Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 15, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.01.008

FOCUS ISSUE: TRANSCATHETER CARDIOVASCULAR THERAPEUTICS Interventional Cardiology

A Randomized Controlled Trial in Second-Generation Zotarolimus-Eluting Resolute Stents Versus Everolimus-Eluting Xience V Stents in Real-World Patients

The TWENTE Trial

Clemens von Birgelen, MD, PhD,*† Mounir W. Z. Basalus, MD,* Kenneth Tandjung, MD,* K. Gert van Houwelingen, MD,* Martin G. Stoel, MD,* J.(Hans) W. Louwerenburg, MD,* Gerard C. M. Linssen, MD, PhD,‡ Salah A. M. Saïd, MD, PhD,§ Miep A. W. J. Kleijne, MD,‖ Hanim Sen, MD,* Marije M. Löwik, PhD,* Job van der Palen, PhD,¶# Patrick M. J. Verhorst, MD, PhD,* Frits H. A. F. de Man, MD, PhD*

Enschede, Almelo, Hengelo, and Winterswijk, the Netherlands

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

Background Only 1 randomized trial previously compared these stents.

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

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

Conclusions Resolute ZES were noninferior to Xience V EES in treating "real-world" patients with a vast majority of complex lesions and "off-label" indications for drug-eluting stents, which were implanted with liberal use of post-dilation. (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting SteNt Study: Head-to-head Comparison of Clinical Outcome After Implantation of Second Generation Drug-eluting Stents in a Real World Scenario; NCT01066650) (J Am Coll Cardiol 2012;59:1350–61) © 2012 by the American College of Cardiology Foundation

Early trials with drug-eluting stents (DES) demonstrated a significant reduction in restenosis and reintervention rates (1,2), which rapidly led to the adaptation of these stents for routine percutaneous coronary interventions (PCI). However, long-term follow-up data of first-generation DES showed that these stents did not improve mortality (3–5).

From the *Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands; †MIRA, Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands; ‡Department of Cardiology, Ziekenhuisgroep Twente, Almelo, the Netherlands; §Department of Cardiology, Ziekenhuisgroep Twente, Hengelo, the Netherlands; ‖Department of Cardiology, Streekziekenhuis Koningin Beatrix, Winterswijk, the Netherlands; ¶Department of Epidemiology, Medisch Spectrum Twente, Enschede, the Netherlands; and the #Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, the Netherlands. This was an investigator-initiated study supported by equal unrestricted grants from Abbott Vascular and Medtronic. Dr. von Birgelen is consultant to and has received lecture fees or travel expenses from Abbott, Medtronic, and Boston Scientific; and has received a speaker's honorarium from MSD. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. von Birgelen and Basalus contributed equally to this work.

Manuscript received November 6, 2011; revised manuscript received January 11, 2012, accepted January 17, 2012.

Several factors and mechanisms have been suggested to be potentially involved. A particularly important factor might be the lack of biocompatibility of coatings on first-generation DES, some of which were shown to be associated with hypersensitivity and vessel wall inflammation that can promote stent thrombosis. In addition, deliverability and side branch access of first-generation DES were somewhat limited (6), and the reduction in reintervention rates in patients with advanced coronary disease was less than expected (7).

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

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

Methods

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

The TWENTE trial complied with the Declaration of Helsinki for investigation in human beings and was approved by the institutional ethics committee of Medisch Spectrum Twente, Enschede, the Netherlands, and the Dutch Central Committee on Research Involving Human Subjects. All patients provided written, informed consent for participation in this trial.

Randomization and study devices. After stratification for sex, randomization was performed on the basis of computer-generated random numbers (block stratified randomization version 5.0 by S. Piantadosi), with sealed, opaque, sequentially numbered allocation envelopes. After passage of the guidewire or pre-dilation (if necessary), patients were assigned in a 1:1 ratio to Resolute ZES or Xience V EES. Patients had no knowledge of the stent type they were allocated to (single-blinded design).

In our center, Resolute ZES were available in diameters of 2.25, 2.50, 3.00, 3.50, and 4.00 mm. Stent length was 8 mm and 14 mm for stents with a diameter ≤2.5 mm; 9 mm and 15 mm for stents with a diameter of ≥3.00 mm; and 12, 18, 24, and 30 mm for all available stent diameters. Xience V EES were available in diameters of 2.25, 2.50, 3.00, 3.50, and 4.00 mm and in lengths of 8, 12, 15, 18, 23, and 28 mm.

Percutaneous intervention and medication. Interventions were performed via femoral or radial route according to standard techniques. Complete lesion coverage was attempted with 1 or more stent(s). Lesion pre-dilation, direct stenting, and/or stent post-dilation were permitted at the discretion of the operators. Operators were encouraged to make liberal use of post-dilation. Although planned staging of PCI was an exclusion criterion, unplanned staged procedures were permitted if the second procedure was performed within 6 weeks after the index procedure (e.g., in unexpected lengthy procedures and/or procedures with excessive contrast use); in such cases, the allocated stent type was used during all stages. During index procedure, mixture of stents was not permitted unless the allocated study stent could not be delivered; then, crossover to another stent was permitted.

Patients who were not taking acetylsalicylic acid received ≥300 mg of acetylsalicylic acid before PCI. In addition, patients received before or at the time of PCI 300 to 600 mg of clopidogrel and at least 5,000 IU or 70 to 100 IU/kg of unfractionated heparin, according to standard protocols.

Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent

JACC Vol. 59, No. 15, 2012
April 10, 2012:1350–61

Administration of glycoprotein IIb/IIIa antagonists was left at the discretion of the operators.

In patients not receiving oral anticoagulation therapy, we prescribed at discharge the combination of 100 mg of acetylsalicylic acid once daily (indefinitely) and clopidogrel 75 mg once daily (12 months). In patients receiving oral anticoagulation therapy, we prescribed 100 mg of acetylsalicylic acid once daily (at least 1 month) and clopidogrel 75 mg daily (12 months) in addition to oral anticoagulation.

Laboratory, electrocardiographic, and angiographic analyses. In all patients, the concentration of creatine kinase was determined before PCI, and the concentration of creatine kinase, creatine kinase-myocardial band, and troponin was measured 6 to 18 h after PCI, with subsequent serial measurements in case of relevant biomarker elevation or complaints. Of the cases, 97% had at least 1 blood sampling performed between 12 and 18 h after PCI. Twelve-lead electrocardiographs were obtained before and after PCI, before discharge, and at suspicion of acute ischemia.

Quantitative coronary angiography was performed offline with use of edge-detection software (QAngio XA version 7.1, Medis, Leiden, the Netherlands) by experienced analysts of Thoraxcentrum Twente, who were blinded as to the type of study device used. All measurements (baseline and final) were conducted according to current standards. Standard offline measurements were obtained over the entire segment, consisting of stented segment plus 5 mm proximal and distal margins. We defined percentage diameter stenosis as: ([reference vessel diameter − minimal lumen diameter]/reference vessel diameter) × 100%. Lesion length was assessed, in general, by quantitative coronary angiography.

Definition of endpoints and data management. The pre-specified primary composite endpoint was the incidence of target vessel failure (TVF) within 1 year, defined as (in hierarchical order) cardiac death, target vessel–related myocardial infarction (MI), or clinically driven target vessel revascularization (TVR) by re-PCI or surgery. All clinical endpoints were defined according to the Academic Research Consortium (17,18). Cardiac death was defined as any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Myocardial infarction was defined as previously outlined in detail. In brief, MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker (creatine kinase-myocardial band fraction or troponin) (18). Moreover, classification of MIs and location of MIs was performed on the basis of laboratory testing, electrocardiographic parameters, angiographic information, and/or clinical data (17,18). A TVR was defined as any repeat coronary revascularization (PCI or surgery) of any segment of the entire major coronary artery and its branches. A TVR (or target lesion revascularization [TLR]) was considered clinically indicated if the angiographic percentage diameter stenosis of the then-treated lesion was ≥50% in the presence of ischemic signs or symptoms or if the diameter stenosis was ≥70%, irrespective of ischemic signs or symptoms (17).

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

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

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

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

Statistical analysis. The main outcome parameter of this noninferiority study was the incidence of TVF at 1 year with 80% power to detect noninferiority at a 1-sided type I error of 0.05. Assuming a median time to TVF of 48 months, on the basis of the Endeavor III (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) trial that had an event rate of 12.8% (19), a hazard ratio of 1.35, an accrual time of 2 years, and an additional follow-up of 1 year for TVF, a total of 1,380 patients was required. On the basis of the aforementioned hazard ratio and assumed event rate, noninferiority would be declared if the upper limit of the 1-sided 95% confidence interval (CI) of the absolute risk difference was ≤4.48%. The Newcombe-Wilson method without continuity correction was used to calculate a CI for the absolute risk difference (20). Analyses were performed on the basis of intention-to-treat principle. Patients were censored when they did not reach any component of the composite primary endpoint. Categorical variables were assessed with use of chi-square or Fisher exact tests, as appropriate, whereas continuous variables were assessed with the Wilcoxon rank-sum test or Student *t* test, as appropriate. The time to the primary endpoint and the components thereof were assessed according to the method of Kaplan-Meier, and the log-rank

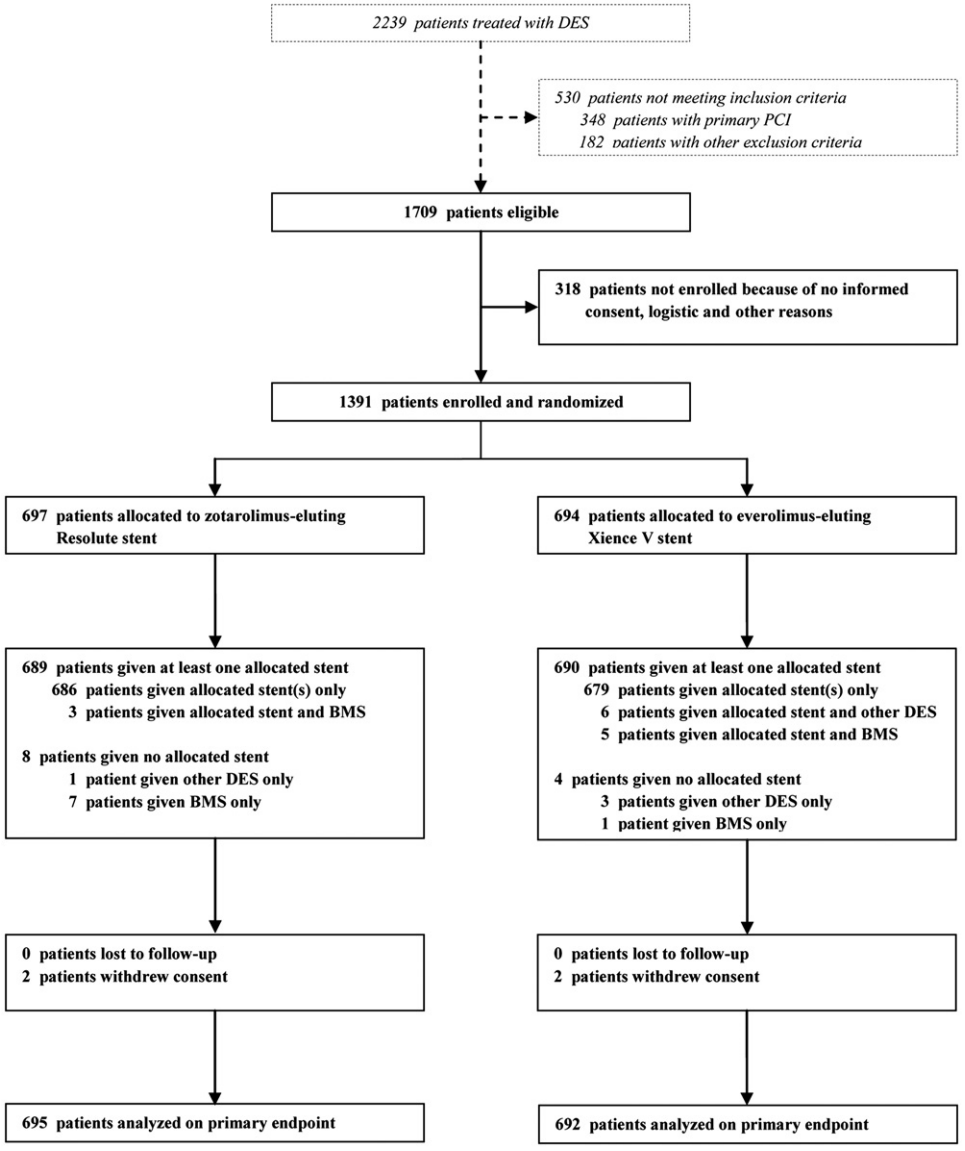

Figure 1 Trial Profile

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

JACC Vol. 59, No. 15, 2012
April 10, 2012:1350–61

test was applied to compare the 2 groups. Kaplan-Meier curves were drawn in accordance with guidelines provided by Pocock et al. (21). Logistic regression was performed to test for interaction between subgroups and stent type with regard to the primary endpoint. A p value <0.05 was considered significant. All p values and CIs were 2-sided, except for those for noninferiority testing of the primary clinical endpoint. After noninferiority was established, we calculated regular 2-sided 95% CIs and 2-sided p values to allow conventional interpretation of results (as for a superiority design). Statistical analyses were performed with SPSS (version 15.0, SPSS, Inc., Chicago, Illinois) and SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina).

Results

Study population. Figure 1 shows the trial profile. Patients (n = 1,391; 81.4% of the eligible patient population) with 2,116 lesions were randomly assigned to Resolute ZES (n = 697, 1,080 lesions) or Xience V EES (n = 694, 1,036 lesions). At least 1 allocated study stent was implanted in 689 (99%) and 690 (99%) patients allocated to Resolute ZES and Xience V EES, respectively. In each study arm, 2 (0.3%) patients withdrew consent before reaching 12-month follow-up. In all other 1,387 patients, complete follow-up information was obtained (100%).

Study groups had similar baseline clinical (Table 1), angiographic (Table 2), and procedural characteristics (Table 3). A total of 52% of patients presented with an acute coronary syndrome. Of the study population, 22% were diabetic. In a high proportion of patients, there was advanced coronary disease with a need for multivessel treatment, bifurcation lesions, long lesions, and small-vessel disease. At least 1 off-label characteristic was present in 77% of patients, and 70% of lesions were complex (type B2/C). Between study

Table 1 Baseline Characteristics of Patients

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

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

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CTO = chronic total occlusion; EES = everolimus-eluting stent(s); PCI = percutaneous coronary intervention; RVD = reference vessel diameter; ZES = zotarolimus-eluting stent(s).

Table 2 Baseline Lesion Characteristics

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

Values are n (%). *Including chronic total occlusion but not grafts and in-stent restenosis. †Thrombus triggering use of thrombus aspiration catheters.
ACC = American College of Cardiology; AHA = American Heart Association; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

groups, there was no difference in the proportion of left main stem and bypass treatment and of recanalization of chronic total occlusions. Direct stenting was performed in 39% of lesions. In 82% of lesions, stents were post-dilated.

Primary and secondary endpoints. Table 4 shows the major adverse cardiac events during 1-year follow-up. Target vessel failure occurred in 57 patients (8.2%) of the Resolute ZES and in 56 patients (8.1%) of the Xience V EES groups. We established noninferiority of the ZES with an absolute risk difference of 0.1% (95% CI: −2.8% to 3.0%) and the upper limit of the 1-sided 95% CI of 2.53% (1-sided p value for noninferiority = 0.001) (Fig. 2A, Table 4).

Between Resolute ZES and Xience V EES groups, there was also no difference in the components of the primary endpoint: cardiac death (1.0% vs. 1.4%, p = 0.46); target vessel–related MI (4.6% vs. 4.6%, p = 0.99); clinically driven TVR at 12-month follow-up (3.3% vs. 2.7%, p = 0.54) (Figs. 2B to 2D, Table 4).

In addition, there was no difference between groups in other secondary endpoints (Table 4), such as the incidence of death from any cause (2.2% vs. 2.0%, p = 0.86).

The results of an exploratory subgroup analysis of the primary endpoint are shown in Figure 3. This analysis suggested a potential interaction between stent type and diabetes mellitus (p = 0.045) with a trend toward a lower rate of TVF in diabetic patients treated with EES (13.9% [22 of 158] vs. 7.7% [11 of 143], p = 0.08; relative risk: 1.81 [95% CI: 0.91 to 3.60] for Resolute ZES and Xience V EES, respectively). In nondiabetic patients, TVF did not differ significantly between stent types (6.5% [35 of 539] vs. 8.2% [45 of 551], p = 0.29; relative risk: 0.80 [95% CI: 0.52 to 1.22] for Resolute ZES and Xience V EES, respectively).

Stent thrombosis. Definite or probable stent thrombosis occurred in 6 patients (0.9%) of the Resolute ZES group (1 death, 4 MI, 1 repeat TVR) and 8 patients (1.2%) of the Xience V EES group (4 death, 4 MI) (p = 0.59) (Fig. 4, Table 4). In the EES arm, probable stent thrombosis beyond day 8 was only observed in patients not adhering to dual antiplatelet therapy (stent thromboses on day 28 and day 136) (Fig. 4). The incidence of definite stent thrombosis was low in both study arms. It occurred in 4 patients (0.6%) of the Resolute ZES arm and in none (0%) of the Xience V EES arm (p = 0.12) (Fig. 4, Table 4). One patient (day 245) was not receiving dual antiplatelet therapy. Three of 4 patients with definite stent thrombosis (75%) survived this event. The only fatal event (day 5) occurred in a patient enrolled for stenting of right and left anterior descending arteries, 7 days after treatment of the circumflex artery with a bare metal stent for a large, subacute non-STEMI. Autopsy revealed thrombus formation and/or coagulated blood in all 3 vessels, and the event was classified as definite stent thrombosis, according to the definition.

JACC Vol. 59, No. 15, 2012
April 10, 2012:1350–61

Table 3 Quantitative Coronary Angiography and Procedural Results

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

Values are median (interquartile range), mean ± SD, n (%), or n/N (%). *Device success is defined as the attainment at the target site of a final residual diameter stenosis of <50% with only the assigned study device. †Lesion success is defined as the attainment at the target site of a final residual diameter stenosis of <50% with any percutaneous method. ‡Procedure success is defined as the attainment at the target site of a final residual diameter stenosis of <50%, together with the absence of any in-hospital major adverse cardiac events.

Abbreviations as in Table 1.

Discussion

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

In the present study, more than 80% of all eligible patients were enrolled. There were only a few exclusion criteria. As a consequence, the majority of patients of this "real-world" patient population were treated in a nonelective setting, and a high proportion of patients had complex lesions and suffered from advanced coronary disease, which required multivessel PCI.

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

To date, there is only 1 other published trial (Resolute All Comers) (15) with a head-to-head comparison of the same stents as in the present study. That trial assessed 1,140 patients in the Resolute ZES arm and 1,152 patients in the EES arm and demonstrated noninferiority of the ZES in a patient population with minimal exclusion criteria. This was confirmed by the present trial.

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

The majority of target vessel–related MIs occur during the periprocedural period. Therefore, the high rate of stent post-dilation in the present trial (82% of lesions) might explain the slightly higher rate of target vessel–related MIs compared with the Resolute All Comers study (15). By contrast, stent post-dilation is likely to improve stent apposition and drug delivery, which might have contributed to the somewhat lower rate of clinically indicated TVR in the present study. In fact, this rate was even lower than that of EES in the SPIRIT IV (Clinical Evaluation of the XIENCE V Everoli-

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

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

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

CI = confidence interval; TVR = target vessel revascularization; ST = stent thrombosis; other abbreviations as in Table 1.

mus Eluting Coronary Stent System) study (3.9%), a multicenter trial that compared EES and paclitaxel-eluting stents in 2,485 and 1,229 patients, respectively (14).

In the TWENTE trial, direct stenting was performed in 39% of lesions. This is similar to the rate of direct stenting in other trials with complex lesions (30% to 40%) (15,22,23). Further mechanistically oriented data analyses of interventional techniques and assessment of their potential relation with clinical outcome will help to define the impact of pre- and post-dilation on the results of the present trial.

Intuitively, one might tend to argue that the lack of inclusion of patients with STEMI in the TWENTE trial might have contributed to a low rate of TVF. However, in the Resolute All Comers trial, the 12% STEMI patients actually had lower rates of TVF and fewer major cardiac events than the overall study population (25). This might partly be explained by the difficulty of identifying periprocedural MI in the setting of STEMI (18). In addition, because of the generally reduced myocardial mass subtended, restenoses of infarct-related arteries are less likely to provoke myocardial ischemia, which can have a lowering effect on the TVR rate. In the COMPARE (Trial of Everolimus-eluting Stents and Paclitaxel-eluting Stents for Coronary Revascularization in Daily Practice), which assessed 897 patients treated with EES and 903 patients treated with paclitaxel-eluting stents, clinically justified TVR in the EES arm (2.1%) (22) was even lower than in the Resolute All Comers study (15) and in the present study. For reasons discussed in the preceding text, the particularly high proportion of STEMI in the COMPARE trial (27%) might have contributed to this difference (22).

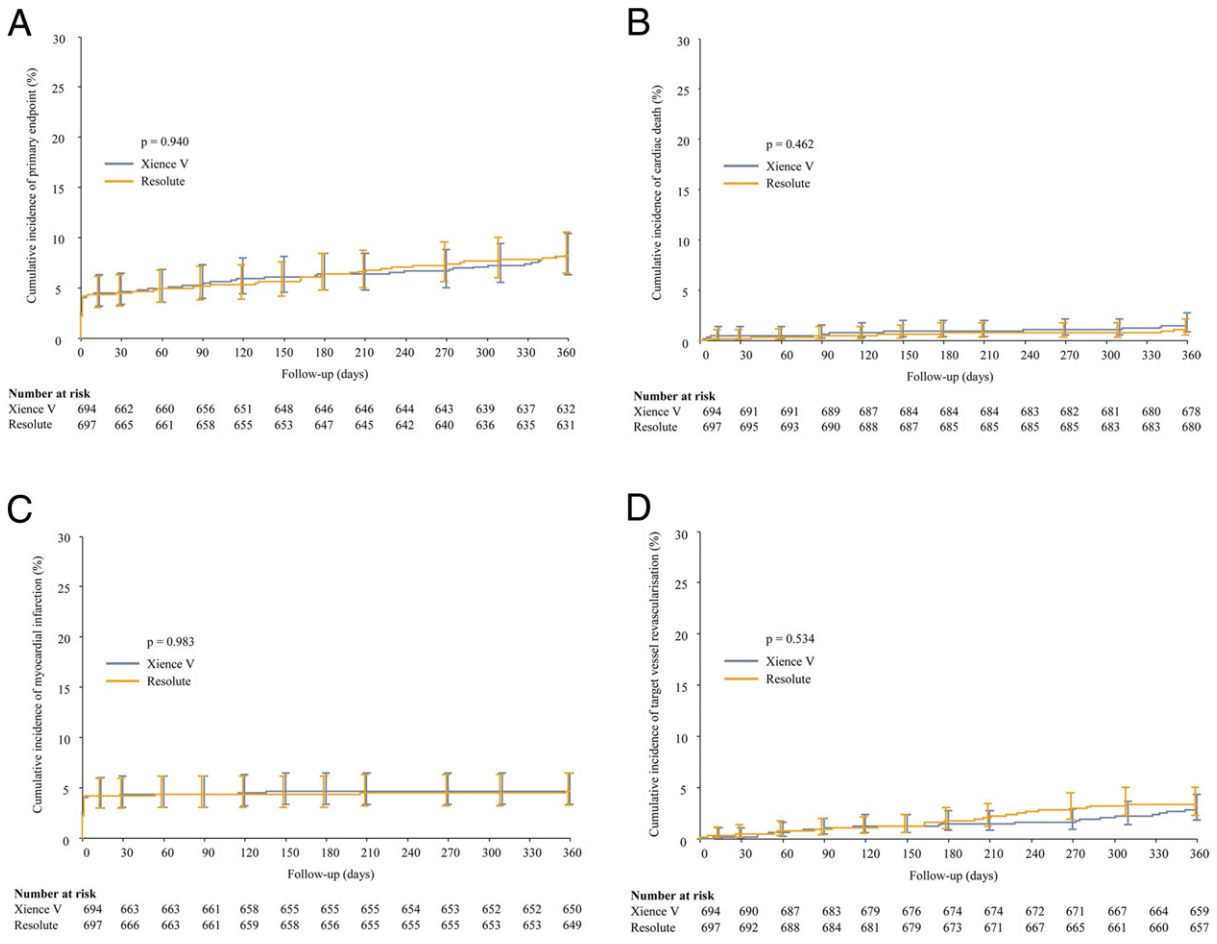

Figure 2 **Kaplan-Meier for Primary Endpoint and the Individual Components of the Primary Endpoint**

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

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

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

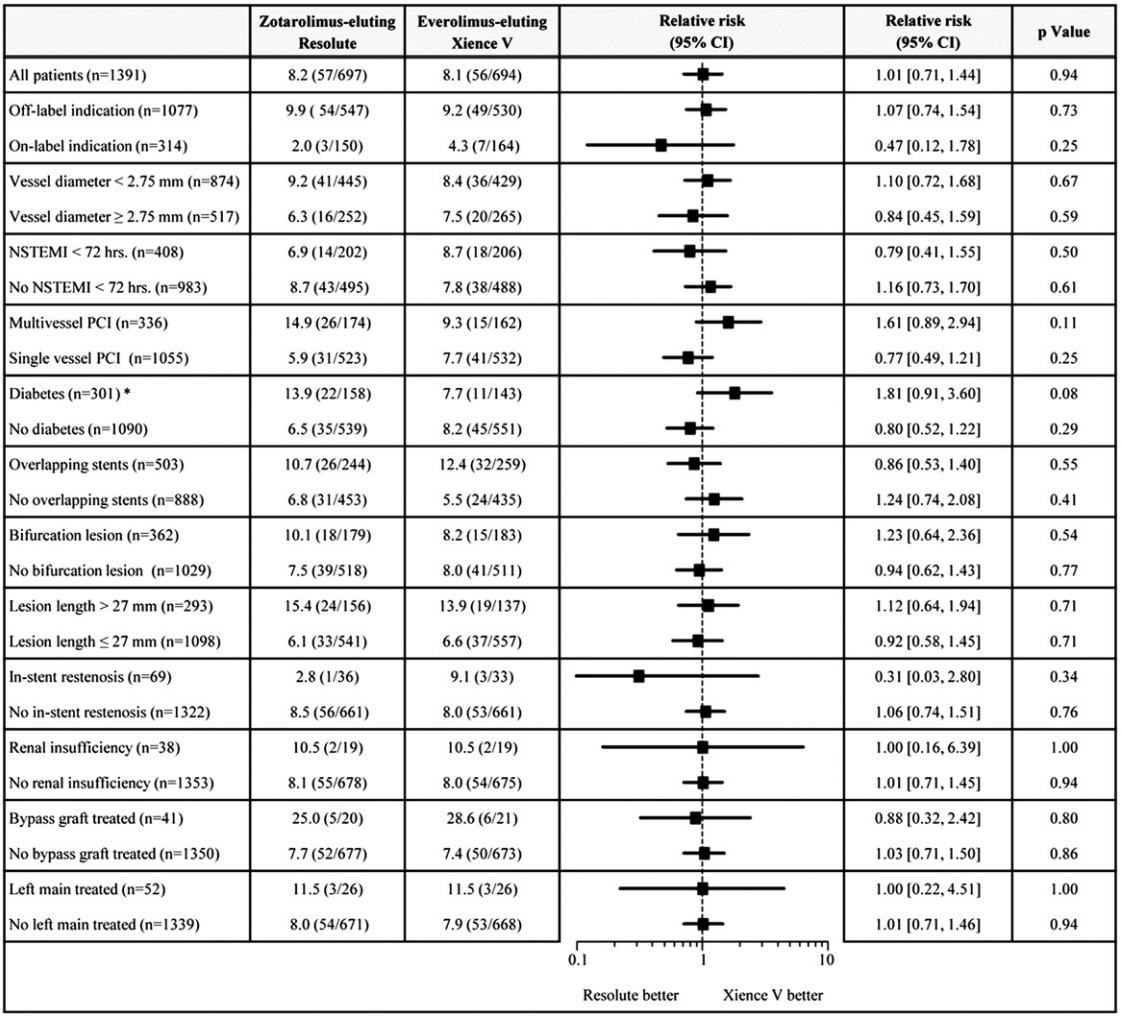

Figure 3 **Subgroup Analysis: Target Vessel Failure at 1 Year**

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

In the present study, the Xience V EES arm showed no definite stent thrombosis at 1-year follow-up. The TWENTE trial is the first randomized trial that showed no definite stent thrombosis in a complex "real-world" patient population with advanced coronary disease and challenging lesions. The use of EES has previously been associated with a relatively low risk of stent thrombosis (28). In the SPIRIT III and IV, COMPARE, and Resolute All Comers trials, definite stent thrombosis rates in EES ranged from 0.3% to 0.8% (10,15,22,29). In contrast to the absence of definite stent thrombosis in the Xience V study arm of the TWENTE trial, there were 8 adverse cardiac events that were adjudicated as probable stent thromboses—4 of them being lethal. However, beyond 8 days after the index procedure, none of these probably thrombotic events occurred in a patient who adhered to dual antiplatelet therapy (the events on day 28 and day 136 occurred in patients not receiving dual antiplatelet therapy) (Fig. 4).

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

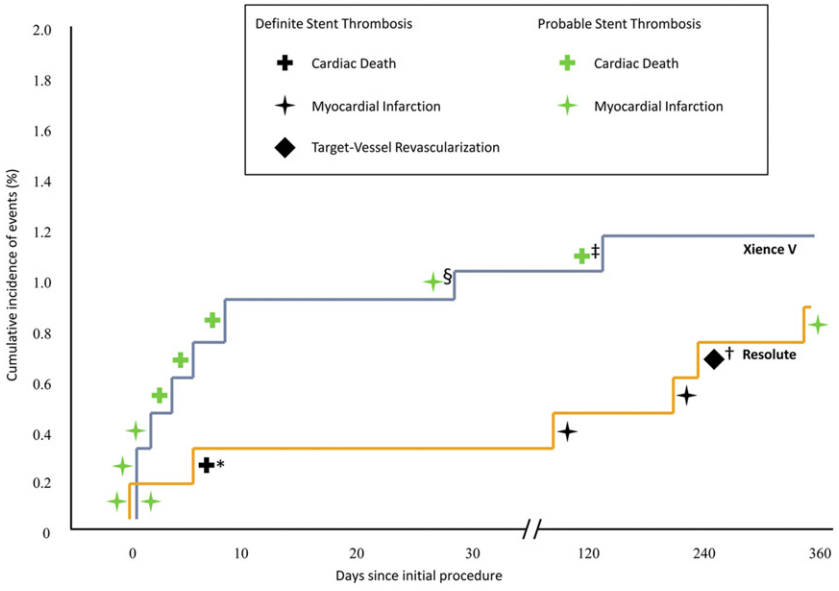

Figure 4 **Cumulative Incidence of Definite or Probable Stent Thrombosis**

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

Study limitations. This trial was performed in a high-volume tertiary center for PCI by 5 experienced operators with relatively uniform procedural strategies and liberal use of stent post-dilation; therefore, generalization of the results might be limited in other settings. The results of the TWENTE trial might not apply to patients with acute STEMI, because they were not studied in this trial. In addition, we did not pre-specify subgroup analysis; however, to avoid a subjective post hoc selection, we used the same subgroups as the Resolute All Comers trial (15).

Conclusions

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

Acknowledgments

The authors thank Dr. M. Brusse-Keizer from Medisch Spectrum Twente in Enschede for the opportunity to discuss our statistical analyses and for statistical advice.

Reprint requests and correspondence: Prof. Clemens von Birgelen, Thoraxcentrum Twente, Department of Cardiology, MST, Haaksbergerstraat 55, 7513ER Enschede, the Netherlands. E-mail: c.vonbirgelen@mst.nl.

REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
2. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
3. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9.
4. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
5. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
6. Basalus MW, van Houwelingen KG, Ankone MJ, Feijen J, von Birgelen C. Micro-computed tomographic assessment following extremely oversized partial postdilatation of drug-eluting stents. EuroIntervention 2010;6:141–8.
7. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
8. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006;2:286–94.
9. Tsuchida K, Piek JJ, Neumann FJ, et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial). EuroIntervention 2005;1:266–72.
10. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.
11. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. J Am Coll Cardiol Intv 2009;2:977–85.

12. Yeung AC, Leon MB, Jain A, et al. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. J Am Coll Cardiol 2011;57:1778–83.
13. Massberg S, Byrne RA, Kastrati A, et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. Circulation 2011;124:624–32.
14. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
15. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136–46.
16. Romagnoli E, Sangiorgi GM, Cosgrave J, Guillet E, Colombo A. Drug-eluting stenting: the case for post-dilation. J Am Coll Cardiol Intv 2008;1:22–31.
17. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
18. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871–4.
19. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440–7.
20. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998; 17:873–90.
21. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359: 1686–9.
22. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
23. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
24. Sakhuja R, Mauri L. Controversies in the use of drug-eluting stents for acute myocardial infarction: a critical appraisal of the data. Annu Rev Med 2010;61:215–31.
25. Windecker S. Clinical and angiographic outcomes in patients with acute myocardial infarction from the RESOLUTE All Comers open label randomized trial: RESOLUTE-AMI. Presented at: TCT 2010; September 22, 2010; Washington, DC.
26. Kereiakes DJ, Cutlip DE, Applegate RJ, et al. Outcomes in diabetic and nondiabetic patients treated with everolimus- or paclitaxel-eluting stents: results from the SPIRIT IV clinical trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System). J Am Coll Cardiol 2010;56:2084–9.
27. Stone GW, Kedhi E, Kereiakes DJ, et al. Differential clinical responses to everolimus-eluting and Paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. Circulation 2011;124:893–900.
28. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011;58:1569–77.
29. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011;377:1241–7.

Key Words: coronary artery disease ■ drug-eluting stent ■ percutaneous coronary intervention ■ randomized controlled trial.