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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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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 $\geq$ 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.

Key words: drug-eluting stent; percutaneous coronary intervention; TWENTE trial; off-label

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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 per 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 $\geq 70\%$, or $\geq 50\%$ 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 $\pm$ standard deviation 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. 1A). 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. 1B–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).

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.

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.

TABLE I. Characteristics of Patients and Procedures

	Resolute ZES ($N = 529$)	Xience V EES ($N = 504$)	*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/m^2)	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
Hypercholesterolemia	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 characteristics			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. of 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 or 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
Aorto-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 descendent	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)	
Postdilation	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, magnetic resonance imaging, or left ventricular 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.

Romagnoli et al. [9] observed cardiac death (3.4%), MI (7.2%; including 3.8% in-hospital MI), and TVR (6.7%). 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

TABLE II. Clinical Outcome

	Resolute ZES ($N = 529$)	Xience V EES ($N = 504$)	P-value
At 30-days			
TVF[a]	29 (5.5)	28 (5.6)	0.96
Cardiac death	1 (0.2)	3 (0.6)	0.36
All target vessel-related MI	27 (5.1)	27 (5.4)	0.86
TVR	2 (0.4)	–	0.50
At 1-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 $\leq$ 48 hr)	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 endpoint	68 (12.9)	58 (11.5)	0.51
Definite or probable stent thrombosis	5 (0.9)	7 (1.4)	0.51
At 2-years			
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 $\leq$ 48 hr)	27 (5.1)	25 (5.0)	0.92
Non-PMI target vessel MI (MI $>$ 48 hr)	5 (0.9)	9 (1.8)	0.24
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)			
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.

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.

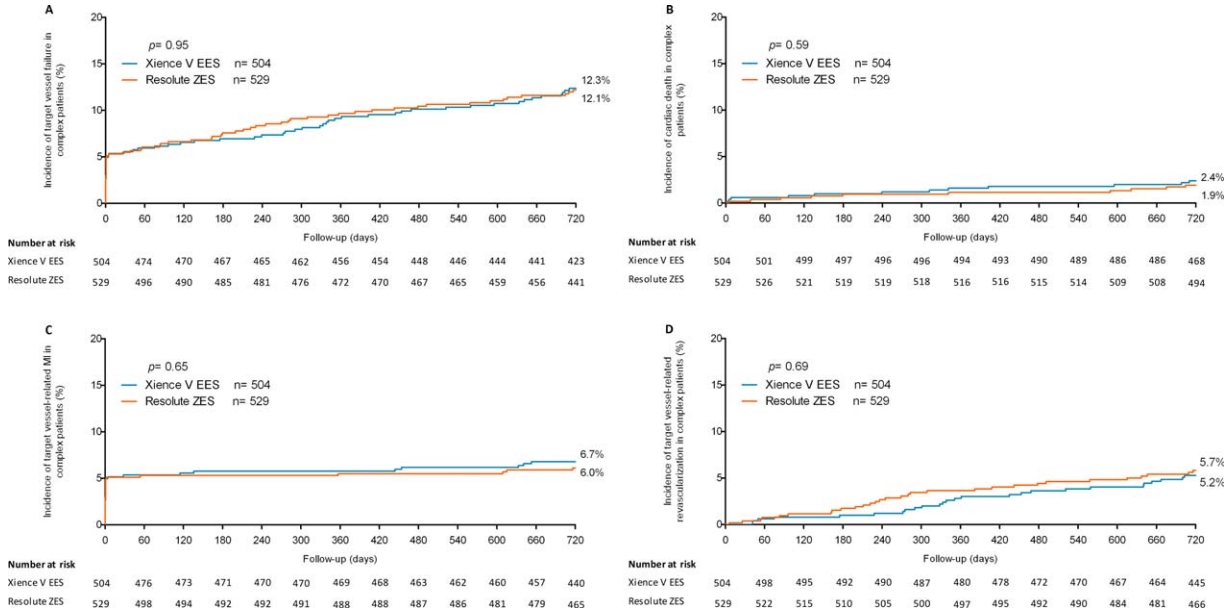

Fig. 1. Kaplan–Meier curves at 2-years for the composite primary endpoint and its individual components in patients treated with Resolute ZES and Xience V EES. (A) Kaplan–Meier cumulative incidence curves at 2-years for TVF, a composite of cardiac death, target vessel-related MI, or TVR for patients 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. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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 (%).

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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