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CME

Clinical Outcome Following Stringent Discontinuation of Dual Antiplatelet Therapy After 12 Months in Real-World Patients Treated With Second-Generation Zotarolimus-Eluting Resolute and Everolimus-Eluting Xience V Stents

2-Year Follow-Up of the Randomized TWENTE Trial

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Clinical Outcome Following Stringent Discontinuation of Dual Antiplatelet Therapy After 12 Months in Real-World Patients Treated With Second-Generation Zotarolimus-Eluting Resolute and Everolimus-Eluting Xience V Stents

2-Year Follow-Up of the Randomized TWENTE Trial

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 antiplatelet 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%, respectively (p = 0.63). Very late definite or probable stent thrombosis occurred only in 2 patients in each study arm (0.3% vs. 0.3%, p = 1.00).

Conclusions 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. (The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente [TWENTE]; NCT01066650) (J Am Coll Cardiol 2013;61:2406–16) © 2013 by the American College of Cardiology Foundation

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 of DES (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, the

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Abbreviations and Acronyms

DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLF = target lesion failure
TLR = target lesion revascularization
TVF = target vessel failure
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent(s)

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 mg once 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 patient's 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 MI (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

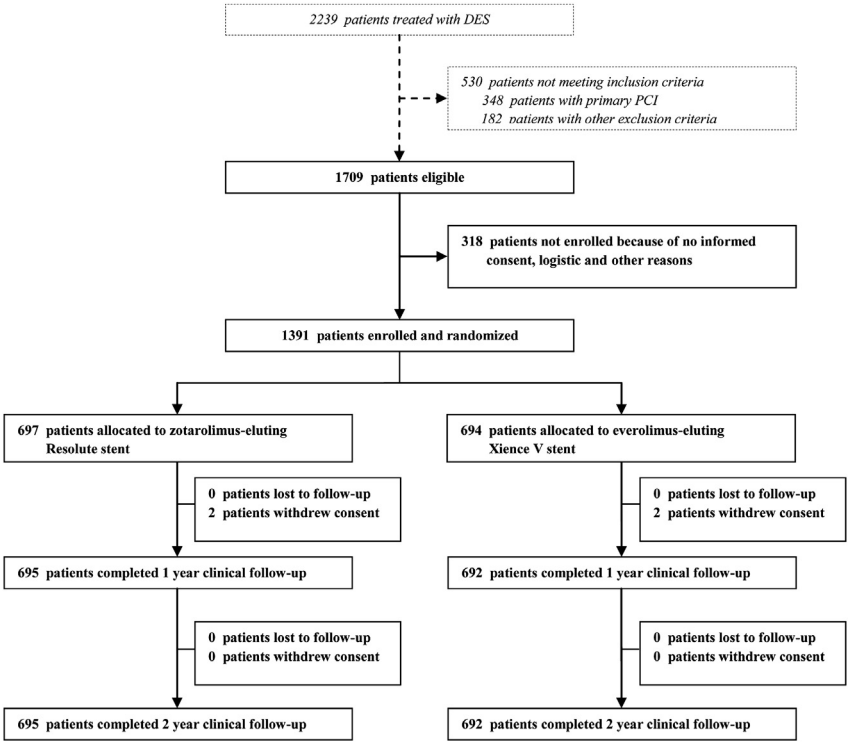

Figure 1 Study Flow Diagram

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

Table 1 Baseline Characteristics of Patients

Variable	Total Population (N = 1,391)	Resolute ZES (n = 697)	Xience V SES (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
Hypercholesterolemia	803/1,357 (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 coronary artery disease	740/1,309 (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 percutaneous coronary intervention	288 (20.7)	139 (19.9)	149 (21.5)	0.48
Previous coronary artery bypass grafting	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 myocardial infarction	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 number of lesions treated per patient				0.49
1	857 (61.6)	422 (60.5)	434 (62.7)	
2	393 (28.3)	198 (28.4)	195 (28.1)	
3 or more	141 (10.1)	77 (11.0)	64 (9.2)	
At least one off-label indication†	1,077 (77.4)	547 (78.5)	530 (76.4)	0.35
Total number of lesions treated	2,116	1,080	1,036	
Number of stents implanted per lesion	1.33 ± 0.62	1.31 ± 0.59	1.35 ± 0.64	0.09
Total stent length per lesion (mm)	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* was defined as a serum creatinine level ≥130 μmol/l. †*Off-label stent use* included renal insufficiency, an ejection fraction <30%, the occurrence of acute myocardial infarction within the previous 72 h, more than one lesion per 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. ‡Thrombus triggering use of thrombus aspiration catheters.

ACC = American College of Cardiology; AHA = American Heart Association.

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.

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,

Table 2 Two-Year Clinical Outcomes

	Resolute ZES (n = 695)	Xience V EES (n = 692)	Difference (95% Confidence Interval)	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 myocardial infarction				
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 target vessel revascularization				
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 target lesion revascularization				
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 myocardial infarction	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 endpoint†	114 (16.4)	118 (17.1)	−0.7 (−4.6 to 3.3)	0.75
Stent thrombosis				
Definite (0–720 days)	6 (0.9)	1 (0.1)	0.7 (−0.0 to 1.5)	0.12
Definite or probable (0–720 days)	8 (1.2)	10 (1.4)	−0.3 (−1.5 to 0.9)	0.63
Definite, probable, or possible (0–720 days)	14 (2.0)	20 (2.9)	−0.9 (−2.5 to 0.8)	0.29
Very late definite or probable (361–720 days)	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, and clinically indicated target lesion revascularization. †*Patient-oriented composite endpoint* is a composite endpoint of all-cause death, any myocardial infarction, and any revascularization.

angiographic, and procedural characteristics of all study patients are summarized in Table 1.

At 2-year follow-up, the composite primary endpoint of TVF occurred in 75 patients (10.8%) in the Resolute ZES group 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. 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).

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).

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 group 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.

The rates of ARC-defined definite 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 stent thrombosis were on acetylsalicylic acid monotherapy

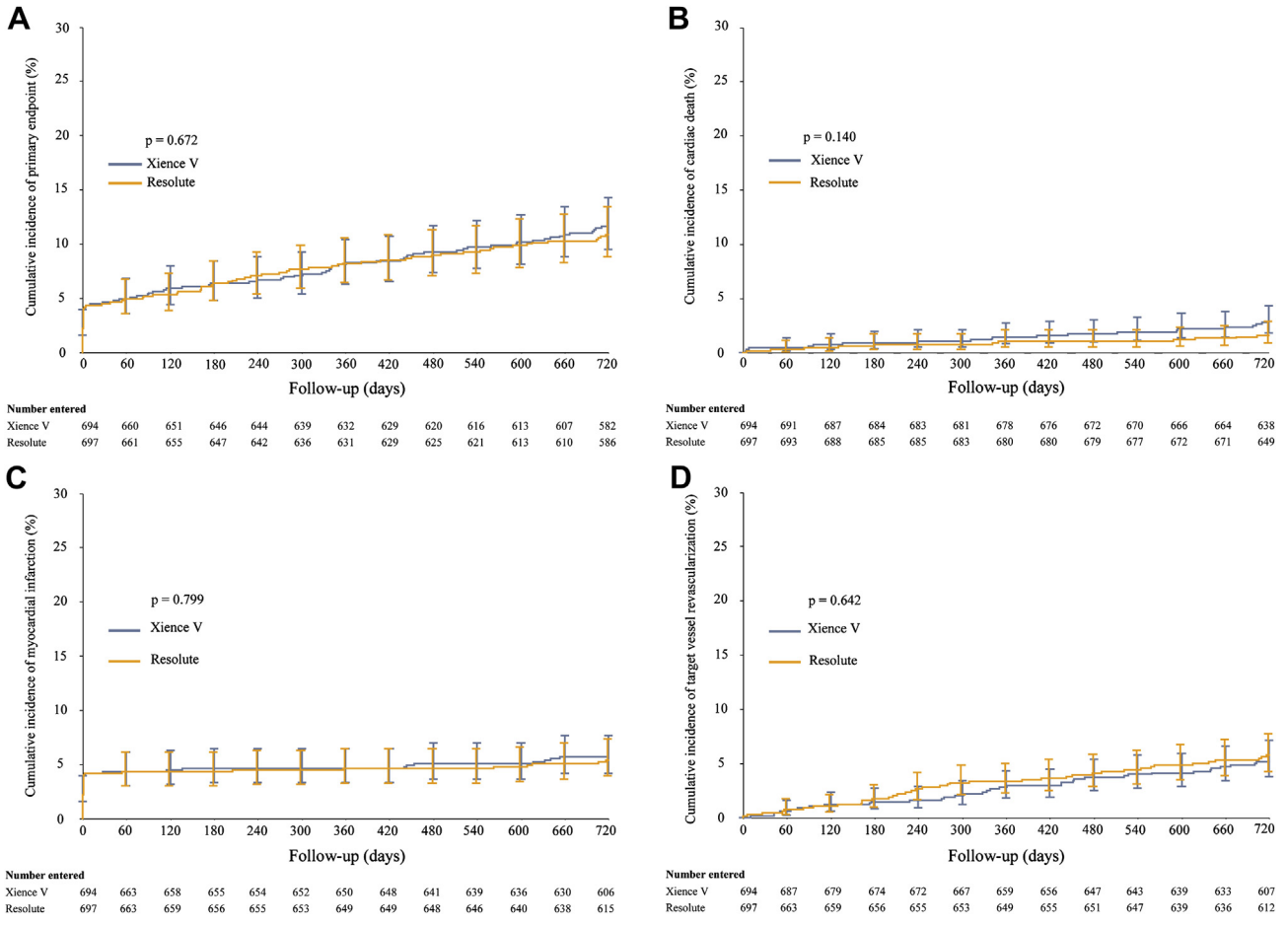

Figure 2 **Kaplan-Meier for Primary Endpoint and the Individual Components of the Primary Endpoint**

Kaplan-Meier cumulative incidence curves at 2 years for the primary endpoint, a composite of cardiac death, target vessel–related myocardial infarction, and 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.

beyond 1 year and there was no clear relation between stent thrombosis and discontinuation of DAPT, with a period of at least 79 days between very late stent thrombosis and discontinuation of DAPT.

Discussion

At the 2-year follow-up of the TWENTE trial, which followed a stringent approach of 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 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 second-generation 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

	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

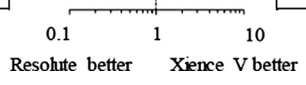

Figure 3 Subgroup Analysis: Target Vessel Failure at 2 Years

Target vessel failure is a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularization. CI = confidence interval; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

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 the Taxus 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

Table 3 Outcome Differences Between 1 and 2 Years

	Resolute ZWS	Xience V EES	Difference (95% Confidence Interval)	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 myocardial infarction	0.8 (5/649)	1.1 (7/650)	−0.3 (−1.4 to 0.7)	0.56
Clinically indicated target vessel revascularization	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 target lesion revascularization	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 endpoint†	6.0 (37/617)	7.4 (46/619)	−1.4 (−4.2 to 1.4)	0.31
Very late stent thrombosis (361–720 days)				
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, and clinically indicated target lesion revascularization. †*Patient-oriented composite endpoint* is a composite endpoint of all-cause death, any myocardial infarction, and any revascularization.

Table 4 Use of Acetylsalicylic Acid, Clopidogrel, and Dual Antiplatelet Therapy

	Resolute ZES	Xience V EES	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 1 year	615 (90.4)	633 (93.4)	
Less than 1 year	13 (1.9)	8 (1.2)	
Continued after 1 year	52 (7.7)	37 (5.5)	
DAPT			0.13
Stopped after 1 year	578 (85.0)	593 (87.5)	
Less than 1 year	57 (8.4)	57 (8.4)	
Continued after 1 year	45 (6.6)	28 (4.1)	
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 concomitant use of a vitamin K antagonist.
DAPT = dual antiplatelet therapy (acetylsalicylic acid and clopidogrel).

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

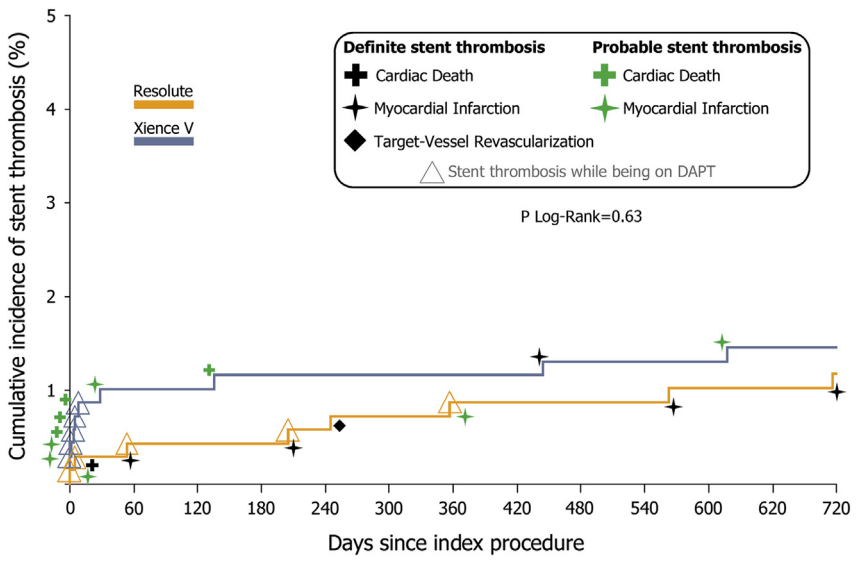

Figure 4 Cumulative Incidence of Definite or Probable Stent Thrombosis Over 2 Years

The cumulative incidence of definite or probable stent thrombosis in 2 years, according to the Academic Research Consortium definition. DAPT = dual antiplatelet therapy (acetylsalicylic acid and clopidogrel).

Table 5 Details on Definite or Probable Stent Thrombosis

Stent/ Thrombosis Type	Indication for PCI	Days to Stent Thrombosis After PCI	Days After Discontinuation of DAPT to Event	Target Vessel	Clinical Event After Stent Thrombosis	Use of Antiplatelet Therapy at Event
Resolute						
Probable	Stable angina	0	NA	RCX, LAD	MI	On DAPT (A + C)
Definite	Unstable angina	5	NA	LAD, RCA	Death	On DAPT (A + C)
Definite	Stable angina	54	NA	RCA, LAD	MI, TLR	On DAPT (A + C)
Definite	Stable angina	205	NA	RCX	MI, TLR	On DAPT (A + C)
Definite	NSTEMI	245	245*	RCA	MI, TLR	Off DAPT (C + VKA)
Probable	Stable angina	357	NA	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	NA	Vein graft, RCA	MI	On DAPT (A + C + VKA)
Probable	Unstable angina	0	NA	RCA	MI	On DAPT (A + C)
Probable	Stable angina	1	NA	RCX, LAD	MI	On DAPT (A + C)
Probable	NSTEMI	3	NA	LAD	Death	On DAPT (A + C)
Probable	NSTEMI	5	NA	RCA, LAD	Death	On DAPT (A + C)
Probable	Stable angina	8	NA	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.

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 of 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 all-comer 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%) (8,29) 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, single-center 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).

Conclusions

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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