%, p=0.89). Figure II shows similar Kaplan Meier curves for TLF in both groups (HR 1.1, 95% CI:0.5-2.2, p=0.85).

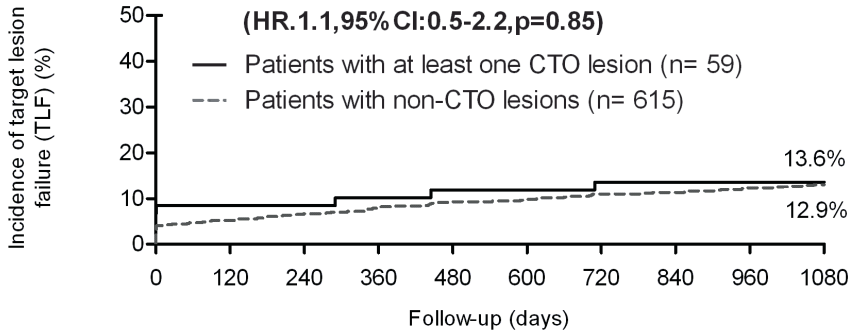

Figure II. Target lesion failure during 3-year follow-up. Kaplan-Meier cumulative event curves for the main outcome parameter target lesion failure (TLF) in patients treated for at least one CTO lesion versus non-CTO lesions only.

Other composite clinical endpoints, such as TVF, MACE, and the most global patient-oriented composite endpoint POCE (18.6% vs. 18.8%, p=0.97), also showed no differences between the two groups (Table II). In addition, the rates of various individual clinical endpoints, such as MI or TVR, were low and did not significantly differ between groups either (Table II). Peri-procedural MI (i.e. MI within the first 48 hours of treatment) occurred numerically more often in the CTO lesion group (8.5% vs. 4.1%, p=0.17), but a maximum creatine kinase level >5x the upper limit of normal was only found in 1.7% patients with treatment of CTO lesions. Among the patients with treatment of CTO lesions, 26 patients were treated with Xience V stents and 33 patients with Resolute stents. Between the two stent-subgroups, there was no significant difference in the incidence of the main outcome parameter TLF (15.4% vs. 12.1%, p=0.72). In addition, within 14 patients in whom complex antegrade techniques were applied, the incidence of target lesion failure was non-significantly higher than in patients without additional complex techniques (21.4% vs. 11.1%, p=0.38).

Table II. Clinical outcome at 3-year follow-up.

	Patients treated for CTO lesions	Patients treated for non-CTO lesions only	P
	N=59	*N=611*	
Target lesion failure (TLF)	8 (13.6%)	79 (12.9%)	0.89
Target vessel failure (TVF)	9 (15.3%)	89 (14.6%)	0.89
Major adverse cardiac events (MACE)	9 (15.3%)	96 (15.7%)	0.93
Patient-oriented composite end-point (POCE)	11 (18.6%)	115 (18.8%)	0.97
Death, any cause	1 (1.7%)	39 (6.4%)	0.25
Death, cardiac cause	0	22 (3.6%)	0.24
MI, any	6 (10.2%)	35 (5.7%)	0.16
MI, target vessel related	6 (10.2%)	34 (5.6%)	0.15
MI, periprocedural	5 (8.5%)	25 (4.1%)	0.17
Revascularization, any	4 (6.8%)	62 (10.1%)	0.41
TVR, clinically indicated	3 (5.1%)	51 (8.3%)	0.61
TLR, clinically indicated	2 (3.4%)	34 (5.6%)	0.76
ST, definite or probable (0-1080 days)	1 (1.7%)	9 (1.5%)	0.89
ST, definite	1 (1.7%)	3 (0.5%)	0.25

Data are number (%). CTO=chronic total occlusion. MI=myocardial Infarction. TVR=target vessel revascularization. TLR=target lesion revascularization. ST=stent thrombosis.

DISCUSSION

To compare the long-term outcome of patients who were treated with second-generation DES implantation for at least one CTO lesion versus patients who were treated for non-CTO lesions only, we analyzed in the present sub-study of the prospective TWENTE trial the data of 674 patients, who had undergone elective PCI for stable angina. Despite various significant differences in patient, lesion, and procedure-related characteristics, 3-year clinical outcome was similar and favorable for both patient groups.

Study population. In the total patient population of the TWENTE trial, 6.8% patients underwent stenting for at least one CTO lesion [16], which is similar to rates (3.0 to 8.0%) in several other randomized DES trials that enrolled broad patient populations [23-26].

The population of the present sub-study consisted of TWENTE patients, who had undergone elective treatment for stable angina and included 59 (8.8%) patients in whom stents were implanted in CTO lesions. For our present study, we did not consider TWENTE patients with non-ST-elevation acute coronary syndromes (Non-ST-ACS) at presentation because in such patients the level of certainty about the duration of an occlusion (> 3 months) is much more often debatable. In clinical practice, lesions will often be labeled as CTO based on (1) the patient-reported course of stable angina symptoms during the last few months prior to the Non-ST-ACS,

(2) the operator's tactile perception of the lesion, and (3) the response of the lesion to the guide wire. In addition, in patients with Non-ST-ACS, event rates may be mostly driven by unstable coronary lesions other than the CTO lesion, and it may be more difficult to prove the occurrence of certain clinical endpoints, such as periprocedural myocardial infarction.

Comparison with results of previous studies. In previous stent studies, treatment of CTO lesions with (mostly) *first-generation* DES was associated with lower Major Adverse Cardiac Events (MACE) rates than after use of bare metal stents, mainly driven by lower revascularization rates. The randomized PRISON II trial showed favorable results and lower TLR rates after 5 years in CTO patients treated with sirolimus-eluting Cypher stents (Cordis, Warren, NJ, USA) versus bare metal stents (12.0% vs. 30.0%, p<0.001) [27]. Siek and coworkers assessed the outcome of 137 patients with CTO lesions who were treated with first and second-generation DES to compare the outcome with 208 CTO lesion patients treated with bare metal stents. In patients treated with DES the incidence of TLR was lower after 1 year (5.1% vs. 14.4%, p<0.01) and after a median follow-up of 23±3 months (7.3% vs. 14.4%, p=0.04) [6]. A large registry, reported by Kato and coworkers, confirmed the relative safety of first-generation sirolimus-eluting Cypher stents in 1210 patients who were treated with CTO lesions; nevertheless, these CTO lesion patients still had a higher TLF rate than patients who were treated with the same DES for non-CTO lesions [18]. In addition, the CATOS Trial showed the efficacy of zotarolimus-eluting Endeavor stents (Medtronic) for the treatment of CTO lesions with a numerically lower TVF rate as compared to the Cypher stent (10.0% vs. 17.5%; p=0.17) [28].

Analyses of long-term clinical outcome following treatment of CTO lesions with *second-generation* DES are scarce, as most studies reported only 1-year follow-up data. The randomized CIBELES Trial found in 207 patients with CTO lesions no difference in 1-year MACE rate between patients treated with first-generation Cypher stents versus second-generation everolimus-eluting Xience V stents (15.9% vs. 11.1%, p=0.34). The TVR rate, however, was lower following the use of Xience V stents (11.6% vs. 7.9%, p=0.53) [29]. The XIENCE V CTO study, which followed 53 patients with CTO lesion treatment for 1 year, showed a TLR rate (6%) that was somewhat higher than in our study after 3-year follow-up (3.4%), which might be related to differences in patient populations, such as a higher prevalence of diabetes in the XIENCE V CTO population (28% vs. 17%) [11].

Clinical perspective. This study assures our present clinical practice as it suggests that the use of second-generation DES for CTO treatment is associated with high and sustained long-term efficacy and safety. The numerically higher rate of periprocedural MI following treatment of CTO lesions could be explained by the occasionally subintimal route of guide wires during the process of CTO recanalization, which may, to some extent, increase the likelihood of occluding minor side branches during the often challenging interventional procedures.

Limitations. Because of the post-hoc nature of the present analysis, the results should only be considered as hypothesis generating. The limited number of patients in the CTO lesion group and

the relatively low event rates did not permit meaningful analyses of smaller subgroups, such as a detailed stent-level analysis. However, the similarity of both DES in clinical outcome until the most recent 3-year follow-up [30] justifies the present pooled analysis. However, our data cannot be generalized to patient populations that are treated with more complex CTO recanalization techniques than used in the present study.

Conclusion. Patients treated with second-generation DES for CTO lesions showed at 3-year follow-up an incidence of adverse clinical events that was low and similar to patients with non-CTO lesions only.

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Chapter 9

Three-year clinical outcome of patients with bifurcation treatment with second-generation Resolute and Xience V stents in the randomized TWENTE trial

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ABSTRACT

Background Only limited data from large randomized clinical trials have been published on the long-term performance of second-generation drug-eluting stents (DES) in bifurcation lesions.

Methods We investigated in patients in the randomized TWENTE trial the long-term safety and efficacy of treating bifurcation lesions with two widely applied second-generation DES, the zotarolimus-eluting Resolute stent (Medtronic Inc., Santa Rosa, CA) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA). Three-year follow-up was available in 99.3%. Patients were categorized into treatment for at least one bifurcation lesion versus treatment for non-bifurcation lesions only.

Results Among the 1,391 patients of the TWENTE trial, 362(26%) were treated for bifurcation lesions. At 3-year follow-up, target-vessel failure (TVF) did not differ between patients treated for bifurcation versus non-bifurcation lesions (13.1% vs. 12.6%; p=0.84), while the periprocedural myocardial infarction rate was higher in patients with bifurcation lesions (6.9% vs. 3.1%; p<0.01). Of the 362 patients with bifurcation lesion treatment, 179 (49.4%) were treated with Resolute and 183(50.6%) with Xience V. There was no significant difference in TVF between the Resolute and Xience V groups with bifurcation treatment (13.6% vs. 12.6%; p=0.78), and their incidence of definite-or-probable stent thrombosis was low and similar (1.1% vs. 0.5%, respectively; p=0.62).

Conclusion Despite a significant difference in periprocedural myocardial infarction, 3-year clinical outcome after implantation of second-generation stents was favorable and similar for patients with and without bifurcation lesions. In addition, we observed no difference in long-term clinical outcome following bifurcation lesion treatment with Resolute and Xience V stents.

INTRODUCTION

Percutaneous coronary interventions (PCI) of bifurcation lesions have been associated with an increased procedural risk and a higher restenosis rate.[1] The introduction of the first generation of drug-eluting stents (DES) reduced the incidence of restenosis.[2-4] Meanwhile, second-generation DES with more biocompatible, durable polymer-based coatings have been developed, such as the zotarolimus-eluting Resolute stent (Medtronic Inc., Santa Rosa, CA) and everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA). Both DES are widely applied, and they have shown favorable clinical results in a large population of all-comer patients[5,6] and in the broad patient population of the TWENTE trial.[7-9] In bifurcation lesions, second-generation DES reduced the risk of restenosis and the need for repeat revascularization, as compared to first-generation DES.[10-12] In addition, a randomized trial that exclusively used second-generation DES recently reported very favorable 2-year outcome data following treatment of bifurcation lesions in an all-comer patient population.[13]

Nevertheless, so far only limited data from large randomized clinical trials have been published on the long-term performance of second-generation DES in bifurcation lesions.[13-15] Therefore, in the present sub-study of the TWENTE trial,[7,8,16] we performed an analysis of the 3-year follow-up data of TWENTE to compare long-term clinical outcome in patient with and without treatment of a bifurcated target lesion. In addition, to evaluate potential between-stent differences, we compared the outcome of patients with bifurcation treatment with Resolute versus Xience V stents.

METHODS

Patient population, interventional procedures, and angiographic analysis

We assessed 1,391 patients in the randomized TWENTE trial (*ClinicalTrials.gov NCT01066650*), which was performed between June 2008 and August 2010 at the Thoraxcentrum Twente, the Netherlands, and has previously been described in detail.[7,9] In brief, a broad and heterogeneous population of PCI patients (but no STEMI within 48 hours) were randomized for treatment with Resolute or the Xience V stents. Interventional procedures and the application of concomitant medication were performed according to institutional protocols and current guidelines. In bifurcations, provisional T-stenting was the generally preferred approach. Nevertheless, the treatment strategy, technique of stenting, and decision to perform a final kissing balloon inflation were left at the operator's discretion. The TWENTE trial was approved by the institutional ethics committee and complied with the Declaration of Helsinki, and all patients provided written informed consent.[7]

For the purpose of the present analysis, patients were categorized into treatment of at least one bifurcation lesion versus treatment of non-bifurcation lesions only. In accordance with the definition of a relevant side-branch in the SYNTAX score,[17] a relevant bifurcation was defined as a junction of a main vessel and a side-branch with minimum lumen diameter ≥ 1.5 mm (after administration of intracoronary nitrates, before PCI), as measured by quantitative coronary angiography (QCA). Angiographic analyses were performed offline by experienced angiographic analysts of the Thoraxcentrum Twente (blinded for stent arm) with the use of edge-detection software (QAngio XA version 7.1; Medis, the Netherlands).[7] In the bifurcation group, a further thorough analysis was performed, comparing the single-stent and the two-stent strategies for bifurcation treatment, the two allocated DES, and the application or omission of a final kissing-balloon inflation.

Follow-up and definition of clinical endpoints

Details of the 3-year clinical follow-up have been reported.[16] Clinical event adjudication was performed by an independent, external clinical event committee, organized by independent clinical research organizations (Cardialysis, Rotterdam, the Netherlands; and Diagram, Zwolle, the Netherlands). Clinical endpoints were defined according to the Academic Research Consortium (ARC).[18,19] *Cardiac death* was defined as any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). *Myocardial infarction* (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 MB fraction or troponin), based on the updated ARC definition of MI. *Periprocedural MI* (PMI) was defined as target-vessel-related MI within 48 hours after PCI.[18,19] Cardiac markers were systematically assessed with subsequent serial measurements in the case of relevant biomarker elevation or complaints. *Stent thrombosis* was defined according to ARC as definite or probable.

The composite endpoint *target-vessel failure* (TVF) was defined as cardiac death, target-vessel-related MI, or clinically driven target-vessel revascularization (TVR). *Target-lesion failure* (TLF) was defined as composite of cardiac death, target-vessel-related MI, and clinically indicated target-lesion revascularization (TLR); and a *patient-oriented composite endpoint* (POCE) as a composite of all-cause mortality, any MI, and any repeat (target- and non-target vessel) revascularization.[7]

Statistics and data analysis

Categorical data were presented as numbers and percentages whereas continuous variables were expressed as mean ± standard deviation (SD). Baseline characteristics were compared using chi-square test or Fisher's exact test for categorical variables and using one-way analyses of variance for continuous variables. Kruskal-Wallis rank-sum test (non-parametric data) was used to compare total number of stents and stent length between treatment for a bifurcation or non-bifurcation target lesion, and results were presented as median and interquartile range (IQR). The time to

clinical endpoint was assessed according to the Kaplan Meier method, and the log-rank test was applied to compare patients with bifurcation treatment versus patients with treatment of non-bifurcation lesions only. Confidence intervals and p-values were two-sided. P-values <0.05 were considered significant. Parameters were considered as potential confounders, if in univariate analyses associations were found with a p-value <0.10. A multivariate Cox regression model was then used to adjust for potential confounders. Analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The TWENTE trial is an investigator-initiated study, supported by equal unrestricted grants from Abbott Vascular and Medtronic. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the paper, and its final contents.

RESULTS

Baseline characteristics of patients, lesions, and procedures

Of the 1,391 patients in the TWENTE trial, 362 (26.0%) patients were treated for bifurcation lesions and 1,029 (74.0%) for non-bifurcation lesions only. Within the bifurcation group, 179 (49.4%) patients were treated with Resolute and 183 (50.6%) with Xience V stents. In bifurcated target lesions, the side-branch lumen measured 2.27±0.41mm with a lesion length of 10.1 ± 6.8mm and a side-branch stenose 62.5 ± 13.6% before PCI. A total of 79.0% of these side-branches had lumen diameters ≥ 2.0 mm by QCA. During follow-up, 10 (0.7%) patients withdrew consent or refused further participation (two in the bifurcation group). In all remaining 1,381 patients (99.3%), follow-up was obtained.

Baseline characteristics of patients, lesions, and procedures are shown in Table 1. Patients with bifurcation treatment had aorto-ostial lesions and a history of previous CABG less often, and they were more often treated in the left anterior descending artery and by post-dilation of the implanted stents (Table 1). Among patients of the bifurcation group treated with Resolute versus Xience V, there was no difference in the technique of stenting and the rate of final kissing balloon inflation (Table 2).

Table 1. Characteristics of all study patients with and without bifurcated target lesions, and of both stent arms in patients with bifurcated target lesions.

	All patients (N=1391)			Patients with bifurcated target lesions (N=362)		
Patient characteristics	**Bifurcated target lesion (N=362)**	**Non-bifurcated target lesion (N=1029)**	**p-value**	**Resolute (N=179)**	**Xience V (N=183)**	**p-value**
Age (yrs)	64.3 (10.5)	64.3 (10.6)	0.98	64.5 (11.1)	64.0 (10.0)	0.68
Female	89 (24.6)	293 (28.5)	0.15	44 (24.6)	45 (24.6)	1.00
BMI (kg/m^2)	27.5 (3.8)/317	27.8 (4.0)/872	0.25	27.1 (3.4)/156	27.9 (4.1)/161	0.05
Diabetes mellitus	75 (20.7)	226 (22.0)	0.62	37 (20.7)	38 (20.8)	0.98
Arterial hypertension	198 (54.7)	575 (55.9)	0.70	95 (53.1)	103 (56.3)	0.54
Hypercholesterolemia	194 (55.1)	609 (60.6)	0.07	93 (52.2)/178	101 (58.0)/174	0.27
Current smoker	95 (26.2)	245 (23.8)	0.35	45 (25.1)	50 (27.3)	0.64
Family history of CAD	188 (51.9)	552 (53.6)	0.58	90 (50.3)	98 (53.6)	0.53
Previous MI	114 (31.5)	336 (32.7)	0.69	55 (30.7)	59 (32.2)	0.76
Previous PCI	66 (18.2)	222 (21.6)	0.18	33 (18.4)	33 (18.0)	0.92
Previous CABG	25 (6.9)	123 (12.0)	<0.01	11 (6.1)	14 (7.7)	0.57
Clinical syndrome			0.65			0.47
Stable angina pectoris	171 (47.2)	503 (48.9)		82 (45.8)	89 (48.6)	
Unstable angina	91 (25.1)	234 (22.7)		50 (27.9)	41 (22.4)	
Non-ST-elevation MI	100 (27.6)	292 (28.4)		47 (26.3)	53 (29.0)	
Lesion/procedural characteristics						
Medina Classification						0.54
0.0.1	30 (8.3%)			17 (9.5)	13 (7.1)	
0.1.0	63 (17.5)			30 (16.8)	33 (18.0)	
0.1.1	43 (11.9)			16 (8.9)	27 (14.8)	
1.0.0	59 (16.3)			27 (15.1)	32 (17.5)	
1.0.1	21 (5.8)			11 (6.1)	10 (5.5)	
1.1.0	62 (17.2)			35 (19.6)	27 (14.8)	
1.1.1	84 (23.1)			43 (24.0)	41 (22.4)	
Multivessel treatment	127 (35.1)	209 (20.3)	<0.01	65 (36.3)	62 (33.9)	0.63
Total no. of lesions treated per patient			<0.01			0.75
One lesion treated	179 (49.4)	678 (65.9)		90 (50.3)	89 (48.6)	
Two or more lesions treated	183 (50.6)	351 (34.1)		89 (49.7)	94 (51.4)	
Treated coronary vessels						
Right coronary artery	70 (19.3)	435 (42.3)	<0.01	34 (19.2)	36 (19.7)	0.91
Left anterior artery	269 (74.3)	455 (44.2)	<0.01	136 (76.8)	132 (72.1)	0.31
Circumflex artery	135 (37.3)	304 (29.5)	<0.01	64 (36.2)	70 (38.3)	0.68
De novo lesions	320 (88.4)	874 (84.9)	0.10	156 (88.1)	162 (88.5)	0.33
Severe calcification	78 (21.5)	197 (19.1)	0.32	38 (21.5)	40 (21.9)	0.93
At least one chronic total occlusion	26 (7.2)	69 (6.7)	0.76	15 (8.4)	11 (6.0)	0.38

At least one in-stent restenosis	14 (3.9)	55 (5.3)	0.27	6 (3.4)	8 (4.4)	0.62
At least one aorto-ostial lesion	25 (6.9)	127 (12.3)	<0.01	10 (5.6)	15 (8.2)	0.34
At least one small-vessel[#]	257 (71.0)	617 (60.0)	<0.01	121 (67.6)	136 (74.3)	0.16
At least one lesion length > 27mm	72 (19.9)	221 (21.5)	0.52	39 (21.8)	33 (18.0)	0.37
Longest lesion length (mm)	22.3 (11.6)	20.4 (13.0)	0.87	20.7 (12.2)	20.0 (11.1)	0.61
Degree of stenosis (pre-PCI)*	67.3 (13.7)	68.0 (14.4)	0.43	68.6 (13.5)	66.1 (13.8)	0.08
Residual in-stent stenosis (post-PCI)*	14.8 (6.1)	13.6 (7.9)	<0.01	14.8 (6.1)	14.8 (6.2)	0.90
Total stent length per patient	40 (24-60)	30 (18-51)	<0.01	42 (24-63)	40 (28-56)	0.98
Number of stents per patient	2.0 (1.0-3.0)	2.0 (1.0-2.0)	<0.01	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.73
Postdilation	343 (94.8)	879 (85.4)	<0.01	170 (96.0)	171 (93.4)	0.27

Values are mean (±SD), n (%)or median (IQR); [#] a reference vessel diameter (RVD) <2.75 mm defined a small vessel; * in case of multiple target lesion, the most severe diameter stenosis was presented.

Clinical outcome

At 3-year follow-up, patients in the bifurcation group showed a higher incidence of target-vessel MI (8.1% vs. 5.0%; p=0.03) but no difference in TVF compared to the non-bifurcation group (Table 3). Among patients with bifurcation lesions, there was no difference in TVF between patients with side-branches ≥2.0mm vs. <2.0mm (13.3% vs. 12.2%; p=0.80; Table 3). The rates of definite-or-probable stent thrombosis were low and similar for both patients with bifurcation lesions and patients with non-bifurcated lesions (0.8% vs. 1.8%; p=0.22). Dual anti-platelet therapy (DAPT) use at 3-year follow-up was slightly lower than after 2 years (70/1302 (5.4%) vs. 91/1312 (6.9%)[9]) and was similar between the bifurcation and non-bifurcation groups (5.0% vs. 5.5%; p=0.70). Among patients with bifurcation lesions, use of a single-stent or a two-stent approach (independent of the allocated stent) and the use or omission of a final kissing balloon inflation were not associated with differences in clinical outcome (Table 3). In patients with bifurcation lesions, there was no difference in TVF and other clinical endpoints between the Resolute and Xience V stent arm (13.6% vs. 12.6%; p=0.78).

Table 2. Techniques applied with Xience V and Resolute stents in both single-stent and two-stent approaches among 362 patients with bifurcated target lesions.

Single-stent approach (N=280)	**Resolute (n=145)**	**Xience V (n=135)**	**p-value**
Main vessel stenting only	137 (94.5)	126 (93.3)	0.69
Side-branch stenting only	8 (5.5)	8 (6.7)	
Use of final kissing balloon inflation	48 (33.1)	55 (40.7)	0.19
Two-stent approach (N=82)	***Resolute (n=34)***	***Xience V (n=48)***	***p-value***
T-stenting	22 (64.7)	26 (54.2)	0.61
Culotte stenting	2 (5.9)	7 (14.6)	
Mini-crush technique	4 (11.8)	7 (14.6)	
Crush technique	4 (11.8)	3 (6.3)	
V-stenting	2 (5.9)	5 (10.4)	
Use of final kissing balloon inflation	27 (79.4)	33 (68.8)	0.28

Figure 1 presents the Kaplan-Meier curves for TVF (Fig. 1A) and the components thereof (Fig. B-D). The abrupt early rise in TVF was numerically higher in patients of the bifurcation group, mainly as the result of a higher incidence of PMI (Fig. 1C). A landmark analysis (Fig. 2) showed that after >48 hours there was no difference between the bifurcation and non-bifurcation group (p=0.37). In addition, the Kaplan Meier curves of TVR for the two study groups showed a somewhat diverging course in favor of patients with bifurcation treatment (Fig. 1D; p=0.06).

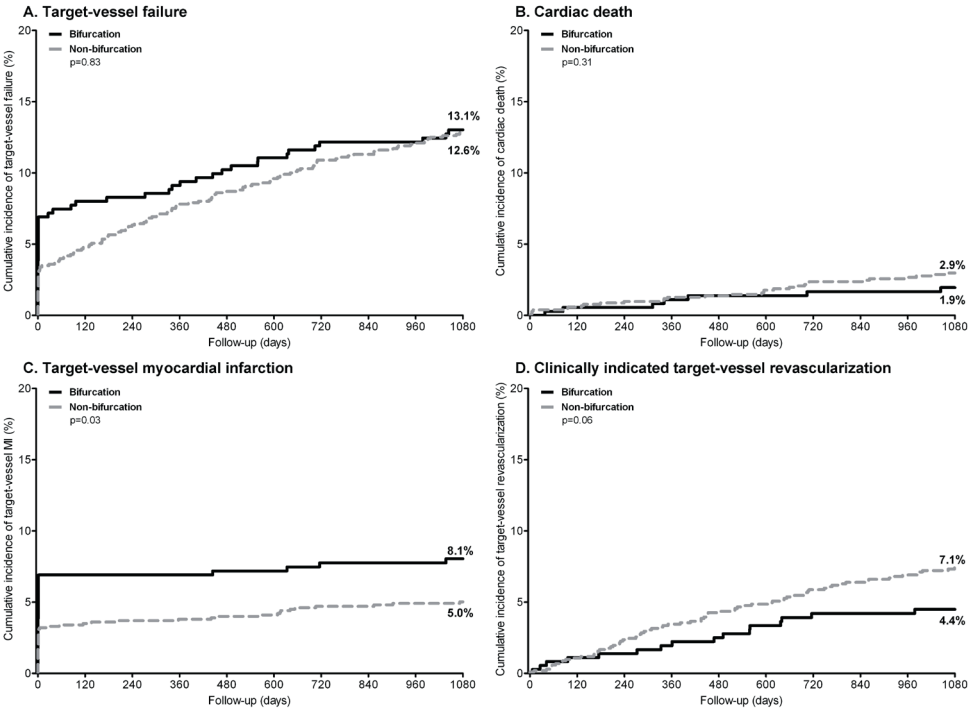

Figure 1. Kaplan Meier curves of the composite clinical endpoint target-vessel failure (TVF) and its individual components.

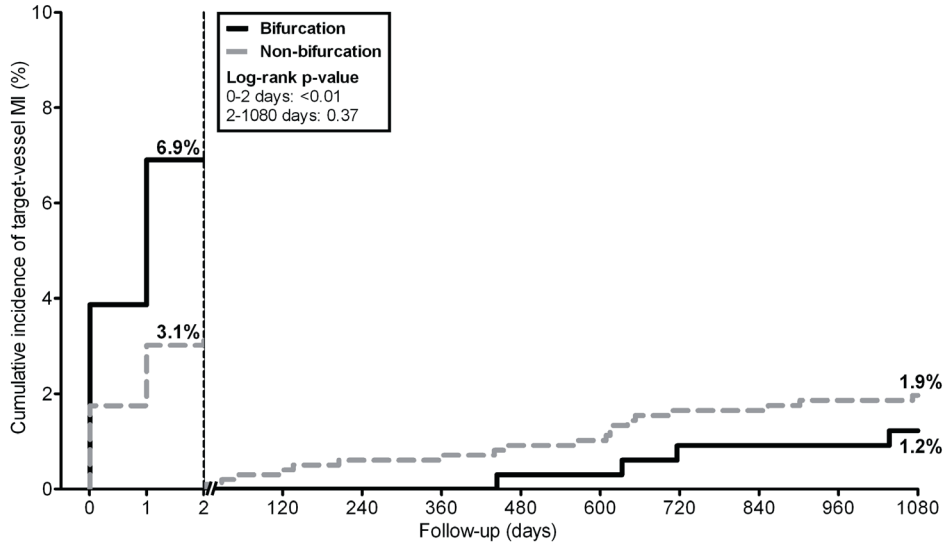

Figure 2. Landmark analysis of target vessel related myocardial infarction at two-years.

Table 3. Three-year clinical outcome in patients with or without treatment of bifurcation lesions

	All patients (N=1381)			Stenting strategy in patients with bifurcated lesion (n=360)		
	Bif. (N=360)	*Non-bif. (N=1021)*	*p value*	*1-stent (N=278)*	*2-stent (N=82)*	*p value*
Death						
All-cause mortality	18 (5.0)	61 (6.0)	0.49	14 (5.0)	4 (4.9)	1.00
Cardiac death	7 (1.9)	30 (2.9)	0.32	5 (1.8)	2 (2.4)	0.66
Myocardial infarction						
Target-vessel MI	29 (8.1)	51 (5.0)	0.03	21 (7.6)	8 (9.8)	0.52
Periprocedural MI	25 (6.9)	32 (3.1)	<0.01	18 (6.5)	7 (8.5)	0.52
Revascularization						
Target-vessel revascularization	16 (4.4)	73 (7.1)	0.07	14 (5.0)	2 (2.4)	0.54
Target lesion revascularization	12 (3.3)	52 (5.1)	0.17	10 (3.6)	2 (2.4)	1.00
Stent thrombosis						
Definite-or-probable (0-1080)	3 (0.8)	18 (1.8)	0.22	1 (0.4)	2 (2.4)	0.13
Very late definite or probable (361-1080)	2 (0.6)	5 (0.5)	1.00	1 (0.4)	1 (1.2)	0.40
Composite endpoints						
Target-vessel failure	47 (13.1)	129 (12.6)	0.84	36 (12.9)	11 (13.4)	0.91
Target lesion failure	44 (12.2)	116 (11.4)	0.66	33 (11.9)	11 (13.4)	0.71
Major adverse cardiac events	52 (14.4)	147 (14.4)	0.98	40 (14.4)	12 (14.6)	0.96
Patient-oriented composite endpoint	59 (16.4)	175 (17.1)	0.74	47 (16.9)	12 (14.6)	0.63

Values are n (%), SB= side-branch. During 3-year follow-up, two patients with bifurcated target lesions and eight patients without bifurcated target lesions withdrew their consent, which explains the minor differences in number of patients as compared to baseline.

Kissing balloon in patients with bifurcated lesions (n=360)			Allocated stent in patients with bifurcation lesions (n=360)			Max. SB diameter in patients with bifurcated lesions (n=360)		
KB (N=162)	*No KB (N=198)*	*p value*	*Resolute (N=177)*	*Xience V (N=183)*	*p value*	*SB ≥ 2.0mm (n=286)*	*SB < 2.0mm (n=74)*	*p value*
10 (6.2)	8 (4.0)	0.36	10 (5.6)	8 (4.4)	0.58	16 (5.6)	2 (2.7)	0.55
4 (2.5)	3 (1.5)	0.71	4 (2.3)	3 (1.6)	0.72	6 (2.1)	1 (1.4)	1.00
13 (8.0)	16 (8.1)	0.98	15 (8.5)	14 (7.7)	0.77	22 (7.7)	7 (9.5)	0.62
13 (8.0)	12 (6.1)	0.47	13 (7.3)	12 (6.6)	0.77	19 (6.6)	6 (8.1)	0.66
9 (5.6)	7 (3.5)	0.36	7 (4.0)	9 (4.9)	0.66	13 (4.5)	3 (4.1)	1.00
5 (3.1)	7 (3.5)	0.81	6 (3.4)	6 (3.3)	0.95	10 (3.5)	2 (2.7)	1.00
0 (0.0)	3 (1.5)	0.26	2 (1.1)	1 (0.5)	0.62	1 (0.3)	2 (2.7)	0.11
0 (0.0)	2 (1.0)	0.50	1 (0.6)	1 (0.5)	1.00	1 (0.3)	1 (1.4)	0.37
25 (15.4)	22 (11.1)	0.23	24 (13.6)	23 (12.6)	0.78	38 (13.3)	9 (12.2)	0.80
22 (13.6)	22 (11.1)	0.48	24 (13.6)	20 (10.9)	0.45	35 (12.2)	9 (12.2)	0.99
26 (16.0)	26 (13.1)	0.43	28 (15.8)	24 (13.1)	0.47	43 (15.0)	9 (12.2)	0.53
30 (18.5)	29 (14.6)	0.32	31 (17.5)	28 (15.3)	0.57	49 (17.1)	10 (13.5)	0.45

Risk factors of target-vessel MI

Cox regression analysis suggested that bifurcation treatment may be associated with an increased risk of target-vessel MI (HR=1.64, 95%CI: 1.04-2.58; p=0.03); but after adjustment for potential confounders (multi-vessel treatment, total stent length, number of stents, post-dilation, treatment of circumflex artery, number of lesions treated, and residual in-stent stenosis following stent implantation) in a multivariate Cox regression model, bifurcation treatment turned out to be no independent predictor of target-vessel MI (adjusted HR=1.29, 95%CI: 0.80-2.06; p=0.30). With an increasing degree of residual in-stent lumen diameter stenosis, there was an increase in the risk of target-vessel MI that was no more than slight (adjusted HR=1.03, 95%CI: 1.01-1.05; p<0.01).

Risk factors of repeat revascularization

Although statistically non-significant, there was a higher risk of TVR in patients with non-bifurcated lesions (HR=1.7, 95%CI: 0.97-2.86; p=0.06). Previous CABG and treatment of (at least one) aorto-ostial lesion were identified as potential confounder and therefore tested in a multivariate Cox regression model which showed that both parameters were predictors of TVR (adjusted HR=2.31, 95%CI: 1.40-3.82, p<0.01; adjusted HR=2.00, 95%CI: 1.18-3.34, p=0.01,

respectively). After adjustment for these confounders, treatment of non-bifurcated lesions did not independently predict TVR (adjusted HR=1.52, 95%CI: 0.89-2.62; p=0.13).

DISCUSSION

Despite a higher incidence of PMI, patients treated for bifurcation lesions with second-generation DES had a favorable long-term clinical outcome that was similar to the outcome of patients with non-bifurcation lesions. In patients with treatment of bifurcated target lesions, different treatment strategies (i.e. single-stent or two-stent approach) and the use of final kissing balloon inflation did not affect long-term outcome. In patients treated with a 2-stent approach, the rate of final kissing balloon inflation was numerically higher in the Resolute group as compared to Xience V group (79.4% vs. 68.8%;p=0.28), which may be related to the more open cell design of the Resolute stent.[20] Nevertheless, there was no difference in clinical outcome between patients treated for bifurcated lesions with Resolute versus Xience V stents.

The numerically higher incidence of TVR in the non-bifurcation group (p=0.06) was attributed to the presence of a more advanced atherosclerotic burden, as shown by the multivariate analysis that demonstrated a significantly higher prevalence of previous CABG and aorto-ostial target lesions in that group. The importance of these two parameters as risk factors of repeat revascularization has previously been shown.[21,22]

The definite-or-probable stent thrombosis rate was numerically higher in the non-bifurcation group versus the bifurcation group (1.8% vs. 0.8%; p=0.22), and in patients with bifurcation treatment with a 2-stent approach versus a single stent (2.4% vs. 0.4%; p=0.13). Although the latter is in line with the sub-study of the Resolute All Comers[13], the stent thrombosis data should be interpreted with caution due to the limited number of events.

Previous bifurcation studies with DES

The introduction of DES has substantially reduced the rate of repeat revascularization following treatment of bifurcation lesions.[2-4] Due to differences in stent design, clinical outcome of bifurcation stenting may differ between DES.[20] The randomized CORpal and SEAside studies compared Xience V and the first-generation sirolimus-eluting Cypher stent (Cordis; Waren, New Jersey, USA) in bifurcation lesions, and found after 12 and 18 months, respectively, no difference in clinical outcome between the two DES.[11,12] However, in a recently reported pooled analysis of both trials, the rate of MACE beyond 1 year was significantly lower (p=0.03) following treatment with Xience V as compared to Cypher,[14] underlining the importance of long-term clinical assessment of DES.[15]

There are somewhat less data available on the Resolute stent in bifurcations lesions. A multicenter registry, comprising 180 patients treated with Resolute, showed a low MACE rate at 9-month

follow-up.[23] In the Z-SEAside study, use of the Resolute stent in bifurcated lesions of 75 patients resulted in a lower procedure-related composite endpoint (as compared to Cypher). Nevertheless, at 2-year follow-up there was no difference in a composite clinical and angiographic endpoint.[24] Overall, Xience V and Resolute have shown favorable results in various patient populations that included patients with bifurcation lesions.[5-7,16,21,25,26] A recent analysis that pooled both stent arms of the RESOLUTE All Comers trial, which used the same DES as the TWENTE trial (and thus our present sub-study), showed similar clinical outcomes for patients treated for bifurcated versus non-bifurcated lesions at 2-year follow-up.[13] In the study reported by Diletti et al. as well as in our present study, there was a higher incidence of PMI in patients with bifurcation lesions. In the absence of an unequivocal cause of PMI in patients with bifurcated target lesions, we speculate that (stent-induced) closures of side-branches may have resulted in PMI. While PMI may be considered a marker of PCI procedure complexity (e.g. treatment of a bifurcated lesion), the clinical impact of PMI remains partly unclear.[27] In addition, in the present study there was no evidence of a relationship between the occurrence of PMI following bifurcation treatment and an adverse clinical outcome. However, in the presence of larger side branches and an increased risk of side-branch occlusion, one may consider the use of an additional guide wire in the side-branch, a more aggressive pharmacological (anti-platelet) therapy, and occasionally the upfront use of a 2-stent approach to protect the patency of the side-branch.

In both studies, the number of patients treated with a two-stent approach was reasonable (81[13] and 82 patients in the present study), representing 20.7% and 22.7% of all patients with bifurcation treatment. In the TWENTE trial population, final kissing balloon inflation was performed in 73.2% of patients treated with the two-stent approach. In the absence of data on the use of final kissing balloon inflation in the RESOLUTE All Comers trial, we can only speculate that potential differences in the frequency of kissing balloon inflation might have played a role.

A randomized bifurcation study with first-generation DES has previously shown a lower restenosis rate of the side-branch in lesions that had been treated with kissing balloon inflation (7.9% vs. 15.4%; p=0.04).[28] In our present clinical study, in the absence of a routine angiographic follow-up, clinical outcome was similar in patients treated for bifurcation lesions with and without final kissing balloon inflation.

Bifurcation analyses should focus on target lesions with side-branches of a relevant size. However, through the various bifurcation studies there was no general consensus on the minimum lumen diameter of side-branches that should be addressed and on the method of assessment (i.e. visually determined or measured by QCA).[11-13,24,28] Compared to visual assessment, QCA is more objective and may be stricter in preventing the inclusion of too small side-branches.[29] In the TWENTE trial and the present bifurcation sub-study, a minimum side-branch diameter ≥1.5 mm by QCA was applied, which is in line with the definition of relevant bifurcations for the SYNTAX score.[17] In addition, almost 80% of our patients with bifurcated target lesions had side-branches ≥2.0mm by QCA, and their TVF rate did not differ from patients with smaller side-branches (p=0.80).

Bifurcations with side-branches ≥2.0mm were also addressed by previous bifurcation studies such as the SEASIDE trial and Z-SEASIDE registry, which included patients based on a visual assessment of the side-branch lumen diameter.[11,24]

Study limitations

Because of the relatively limited sample size and the low event rates, no definite conclusion can be drawn from the present post hoc analysis, and findings should be considered hypothesis generating. Nevertheless, because of the low event rates with the study stents used, the analysis was based on the 3-year clinical outcome data (which increased the overall number of adverse events). In addition, the comparison between the outcome of patients treated with two-stent versus single stent approach and of patients treated with kissing balloon inflation versus the omission thereof are limited by the small size of these patient subgroups. Similar to previous bifurcation studies that used several different definitions of bifurcated target lesion and relevant side-branch, the comparability of our findings with data of trials that used different definitions and/or addressed dissimilar patient populations may be limited. We did not measure the bifurcation angle; a dedicated three-dimensional reconstruction and analysis software for bifurcations may be a promising tool to obtain reliable data on true lesion geometry.[30] The TWENTE trial did not comprise a routine angiographic follow-up; as such, no angiography-based sub-analyses of side-branch patency could be performed.

Clinical implications

The present analysis of the randomized TWENTE trial, which enrolled a broad study population of patients with advanced coronary disease and complex coronary lesions in the majority of patients, reassures that use of the study stents for the treatment of bifurcated coronary lesions is safe and effective. These findings are relevant, as in most patients with bifurcation lesions a simple approach with provisional T-stenting was applied, which is currently the recommended approach.[31,32] The favorable outcome of various subgroups of patients suggest that, with the use of second-generation DES, long-term clinical outcome is favorable and similar for bifurcation treatment with a single-stent or two-stent approach, and with or without kissing balloon inflation.

Conclusions

Despite a significant difference in periprocedural myocardial infarction, 3-year clinical outcome after implantation of second-generation stents was favorable and similar for patients with and without bifurcation lesions. In addition, we observed no difference in long-term clinical outcome following bifurcation lesion treatment with Resolute and Xience V stents.

Acknowledgements

We thank Mrs. Jacqueline C. Jonge Poerink (Thoraxcentrum Twente, MST, Enschede, Netherlands) for performing QCA measurements of the bifurcated target lesions.

Disclosures

Conflict of Interest: Clemens von Birgelen is or has been consultant to and has received lecture fees or travel expenses from Abbott Vascular, Boston Scientific, and Medtronic; he received travel expenses from Biotronik and lecture fees from MSD; the institution has received research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. All other authors declare that they have no conflict of interest. The TWENTE trial is an investigator-initiated study, supported by equal unrestricted grants from Abbott Vascular and Medtronic.

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Safety and efficacy of novel DES in all comers

Chapter 10

Highly deliverable third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients (DUTCH PEERS): A randomised trial

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Lancet. 2014 Feb 1;383(9915):413-23.

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%). This trial is registered with ClinicalTrials.gov, number NCT01331707.

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 reported,[11,19] 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 centres (Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Scheper Hospital, Emmen;

and Medisch Centrum Alkmaar, Alkmaar). In this investigator-initiated study, single-blind, multi-centre, randomised, two-arm, non-inferiority trial,[10] all-comer patients aged 18 years and older, who were capable of providing informed consent and who required a percutaneous coronary intervention with implantation of a drug-eluting stent, were randomly assigned for treatment with one of the two study stents. All coronary syndromes, de-novo and restenotic lesions, and coronary artery or bypass stenoses were permitted (with no limit for lesion length, reference size, or number of lesions or diseased vessels). Exclusion criteria were: participation in another randomised study for a drug or medical device that had not reached its primary endpoint; planned surgery within the next 6 months unless dual antiplatelet therapy was maintained; known intolerance to a P2Y12 receptor antagonist that would prevent adherence to dual antiplatelet therapy, or intolerance to aspirin, heparin, or components of drug-eluting stents; known pregnancy; and life expectancy of less than 1 year. The study complied with the CONSORT 2010 statement and the Declaration of Helsinki and was approved by the independent Medical Ethics Committee Twente and the institutional review boards of all participating centres. All patients provided written informed consent.

Randomisation and masking

After guide wire passage (or predilation), patients were randomly assigned in blocks of eight and four in random order by a computer program (block stratified randomisation 5.0 by S. Piantadosi). Patients were assigned in a 1:1 ratio to one of the drug-eluting stents. Patients and all analysts were masked to the allocated stent, but treating clinicians were not. The random allocation was implemented by use of sequentially numbered, opaque, sealed envelopes.

Procedures

The third-generation cobalt-chromium-based zotarolimus-eluting (Resolute Integrity, Medtronic, Santa Rosa, CA, USA) stent uses 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 that consists of zotarolimus and the BioLinx polymer system, which have been efficacious in the second-generation Resolute stent (Medtronic).[7,8,21] 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 81 μm) of the third-generation everolimus-eluting Promus Element stent 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 (ie, radiopacity), is covered by a 7 μm everolimus-eluting fluoropolymer coating that has been efficacious in the second-generation cobalt chromium-based everolimus-eluting Xience V/Promus stent (Xience V, Abbott Vascular Devices, Santa Clara, CA, USA; Promus, Boston Scientific, Natick, MA, USA).[5,8] Everolimus-eluting stents were available in diameters of 2.25–4.0 mm and lengths of 8–38 mm.

Interventions were done with standard techniques. Lesion pre-dilation, use of glycoprotein IIb/IIIa receptor antagonists, direct stenting, and stent post-dilation were left to the operator's discretion. Staged procedures with allocated stents were allowed within 6 weeks. Concomitant drugs did not differ from routine treatment; further medical treatment was provided in accordance with medical guidelines and the physician's judgment.[10] Generally, dual antiplatelet therapy was prescribed for 1 year after stent insertion.

Electrocardiographs(ECGs) were systematically assessed before and after the intervention, before discharge, and at suspicion of ischaemia, and were recommended at 12-month follow-up. Laboratory tests included systematic assessment of cardiac markers after the intervention and subsequent serial measurements in the case of relevant raised markers or chest pain. In patients with acute coronary syndromes, cardiac markers were also assessed before the intervention.[10]

Angiographic analysts at Thoraxcentrum Twente, who were masked to the assigned stent type, did subsequent quantitative coronary angiography for study participations from all centres in accordance with present standards (QAngio XA 7.2, Medis, Leiden, 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 after initially successful deployment.[16–18] On angiography, longitudinal stent deformation was identified as a localised change in radiopacity pattern of a stent, that occurred between initial deployment and the end of the procedure, after manipulations with the guiding catheter or after the use of further catheter-based devices (eg, an attempt to recross 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, who was masked to reported longitudinal stent deformation and allocated stent type. Measurement of stent length both final (ie, after completion of the interventional procedure) and immediately after deployment, and calculation of the post-deployment stent length ratio (stent length final divided by stent length after deployment) were done for cases in which longitudinal stent deformation was noted by the operator or indentified identified by the analyst.[19]

Clinical endpoints were defined as proposed by the Academic Research Consortium, including the addendum on myocardial infarction.[10,22,23] The pre-specified composite pimary 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, and clinically indicated target-vessel revascularisation (components listed in hierarchical order by importance). Death was regarded as cardiac unless an unequivocal non-cardiac cause could be established. Myocardial infarction was defined by a creatine kinase concentration of more than double the upper limit of normal with raised confirmatory cardiac biomarkers.[23] A target-vessel-related myocardial infarction was related to the target vessel or could not be related to another vessel; further classification could be based on laboratory, ECG, angiographic, or clinical data.[10] Revascularisation procedures were regarded as clinically indicated (ie, there was sufficient objective evidence of a clinically significant lesion)

if the angiographic diameter stenosis of the then treated lesion was 50% or more in the presence of ischaemic signs or symptoms, or if the diameter stenosis was 70% or more irrespective of ischaemic signs or symptoms.[23]

Prespecified secondary endpoints included: the separate components of the primary endpoint; all-cause mortality; any myocardial infarction; clinically indicated target-lesion revascularisation; and stent thrombosis.[10,22] Prespecified secondary composite endpoints (components in hierarchical order of importance) were: a composite of *target-lesion failure*, consisting of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-lesion revascularisation; a composite of *major adverse cardiac events*, consisting of all-cause mortality, any myocardial infarction, emergent coronary bypass surgery, and clinically indicated target-lesion revascularisation; and a more comprehensive *patient-oriented composite,* consisting of all-cause mortality, any myocardial infarction, and any coronary revascularisation. A final residual diameter stenosis of less than 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. We also did a post-hoc exploratory subgroup analysis of the primary endpoint in line with previous trials.[7,8,21]

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

The CRO Diagram (Zwolle, Netherlands) did the data monitoring, which consisted of: informed consent and type and size of stent (all patients); all potential clinical events reported by investigators or patients (all event triggers); and further in-depth monitoring of all demographic, procedural, and clinical outcome data (at random in 10% of patients).

The CRO Cardialysis (Rotterdam, Netherlands) did the processing of clinical outcome and clinical event adjudication. The clinical event committee in Rotterdam, which was masked to the assigned treatment, adjudicated all clinical endpoints, with the only exception being the secondary endpoint of *non-target-vessel revascularisation* which was adjudicated by Cardio Research Enschede. Members of the clinical event committee are listed at the end of the report.

Statistical 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 the $\chi 2$ test with at least 80% power to detect non-inferiority at a one-sided type I error of 0.05.[24] 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

did a per-protocol analysis of the primary endpoint. Categorical variables were assessed with the $\chi 2$ test, whereas continuous variables were assessed with the Student's t test or the Wilcoxon rank-sum test, as appropriate. The time to primary endpoint and the components thereof were assessed by to Kaplan-Meier analysis;[25] 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 of less than 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,[26] 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 the study had no role in study design, data collection and monitoring, data analysis, data interpretation, or writing of the report. They had no access to the clinical trial database. The authors had full access to all the data in the study. 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).

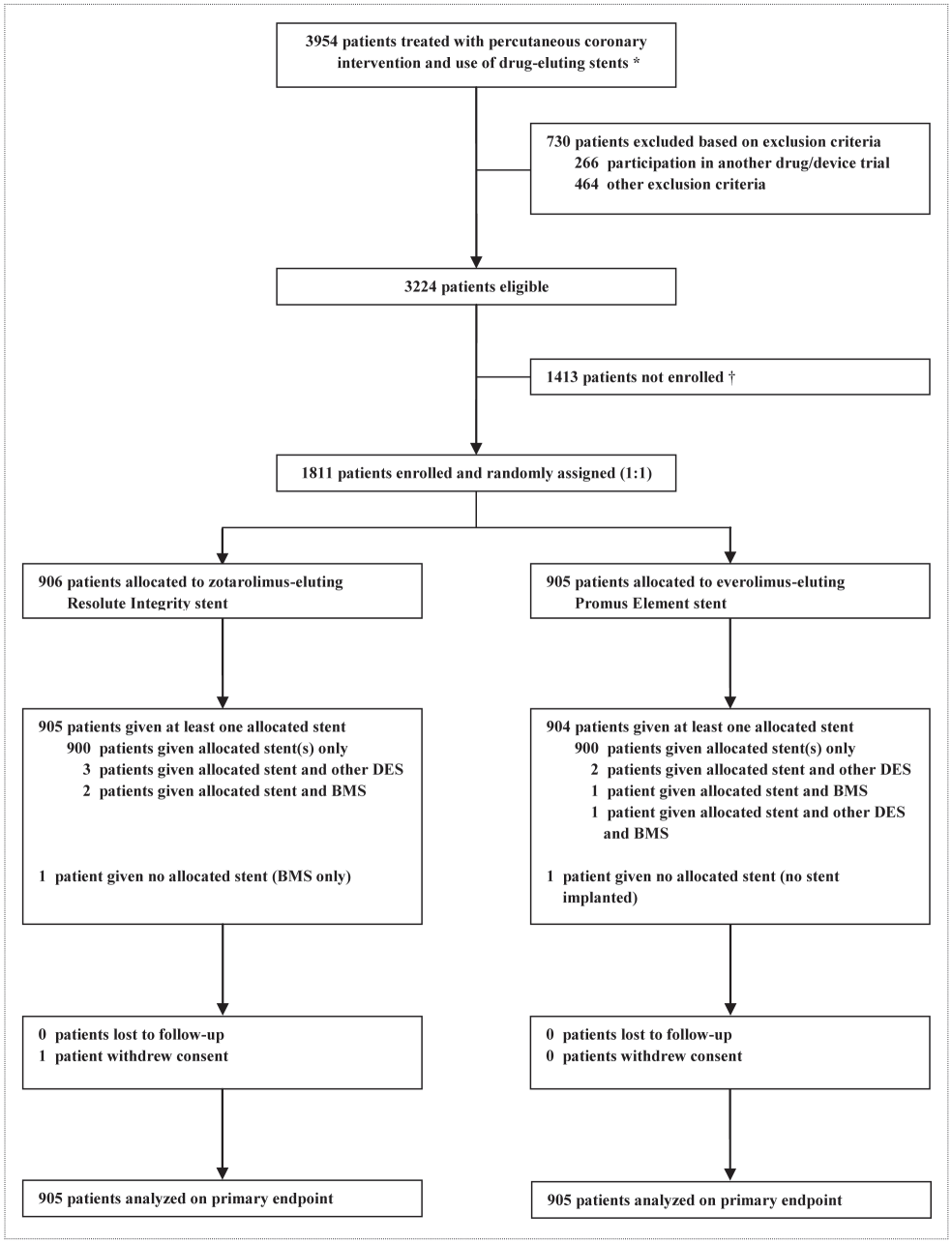

Figure 1. Trial profile

* Total number of patients at the four study centres who had percutaneous coronary intervention with use of drug-eluting stents during the study enrolment period, irrespective of inclusion and exclusion criteria.
† No reliable data are available for the reasons why eligible patients were not enrolled.

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 findings (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 1. Baseline characteristics of patients

	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)

Data are n (%) or median (IQR). Baseline patient characteristics did not differ significantly between treatment arms;p values were greater than 0.10, apart from those for clinical syndrome at presentation (p=0.07) and bifurcation with main-vessel and side-branch stenting (p=0.052). RVD=reference vessel diameter. *Data from 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. ‡Data from 903 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group. §Data from 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; data from 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.

Table 2. Baseline characteristics of target lesions

	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 n (%) or median (IQR). Baseline lesion characteristics did not differ significantly between treatment arms; p values were greater than 0.10, apart from that for severe calcification (p=0.052). ACC/AHA=American College of Cardiology/American Heart Association. TIMI=thrombolysis in myocardial infarction. *Including chronic total occlusion, but not grafts or in-stent restenosis. †Only thrombi that triggered use of a thrombus aspiration catheter were counted.

Table 3. 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 n (%). *Data are per patient (906 patients in the zotarolimus-eluting stent group and 905 patients in the everolimus-eluting stent group). †Data from 1204 lesions in the zotarolimus-eluting stent group and 1165 lesions in the everolimus-eluting stent group. ‡Device success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50% with only the assigned study device. §Lesion success was defi ned as the attainment at the target site of a final residual diameter stenosis of less than 50% by any percutaneous method. ¶Procedure success was defined as the attainment at the target site of a final residual diameter stenosis of less than 50%, together with the absence of any in-hospital major adverse cardiac events.

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).

Table 4. One-year clinical outcomes

	Total patients (N=1810)	Zotarolimus-eluting stent (905 patients)	Everolimus-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 n (%), unless otherwise indicated. *The primary endpoint of target-vessel failure is a composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-vessel revascularisation. †Target-lesion failure is a composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-lesion revascularisation. ‡Major adverse cardiac events is a composite of all-cause death, any myocardial infarction, emergent coronary-artery bypass surgery, and clinically indicated target-lesion revascularisation. §The patient-oriented composite endpoint is a composite of all-cause death, any myocardial infarction, and any revascularisation.

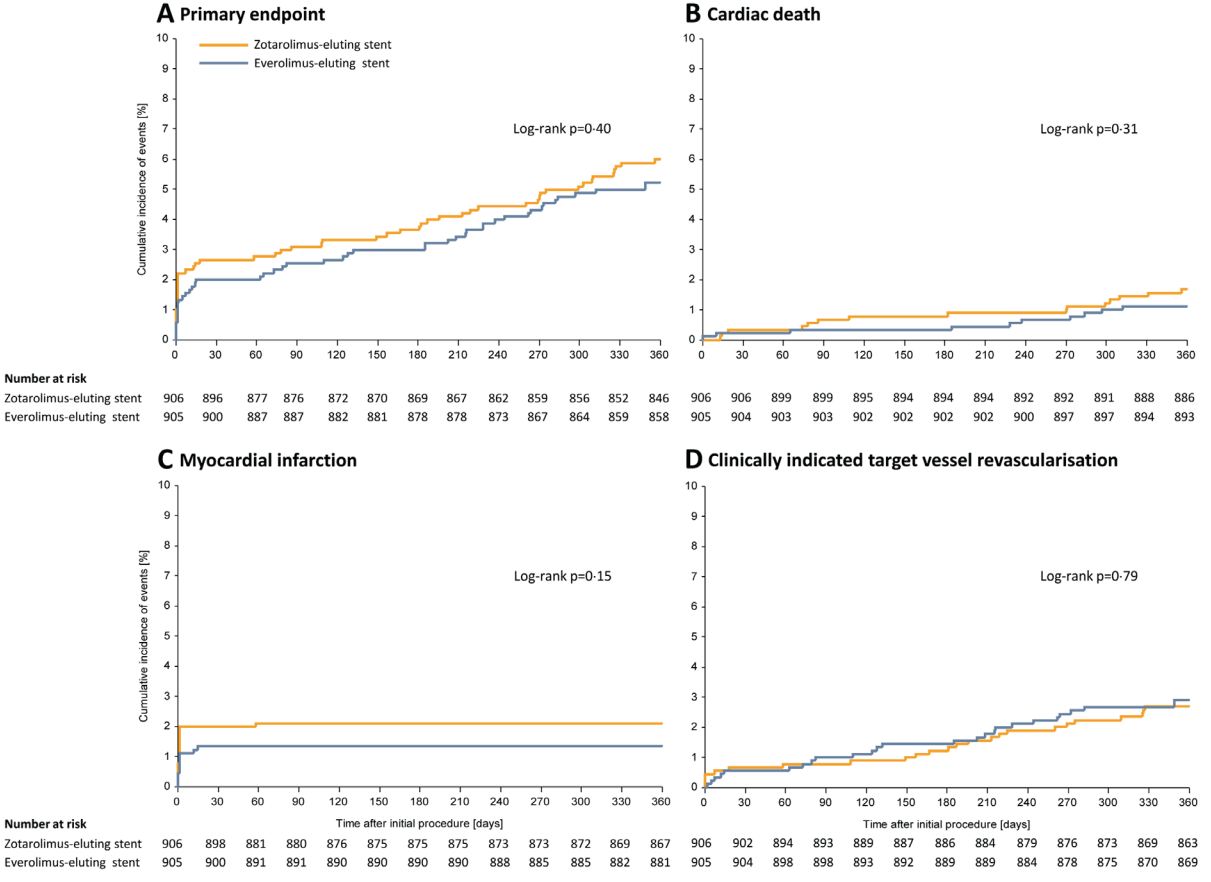

Figure 2: Kaplan-Meier cumulative event curves for the primary combined safety and effi cacy endpoint and its individual components at 12 months

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

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 about corresponding clinical events.

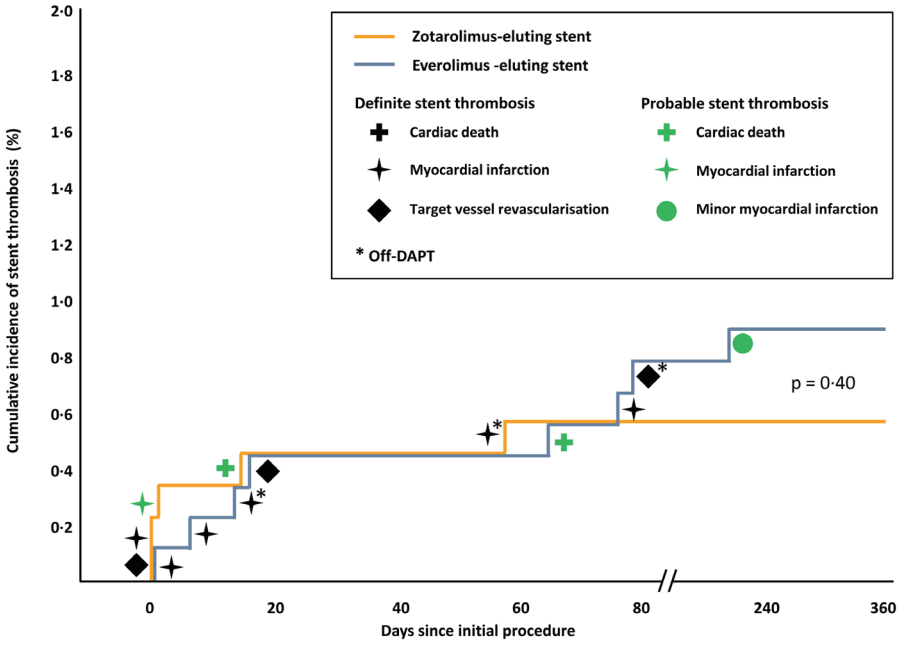

Figure 3. Cumulative incidence of definite or probable stent thrombosis

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).

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 the third-generation zotarolimus-eluting Resolute Integrity and everolimus-eluting Promus Element stents. It is also the first trial ever to investigate the Resolute Integrity stent. In this all-comer patient population, no significant difference was seen between stent groups in the primary endpoint of 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 with the everolimus-eluting Promus Element stent (panel). 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.[7,19,27–29] The proportions of patients with complex type B2 or C coronary lesions and bifurcation lesions were also high compared with other trials.[6–8,19,28,29]

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 drug-eluting stent groups of various

other randomised trials, such as TWENTE,[8] RESOLUTE All-Comers,[7] COMPARE II,[30] and LEADERS,[27] across which treatment of 1.6–5.3% of patients deviated from the assigned stents.
Up to now, the third-generation Promus Element stent *has only been compared with second-generation* drug-eluting stent.[11,19] In the PLATINUM trial,[11] which enrolled patients at low-to-moderate risk of adverse cardiovascular events, the Promus Element stent was shown to be non-inferior to the second-generation cobalt-chromium-based everolimus-eluting Xience V/Promus stent ,and only a small proportion of patients (4.2%) met the target-vessel-related composite endpoint.[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[19] trial has compared the Promus Element stent with the second-generation zotarolimus-eluting Resolute stent in an all-comers population in South Korea (patients with a reference vessel diameter less than 2.5mm or heart failure were excluded). The investigators attributed the very low frequencies of clinical endpoints to the excellent device characteristics and generally lower clinical event frequencies 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 this 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 (class B2 or C, 66% vs 51%) and treatment of more lesions in small vessels (by not excluding patients with a reference vessel diameter of less than 2.5 mm). Moreover, investigators of a very small randomised study[31] from Spain also reported favourable outcome data for 150 patients treated with Promus Element stents, but this study did not permit a meaningful between-stent comparison. Compared with the second-generation everolimus-eluting stent in the TWENTE[8] and RESOLUTE All-Comers[7] trials, which recruited broad patient populations, the Promus Element stent group in our trial showed lower frequencies of both target-vessel-related (5.2% vs 8.1– 9.6%) and target- lesion-related composite endpoint events (4.5% vs 6.8–8.3%).
Only a small-scale, first-in-man study reported data for the bare-metal stent platform that is used 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 counterpart in the randomised TWENTE[8] and RESOLUTE All-Comers[7] trials (target-vessel-related composite endpoint: 6.1% vs 8.2–9.0%; definite stent thrombosis 0.3% vs 0.6–1.2%).
A potential trade-off of the novel, flexible designs of third-generation drug-eluting stents might be a reduced longitudinal stability.[15,16] Since the introduction of the Promus Element stent, longitudinal stent deformation has been reported much more frequently.[18] Retrospective analyses[16,17] have shown longitudinal deformation to occur at a frequency of 0.3–0.9% per Promus Element stent implanted, although such deformations are associated with a mostly benign

clinical course. In the HOST-ASSURE trial, [19] longitudinal deformation of the Promus Element stent was noted in seven (0.2%) of 2938 patients, but was 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[19,32] 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 of target- lesion failure has been advocated as primary endpoint,[22] DUTCH PEERS used the composite 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.[27-29] 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 significant 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 frequencies of primary endpoint events affect the robustness of the results, particularly the results of the post-hoc subgroup analysis. When designing the DUTCH PEERS trial, we assumed that the tested devices would have an event risk that was in the range of their second-generation counterparts tested in the RESOLUTE All-Comers trial,[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 [19,30] 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

frequency), the primary outcome of non-inferiority of the Resolute Integrity stent compared with the Promus Element stent was unchanged. A one-sided α of 0.05, which is also used by other DES trials in all-comers[7,29,30]—is less conservative in establishing non-inferiority of two treatments, but the use of a one-sided α of 0.025 would not have had an effect on the outcome of our study (ie, 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

We searched PubMed for reports with an abstract in English published up to Aug 26, 2013, and checked the listings of the EuroPCR, Transcatheter Cardiovascular Therapeutics, and American College of Cardiology conferences (from 2009 onwards) for reports of randomised trials that compared 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 'zotarolimus',

'everolimus', 'Resolute Integrity', 'Promus Element', 'platinum', 'randomised', and 'randomized'. The third-generation Resolute Integrity stent had not yet been assessed in a randomised trial. The Promus Element stent had been assessed in two randomized clinical trials.[11,19] In the PLATINUM trial,[11] Promus Element was non-inferior to the cobalt-chromium-based Xience V stent in patients at low-to-moderate risk of adverse cardiovascular events. Preliminary data from the HOST-ASSURE trial[19] in allcomer patients in South Korea showed very low event frequencies for both the Promus Element and the second-generation Resolute stent.

Interpretation

DUTCH PEERS was the first randomised trial to investigate the Resolute Integrity stent. The third-generation, permanent-polymer zotarolimus-eluting (Resolute Integrity) and everolimus-eluting (Promus Element) stents were similarly efficacious and safe, with excellent clinical outcomes in a real all-comer patient population.

Contributors

CvB, KT and MWZB designed the trial. CvB, PWD, and GAJJ were the trial steering committee. CvB wrote the first draft of the report with the participation of KT, HS, MKL, MGS, MML and GCML. RWMH, GKvH, ARS, RMTJG, JWL, FHAFdM, SAMS, MBN, and PMJV revised the draft for important intellectual content. HS, MKL, MML, and KT gathered and analysed data. KT and CJMD did the statistical analyses. CvB, HS, MKL, MML, CJMD, and KT interpreted the data. All authors read and approved the final submitted version of the report.

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Conflicts of interest

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

Acknowledgments

Boston Scientific and Medtronic equally supported this investigator-initiated study.

We thank Job van der Palen (Medisch Spectrum Twente and University of Twente, Enschede, Netherlands) for providing statistical advice and Liefke van der Heijden for data retrieval and verification (Medisch Spectrum Twente, Enschede, Netherlands). We are grateful for the invaluable support of the cardiologists and other staff the research departments, catheterisation

laboratories, wards, and administrative departments of the study centres and referring hospitals, and of the various general physicians and pharmacists involved in the treatment of our patients.

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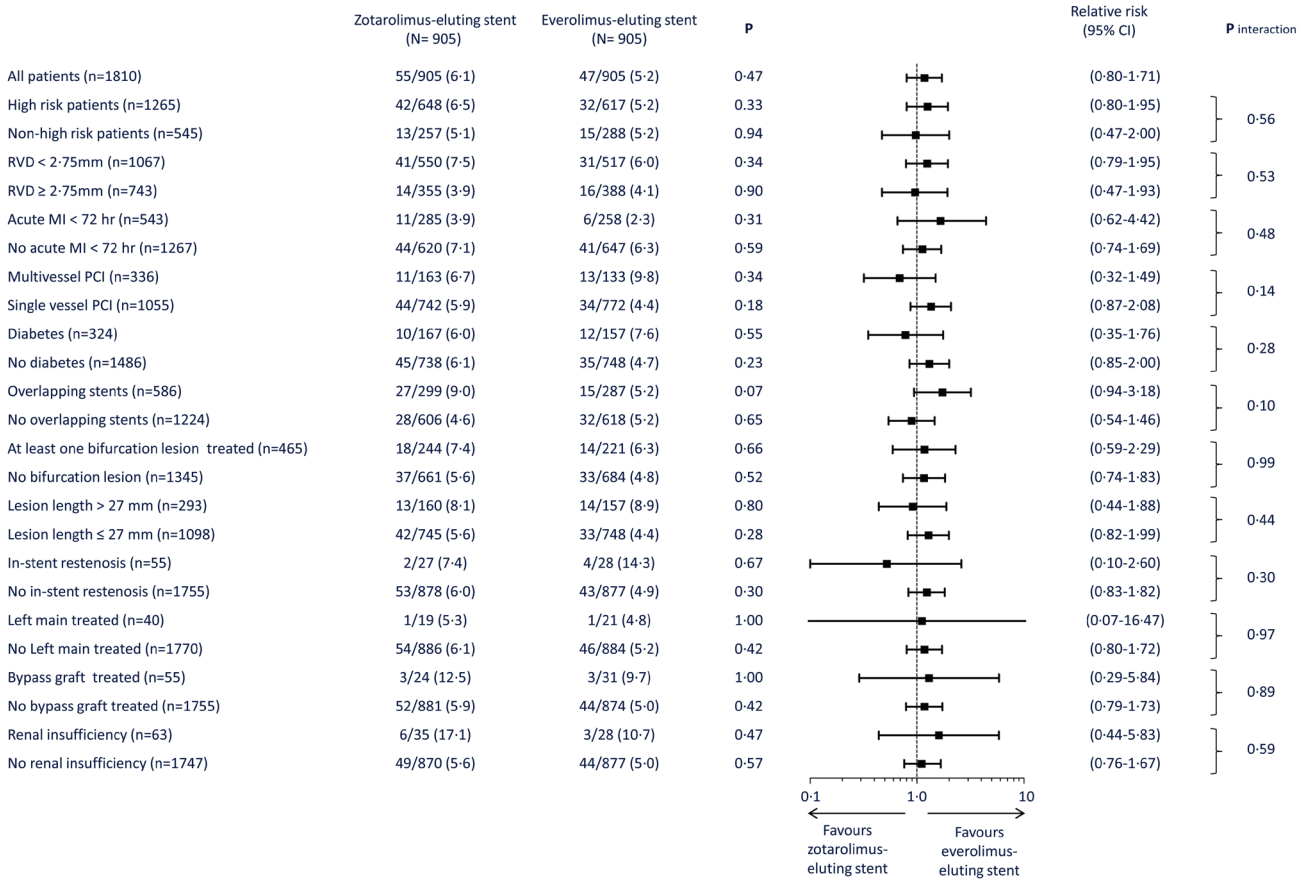
	Zotarolimus-eluting stent (1205 lesions)	Everolimus-eluting stent (1166 lesions)	p value
Implantation of assigned stents only	1195 (99.2)	1161 (99.6)	0.36
Number of stents per lesion	1.35 (0.68)	1.36 (0.70)	0.70
Total stent length per lesion (mm)	22 (18-36)	24 (16-38)	0.20
Maximum nominal stent diameter 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

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

	Zotarolimus-eluting stent (906 patients)	Everolimus-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 (0.54-187)	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

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

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

Web Appendix IV. Longitudinal stent deformation, classified according to presumed cause 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 11

Clinical events and patient-reported chest pain in all-comers treated with esolute Integrity and Promus Element stents: Two-year follow-up of the randomized DUTCH PEERS (TWENTE II) trial

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ABSTRACT

Objectives: We assessed clinical events and patient-reported chest pain 2 years after treatment of all-comers with Resolute Integrity zotarolimus-eluting stents (ZES) (Medtronic Vascular) and Promus Element everolimus-eluting stents (EES) (Boston Scientific).

Background: For both drug-eluting stents (DES), no all-comer outcome data >12 months were published. While there is increasing interest in patient-reported chest pain following stenting, data with novel DES are scarce.

Methods: The DUTCH PEERS multicenter trial (TWENTE II) randomized 1,811 all-comer patients to treatment with one DES type. Monitoring and event adjudication were performed by independent contract research organizations.

Results: 2-year follow-up of 1,810 patients (99.9%) was available. The primary composite endpoint target vessel failure (TVF) occurred in 8.6% and 7.8% of patients treated with ZES and EES (p=0.55). Rates of components of TVF were: cardiac death (2.4% vs. 1.9%, p=0.42); target vessel-related myocardial infarction (2.4% vs. 1.8%, p=0.33); clinically-indicated target vessel revascularization (TVR) (4.6% vs. 4.9%, p=0.83). At 1 and 2-year follow-up, >80% of patients were free from chest pain (no between-stent difference). In addition, >87% of patients were either free from chest pain or experienced pain only at maximum physical exertion, but not during normal daily activities. Patients with chest pain after 12 months at no more than moderate physical effort had a higher TVR risk during the following year (HR: 1.89 (95%-CI: 1.05-3.39), p=0.03).

Conclusion: During the second year of follow-up, the incidence of adverse clinical endpoints remained similar and low for both DES. The vast majority of patients were free from chest pain.

KEYWORDS

randomised (randomized) clinical trial - all-comer / all-comers - percutaneous coronary intervention - Resolute Integrity cobalt-chromium zotarolimus-eluting stent (ZES) Promus Element platinum-chromium everolimus-eluting stent (EES) -drug-eluting-stents (DES)

CONDENSED ABTRACT

The 2-year analysis of the randomized DUTCH PEERS trial (TWENTE II) compared clinical events and patient-reported chest pain between all-comer patients treated with novel, highly flexible zotarolimus-eluting and everolimus-eluting stents (Resolute Integrity vs. Promus Element). The rates of the primary endpoint target-vessel failure (8.6% vs. 7.8%, p=0.55) and its components were low and similar between stent-groups. At 1 and 2-year, >80% of patients were free from any chest pain (no between-stent difference); >87% were free from chest pain during normal daily activities. Chest pain at 1-year at mild-to-moderate physical effort was associated with a higher risk of consecutive target-vessel revascularization.

INTRODUCTION

Drug-eluting stents (DES) have revolutionized the treatment of obstructive coronary disease. Since their introduction, these devices have undergone major improvements (1). These include an increase in biocompatibility of their durable polymer-based coatings in the second-generation DES (2,3) and an improvement in flexibility and deliverability of their metallic stent platforms in the more recent generation of DES, using the same coatings (4-6).

The cobalt-chromium-based Resolute Integrity zotarolimus eluting stent (ZES) (Medtronic, Santa Rosa, CA, USA) and the platinum-chromium-based Promus Element everolimus-eluting stent (EES) (Promus Element, Boston Scientific, Natick, MA, USA) are two such novel, highly flexible DES, which have recently been compared in the randomized, multi-center DUTCH PEERS trial in all-comers (4). DUTCH PEERS is the first randomized trial that reports outcome data of Resolute Integrity ZES and the first trial to provide a head-to-head comparison of the two durable coating-based DES, showing low clinical event rates at 1 year (4). Follow-up information after the cessation of dual-antiplatelet therapy (DAPT) at 1 year is of interest to demonstrate or exclude any potential late catch-up in adverse events.

In the presence of very low rates of traditional clinical endpoints following percutaneous coronary interventions (PCI) with novel DES (4-6), there is growing interest in the assessment of patient-reported chest pain – the principal anginal symptom and main trigger of repeat cardiac assessment despite a successful PCI (7,8). Moreover, long-lasting absence of chest pain determines to a great extent the "patient satisfaction" with PCI. Therefore, in the present 2-year analysis of the DUTCH PEERS all-comers population, we investigated both clinical event rates and patient-reported chest pain following treatment with Resolute Integrity ZES and Promus Element EES.

METHODS

Study design, patients, and procedures. The DUTCH PEERS trial has previously been described in detail (4). In brief, DUTCH PEERS is a multicenter, prospective, randomized, single-blinded, investigator-initiated trial in an all-comers patient population. Study enrollment was performed between November 25, 2010, and May 24, 2012. There was no limit for lesion length, reference size, and number of lesions or diseased vessels to be treated. Interventional procedures were performed according to standard techniques and routine clinical protocols. The study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee Twente and the institutional review boards of all participating centers. All patients provided written informed consent. Patients were randomly assigned, in a 1:1 fashion, to treatment with one of the two study stents.

Resolute Integrity ZES releases zotarolimus from the 6 µm BioLinx conformal, permanent polymer system (blend of 3 polymers), which has been highly effective on Resolute stents (2,3,9), and uses the novel, sinusoid-shaped single cobalt-chromium wire-based, open-cell design Integrity stent platform (91 µm round struts) (4) (4) with slightly more strut connections in close vicinity to its proximal and distal ends.Promus Element EES releases everolimus from a 7 µm conformal, permanent fluoropolymer coating that recently demonstrated its efficacy in other patient populations (2,3,9-12) and uses the novel, laser-cut, platinum-chromium alloy (highly radiopaque), open-cell design (serpentine rings connected by links) Element stent platform (81 µm struts) for improved deliverability (4,13,14). Novel flexible, highly deliverable stents may be less longitudinally stable, which can sometimes result in a distortion or shortening of an initially successfully implanted stent in the longitudinal axis; differences in stent design and radiographic visibility may explain between-stent differences. In DUTCH PEERS, a dedicated angiographic analysis confirmed longitudinal stent deformations in 1% of patients treated with Promus Element (no clinical consequences up to 1-year follow-up) and in none of the patients treated with Resolute Integrity (4).

Interventions were performed according to standard techniques. Patients were pre-treated with acetylsalicylic acid and clopidogrel. Lesion pre-dilation, use of glycoprotein IIb/IIIa receptor antagonists, direct stenting, and stent post-dilation were left at the operator's discretion. Operators were requested to report evident (or suspected) longitudinal stent deformation, defined as distortion or shortening of initially successfully implanted stents in the longitudinal axis (15,16). In general, dual anti-platelet therapy was prescribed for 1 year. Systematic laboratory and electrocardiographic testing were performed as previously described (4) to identify peri-procedural myocardial infarction (MI). The follow-up procedures of the study have previously been reported (4,17). At 1 and 2-year follow-up, research nurses and analysts who were blinded to the assigned stent type obtained information on chest pain by use of a medical questionnaire or, in the absence of a response, a telephone follow-up that used the same questions.

Angiographic analysts, blinded to the stent type used, performed off-line quantitative coronary angiography according to current standards (QAngio XA 7.2, Medis, Leiden, The Netherlands). The CRO Cardio Research Enschede (Enschede, The Netherlands coordinated the trial and data management. Regular safety data were reported to the independent Medical Ethics Committee Twente. Data monitoring was performed by the independent CRO Diagram (Zwolle, the Netherlands). Processing of clinical outcome data and clinical event adjudication were performed by the independent CRO Cardialysis (Rotterdam, the Netherlands).

Definition of clinical endpoints. Definitions of all predefined clinical endpoints have previously been described in detail (4,17). Clinical endpoints were defined according to the Academic Research Consortium (ARC), including the addendum on myocardial infarction (4, 17-19). In brief, *Target Vessel Failure* (TVF), the primary endpoint of DUTCH PEERS is a composite of cardiac death, target vessel-related MI, or clinically-indicated target vessel revascularization (TVR).

Death was considered cardiac, unless an unequivocal non-cardiac cause could be established. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated confirmatory cardiac biomarkers. A target vessel-related MI was related to the target vessel or could not be related to another vessel. TVR and target lesion revascularization (TLR) were considered clinically-indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms. Stent thrombosis was classified according to the ARC definitions (19,20).

Predefined secondary endpoints included the components of the primary endpoint; all-cause mortality; any MI; clinically-indicated TLR; stent thrombosis and longitudinal stent deformation. Other composite parameters were (in hierarchical order): *Target Lesion Failure* (TLF), a composite of cardiac death, target vessel-related MI, or clinically indicated TLR; *Major Adverse Cardiac Events* (MACE), a composite of all-cause death, any MI, emergent coronary bypass surgery, or clinically indicated TLR; *Patient-Oriented Composite Endpoint* (POCE), a composite of all-cause death, any MI, or any coronary revascularization. An exploratory subgroup analysis of the primary endpoint was performed in line with previous trials (2,3).

Patient-reported chest pain, the principal symptom of angina pectoris and a surrogate for myocardial ischemia, was classified into four scores: 0= no chest pain at all; 1= chest pain only during most severe physical exertion; 2= chest pain at moderate physical effort (during moderate/normal daily activities); 3= chest pain at mild physical effort or at rest.

Statistical analysis. Data were reported as frequencies and percentages for dichotomous and categorical variables, while continuous variables were expressed as mean ± standard deviation (SD) for continuous variables. Differences in dichotomous and categorical variables were assessed with the Chi-square or Fisher's exact tests, while continuous variables were assessed with the student's t-test or the Wilcoxon rank-sum test, as appropriate. The Kaplan-Meier analysis was used to calculate the time to clinical endpoints and the Log-rank test was applied to compare between-group differences. A landmark analysis was performed at 1 year for various adverse clinical events expressed as a difference in proportion and 95% confidence interval (21). The Cox proportional-hazards regression analysis was performed to test for interaction between subgroups and stent type with regard to the clinical endpoint TVF. All p-values and confidence intervals were two-sided and a p-value <0.05 was considered significant. Data analysis was performed with SPSS (version 17, SPSS Inc., Chicago, IL) and SAS v.9.2 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 1,811 patients were randomly assigned to treatment with Resolute Integrity ZES (906 patients) or Promus Element EES (905 patients). The main clinical, procedural, and angiographic characteristics of both study groups are summarized in Table 1. Two-year follow-up data was

obtained from all but one patient, who withdrew consent (Supplement I shows trial consort diagram).

Table 1. Characteristics of Patients, Target Lesions, and Interventional Procedures.

	Resolute Integrity ZES	Promus Element EES	p value
Patients data	**N=906 patients**	**N=905 patients**	
Age (years)	63.9 ± 10.6	63.9 ± 11.0	0.97
Men	665 (73.4)	675 (72.6)	0.70
Diabetes mellitus (any)	167 (18.4)	157 (17.3)	0.55
Arterial hypertension	500 (55.2)	484 (53.5)	0.47
Hypercholesterolemia	418 (46.1)	430 (47.5)	0.56
Current smoker*	213 (23.6)	231 (25.5)	0.32
Family history of CAD†	452 (50.1)	451 (49.9)	0.98
Previous myocardial infarction	207 (22.8)	190 (21.0)	0.34
Previous percutaneous coronary intervention	182 (20.1)	167 (18.5)	0.38
Previous coronary bypass surgery	84 (9.3)	89 (9.8)	0.68
Clinical syndrome at presentation:			0.07
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)	
At least one small-vessel (RVD <2.75mm)	551 (60.8)	517 (57.1)	0.11
At least one lesion length >27 mm	161 (17.8)	157 (17.3)	0.81
At least one chronic total occlusion	38 (4.2)	38 (4.2)	1.00
Glycoprotein IIb/IIIa antagonist	262 (28.9)	259 (28.6)	0.89
Number of lesions treated per patient:			0.32
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)	
Lesions and Interventional procedures data	**N=1205 lesions**	**N=1166 lesions**	
ACC/AHA lesion class B2/C	793 (65.8)	765 (65.6)	0.92
De novo lesion‡	1147 (95.2)	1103 (94.6)	0.51
Reference vessel diameter (mm)	2.68 ± 0.59	2.70 ± 0.59	0.32
Implantation of assigned stents only	1195 (99.2)	1161 (99.6)	0.22
Number of stents per lesion	1.35 ± 0.68	1.36 ± 0.70	0.70
Total stent length per lesion (mm)	28.60 ± 18.51	29.71 ± 19.11	0.15
Direct stenting	352 (29.2)	326 (28.0)	0.50
Stent postdilation	887 (73.6)	920 (78.9)	<0.01

Data are number (%) or mean ± SD. CAD = coronary artery disease. RVD = reference vessel diameter. ACC/AHA=American College of Cardiology/American Heart Association.
*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.
‡Including chronic total occlusion, but not grafts or in-stent restenosis.

Rates of adverse clinical events. At 2-year follow-up, the composite primary endpoint TVF occurred in 78 patients (8.6%) treated with Resolute Integrity ZES and in 71 patients (7.8%) treated with Promus Element EES (p=0.55) (Table 2 and Figure 1). The incidence of the individual components of TVF was similar for both stent arms: cardiac death (2.4% vs. 1.9%, p=0.42); target vessel-related MI (2.4% vs. 1.8%, p=0.33); clinically-indicated target vessel revascularization (4.6% vs. 4.9%, p=0.83).

An exploratory subgroup analysis revealed no significant between-stent difference in TVF at 2 years across various subgroups (Figure 2). In addition, there was also no significant difference in various event rates between 1 and 2-year follow-up (Table 3). None of the 9 patients who had developed longitudinal stent deformation in Promus Element EES during the index PCI procedure experienced an adverse clinical event during the second year of follow-up, although DAPT was discontinued after 12 months in all but one patient, who continued DAPT at physician discretion (Supplement II).

The incidence of definite-or-probable stent thrombosis was 1.1% for both DES at 2-year follow-up (Figure 3), and the rate of definite stent thrombosis was similar in patients treated with Resolute Integrity ZES and Promus Element EES (0.8% vs. 0.9%, p=0.80; Table 2). Very late definite stent thrombosis occurred in 4 (0.4%) vs. 2 (0.2%) patients, respectively. At 2-year follow-up, 8.9% (78/872) and 9.0% (79/881) of the (surviving) patients in both stent arms were still on DAPT (Supplement III).

Table 2. Two-Year Clinical Outcome in Treatment Arms.

	Total patients N=1810	Resolute Integrity ZES N=905 patients	Promus Element EES N=905 patients	Relative Risk (95% CI)	p value
Death					
Any cause	57 (3.1)	33 (3.6)	24 (2.7)	1.38 (0.82-2.31)	0.23
Cardiac cause	39 (2.2)	22 (2.4)	17 (1.9)	1.29 (0.69-2.42)	0.42
Target vessel-related myocardial infarction					
Any	38 (2.1)	22 (2.4)	16 (1.8)	1.38 (0.73-2.60)	0.33
Q-wave	10 (0.6)	5 (0.6)	5 (0.6)	1.00 (0.29-3.44)	1.00
Non-Q-wave	28 (1.5)	17 (1.9)	11 (1.2)	1.55 (0.73-3.28)	0.34
Periprocedural (<48h from index procedure)	30 (1.7)	19 (2.1)	11 (1.2)	1.74 (0.83-3.61)	0.14
Target vessel revascularization, any	88 (4.9)	43 (4.8)	45 (5.0)	0.96 (0.64-1.44)	0.83
Target vessel revascularization, clinically indicated	86 (4.8)	42 (4.6)	44 (4.9)	0.96 (0.63-1.44)	0.83
Target lesion revascularization, clinically indicated	66 (3.6)	34 (3.8)	32 (3.5)	1.06 (0.66-1.71)	0.80
Target vessel failure*	149 (8.2)	78 (8.6)	71 (7.8)	1.10 (0.81-1.50)	0.55
Target lesion failure†	131 (7.2)	71 (7.8)	60 (6.6)	1.18 (0.85-1.65)	0.32
Major adverse cardiac events‡	156 (8.6)	83 (9.2)	73 (8.1)	1.14 (0.84-1.54)	0.40
Patient-oriented composite endpoint§	228 (12.6)	114 (12.6)	114 (12.6)	1.00 (0.78-1.27)	0.99
Stent thrombosis (0-360 days)					
Definite, any (0-720 days)	15 (0.8)	7 (0.8)	8 (0.9)	0.88 (0.32-2.40)	0.80
Definite, very late (360-720 days)	6 (0.3)	4 (0.4)	2 (0.2)	2.00 (0.37-10.89)	0.69
Definite or probable, any (0-720 days)	20 (1.1)	10 (1.1)	10 (1.1)	1.00 (0.42-2.39)	1.00
Definite or probable, very late (360-720 days)	7 (0.4)	5 (0.6)	2 (0.2)	2.50 (0.49-12.85)	0.45
Definite, probable, or possible, any (0-720 days)	46 (2.5)	23 (2.5)	23 (2.5)	1.00 (0.57-1.77)	1.00

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 revascularization.
† Target lesion failure is a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target lesion revascularization.
‡ Major adverse cardiac events is a composite of all cause death, any myocardial infarction, emergent coronary-artery bypass surgery, or clinically indicated target lesion revascularization.
§ Patient-oriented composite end-point is a composite of all cause death, any myocardial infarction, or any revascularization.

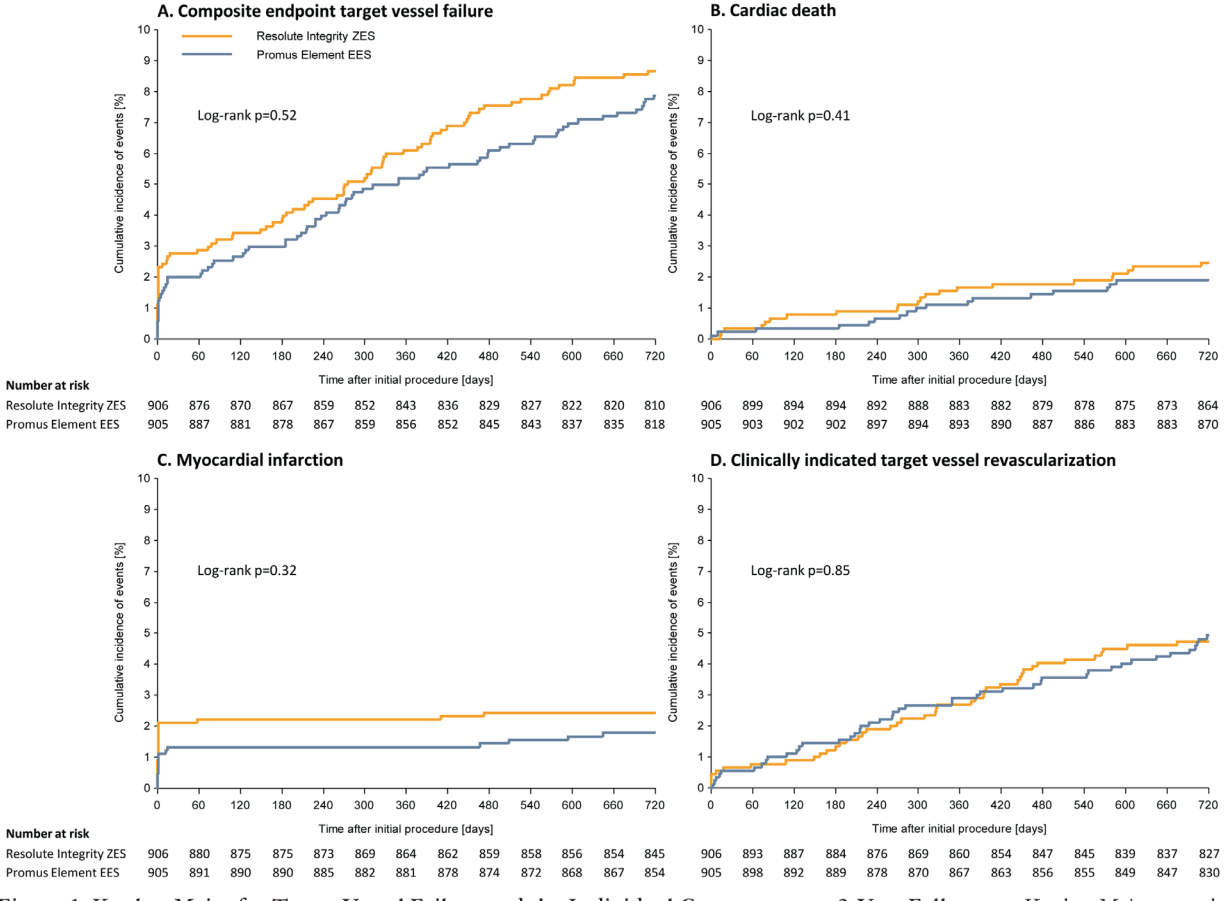


Figure 1. Kaplan-Meier for Target Vessel Failure and the Individual Components at 2-Year Follow-up. Kaplan-Meier cumulative incidence curves for: the primary endpoint target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization (A); cardiac death (B); target vessel -related myocardial infarction (C); target-vessel revascularization (D) for patients treated with Resolute Integrity ZES or Promus Element EES.

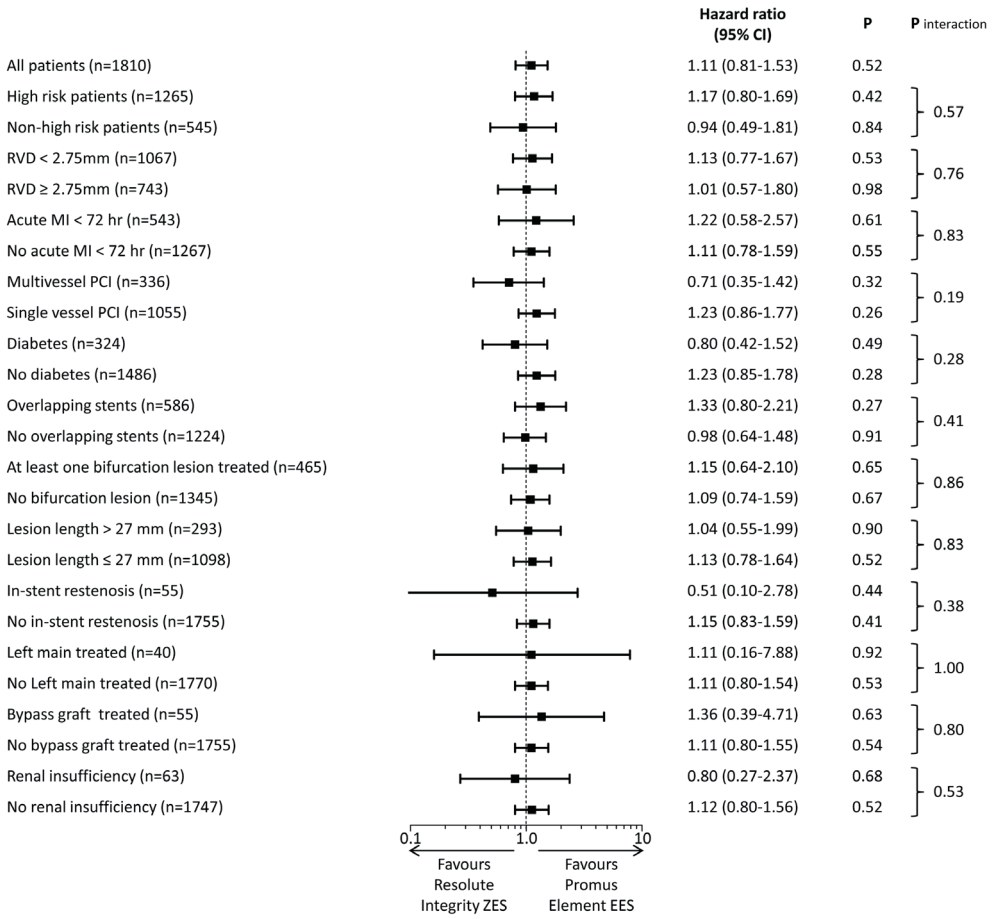


Figure 2. Subgroup Analysis: Target Vessel Failure at 2-Year Follow-up. Target vessel failure (TVF) is a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularization. CI=confidence interval; RVD=reference vessel diameter; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Table 3. Outcome Differences Between 1 and 2-Year Follow-up.

	Resolute Integrity ZES	Promus Element EES	Difference (95% CI)	p value
Death				
Any cause	1.2 (11/883)	1.3 (12/893)	-0.10 (-1.03—1.23)	0.86
Cardiac cause	0.8 (7/893)	0.8 (7/883)	-0.01 (-0.91—0.94)	0.98
Target vessel-related myocardial infarction	0.2 (2/864)	0.5 (4/881)	-0.22 (-0.45—0.95)	0.69
Target vessel revascularization, clinically indicated	2.1 (18/860)	2.1 (18/867)	0.02 (-1.43—1.39)	0.98
Target lesion revascularization, clinically indicated	1.6 (14/864)	1.4 (12/873)	0.25 (-1.48—0.96)	0.67
Target lesion failure*	2.4 (20/847)	2.2 (19/862)	0.16 (-1.64—1.31)	0.83
Target vessel failure†	2.7 (23/843)	2.8 (24/856)	-0.08 (-1.54—1.69)	0.93
Major adverse cardiac events‡	3.0 (25/847)	3.4 (29/861)	-0.42 (-1.29—2.13)	0.62
Patient-oriented composite endpoint§	3.7 (30/821)	5.0 (42/833)	-1.39(-0.60—3.41)	0.17
Stent thrombosis				
Definite	0.5 (4/880)	0.2 (2/887)	0.23 (-0.96—0.43)	0.41
Definite or probable	0.6 (5/879)	0.2 (2/886)	0.34 (-1.12—0.33)	0.29

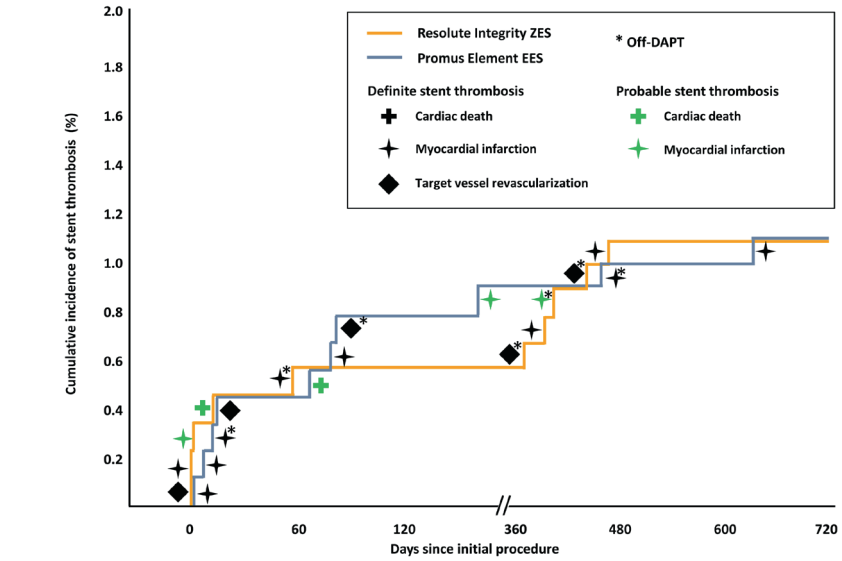
Values are % (n/N) or % difference (95%CI). Analyses were performed among survivors of the first year of follow-up who did not experience the respective adverse event during 1-year follow-up.

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

† Primary endpoint target vessel failure is a composite of cardiac death, target vessel-related Myocardial infarction, or clinically indicated target vessel revascularization.

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

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



Number at risk							
Resolute Integrity ZES	906	895	890	879	872	869	858
Promus Element EES	905	899	896	886	879	875	861

Figure 3. Cumulative Incidence of Definite or Probable Stent Thrombosis.
Symbols indicate the hierarchically highest adverse events, associated with stent thrombosis. Black symbols signify definite stent thrombosis. Green symbols signify probable stent thrombosis. *Off-DAPT indicates stent thrombosis in patients not 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).

Patient-reported chest pain. At 1-year follow-up, 1,647(92.7%) of all 1,776 surviving patients provided information about the presence or absence of chest pain (Figure 4, panel A). Most of these patients had no chest pain at all, and there was no difference between stent arms (81.6% vs. 81.0%, p=0.96). In addition, 88.2% and 87.4% of patients in both stent arms had either no chest pain at all or chest pain only during maximal exertion (p=0.96). Patients with a chest pain score of 2 or 3 at 1-year follow-up had an almost two-fold increase in risk of clinically-indicated TVR during the second year of follow-up (HR 1.89 (1.05-3.39), p=0.03) compared to those with a chest pain score of 0 or 1.

Chest pain data at 2-year follow-up was available from 1,606/1,753 (91.6%) of the surviving patients with pain scores that were similar to 1-year (Figure 4, panel B). At 2-year follow-up, new onset (as compared to 1-year) chest pain was reported by 8.8% of patients. Between 1 and 2-year follow-up, 77.9% (of the 1572 patients who were alive at 2 years and answered the chest pain questionnaire at both 1 and 2 years) in both stent arms showed no change in chest pain score (Figure 4, panel C), while only 10.6% and 12.2% of patients in the respective stent arms reported an increase and 11.6% and 9.9% a decrease (p=0.30). Restricting the analysis of chest pain score at 1 and 2-year to patients who provided *chest pain information at both times* (Supplement IV) lead to results which were similar to findings in all responding patients at the individual times of follow-up (Figure 4, panels A and B).

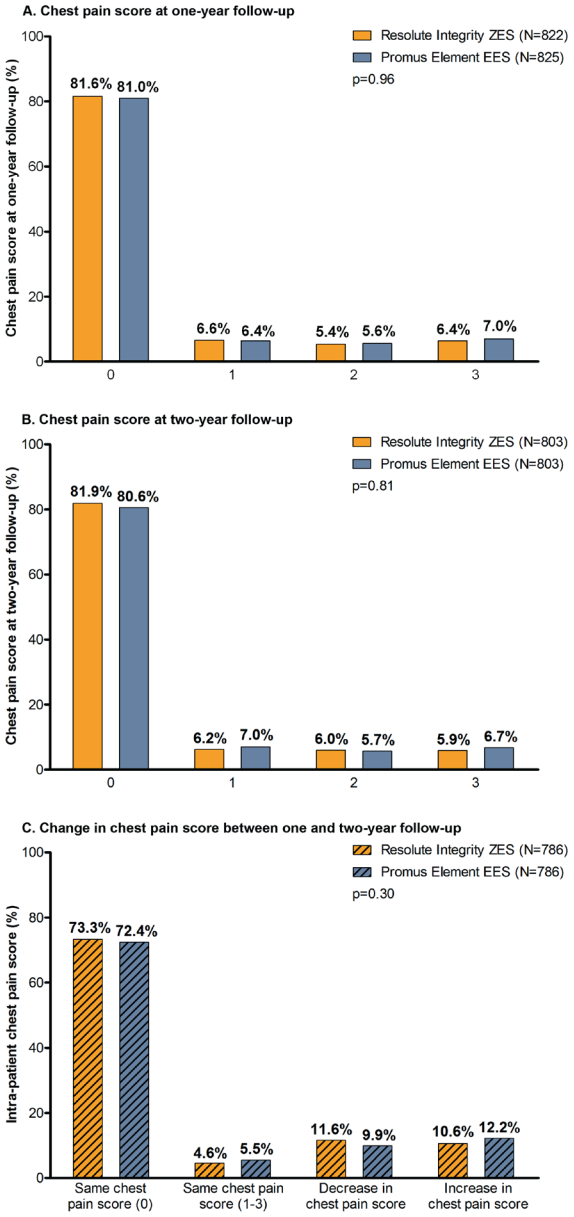


Figure 4. Patient-Reported Chest Pain at 1 and 2-Years.
Patient-reported chest pain classified into 4 scores: 0= no chest pain at all; 1= chest pain only during most severe physical exertion; 2= chest pain at moderate physical effort (during moderate/normal daily activities); 3= chest pain during mild physical exertion or at rest.
Panels A and B provide information about the presence and extent (i.e., pain score) of chest pain at 1 and 2-year follow-up in all (surviving) patients who provided chest pain information at the two individual time points (1,647 and 1,606 patients, respectively). Panel C shows the *change* in chest pain score between 1 and 2-year follow-up in 1,572 patients, who were alive at 2-year follow-up and answered the chest pain questionnaire both times.

DISCUSSION

At 2-year follow-up of the DUTCH PEERS trial, the incidence of the primary endpoint TVF was low and similar in both stent arms. The rates of cardiac death, target vessel-related MI, and clinically-indicated TVR (i.e., the individual components of TVF), were also low and similar. In addition, despite enrollment of an all-comers population that included many high-risk patients and complex lesions, the incidence of very late stent thrombosis was extremely low. None of the few patients who initially had developed longitudinal deformation in Promus Element stents experienced a very late clinical event after cessation of DAPT.

At 1 and 2-year follow-up, more than 80% of patients in both stent arms were free from chest pain. In addition, more than 87% were either symptom-free or experienced chest pain only at the very maximum level of physical exertion, in that the pain did not limit the daily activities of this large group of patients.

Previous DES trials with the examined stents. The present analysis from the DUTCH PEERS randomized trial is the first report of 2-year clinical outcome data in all-comers treated with the Resolute Integrity or Promus Element stents. The PLATINUM trial, which assessed patients with low-to-moderate cardiovascular event risk, has previously demonstrated non-inferiority of the Promus Element stent as compared to the second-generation Xience V/Promus stent (Abbott Vascular, Santa Clara, California / Boston Scientific) (13), showing a favorable rate of the primary endpoint TLF (5.9%) for Promus Element after 3 years (14). The HOST-ASSURE trial has compared Promus Element with the second-generation Resolute stent in South Korean patients in coronary vessels >2.5mm, showing a similar clinical performance of both stents at 1 year (5). So far, the SORT-OUT VI all-comers trial is the only other randomized study that has also examined the Resolute Integrity stent, showing at 1 year an incidence of the primary endpoint MACE that was similar to the comparator, the bioresorbable coating-based BioMatrix Flex stent (Biosensors, Singapore) (5.3% versus 5.1%) (6).

Chest pain following PCI. Chest pain, the principal symptom of angina pectoris, is the main trigger for patients to consult medical professionals following a successful PCI procedure, and it is frequently associated with further cardiac assessment and increased costs (8). The prevalence and recurrence of angina pectoris after coronary revascularization had previously been investigated in randomized studies that compared balloon angioplasty with coronary bypass surgery (22,23) or with PCI, using bare metal stents (24,25). However, randomized trials with DES were mostly focused on device-oriented endpoints (26). Nowadays, there is a growing interest in the assessment of angina pectoris following the implantation of novel DES and bioresorbable scaffolds (7). But so far, there is a lack of published data about this matter regarding treatment with newer generation DES.

In the DUTCH PEERS trial, there was no difference in chest pain between the two stent arms, at both 1 and 2-year follow-up. More than 80% of our patients were entirely free from chest

pain. This rate is similar to or higher than the prevalence of angina in several studies with bare metal stents or DES, reporting 66% to 79% of the patients to be angina-free at 1 year (7,27-30). However, none of these studies applied the highly deliverable DES that were used in DUTCH PEERS. A substudy of the FREEDOM trial, which assessed diabetic patients with multi-vessel disease being treated with PCI or CABG, found 79.5% and 81.0% of patients to be free from angina at 1 and 2-year follow-up after PCI with first-generation sirolimus-eluting stents (27), but this excellent result may be partly attributed to the general lower incidence of angina in diabetic patients. In the SYNTAX trial, which assessed angina after PCI for the treatment of three-vessel or left-main coronary disease with first-generation paclitaxel-eluting stents, 71.6% of patients were free from angina at 1-year follow-up (28).

The two aforementioned studies used the Seattle Angina Questionnaire, which is a validated method to assess anginal stability and frequency, physical limitation, treatment satisfaction, and disease perception by use of a list of standardized questions (31). This approach requires patients to answer a considerable number of questions, which might sometimes have a negative effect on the overall response rate of a study (32).

In the present study, we did not assess angina but scored the patient-reported chest pain in relation to the individual range of physical activities of a patient. While this approach does not attempt to distinguish between angina and atypical chest pain, it tackles the key issue of "patient satisfaction", which is greatly independent of the classification of chest pain into angina or atypical chest pain (26). We assessed *whether an individual patient felt chest pain during (individually graded) levels of physical activity*, as this will generally determine whether a patient seeks further medical advice and/or repeat cardiac assessment. Notably, we found a significant relation between chest pain at 1-year follow-up and repeat clinically-indicated TVR during the second year of follow-up.

Limitations. We did not pre-specify the analysis of the primary endpoint TVF across the various subgroups; to avoid subjectivity, we applied subgroup definitions of previous DES trials (2,3). Rigorous embracing of the principle of ischemia-driven PCI may have contributed to the relatively low rate of residual chest pain following PCI with novel generation DES in DUTCH PEERS. Knowledge on the completeness of coronary revascularization would have facilitated the interpretation of the chest pain data, but as most other all-comer DES trials, DUTCH PEERS did not assess this matter. It is desirable that future randomized clinical trials prospectively address this issue.

Conclusions. During the second year of follow-up, the incidence of adverse clinical endpoints remained similar and low for both DES. The vast majority of patients were free from chest pain after 1 and 2 years.

ACKNOWLEDGMENTS

We thank Mrs. Ilona Valkenburg for performing QCA measurements and also for her great commitment during the collection of follow-up data; Mrs. Jacqueline C. Jonge Poerink for performing QCA measurements and Mrs. Renate E. van der Leest for her great commitment during the collection of follow-up data (all from Thoraxcentrum Twente, MST, Enschede, the Netherlands).

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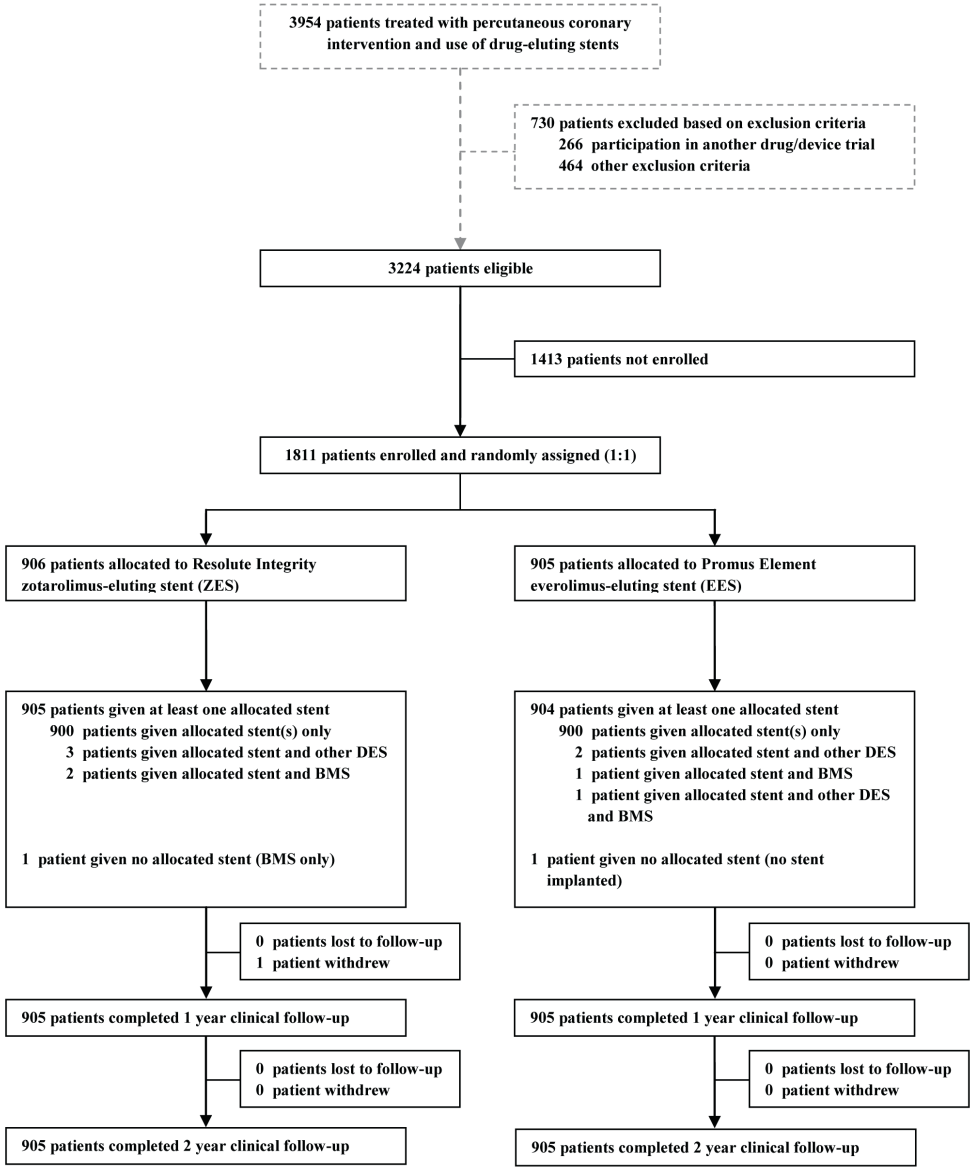


Supplement I. Trial Profile.
Of all patients who underwent percutaneous coronary intervention with DES during the study period, 3,224 patients were eligible. A total of 1,811 patients (56%) were enrolled and randomly assigned to the stent types. Two-year follow-up data was obtained from 1,810 patients (one patient withdrew consent). BMS=bare metal stent. DES=drug-eluting stent.

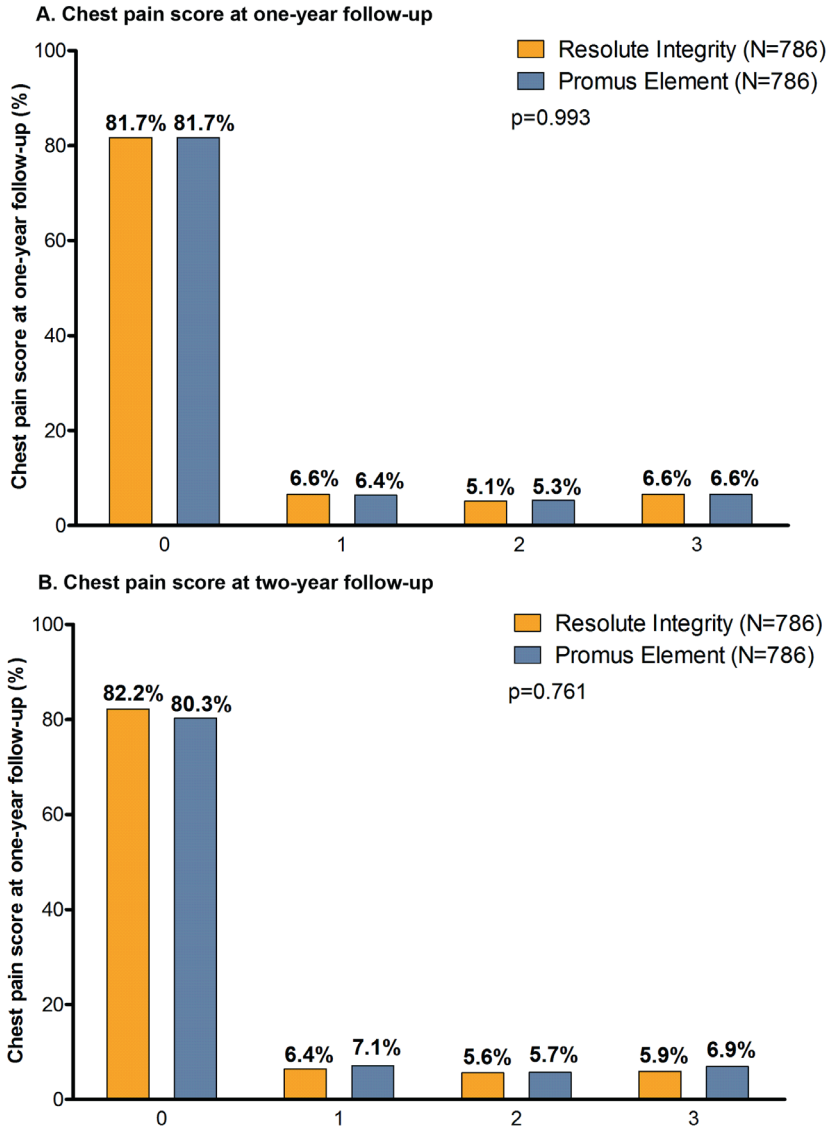
Case	Vessel and segment	Lesion characteristics	ACC/AHA lesion class	Stent size (mm)	Proximal/ distal location in stent	Post-dilation of stent performed	Procedural consequences	DAPT use at 2-year follow-up	Consecutive adverse clinical events until 2-year follow-up
1	LAD, mid	bifurcation lesion	C	3.0 x 38	proximal	+	additional proximal stent	–	–
2	RCA, mid	severe calcification	C	2.5 x 32	proximal	+	additional proximal stent	–	–
3	LAD, prox.	bifurcation lesion	C	3.5 x 24	proximal	+	additional proximal stent	–	–
4	LAD, prox.	bifurcation lesion	C	2.25 x 16	proximal	–	additional proximal stent	–	–
5	LAD, prox.	severe calcification	C	2.25 x 22	proximal	+	additional proximal stent	–	–
6	Left main	bifurcation lesion	B2	3.5 x 16	proximal	+	postdilation of stent	–	–
7	RCA, distal	bifurcation lesion	C	2.5 x 32	proximal	+	additional proximal stent	+	–
8	LAD, prox.	moderate calcification	C	3.0 x 12	proximal	+	additional proximal stent	–	–
9	RCA, mid	severe calcification	C	3.0 x 24	proximal	+	postdilation of stent	–	–

Supplement II. Outcome of patients in whom longitudinal stent deformation had been observed (all Promus Element stent group).
ACC/AHA=American College of Cardiology/American Heart Association; LAD=left anterior descending artery; Prox.=proximal; RCA=right coronary artery; DAPT=dual antiplatelet therapy. +=yes; –=no.

Data except results of 2-year follow-up have previously been reported in: von Birgelen C, Sen H, Lam MK, 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;383:413-23.

	Total	Resolute Integrity ZES	Promus Element EES	p value
At 1 year	**N=1776**	**N=883**	**N=883**	
Ascal	1575 (88.7)	786 (89.0)	789 (88.4)	0.66
P2Y12 inhibitor	437 (24.2)	227 (25.7)	210 (23.5)	0.28
DAPT	1534 (86.4)	765 (86.6)	769 (86.1)	0.75
Vitamin K antagonist	195 (11.0)	90 (10.2)	105 (11.8)	0.29
At 2 years	**N=1753**	**N=872**	**N=881**	
Ascal	1523 (86.9)	760 (87.2)	763 (86.6)	0.73
P2Y12 inhibitor	205 (11.7)	102 (11.7)	103 (11.7)	1.00
DAPT	157 (9.0)	78 (8.9)	79 (9.0)	0.99
Vitamin K antagonist	214 (12.2)	98 (11.2)	116 (13.2)	0.22

Supplement III. Anticoagulant Use at 1 and 2-Year Follow-up.
Values are % (n/N). DAPT= dual-antiplatelet therapy. Analysis based on survivors at 1 and 2-years, respectively.



Supplement IV. Patient-Reported Chest Pain at 1 and 2-Years (in Patients who Provided Chest Pain Information at Both Times).

Patient-reported chest pain classified into 4 scores: 0= no chest pain at all; 1= chest pain only during most severe physical exertion; 2= chest pain at moderate physical effort (during moderate/normal daily activities); 3= chest pain during mild physical exertion or at rest.

Panels A and B provide information about the presence and extent (i.e., pain score) of chest pain at 1 and 2-year follow-up in 1,572 patients, who were alive at 2-year follow-up and answered the chest pain questionnaire both times.

Chapter 12

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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Am Heart J. 2014 Apr;167(4):445-51.

ABSTRACT

Aim To evaluate the safety and efficacy of 2 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 3540 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 at 1 year, consisting of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization. Power calculation assumes a target vessel failure rate of 8.5% with a 3.5% non-inferiority margin, giving the study a power of 85% (α level .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 3540 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) 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) 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 (7.4 vs. 3.5 μm, 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 60 μm in stents with a nominal diameter ≤ 3.0 mm and 80 μm in stents with a nominal diameter >3.0 mm. 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, CA).[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 74 μm 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 -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 91 μm 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).

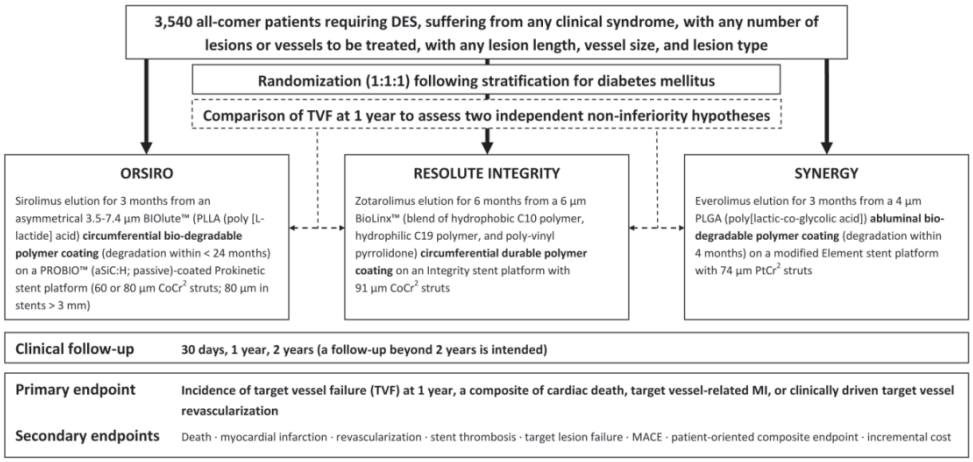

Figure 1. Study Design

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 3540 all-comer patients (age ≥18 years) 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 consent. 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 in spring 2015.

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

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 for the assessment of angiographically intermediate stenoses is recommended. If clinically indicated, intravascular ultrasound or optical coherence tomography 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 optical coherence tomography or intravascular ultrasound 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 Fractional Flow Reserve 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 is recommended for 6 to 12 months according to current medical guidelines. In patients on oral anticoagulation (eg, for atrial fibrillation), triple therapy is recommended for at least 1 to 3 month(s), after which oral anticoagulation in combination with clopidogrel, ticagrelor, or prasugrel is prescribed for 6 to 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 myocardial infarctions 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 (eg, 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, major adverse cardiac events, patient-oriented composite endpoint as previously described,[8] and stent thrombosis according to the Academic Research Consortium 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 BIO-RESORT 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 $\chi 2$ test. A total of 3540 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 α level of .025 (from .05 adjusted for multiple testing to .025) and allowing for up to 3% loss to follow-up. The sample size calculation was performed with PASS software (NCSS, Kaysville, UT).

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 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 1-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 2-sided 95% CIs. 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, NJ) 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.[5,38] 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.[2,6,13,17,30,31] A recent analysis of data of the TWENTE trial demonstrated an increased incidence of peri-procedural MI in patients with previously undetected diabetes.[39] 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, multicenter trial with three arms, comparing in 3540 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.

Disclosures

Conflict of Interest: Clemens von Birgelen is consultant to and has received lecture fees or travel expenses from Abbott Vascular, Boston Scientific, and Medtronic; he received travel expenses from Biotronik and lecture fees from MSD. The institution has received research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. The BIO-RESORT trial is equally funded by Medtronic, Biotronik, and Boston Scientific.

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Chapter 13

GENERAL DISCUSSION and FUTURE PERSPECTIVES

Percutaneous coronary intervention (PCI) with balloon angioplasty and with implantation of bare metal stents (BMS) or early drug-eluting stents (DES) showed worse clinical outcomes in patients with complex coronary lesion morphologies and certain conditions or co-morbidities that increased the risk of PCI.[1, 2] After treatment with first-generation DES, patients with such features that are called "off-label" criteria, had a higher risk of death, myocardial infarction (MI), and stent thrombosis than patients with on-label DES use.[3-5] Randomized studies in broad and so-called all-comer populations provide interesting insights into the clinical outcome of "real-world" patient populations. Many all-comer patients have one or more "off-label" criteria. An example of such a study with a vast majority of complex patients is the TWENTE trial.[6] This randomized comparative DES study showed similar safety and efficacy for the second-generation Resolute and Xience V DES. The favorable outcome was sustained until the two-year follow-up, which is reported in chapter 4 of this thesis. Although most comparative DES studies in broad patient populations applied only few exclusion criteria, merely a part of the eligible patients was finally enrolled and randomized. But what do we know about potential dissimilarities between the randomized trial participants and the eligible, non-enrolled patients? In fact, such interesting information is sparse and only available from a few studies.[7, 8] Therefore, we collected data of the eligible, non-enrolled patients and compared it with corresponding data of the participants of the TWENTE trial. As shown in chapter 2, patients enrolled in the TWENTE trial largely reflected daily clinical practice, as their clinical outcome was similar to the outcome of the non-enrolled, eligible patients who were treated with the same DES. These findings underline that studies in broad patient populations and, in particular, the TWENTE trial, may provide insights with a high clinical relevance.

In chapter 5, we reported that complex TWENTE trial patients with off-label DES use, who had a higher risk profile than TWENTE trial patients with on-label DES use, showed no significant difference in clinical outcome versus less complex patients, with the only exception being a higher periprocedural MI risk. In addition, in complex patients in the TWENTE trial there was no difference in outcome between the two second-generation DES (chapter 6). The favorable outcome of complex patients treated with second-generation DES is furthermore supported by the results of thorough analyses of subgroups of patients who were treated for chronic total occlusion (CTO) lesions and bifurcation lesions (chapters 8 and 9 of this thesis). Until three-year follow-up, treatment of CTO lesions was not associated with an inferior outcome (chapter 8) and treatment of bifurcation lesions was only associated with a higher risk of periprocedural MI.

In the era of BMS and first-generation DES, patients with previous coronary artery bypass grafting (CABG) had a higher incidence of target vessel revascularization than patients without previous CABG. Although the TWENTE trial studied second-generation DES that generally are more effective in preventing restenosis, patients with previous CABG had a four-fold higher repeat revascularization rate following PCI, which was mainly driven by more repeat revascularizations in degenerated vein grafts, as reported in chapter 3. Thus, PCI of a graft vessel, one of the off-label

criteria, was still associated with a higher risk of repeat revascularization. In addition, as shown in chapter 7, patients undergoing treatment of an aorta-ostial lesion also had a higher risk of a repeat target vessel revascularization.

All PCI in CTO lesions are by definition "off-label" procedures. However, as shown in chapter 8, the clinical event risk of PCI with second-generation DES was not significantly increased after the treatment of CTO lesions that had been successfully recanalized with relatively atraumatic, antegrade approaches. On the other hand, based on the higher rate of repeat revascularization (chapter 3), PCI in graft lesions are rightfully considered to be "off-label". As a consequence, the question arises whether the definition of off-label DES use, which combines several lesion and patient characteristics of which only some are relevant for PCI with second-generation DES, is still appropriate to classify patients with an increased event risk. Based on the findings of the present thesis, one may answer *no* to this question. Our findings suggest that with the use of second-generation DES the definition of "off-label" DES use is actually outdated and only of historical interest. Therefore, in current clinical practice and in future clinical trials, it is unnecessary to make a distinction between patients with off-label and on-label indications for DES use. Instead, it makes sense to concentrate on specific subgroups of patients which have been shown to be still associated with an increased risk of cardiovascular events. Examples of such patient subgroups have been studied in chapters 3 and 7 of this thesis. In addition, for the interpretation of clinical trials and the comparison of the results with other studies, more attention should be paid to the proportion of patients with lesion characteristics or co-morbidities that have an increased event rate, even with the use of contemporary DES.

But what can we say about the most recently developed, flexible, highly deliverable durable polymer-based metallic DES? The increased flexibility of these devices allows operators to treat obstructed coronary arteries with very high lesion complexity and vessel tortuosity, but it is also known to reduce the longitudinal stability of some devices.[9] Highly flexible DES, such as Resolute Integrity and Promus Element stents, had similar efficacy and safety at one and two-year follow-up (chapters 10 and 11), but their increased device flexibility was not associated with adverse clinical events.[10, 11] This is an unambiguous safety signal for the use of these DES in complex lesion anatomies. Moreover, there was no significant between-group difference in the composite primary endpoint between patients with high versus low risk profiles and across various subgroups of patients that were defined by several individual off-label criteria. The largely favorable results with modern, highly flexible and deliverable DES underline that newer generation DES are safe, even in patients and lesions that are traditionally considered as high-risk.

Metallic DES with biodegradable polymer coatings were developed because of concerns about the long-term safety of durable polymers, which may trigger vessel wall inflammations that promote late and very late stent thrombosis.[12-14] The favorable results of early-generation biodegradable coating DES, which after resorption of the coating leave only a bare metal stent behind,[14] might be further improved by novel devices that have thinner struts,[15, 16] higher flexibility, and novel

coatings. Future studies and ongoing clinical trials, such as the BIO-RESORT trial (chapter 12) will examine whether the outcome of PCI can be further improved by the use of such modern biodegradable coating DES. The clinical outcome of various subgroups of complex patients treated with these devices will be of interest. Moreover, results of studies with early-generation biodegradable coating DES suggest that assessment of long-term clinical outcome will be required.

A polymer-based fully bioresorbable scaffold (BRS) has recently been introduced into the clinical arena, and it may be expected that its use will further increase in the near future. The device undergoes a process of polymer degradation before it is fully resorbed from the treatment site.[17] As the first-generation commercially available BRS has relatively thick struts that may partly obstruct the ostium of side branches and is susceptible to oversized postdilatation, identification and careful assessment of patient and lesion subgroups with an increased risk of clinical events following BRS implantation will be very important to better define indications for BRS use in routine clinical practice and to guide the indispensable process of device refinement.

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Chapter 14

Summary and conclusion

SUMMARY

DES are constantly being refined to improve safety (as compared to first-generation DES) while maintaining high efficacy in preventing the occurrence of in-stent restenosis and reducing the need for repeat revascularization. After the approval of the first DES for clinical use, these devices were initially implanted in low-risk patients who did not reflect routine clinical practice, in which the majority of patients were complex and underwent PCI for at least one off-label indication. Complex patients were characterized by a higher clinical event risk and more challenging lesion anatomies. Only limited data were available on the clinical outcome of complex patients who were treated with new devices. This thesis provides insight into the performance of several types of DES in complex patients undergoing PCI.

Chapter 1 serves as an introduction to this thesis and provides background information on DES and their use in complex patients.

In **Chapter 2,** we evaluate whether eligible, non-enrolled patients (Non-Enrolled TWENTE study) differed from the randomized TWENTE trial population, who were treated with the same DES (Endeavor Resolute and Xience V) in baseline characteristics and clinical outcome. The non-enrolled patients (n=318) and patients from the randomized TWENTE trial (n=1391) differed only in age and cardiovascular history. At one-year, non-enrolled and randomized patients did not differ in clinical outcome; the primary composite endpoint target vessel failure (TVF) occurred in 9.8% of the non-enrolled patients and 8.1% of the randomized TWENTE trial patients (p=0.34). The findings of this chapter show that *despite some differences in baseline characteristics, non-enrolled and randomized patients did not differ in one-year clinical outcome, which was favorable for both populations and may be related to the DES used.*

Chapter 3 demonstrates the impact of previous coronary artery bypass surgery (CABG) on clinical outcome after PCI with second-generation DES in a pooled population of 1709 patients from the TWENTE trial and the Non-Enrolled TWENTE study. Of all the patients, 202 (11.8%) had a history of previous CABG. Patients with previous CABG were significantly older, had a higher prevalence of diabetes mellitus, and had more often undergone previous PCI (vs. patients without previous CABG). Despite the extended risk profile at baseline, patients with previous CABG had only a significantly higher rate of target vessel revascularization (TVR) (9.4% vs. 2.3%, p<0.001) at one year. Among the 1638 patients who were treated for target lesions located in native coronary vessels, patients with versus without previous CABG did not differ significantly in TVR rate. However, among all 202 patients with previous CABG, the TVR rate was significantly higher in patients treated for vein graft lesions than in patients treated for native coronary lesions only (18.5% vs. 5.1%, P = 0.002). The results of this chapter *demonstrate that patients with previous*

CABG have a favorable safety profile after PCI with second-generation DES. Nevertheless, their TVR rate was still much higher, mainly driven by more repeat revascularizations following PCI for lesions in degenerated vein grafts.

Chapter 4 presents the two-year outcome data of 1391 patients from the TWENTE trial, who were treated with the second-generation Resolute or Xience V stent and followed a stringent discontinuation of dual anti-platelet therapy (DAPT) after 12 months from stenting. Two-year follow-up was obtained from all but four patients, who withdrew consent. After two years, the rate of target lesion revascularization differed significantly (4.9% vs. 2.6%, p=0.03), but this did not translate into a significant between-DES difference in TVF (10.8% vs. 11.6%, p=0.65). The rate of definite or probable stent thrombosis was low (1.2% vs. 1.4%, p=0.63) and very late definite-or-probable stent thrombosis occurred only in two patients per stent group (0.3% vs. 0.3%, p=1.0), despite the low rate of continuation of DAPT after 12 months (5.4%). This chapter demonstrates that *after two years of follow-up and stringent discontinuation of DAPT beyond 12 months, Resolute and Xience V showed 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 5 compares the two-year clinical outcome of TWENTE trial patients who underwent PCI with second-generation DES implantation for off-label indications versus on-label indications.
Off-label indications included: renal insufficiency (creatine ≥140 µmol/l); ejection fraction <30%; acute myocardial infarction within previous 72 hours; >1 lesion/vessels; >2 vessels treated; lesion length >27 mm; bifurcation; saphenous vein graft lesion; arterial bypass graft lesion; in-stent restenosis; unprotected left main lesion; lesion with thrombus; or lesion with total occlusion.
Of all the TWENTE trial patients, 1033 were treated for off-label indications and more often had diabetes, previous myocardial infarctions, type B2/C lesions, and acute coronary syndromes at presentation. At two-year follow-up, patients with off-label DES use had, despite their higher risk profile, rates of cardiac death, TVR, and stent thrombosis that were low and similar to patients with on-label DES use only. Compared to patients with on-label DES use, the off-label patients had a significantly higher rate of periprocedural MI (5.0% vs.1.4%, p=0.003), but only 1.1% had creatine kinase levels of more than five times the upper limit of normal. This chapter shows that, *despite significant differences in risk profile, patients with off-label DES use did not differ in clinical endpoints from patients with on-label DES use, with the only exception being periprocedural MI. These largely positive findings underline the favorable safety profile of second-generation DES.*

Chapter 6 describes in depth the clinical outcome of complex patients with off-label indications for DES use. Among the complex patients, 529 (51%) patients were treated with Resolute and 504 (49%) patients with Xience V stents. Baseline clinical characteristics were similar between the two DES groups. At two-year, the rates of the clinical endpoints were similar; in particular,

the rate of TVF was 12.1% in the Resolute and 12.3% in the Xience V group (p=0.92). The incidence of definite-or-probable stent thrombosis was low and also did not differ between the two DES groups (p=0.53). This chapter shows that *complex patients treated with Resolute and Xience V stents have similar safety and efficacy endpoints during the second year of follow-up.*

Chapter 7 shows the impact on clinical outcome of right coronary artery (RCA) ostial coverage with second-generation DES at two-year. Among all 1391 patients from the TWENTE trial, 321 patients with single-vessel RCA treatment were divided into patients with versus without aorta-ostial stent covarage (aorta-ostial region comprises proximal 3 mm from aortic orifice). Patients with aorta-ostial coverage had significantly more calcified lesions than patients without aorta-ostial coverage (31.3% vs. 12.6%, p<0.01). At two-year follow-up, patients with aorta-ostial lesion coverage showed a four-fold increase in risk of target lesion revascularization (HR: 4.1, 95%CI: 1.17-14.39,p=0.03) compared to patients without aorta-ostial coverage. This chapter demonstrates that *aorta-ostial treatment with second-generation DES is feasible, but it is a predictor for target lesion revascularization.*

Chapter 8 presents the three-year clinical outcome of the TWENTE trial patients treated for chronic total occlusion lesions (CTO) versus patients who were treated for non-CTO lesions. Lesions were classified as CTO lesions in the presence of a total luminal obstruction with TIMI flow grade 0 within the occluded segment and duration of the occlusion of more than three months.
Patients treated for at least one CTO lesion (n=59) (of which the majority had J-CTO scores ≥2 (56%), reflecting the fact that most CTO lesions were classified as difficult to cross) were more often treated for lesions in small vessels, long lesions, and lesions in multiple vessels, and they were less often male than patients with non-CTO lesions (n=615). After three-year follow-up, the rate of the more lesion-oriented combined endpoint target lesion failure was similar for both groups (13.6% vs. 12.9%, p=0.89). The patient-oriented composite endpoint was also similar between the two DES groups (18.6% vs. 18.8%, p=0.97). This chapter demonstrated that *patients treated with second-generation DES for CTO lesions showed at three-year follow-up a low incidence of adverse clinical events, similar to patients with non-CTO lesions only.*

In Chapter 9, we investigate, in patients in the TWENTE, trial the long-term safety and efficacy of treating bifurcation lesions with second-generation DES. Within the population of the TWENTE trial, 362 patients were treated for bifurcation lesions. Despite the significantly higher rate of periprocedural MI in patients with treatment of bifurcation lesions (6.9% vs. 3.1%, p<0.01), the incidence of TVF did not differ at three-year follow-up (13.1% vs. 12.6%, p=0.84). Among the 362 patients with treatment of bifurcation lesion, there was no statistically significant difference in clinical endpoints between the two DES groups. This chapter demonstrates that

despite a difference in periprocedural MI, three-year clinical outcome after treatment of second-generation DES was favorable and similar for patients with and without bifurcation lesions.

Chapter 10 presents the main one-year clinical outcome of the randomized DUTCH PEERS trial, an investigator-initiated, randomized, multicenter non-inferiority trial that compares the safety and efficacy of the Resolute Integrity and Promus Element stents. A total of 1811 patients were randomly assigned (1:1) to treatment with Resolute Integrity (n=906) and Promus Element stents (n=905). The study population comprised 59% patients with ACS (20% of all patients presented with an acute ST-elevation MI) and 18% had diabetes. The primary endpoint, TVF at one-year, was met by 6.1% of patients in the Resolute Integrity group and 5.2% of the patients in the Promus Element group (P non-inferiority=0.006). Follow-up was obtained from all but one patient, who withdrew consent after one day. The incidence of the individual components of TVF (cardiac death; target vesssel-related MI; and clinically-indicated TVR) was also similar between the two DES. Definite-or-probable stent thrombosis occurred in 0.6% of the patients treated with Resolute Integrity versus 0.9% patients of the Promus Element group (p=0.40). Longitudinal stent deformation was only observed in the Promus Element group (1.0%), but did not lead to an adverse clinical event. The findings of this randomized multicenter trial demonstrate that *Resolute Integrity and Promus Element were similarly efficacious and safe in the treatment of all-comers with an excellent clinical outcome in a high number of patients presenting with ACS.*

In Chapter 11, we assess two-year adverse clinical events and patient-reported chest pain in 1811 patients, who were treated with Resolute Integrity and Promus Element in the DUTCH PEERS trial. At two-year, the primary endpoint TVF (8.6% vs. 7.8%, p=0.55) did not differ between patients treated with Resolute Integrity and Promus Element, respectively. The rate of very late definite-or-probable stent thrombosis was low and similar for the two DES (0.6% vs. 0.2%, p=0.45), while at two-year 9% of the patients were still on DAPT. At one and two-year follow-up more than 80% of the patients were free from chest pain. In addition, more than 87% of all patients were either free from chest pain or experienced chest pain only during maximal exertion, without any difference between the two device groups. Patients who reported chest pain during moderate/mild physical effort or at rest at one-year, had an almost two-fold risk of clinically-indicated TVR during the second year (HR: 1.89, 95%CI: 1.05-3.39, p=0.03) compared with patients who were free from chest pain or experienced chest pain only during maximal exertion. This chapter demonstrates that *at two-year follow-up the incidence of adverse clinical events remains low and similar for both DES of the DUTCH PEERS trial. The vast majority of patients were free from chest pain after one and two years and were therefore not limited by pain in their daily activities.*

Chapter 12 describes the rationale and design of the BIO-RESORT trial. The BIO-RESORT trial is an investigator-initiated, patient-blinded, randomized multicenter trial to compare the safety

and efficacy of two novel DES with biodegradable polymer coatings, ORSIRO and SYNERGY, with that of the durable coating-based Resolute Integrity DES. 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. Randomization is being performed in a 1:1:1 fashion in a population of at least 3540 patients between the ORSIRO stent with circumferential biodegradable coating, the SYNERGY stent with abluminal biodegradable coating, and the Resolute Integrity stent with durable coating. The primary endpoint is TVF at one-year. The trial evaluates two hypotheses: the safety and efficacy of ORSIRO is non-inferior to that of Resolute Integrity, and the safety and efficacy of SYNERGY is non-inferior to that of Resolute Integrity. This chapter *provides information on rationale and design of the BIO-RESORT trial, a study that will provide novel insights in the clinical outcome with modern DES.*

In Chapter 13, we conduct a general discussion of the findings of this thesis. In addition, future perspectives are outlined.

CONCLUSIONS

Drug-eluting stents have revolutionized the treatment of obstructive coronary disease and are widely used in daily clinical practice. The majority of patients treated by PCI in daily clinical practice are complex with at least one off-label indication for DES use. Complex patients are characterized by a higher clinical event risk and more challenging lesion anatomies. This thesis provides insight into the performance of several novel types of DES in complex patients treated by PCI in two randomized trials. In both TWENTE and DUTCH PEERS, the vast majority of patients were complex. The TWENTE trial reflects a "real-world" situation, as non-enrolled patients and patients of the randomized trial did not differ in several clinical endpoints. The complex patients with off-label indications for DES use, enrolled in the TWENTE trial, did not differ significantly in clinical event rates from patients with on-label DES use, with the only exception being a higher incidence of periprocedural MI. Treatment of a graft vessel, one of the off-label criteria for DES use, is associated with a higher revascularization rate, mainly driven by more repeat revascularizations in degenerated vein grafts. Treatment of CTO lesions, which is also one of the off-label criteria for DES use, is no longer associated with inferior clinical outcome, even three years after PCI with second-generation DES. Treatment of an aorta-ostial lesion, however, which is not a "classical" off-label criterion, generally indicates the presence of extensive coronary disease and is a predictor for target lesion revascularization. The novel, highly flexible, durable polymer coating Resolute Integrity and Promus Element stents showed an excellent deliverability in the DUTCH PEERS trial, even in complex anatomies, and similar and excellent clinical outcomes at one and two- year follow-up. The vast majority of patients

who were treated with these novel DES were not limited by pain in their daily activities after one and two years. DES with a biodegradable polymer coating have been developed because of concerns about durable polymers as potential trigger of vessel wall inflammation and very late stent thrombosis. The ongoing BIO-RESORT randomized trial assesses the non-inferiority of the Synergy and Orsiro stents, two novel, highly flexible, biodegradable polymer coating DES, as compared to the durable polymer-based Resolute Integrity DES, which serves as reference.

Chapter 15

Nederlandse samenvatting en Conclusie

Dankwoord

Curriculum Vitae

Publicaties

NEDERLANDSE SAMENVATTING EN CONCLUSIE

Samenvatting

DES (drug-eluting stents; medicijn-afgevende stents) zijn ontwikkeld om de effectiviteit van een percutane coronaire interventie (PCI, in de volksmond ook wel dotterprocedure) te vergroten. De voorheen gebruikte metalen stents zonder medicijnafgifte hadden namelijk als belangrijke complicatie het opnieuw dichtgroeien van het vat, waardoor herhaalde revascularisaties noodzakelijk waren. Hoewel deze zogenaamde in-stent restenoses door de komst van eerste generatie DES aanzienlijk afnamen, bleken zij ook ongewenste neveneffecten te hebben zoals een vergrootte kans op stenttrombose. Sinds de ontwikkeling van de eerste generatie zijn DES voortdurend onderhevig aan verfijning om ook de veiligheid ervan te verbeteren.
Na de goedkeuring voor klinisch gebruik van de eerste DES, werden deze stents in eerste instantie alleen in laag-risico patiënten (on-label) geïmplanteerd. Echter, in de dagelijkse klinische praktijk hebben de meeste patiënten die een PCI ondergaan tenminste één off-label criterium (een andere indicatie dan geregistreerd) en na de eerste positieve onderzoeken werd het gebruik van DES ook bij deze complexe patiënten geïntroduceerd. Complexe patiënten hebben een verhoogd klinisch risico en meer complexe laesies met een uitdagende coronaire anatomie. Dit proefschrift geeft inzicht in de prestaties van verschillende soorten DES in complexe patiënten die een PCI hebben ondergaan.

Hoofdstuk 1 dient als een inleiding op dit proefschrift en geeft achtergrondinformatie over het gebruik van DES in complexe patiënten.

In **hoofdstuk 2** evalueren we of de geschikte, maar niet-geïncludeerde patiënten behandeld met dezelfde DES (Endeavor Resolute en Xience V) (Non-Enrolled TWENTE studie) verschilden van de gerandomiseerde TWENTE studiepopulatie in baseline karakteristieken en klinische uitkomsten.
De non-enrollers (n = 318) en de patiënten van de gerandomiseerde TWENTE studiepopulatie (n = 1391) verschilden alleen in leeftijd en cardiovasculaire voorgeschiedenis. Na een jaar verschilden de non-enrollers niet van de patiënten geïncludeerd in de TWENTE studie voor wat betreft de klinische uitkomsten; het gecombineerde primaire eindpunt target vessel failure (TVF) trad op bij 9.8% van de non-enrollers en bij 8.1% van de patiënten van de gerandomiseerde TWENTE studiepopulatie (p = 0.34). De bevindingen van dit hoofdstuk laten zien dat, ondanks enkele verschillen in de baseline karakteristieken, de non-enrollers en de gerandomiseerde patiënten niet verschilden in klinische uitkomsten na één jaar, wat gunstig was voor beide populaties en gerelateerd kan worden aan de gebruikte DES.

Hoofdstuk 3 toont de impact van een eerdere coronaire bypassoperatie (CABG) op de klinische uitkomsten na een PCI met tweede generatie DES in een gepoolde populatie van 1709 patiënten van de TWENTE en de Non-Enrolled TWENTE studie.
Van alle patiënten, hadden 202 patiënten (11,8%) een voorgeschiedenis met eerdere CABG. Patiënten met eerdere CABG waren significant ouder, hadden een hogere prevalentie van diabetes mellitus, vaker PCI in de voorgeschiedenis (ten opzichte van patiënten die geen eerdere CABG gehad hebben). Ondanks deze hogere risicoprofiel bij baseline hadden patiënten met een CABG in de voorgeschiedenis na één jaar alleen een significant hogere incidentie van target vessel revascularisatie (TVR) (9.4% vs. 2.3%, p <0,001). Tevens was binnen de 202 patiënten met CABG in de voorgeschiedenis de TVR ratio significant hoger bij patiënten die behandeld waren voor veneuze bypass graft laesies vergeleken met patiënten die alleen behandeld waren voor laesies in de natieve coronairvaten (18.5% vs. 5.1%, p = 0.002). De resultaten van dit hoofdstuk tonen aan dat patiënten met een CABG in de voorgeschiedenis een gunstig veiligheidsprofiel hebben na een PCI met tweede generatie DES. Desondanks was de incidentie van TVR nog veel te hoog, met name te wijten aan de herhaalde revascularisaties aan de gedegeneerde vene grafts.

Hoofdstuk 4 presenteert de tweejaars klinische resultaten van 1391 patiënten van de TWENTE studie, die behandelt zijn met de tweede generatie Resolute of Xience V stents en een strikt stopzettingsbeleid opvolgden van de dubbele anti-trombocyten aggregatie remming (DAPT), 12 maanden na de PCI. De tweejaars follow-up gegevens werden van alle patiënten verzameld, behalve van vier patiënten die hun informed consent hadden ingetrokken. Na twee jaar verschilde de incidentie van target laesie revascularisatie significant (4.9% vs. 2.6%, p=0.03), maar dit vertaalde zich niet in een significant verschil in TVF tussen de twee stentgroepen (10.8% vs. 11.6%, p=0.65). Het percentage definitieve-of- waarschijnlijke stent trombose was laag (1.2% vs. 1.4%, p=0.63) en erg late definitieve-of- waarschijnlijke stent trombose trad alleen in twee patiënten per stentgroep op (0.3% vs. 0.3%, p=1.0), ondanks een lage percentage van DAPT gebruik na 12 maanden (5.4%). Dit hoofdstuk laat zien dat na twee jaar follow-up en een strikt stopzettingsbeleid van DAPT na 12 maanden, de Resolute en Xience V stents vergelijkbare resultaten laten zien voor wat betreft de veiligheid en effectiviteit in het behandelen van patiënten die grotendeels complexe laesies en off-label indicaties voor het gebruik van DES hadden.

Hoofdstuk 5 vergelijkt de tweejaars klinische uitkomsten van de TWENTE studie patiënten die een PCI ondergingen met een tweede generatie DES voor off-label en on-label indicaties.
Off-label indicaties waren: nierinsufficiëntie (creatine ≥140 umol/ l); ejectiefractie <30%; acuut myocardinfarct in de afgelopen 72 uur; >1 laesie/vat; >2 vaten behandeld; laesie lengte> 27 mm; bifurcaties; vene graft laesie; arteriële bypass graft laesie; in-stent restenose; onbeschermde hoofdstam laesie; laesie met trombus; of een laesie met een totale occlusie.

Van alle TWENTE studie patiënten werden 1033 behandeld voor off-label indicaties en zij hadden vaker diabetes, een eerder doorgemaakte hartinfarct, type B2/C laesies en acuut coronair syndromen bij presentatie. Na twee jaar follow-up, hadden patiënten met off-label gebruik van DES, ondanks hun verhoogd risicoprofiel, een vergelijkbare lagere incidentie van cardiale sterfte, TVR en stent trombose als patiënten met on-label gebruik van DES. Ten opzichte van patiënten met on-label gebruik van DES, hadden off-label patiënten een significant hogere percentage periprocedurele MI (5.0% vs.1.4%, p = 0.003), van wie slechts 1.1% een creatine kinase level van meer dan vijf keer de bovengrens van normaal had. Dit hoofdstuk laat zien dat ondanks de grote verschillen in het risicoprofiel, de patiënten met off-label gebruik van DES niet verschilden in klinische eindpunten ten opzichte van patiënten met on-label gebruik van DES, met als enige uitzondering de periprocedurele MI. Deze grotendeels positieve bevindingen benadrukken het gunstige veiligheidsprofiel van de tweede generatie DES.

Hoofdstuk 6 beschrijft in detail de klinische uitkomsten van complexe patiënten met off-label indicaties voor gebruik van DES. Van de complexe patiënten werden 529 (51%) patiënten behandeld met de Resolute en 504 (49%) patiënten met de Xience V stents. De baseline klinische karakteristieken waren vergelijkbaar tussen de twee groepen DES. Na twee jaar, waren de incidenties van de klinische eindpunten vergelijkbaar; in het bijzonder voor het percentage van TVF, dat 12.1% in de Resolute en 12.3% in de Xience V groep was (p = 0.92). De incidentie van definitieve-of- waarschijnlijke stent trombose was laag en ook niet verschillend tussen de twee DES groepen (p = 0.53). Dit hoofdstuk laat zien dat complexe patiënten die behandeld zijn met de Resolute en Xience V stents vergelijkbare veiligheid en effectiviteits eindpunten hebben gedurende het tweede jaar van follow-up.

Hoofdstuk 7 geeft de invloed weer van ostiale bedekking van de rechter kransslagader (RCA) met een tweede-generatie DES op de klinische uitkomst na twee jaar. Van alle 1391 patiënten van de TWENTE studie werden 321 patiënten die alleen in de RCA werden behandeld verdeeld in patiënten met en zonder aorta-ostiale stent bedekking (aorta-ostiale regio bestaat uit de 3 mm proximale gedeelde van de aorta opening). Patiënten met een aorta-ostiale bedekking hadden significant meer verkalkte laesies dan patiënten zonder aorta-ostiale bedekking (31.3% vs. 12.6%, p <0.01). Na twee jaar follow-up, toonden patiënten met aorta-ostiale laesie bedekking een viervoudige toename van het risico op target laesie revascularisatie (HR: 4.1, 95% CI: 1.17-14.39, p = 0.03) vergeleken met patiënten zonder aorta- ostiale bedekking. Dit hoofdstuk toont aan dat aorta-ostium behandeling met tweede generatie DES haalbaar is, maar dat het een voorspeller is voor target laesie revascularisatie.

Hoofdstuk 8 presenteert de driejaars klinische uitkomsten van de TWENTE trial patiënten die behandeld zijn voor chronische totale occlusie laesies (CTO) ten opzichte van patiënten die behandeld zijn voor niet-CTO laesies. Laesies werden geclassificeerd als CTO laesies indien er sprake was van een totale lumen obstructie met TIMI flow graad 0 in het afgesloten segment en indien de duur van de occlusie meer dan drie maanden was.
Patiënten die tenminste voor één CTO laesie werden behandeld (n = 59) (waarvan de meerderheid een J-CTO score had van ≥2 (56%), duidend op een moeilijke passage van de meeste CTO laesies) werden vaker behandeld voor laesies in kleine vaten, lange laesies en laesies in meerdere vaten en waren minder vaak van het mannelijk geslacht dan patiënten zonder CTO laesies (n = 615). Na drie jaar follow-up, was het percentage van het meer laesie-georïenteerde gecombineerde eindpunt, target lesion failure, gelijk voor beide groepen (13.6% vs. 12.9%, p = 0.89).Het patiënt-georïenteerde gecombineerde eindpunt was ook vergelijkbaar tussen de twee groepen DES (18.6% vs. 18.8%, p = 0.97). In dit hoofdstuk wordt aangetoond dat patiënten die behandeld worden met de tweede generatie DES voor CTO laesies na drie jaar follow-up een vergelijkbare lage incidentie van klinische events tonen als patiënten zonder CTO laesies.

In hoofdstuk 9 onderzoeken we bij de TWENTE studie patiënten, de veiligheid en effectiviteit op lange termijn van het behandelen van bifurcatie laesies met de tweede generatie DES. Binnen de populatie van de TWENTE studie werden 362 patiënten behandeld voor bifurcatie laesies. Ondanks het significant hogere percentage van periprocedurele MI bij patiënten die voor bifurcatie laesies werden behandeld (6.9% versus 3.1%, p <0.01), verschilde de incidentie van TVF niet significant na drie jaar follow-up (13.1% versus 12.6%, p = 0.84). Van de 362 patiënten die voor bifurcatie laesies zijn behandeld, was er statistisch geen significant verschil in de klinische eindpunten tussen de twee groepen DES. Dit hoofdstuk demonstreert dat ondanks een verschil in periprocedurele MI, de drie-jaars klinische uitkomst na behandeling met de tweede generatie DES gunstig was en vergelijkbaar met patiënten zonder bifurcatie laesies.

Hoofdstuk 10 presenteert de éénjaars klinische resultaten van de gerandomiseerde DUTCH PEERS studie; een onderzoeker geïnitieerde, gerandomiseerde, multicenter, non-inferioriteit studie die de veiligheid en de effectiviteit van de Resolute Integrity en de Promus Element stents met elkaar vergelijkt. In totaal werden 1811 patiënten (1: 1) gerandomiseerd voor de behandeling met Resolute Integrity (n = 906) of Promus Element stent (n = 905). De studie populatie bestond uit 59% patiënten met ACS (20% van alle patiënten hadden een acuut ST-elevatie MI) en 18% had diabetes. Follow-up gegevens werd van iedereen verkregen met de uitzondering van één patiënt, die na een dag zijn/haar toestemming had ingetrokken. Het primaire eindpunt, TVF na één jaar, trad op in 6.1% van de patiënten in de Resolute Integrity-groep en in 5.2% van de patiënten in de Promus Element groep (P non-inferioriteit = 0.006). De incidentie van de individuele componenten van TVF (cardiale sterfte, target vesssel-gerelateerde

MI en klinisch geïndiceerde TVR) was vergelijkbaar tussen de twee DES groepen. Definitieve-of- waarschijnlijke stent trombose trad op bij 0.6% van de patiënten die behandeld waren met Resolute Integrity tegenover 0.9% van de patiënten in de Promus Element groep (p = 0.40). Longitudinale stent vervorming werd alleen waargenomen in de Promus Element groep (1.0%), maar heeft niet geleid tot een klinisch event. De resultaten van dit gerandomiseerde multicenter trial tonen aan dat de Resolute Integrity en Promus Element stents even effectief en veilig zijn en uitstekende klinische resultaten laten zien in een populatie waarin een groot deel van de patiënten zich met ACS presenteert.

In hoofdstuk 11 beoordelen we de tweejaars klinische resultaten en patiënt-gerapporteerde pijn op de borst in 1811 patiënten die behandeld waren met Resolute Integrity en Promus Element stents in de DUTCH PEERS studie. Na twee jaar, verschilde het primaire eindpunt TVF (8.6% vs. 7.8%, p = 0.55) niet significant tussen de patiënten die behandeld waren met de Resolute Integrity of Promus Element stents, respectievelijk. Het percentage van erg late definitieve-of-waarschijnlijke stent trombose was laag en vergelijkbaar voor de twee DES typen (0.6% vs. 0.2%, p = 0.45), terwijl na twee jaar 9% van de patiënten nog DAPT hadden. Na één en twee jaar follow-up waren meer dan 80% van de patiënten vrij van pijn op de borst. Daarnaast waren meer dan 87% van alle patiënten vrij van pijn op de borst of hadden pijn op de borst alleen bij maximale inspanning, zonder enig verschil tussen de twee stentgroepen. Patiënten die één jaar na PCI tijdens matige / milde lichamelijke inspanning of in rust pijn op de borst klachten hadden, hadden een bijna tweevoudig verhoogd risico op een klinisch-geïndiceerde TVR in het tweede jaar (HR: 1.89, 95% CI: 1.05-3.39, p = 0.03) vergeleken met patiënten die alleen bij maximale inspanning pijn op de borst hadden of helemaal pijnvrij waren. Dit hoofdstuk toont aan dat na twee jaar follow-up, de incidentie van ongewenste klinische events laag en vergelijkbaar waren voor beide DES van de DUTCH PEERS studie. De meerderheid van de patiënten waren na één en twee jaar vrij van pijn op de borst en werden niet door pijn beperkt in hun dagelijkse activiteiten.

Hoofdstuk 12 beschrijft de rationale en het ontwerp van de BIO-RESORT studie. De BIO-RESORT studie is een onderzoeker geïnitieerde, patiënt geblindeerde, gerandomiseerde multicenter studie om de veiligheid en effectiviteit van twee nieuwe DES met biologisch afbreekbare polymeer coatings, de ORSIRO en SYNERGY, te vergelijken met een DES met een permanente coating, de Resolute Integrity. De studie vergelijkt niet alleen drie stents met elkaar, maar ook drie verschillende "filosofieën", omdat beide biologisch afbreekbare coatings van de DES significant verschillen in de verdeling van de coating op het stent oppervlak en de snelheid waarmee deze coatings worden afgebroken. De randomisatie wordt 1: 1: 1 uitgevoerd in een populatie van ten minste 3540 patiënten, voor de ORSIRO stent met circumferentiëel biologisch afbreekbare coating, voor de SYNERGY stent met abluminaal biologisch afbreekbare coating en voor de Resolute Integrity stent met permanente coating. Het primaire eindpunt is

het optreden van TVF na één jaar. De studie toetst twee hypothesen: de veiligheid en effectiviteit van de ORSIRO is niet inferieur aan die van de Resolute Integrity, en dat de veiligheid en effectiviteit van de SYNERGY niet inferieur is aan die van de Resolute Integrity. Dit hoofdstuk geeft informatie over de rationale en het ontwerp van de BIO-RESORT studie, een studie dat nieuwe inzichten zal verschaffen in de klinische uitkomst van moderne DES.

In **hoofdstuk 13** bespreken we de bevindingen van dit proefschrift en geven we toekomst-perspectieven weer.

Conclusie

Drug-eluting stents (DES) hebben de behandeling van obstructieve coronair aandoeningen gerevolutioneerd en worden veel gebruikt in de dagelijkse klinische praktijk. De meerderheid van de patiënten die met PCI worden behandeld zijn complex en hebben ten minste één off-label indicatie voor gebruik van DES. Complexe patiënten worden gekenmerkt door een verhoogd klinisch risico en hebben meer complexe laesies met een uitdagende coronair anatomie. Dit proefschrift geeft inzicht in de prestaties van de verschillende nieuwe soorten DES in complexe patiënten die een PCI ondergaan in twee gerandomiseerde studies. In zowel de TWENTE als de DUTCH PEERS studie waren de meerderheid van de behandelde patiënten complex. De TWENTE studie representeert de "real-world" situatie, omdat de niet-geïncludeerde patiënten en patiënten van de gerandomiseerde studiepopulatie niet verschilden in klinische eindpunten. De complexe patiënten met off-label indicaties voor gebruik van DES, geincludeerd in de TWENTE studie, verschilden niet significant in het optreden van klinische events vergeleken met de patiënten met on-label gebruik van DES, met als enige uitzondering een hogere incidentie van periprocedurele MI. De behandeling van een graft, als één van de off-label criteria voor DES gebruik, is geassocieerd met een hogere incidentie van revascularisatie, voornamelijk door meer herhaalde revascularisaties in gedegenereerde vene grafts. De behandeling van een CTO laesie, die ook een van de off-label criteria voor DES gebruik is, heeft geen slechtere klinische resultaten, zelfs niet drie jaar na PCI met een tweede generatie DES.
De behandeling van een aorta-ostium laesie, welke geen "klassieke" off-label criterium is, geeft echter wel de aanwezigheid van een uitgebreide coronaire ziekte aan en is een voorspeller voor target laesie revascularisatie.
De nieuwe, zeer flexibele stents met permanente polymeer coating, de Resolute Integrity en de Promus Element stents lieten een uitstekende plaatsbaarheid zien in de DUTCH PEERS studie, zelfs in complexe anatomie en toonden vergelijkbare en uitstekende klinische resultaten na één en twee jaar follow-up. De meerderheid van deze patiënten die behandeld zijn met deze nieuwe DES werden na één en twee jaar niet door pijn beperkt in hun dagelijkse activiteiten.

DES met een biologisch afbreekbaar polymeer coating zijn ontwikkeld als gevolg van bezorgdheid over permanente polymeren als mogelijke oorzaak van de vaatwand ontsteking en zeer late stent trombose. De lopende BIO-RESORT gerandomiseerde studie onderzoekt de non-inferioriteit van de Synergy en Orsiro stents, twee nieuwe, zeer flexibele, biologisch afbreekbare polymeer coating DES, in vergelijking met de permanente polymeer-gebaseerde Resolute Integrity DES, die als referentie dient.

DANKWOORD

Allereerst wil ik iedereen bedanken die ik hieronder niet bij naam zal noemen, degenen die mij hebben gesteund in mijn werk de afgelopen jaren en hebben bijgedragen tot het totstandkomen van dit proefschrift. De volgende mensen wil ik in het bijzonder bedanken:

Mijn promotor Clemens von Birgelen, beste Clemens, terugkijkend hoe ik als co-assistent contact met je opnam om de mogelijkheden voor wetenschappelijke stage te bespreken was ik erg verrast over het feit hoe snel het allemaal geregeld werd. Ik bedank je voor de mogelijkheid om wetenschappelijk onderzoek te mogen doen. Bovendien bedank ik je voor je steun, inzet en geduld. Zonder jouw intensieve begeleiding had ik hier nu niet gestaan.

De cardiologen en arts-assistenten van het Thoraxcentrum Twente en in het bijzonder mijn opleiders Patrick Verhorst en Marcoen Scholten wil ik graag bedanken voor hun steun en de mogelijkheid dat ze me hebben gegeven om wetenschappelijk onderzoek te doen alsmede voor hun begeleiding om uiteindelijk een goede klinische cardioloog te worden.

Ik bedank alle interventiecardiologen van het Thoraxcentrum Twente voor hun inzet in de TWENTE, DUTCH PEERS en de BIO-RESORT trial alsmede de interventiecardiologen van Emmen, Arnhem en Alkmaar voor hun inzet in de DUTCH PEERS trial. Dankzij jullie werk, jullie inclusie, hebben we data verkregen dat mogelijk gemaakt heeft om onderzoek te doen en te staan waar ik nu sta. Dank jullie allen.

Naast de interventiecardiologen wil ik de laboranten, verpleegkundigen en de secretaressen bedanken voor hun inzet in de TWENTE trials.

Mijn commissieleden: Prof. dr. M. IJzerman, Prof. dr. J. Grandjean, Prof. dr. J. van der Palen, Prof. dr. J.C.A. Hoorntje, Prof. dr. F. Zijlstra en Prof. dr. M.J. de Boer wil ik bedanken voor de beoordeling van mijn proefschrift.

De medewerkers van CardioResearch van het Thoraxcentrum Twente: Harald, Jan, Henny, Gera, Martina, Petra, Eva, Jolande, Wendy en Ester. Bij jullie kon ik altijd terecht voor vragen en advies en natuurlijk voor de heerlijke koffie. In het bijzonder wil ik Harald bedanken voor zijn goede steun. Harald, dankjewel voor het optreden als mentor/manager, je gaf me zoveel praktische adviezen en wijze raad.

Mijn collega's van het onderzoek, oftewel de leden van het 'Hok': Kenneth, Ming Kai, Marije, Jacqueline, Ilona, Renate, Liefke en Marlies, maar ook de eerdere onderzoekers: Mounir, Jennifer,

Marlon, Bob, Karin en de huidige onderzoekers van de elektrofysiologie Tim en Marleen. In het 'Hok' hebben we zoveel data verzameld en aan papers geschreven, maar we wisselden die momenten af met kofiepauzes en het voeren van 'bijzondere en leerzame gesprekken'. In het bijzonder wil ik Kenneth bedanken voor zijn begeleiding van mijn wetenschappelijke stage en zijn enthousiasme voor de cardiologie die hij op mij heeft overgedragen.

Mijn buren van het 'Hok', de leden van de medical school, bedankt voor de vele theezakjes en de koffie die we bij jullie mochten halen. Mijn dank eveneens voor de gezellige gesprekken in de pauzes.

Mijn paranimfen, mijn collega Marije Löwik en mijn broertje Taner Şen. In het bijzonder wil ik Marije bedanken, beste Marije, je bent mijn rechterhand geweest sinds ik met het onderzoek ben begonnen. Bij jou kon ik altijd terecht. Ik dank je zeer voor je geduld en begrip. Dank ook voor het tegenlezen van mijn proefschrift.

Ik wil mijn ouders Mustafa Şen en Sonay Şen-Yucel bedanken voor hun stimulatie en vertouwen, al vanaf het begin van mijn opleiding geneeskunde. Jullie stonden altijd achter me en stimuleerden mij om door te zetten. Ik wil mijn opa Şen bedanken die er niet meer is. Hij geloofde erin dat ik het pad van de cardiologie zou betreden al voordat ik aan mijn studie geneeskunde was begonnen.

Als laatste wil ik mijn partner Sinan Özdil bedanken. Lieve Sinan dankjewel voor je liefde en steun. Op heel korte termijn gaan we samen het huwelijksbootje instappen en ik hoop dat we nog lang samen gelukkig mogen zijn…

CURRICULUM VITAE

Hanim Şen werd geboren op 24 oktober 1986 te Amelo. In 2005 behaalde zij haar VWO diploma aan het OSG Erasmus te Almelo. Daaropvolgend begon ze in 2005 met de studie Geneeskunde aan de Rijksuniversiteit te Groningen. Ze volgde haar senior-coschappen tussen 2009/2010 bij de diverse afdelingen van het Medisch Spectrum Twente te Enschede. Vanaf september 2010 zette ze haar opleiding Geneeskunde voort bij de afdeling cardologie van het Thoraxcentrum Twente, te Enschede. Na haar afstuderen, ging ze verder met haar onderzoek dat ze in het kader van haar wetenschappelijke stage had verricht. Zij begon met haar promotie-onderzoek binnen het Thoraxcentrum vanaf 2011 bij de interventie-cardiologie onder begeleiding van C. von Birgelen en dat geleid heeft tot dit proefschrift. Per 1 december 2014 is ze gestart met de opleiding tot cardioloog onder leiding van de opleiders dr. P.M.J Verhorst en dr. M.F.Scholten en de eerste twee jaren vooropleiding Interne Geneeskunde onder leiding van dr. W.M.Smit. Hanim Şen is de partner van Sinan Özdil.

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