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Five-Year Outcome After Implantation of Zotarolimus- and Everolimus-Eluting Stents in Randomized Trial Participants and Nonenrolled Eligible Patients

A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Long-term follow-up after a clinical trial of 2 often-used, newer-generation drug-eluting stents (DESs) in a broad patient population is of interest. Comprehensive long-term outcome of eligible nonenrolled patients has never been reported.

OBJECTIVE To assess 5-year safety and efficacy of 2 newer-generation DESs in randomized participants with non–ST-elevation acute coronary syndromes or stable angina and to evaluate long-term outcomes of nonenrolled eligible patients treated with the same DESs.

DESIGN, SETTING, AND PARTICIPANTS The TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial is an investigator-initiated, patient-blinded, randomized, comparative DES trial that enrolled patients from June 18, 2008, to August 26, 2010. Most patients had non–ST-elevation acute coronary syndromes and complex lesions. Of all 1709 eligible patients, 1391 (81.4%) were treated in the TWENTE trial with zotarolimus-eluting (ZES, n = 697) or everolimus-eluting (EES, n = 694) cobalt-chromium stents. The remaining 318 eligible patients (18.6%) were not enrolled but underwent nonrandomized treatment with the same DESs. Data were analyzed from August 26, 2015, to October 11, 2016. Event rates (percentages) were derived from log-rank analysis and may differ from straightforward calculation (nominator/denominator). The 5-year follow-up of the TWENTE participants was prespecified in the trial protocol; that of the nonenrolled participants was ad hoc.

MAIN OUTCOMES AND MEASURES Target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction, or target vessel revascularization.

RESULTS Of 1709 eligible participants, 1233 (72.1%) were men, 476 (27.9%) were women, and mean (SD) age was 64.6 (10.6) years. Among the 1370 of 1391 TWENTE trial participants (98.5% follow-up), TVF was similar between those in the ZES (16.1%) and EES (18.1%) groups ($P = .36$). Stent thrombosis rates were low: definite (7 of 697 [1.0%] vs 4 of 694 [0.6%]; $P = .37$) and occurred after more than 1 year in 3 (0.4%) with ZES vs 4 (0.6%) with EES ($P = .69$). The 318 nonenrolled eligible patients (308 patients [96.9%] of whom were followed up) were older and had more advanced disease than trial participants. Their TVF rate was higher than that of trial participants (71 of 318 [23.3%] vs 233 of 1391 [17.1%]; $P = .02$), which partly reflects a difference in cardiac mortality (23 of 318 [7.7%] vs 60 of 1391 [4.5%]; $P = .03$). Similar 5-year rates were found for myocardial infarction (91 of 1391 [6.7%] vs 22 of 318 [7.2%]; $P = .80$) and target vessel revascularization (129 of 1391 [9.7%] vs 34 of 318 [11.4%]; $P = .36$) between trial participants and nonenrolled eligible patients. In all eligible patients (ie, trial participants plus nonenrolled eligible patients), the TVF rate was only slightly higher than in trial participants only (18.3% vs 17.1%).

CONCLUSIONS AND RELEVANCE Long-term outcome data from nonenrolled eligible patients support the validity of the TWENTE trial findings and present, with the trial, a strong case for the long-term safety and efficacy of the newer-generation DESs used.

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Randomized clinical trials that compare novel drug-eluting stents (DESs) in large, greatly unrestricted patient populations are indispensable because they permit a reliable evaluation of the efficacy and safety of these devices.[1-8] Availability of long-term follow-up from such trials in all comers is a prerequisite for trustworthy judgment of the long-term effects of percutaneous coronary interventions (PCIs) using these devices.[5] However, almost all randomized clinical trials (RCTs) in broad patient and all-comer populations involve some selection.[9-11] Information on the clinical characteristics and short-term mortality of patients who did not participate in an RCT is infrequently reported.[4,12,13]

The zotarolimus-eluting stent (ZES) (Resolute; Medtronic Inc) and the everolimus-eluting stent (EES) (Xience V; Abbott Vascular) are newer-generation DESs that were developed to increase device biocompatibility and improve long-term outcomes.[2,3,14] The randomized TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial demonstrated noninferiority of the ZES vs EES in 1391 patients, representing 81.4% of all 1709 eligible patients of a broad population.[7] The Nonenrolled TWENTE registry compared the clinical characteristics and outcomes of the 1391 trial participants vs 318 nonenrolled eligible patients who were treated with the same DESs.[13] After 12 months, the rates of adverse events were fairly similar for all trial participants (treatment arms pooled) vs the nonenrolled eligible patients.[13]

Five-year outcome data from randomized comparisons of the ZES and EES are of clinical interest but are so far only available from the RESOLUTE AC (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial.[15] In addition, long-term outcome data from eligible nonenrolled patients treated with the same stents as the randomized patients have not yet been reported. In the present study, we report the 5-year clinical outcomes of patients enrolled in the randomized TWENTE trial and eligible nonenrolled patients.

Key Points

Questions Are newer-generation drug-eluting stents safe and efficacious at the 5-year follow-up, and do outcomes of eligible nonenrolled patients treated with the same stents support the randomized clinical trial findings?

Findings In this secondary analysis of the TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) randomized clinical trial, which examined 81% of all the eligible patients, the rate of the main composite clinical end point of target vessel failure was similar for zotarolimus- and everolimus-eluting stents. In all eligible patients, the event rate was only slightly higher than in trial participants only.

Meaning At long-term follow-up of this randomized clinical trial, newer-generation stents were safe and efficacious, and the outcomes of nonenrolled eligible patients support the trial's validity.

Methods

Study Design and Patient Populations

The TWENTE trial is an investigator-initiated, patient-blinded, randomized, comparative DES trial with limited exclusion criteria.[7] During the RCT, nonenrolled eligible patients were treated at the operator's discretion with one of the European Conformity–certified DESs that were also examined in the randomized trial (ie, ZES or EES), using the same routine clinical and procedural strategies. The RCT and registry complied with the Declaration of Helsinki[16] for investigation in human beings and were approved by the medical ethical committee of Twente and the institutional review board. All participants in the RCT provided written informed consent. For the Nonenrolled TWENTE registry, patients were not required to change their behavior or take action other than following their regular treatment; therefore, according to Dutch law and as approved by the medical ethical committee of Twente, written informed consent from patients in this registry was not required.

Patients were enrolled in the TWENTE trial from June 18, 2008, to August 26, 2010, at Thoraxcentrum Twente, Enschede, the Netherlands. Patients were randomized in a 1:1 ratio for treatment with the cobalt-chromium ZES or EES. No limit for lesion length, reference vessel size, number of target lesions, or number of vessels to be treated was applied. The main exclusion criterion was an ST-segment elevation myocardial infarction (MI) before PCI (<48 hours).[7] Outcomes of the TWENTE trial participants were reported until the 3-year follow-up.[17,18] Operators generally avoided the use of different stents in a single patient. Procedural details and the 12-month clinical course of the nonenrolled eligible patients have been published elsewhere.[13] The outcomes of all eligible patients were followed up as participants of the TWENTE trial or within the Nonenrolled TWENTE registry. Stent-level analyses were only performed in participants of the TWENTE trial.

Definition of Clinical End Points

The same end point definitions were applied in the Nonenrolled TWENTE registry as used for the randomized TWENTE trial.[7,13] Clinical end points, including stent thrombosis, were defined according to the Academic Research Consortium, including the addendum on the definition of MI.[19,20] The prespecified main end point of the RCT—target vessel failure (TVF)—was composed (in hierarchical order) of cardiac death, target vessel–related MI, or clinically indicated target vessel revascularization.[9] Death was considered cardiac unless an unequivocal noncardiac cause could be established. Myocardial infarction was defined by any creatine kinase concentration of more than double the upper reference limit with elevated confirmatory cardiac biomarkers.[20] A target vessel–related MI was related to the target vessel or could not be related to another vessel; further MI classification was based on laboratory, electrocardiographic, angiographic, and/or clinical data.[7,20] Revascularization procedures were considered clinically indicated if the visually assessed angiographic percentage diameter of stenosis was at least 50% in the presence of ischemic signs or symptoms or if the diameter stenosis was at least 70% irrespective of ischemic signs or symptoms.[20]

Table 1. Five-Year Clinical Outcome of TWENTE Randomized Trial Participants According to Assigned DES

Outcome	DES Group, No. (%)[a]		HR (95% CI)	*P* Value for Log-Rank Test
	ZES (n = 697)	EES (n = 694)		
Death				
Any	62 (9.0)	80 (11.6)	0.77 (0.55-1.07)	.12
Cardiac death	25 (3.7)	35 (5.2)	0.71 (0.42-1.18)	.18
MI				
Any	49 (7.2)	52 (7.7)	0.94 (0.63-1.38)	.73
Target vessel–related	46 (6.8)	45 (6.6)	1.02 (0.67-1.53)	.94
Revascularization				
Any	95 (14.1)	105 (15.9)	0.90 (0.68-1.18)	.43
Clinically indicated target				
Vessel	60 (8.9)	69 (10.5)	0.86 (0.61-1.22)	.41
Lesion	47 (7.0)	50 (7.7)	0.94 (0.63-1.40)	.77
Target				
Vessel failure	110 (16.1)	123 (18.1)	0.89 (0.69-1.15)	.36
Lesion failure	102 (15.0)	110 (16.2)	0.93 (0.71-1.21)	.58
Major adverse cardiac events	138 (19.9)	157 (22.7)	0.88 (0.70-1.10)	.26
Patient-oriented composite end point	176 (25.4)	196 (28.4)	0.89 (0.73-1.10)	.27
Definite or probable stent thrombosis	13 (1.9)	14 (2.1)	0.92 (0.43-1.96)	.83
Definite stent thrombosis	7 (1.0)	4 (0.6)	1.74 (0.51-5.94)	.37

Abbreviations: DES, drug-eluting stent; EES, everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; TWENTE, Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente; ZES, zotarolimus-eluting stent.

[a] Five-year follow-up information was obtained from 1370 of 1391 participants (98.5%) in the TWENTE trial, including 683 of 697 (98.0%) in the ZES group (Resolute; Medtronic Inc) and 687 of 694 (99.0%) in the EES group (Xience V; Abbott Vascular). Data were analyzed using the Kaplan-Meier method, which implies that patients who could not be followed up for the entire 5 years because of death, consent withdrawal, or loss to follow-up were censored at the exact moment of dropout. Please note that the percentages provided in the Table may therefore differ slightly from the results of straightforward calculations of nominator divided by denominator.

Prespecified secondary end points included the individual components of TVF, all-cause mortality, and stent thrombosis. Further composite end points included target lesion failure (cardiac death, target vessel–related MI, or clinically indicated target lesion revascularization), major adverse cardiac events (all-cause death, any MI, emergent coronary bypass surgery, or clinically indicated target lesion revascularization), and a more global patient-oriented composite end point (all-cause death, any MI, or any coronary revascularization).

Acquisition and Analysis of Clinical Follow-up Data

We obtained clinical follow-up data at visits to outpatient clinics, by medical questionnaire, and/or by telephone follow-up (with staff blinded to the assigned DES). The contract research organization CardioResearch Enschede BV, Enschede, the Netherlands, coordinated the trial and data management. The independent contract research organizations Cardialysis, Rotterdam, the Netherlands, and Diagram, Zwolle, the Netherlands, which were blinded to the assigned DES, performed the adjudication of adverse clinical events for all patients. Angiographic analysts performed a visual assessment of target lesion characteristics offline.

Assessment of Reasons for Nonenrollment and Potential Selection

To identify the explicitly stated and implicit reasons for nonenrollment of eligible patients, 5 members of the research group reviewed all medical files available. If the reason for nonenrollment was not explicitly stated, the presumed reason for nonenrollment was retrospectively established by consensus of the committee members. Reasons for nonenrollment were classified into 1 of the following categories: (1) explicit refusal of the informed patient; (2) inability of the operator to obtain informed consent (eg, owing to severe anxiety or partial deafness); (3) logistic aspects (eg, no randomization envelopes available, forgotten to randomize, or time pressure); (4) omission of informing the patient before treatment on the ward; and (5) unknown. In the absence of (conceivable) reasons, the committee also searched for indications of potential selection, which was suspected if vessels with particularly high risk were treated (eg, left main stem, degenerated vein grafts, or all 3 coronary arteries) or if operators indicated an increased procedural risk, high technical complexity of the procedure, or serious comorbidities.

Statistical Analysis

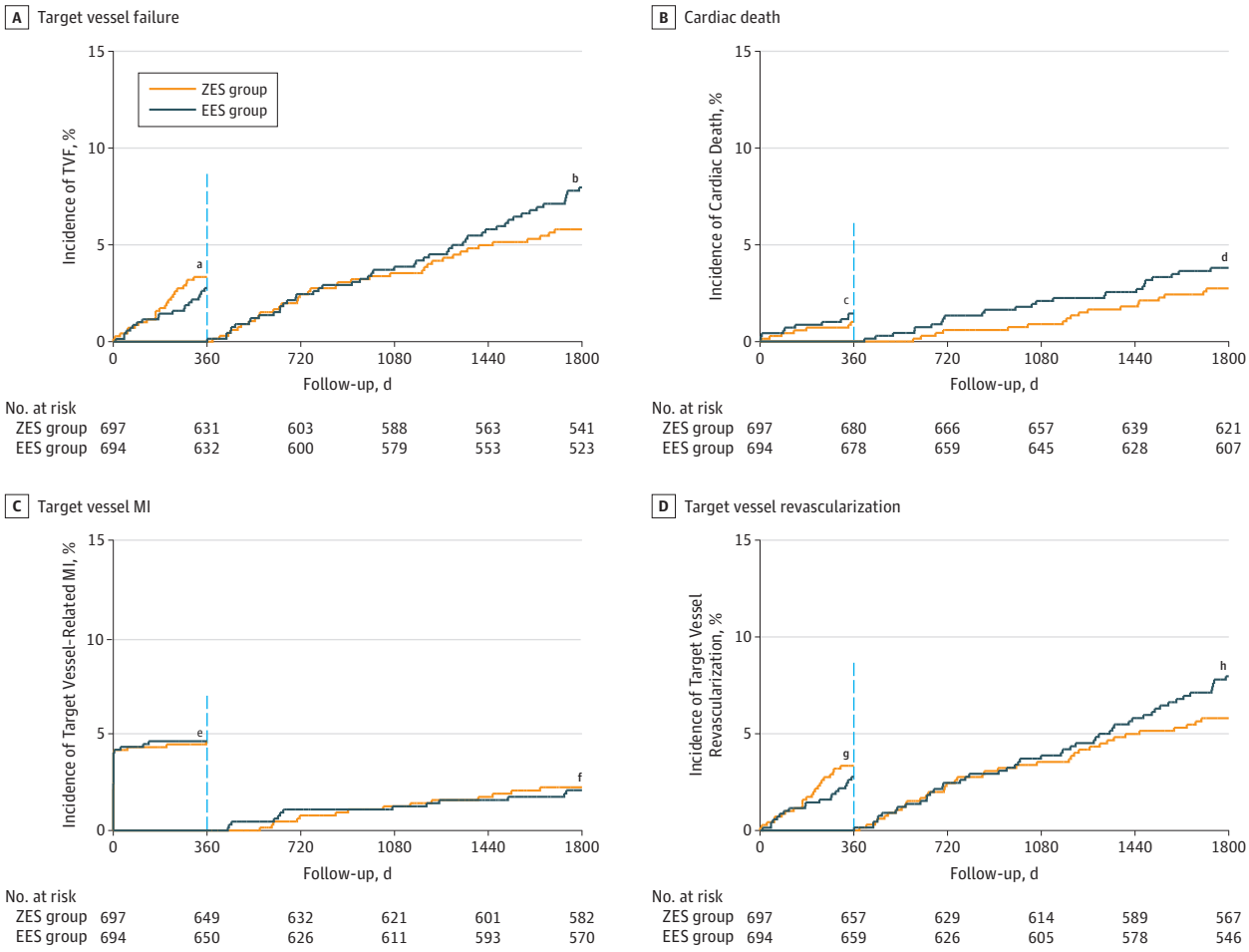
Data were analyzed from August 26, 2015, to October 11, 2016. The 5-year follow-up of the TWENTE participants was prespecified in the trial protocol; that of the nonenrolled participants was ad hoc. Analyses were based on intention to treat using SPSS software (version 22.0; SPSS Inc). Categorical variables were assessed with the use of χ^2 or Fisher exact tests, whereas continuous variables were assessed with the Wilcoxon rank sum test or 1-sample *t* test. The time to the main end point and its components was assessed according to the Kaplan-Meier method, and the log-rank test was applied to compare groups. Therefore, percentages of outcome factors may differ slightly from the results of a straightforward calculation of nominator divided by denominator. We calculated hazard ratios using Cox proportional hazards regression analysis. Logistic regression was used to test for interaction between subgroups and stent type with respect to the main end point. Unless otherwise specified, *P* values and CIs were 2 sided. $P < .05$ was considered significant.

Results

Clinical Outcome of the TWENTE Trial

A total of 1709 eligible participants (1233 men [72.1%] and 476 women [27.9%]; mean [SD] age, 64.6 [10.6] years) were

Figure 1. Kaplan-Meier Cumulative Event Curves for Stent Groups



Kaplan-Meier cumulative incidence curves at 5 years are given for participants in the randomized TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial for the zotarolimus-eluting stent (ZES) (Resolute; Medtronic Inc) and the everolimus-eluting stent (EES) (Xience V; Abbott Vascular) for target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction (MI), or target vessel revascularization.

[a] $P = .94$ for comparison between groups, log-rank test.

[b] $P = .18$ for comparison between groups, log-rank test.

[c] $P = .46$ for comparison between groups, log-rank test.

[d] $P = .28$ for comparison between groups, log-rank test.

[e] $P = .99$ for comparison between groups, log-rank test.

[f] $P = .87$ for comparison between groups, log-rank test.

[g] $P = .54$ for comparison between groups, log-rank test.

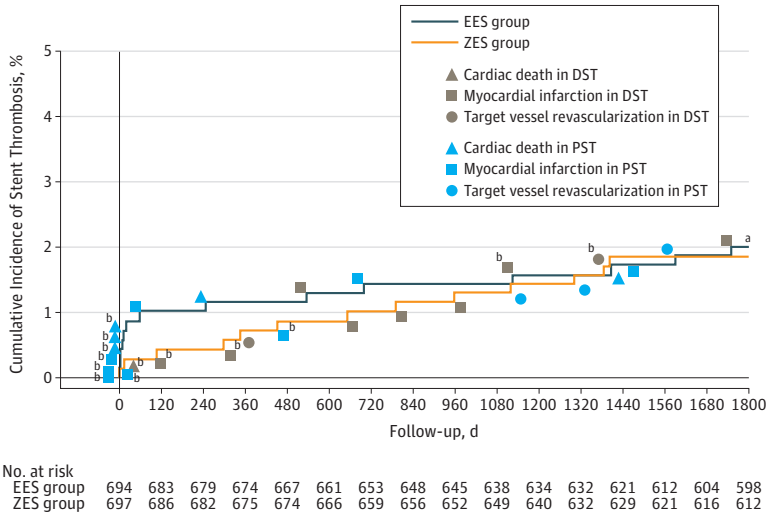
[h] $P = .15$ for comparison between groups, log-rank test.

included in the analysis. Of 1391 TWENTE trial participants (1009 men [72.5%]; 382 women [27.5%]), 5-year follow-up was obtained from 1370 (98.5%), including 683 of 697 patients (98.0%) randomized to ZES and 687 of 694 (99.0%) randomized to EES (eFigure 1 in the Supplement). Between stent groups, no difference was found in baseline patient, lesion, and procedural characteristics (eTable 1 in the Supplement). At the 5-year follow-up, 61 of the 1228 trial participants (5.0%) were receiving dual antiplatelet therapy without any between-stent difference.

The main end point of TVF was met by 110 of 697 patients (16.1%) in the ZES group vs 123 of 694 (18.1%) in the EES group (hazard ratio, 0.89; 95% CI, 0.69-1.15; $P = .36$) (**Table 1** and **Figure 1**). No significant difference was seen in the individual components of TVF, including cardiac death (25 of 697 [3.7%] vs 35 of 694 [5.2%]; $P = .18$), target vessel–related MI (46 of 697 [6.8%] vs 45 of 694 [6.6%]; $P = .94$), and clinically driven target vessel revascularization (60 of 697 [8.9%] vs 69 of 694 [10.5%], respectively; $P = .41$). In addition, the rates of other composite end points were similar for both DESs (Table 1). An exploratory subgroup analysis of the main end point of TVF showed consistent results across subgroups, with the only exception being single-vessel treatment, favoring ZES (67 of 523 [12.8%] vs 92 of 532 [17.3%], respectively; $P = .05$; $P = .03$ for interaction) (eFigure 2 in the Supplement).

For ZES and EES, the rates of definite (7 of 697 [1.0%] vs 4 of 694 [0.6%]; $P = .37$) and definite or probable (13 of 697 [1.9%] vs 14 of 694 [2.1%], respectively; $P = .83$) stent thrombosis were low and similar (**Figure 2**). Very late definite stent thrombosis (>1 year) occurred in 3 patients in the ZES group (0.4%) vs 4

Figure 2. Cumulative Incidence of Definite (DST) or Probable (PST) Stent Thrombosis in the Randomized Trial



Data include participants in the randomized TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial for the zotarolimus-eluting stent (ZES) (Resolute; Medtronic Inc) and the everolimus-eluting stent (EES) (Xience V; Abbott Vascular). Stent thrombosis was adjudicated by the Academic Research Consortium definition.

[a] $P = .83$ for comparison between groups, log rank test.

[b] Indicates dual antiplatelet therapy (acetylsalicylic acid plus P2Y12 receptor antagonist).

patients in the EES group (0.6%) ($P = .69$). In eTable 2 in the Supplement, annual cumulative event rates for both stent groups are presented.

Nonenrolled Eligible Patient Population

Five-year follow-up data were available for 308 of 318 eligible patients (96.9%) (224 men [70.4%]; 94 women [29.6%]) who had not been enrolled in the randomized trial (eFigure 1 in the Supplement). Reasons for nonenrollment included (1) explicit refusal to participate (33 of 318 [10.4%]); (2) inability to obtain informed consent (57 [17.9%]); (3) logistic aspects (40 [12.6%]); (4) omission of informing the patient before treatment (113 [35.5%]); and (5) unknown reasons (75 [23.6%]). Indications of potential selection were found in 61 of 318 (19.2%) nonenrolled eligible patients, representing 3.6% of all 1709 eligible patients. Nonenrolled eligible patients were significantly older than randomized participants (66.0 [10.9] vs 64.2 [10.8] years; $P = .01$), significantly more often had a history of MI (137 [43.1%] vs 450 [32.4%]; $P < .001$), PCI (92 [28.9%] vs 288 [20.7%]; $P = .001$), and bypass surgery (54 [17.0%] vs 148 [10.6%]; $P = .002$), and significantly more often had chronic renal failure (21 [6.6%] vs 38 [2.7%]; $P = .001$) and a left ventricular ejection fraction of less than 30% (13 of 199 [6.5%] vs 32 of 1051 [3.0%]; $P = .02$). In addition, they were treated more often for complex target lesions (355 of 466 [76.2%] vs 1484 of 2116 [70.1%]; $P = .009$) and in-stent restenosis (37 of 466 [7.9%] vs 75 of 2116 [3.5%]; $P < .001$) (eTable 3 in the Supplement). At the 5-year follow-up, 19 of 264 patients (7.2%) were receiving dual antiplatelet therapy ($P = .15$ vs RCT participants).

TWENTE Trial Participants vs Nonenrolled Eligible Patients

The TWENTE trial participants and nonenrolled eligible patients differed in TVF (233 of 1391 [17.1%] vs 71 of 318 [23.3%]; $P = .02$), which was partly attributable to a difference in cardiac death (60 of 1391 [4.5%] vs 23 of 318 [7.7%]; $P = .03$). The Kaplan-Meier curves showed that, until the 4-year follow-up, the cardiac death rates were similar, after which the slope of the curve increased for nonenrolled patients (**Figure 3**). Both patient groups had quite similar 5-year rates of target vessel–related MI (91 of 1391 [6.7%] vs 22 of 318 [7.2%]; $P = .80$) and target vessel revascularization (129 of 1391 [9.7%] vs 34 of 318 [11.4%]; $P = .36$). The 5-year definite-or-probable stent thrombosis rate was low in trial participants and nonenrolled eligible patients (27 of 1391 [2.0%] vs 3 of 318 [1.0%]; $P = .23$). Further outcome data are presented in **Table 2**, and landmark analyses for TVF and its components are presented in eFigure 3 in the Supplement.

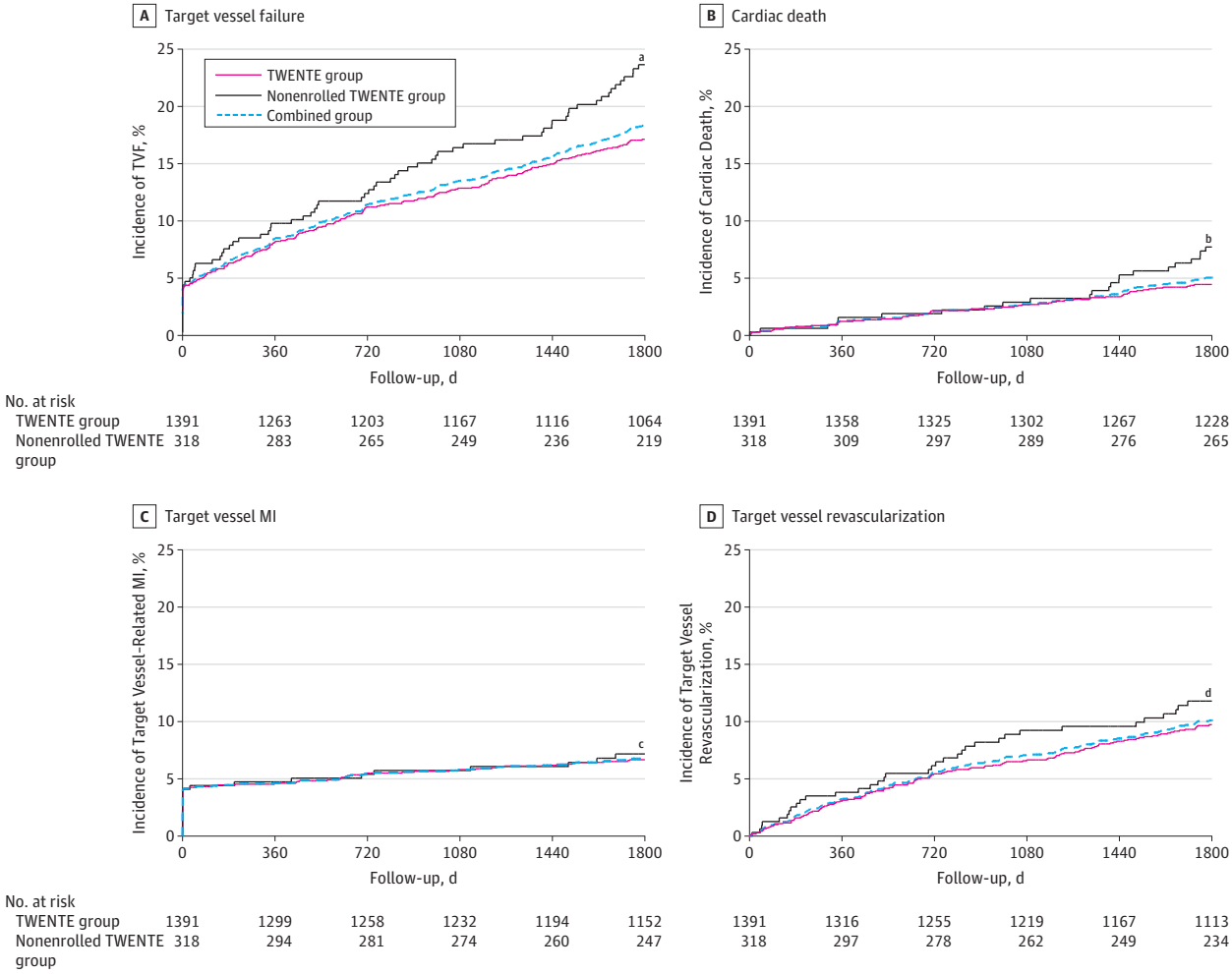
Table 2 also shows the event rates of all eligible patients (ie, a pooled population of trial participants and nonenrolled eligible patients). The 5-year TVF rate was 304 of 1709 (18.3%) in all eligible patients and 233 of 1391 (17.1%) in randomized trial participants only (stent arms pooled); this finding is also visualized in eFigure 4 in the Supplement.

Discussion

Randomized studies generally do not randomize every eligible patient and are therefore susceptible to selection.[9-11] The TWENTE trial enrolled a large proportion of all eligible patients (81.4%), whereas excellent multicenter DES trials[9-11] previously enrolled 40% of eligible patients or did not report such details. Minor selection cannot be excluded and may—from a clinician's perspective—sometimes appear reasonable in patients with end-stage coronary heart disease or excessive comorbidities. The present analysis is special in that it reports long-term outcome data from the randomized trial and a registry of nonenrolled eligible patients, which together provide unique, complementary insights.

In the present study, TWENTE trial participants treated with ZES vs EES showed 5-year TVF rates that were relatively low (16.1% vs 18.1%) in both treatment arms, as were the rates of the individual components of TVF. Our findings are in line with those of other RCTs that compared similar ZESs and

Figure 3. Kaplan-Meier Cumulative Event Curves for All Comers



Kaplan-Meier cumulative incidence curves at 5 years are given for the randomized TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial participants (n = 1391), nonenrolled eligible patients (n = 318), and both groups combined (n = 1709) for target vessel failure (TVF), a composite of cardiac death, target vessel–related myocardial infarction (MI), or target vessel revascularization. Blue dotted lines represent the cumulative event incidence for the pooled patient population of TWENTE trial participants and nonenrolled eligible patients.

[a] $P = .02$ for comparison between groups, log-rank test.

[b] $P = .03$ for comparison between groups, log-rank test.

[c] $P = .80$ for comparison between groups, log-rank test.

[d] $P = .36$ for comparison between groups, log-rank test.

EESs,[3,8,21,22] network meta-analyses that—among other DESs—constituted the 2 DESs assessed in the TWENTE trial,[23,24] and a dedicated meta-analysis.[25]

Comprehensive information was available also on the long-term outcome of nonenrolled eligible patients, who were treated in a nonrandomized fashion with the same DESs. The adverse events of these 2 patient populations were adjudicated by the same independent clinical event committee, which further increases the usefulness of these data. Moreover, 5-year follow-up rates of trial participants and nonenrolled eligible patients were high (98.5% and 96.9%, respectively). In nonenrolled eligible patients, who were older and more often had a history of coronary revascularizations and MI than RCT participants, the TVF rate was higher (23.3% vs 17.1%). Until the 4-year follow-up, the rate of cardiac death remained similar in both patient groups. During the fifth year of follow-up, cardiac mortality increased more noticeably in the nonenrolled patients. The 5-year cardiac death rate (7.7% vs 4.5%) reflected the more advanced age and disease stage of the nonenrolled patients and contributed to the aforementioned difference in TVF. Our data suggest that if all eligible patients had been randomized, clinical event rates might still have been favorable and, in general, only slightly higher than those actually obtained for the randomized population. Hence, the long-term outcome data from the nonenrolled eligible patients support the external validity and findings of the TWENTE trial.

Previous Studies Addressing Nonenrolled Patients

Patients enrolled in coronary intervention trials are often not fully representative of patients in clinical practice.[9-11] Never-

Table 2. Five-Year Clinical Outcomes of the TWENTE Randomized Trial Participants vs Nonenrolled Eligible Patients

Outcome	Population, No. (%)[a]			HR (95% CI)	*P* Value for Log-Rank Test
	All Eligible Patients (n = 1709)	TWENTE Trial (n = 1391)	Nonenrolled Eligible Patients (n = 318)		
Death					
Any	185 (10.9)	142 (10.3)	43 (13.8)	0.74 (0.52-1.04)	.08
Cardiac death	83 (5.0)	60 (4.5)	23 (7.7)	0.58 (0.36-0.94)	.03
MI					
Any	129 (7.8)	101 (7.5)	28 (9.3)	0.82 (0.54-1.24)	.34
Target vessel-related	113 (6.8)	91 (6.7)	22 (7.2)	0.94 (0.59-1.50)	.80
Revascularization					
Any	250 (15.3)	200 (15.0)	50 (16.7)	0.89 (0.65-1.21)	.45
Clinically indicated target					
Vessel	163 (10.0)	129 (9.7)	34 (11.4)	0.84 (0.57-1.22)	.36
Lesion	123 (7.6)	97 (7.3)	26 (8.7)	0.83 (0.54-1.27)	.38
Target					
Vessel failure	304 (18.3)	233 (17.1)	71 (23.3)	0.73 (0.56-0.95)	.02
Lesion failure	277 (16.6)	212 (15.6)	65 (21.3)	0.73 (0.55-0.96)	.02
Major adverse cardiac events	382 (22.5)	295 (21.3)	87 (27.8)	0.75 (0.59-0.95)	.02
Patient-oriented composite end point	476 (28.0)	372 (26.9)	104 (33.2)	0.79 (0.63-0.98)	.03
Definite or probable stent thrombosis	30 (1.8)	27 (2.0)	3 (1.0)	2.03 (0.62-6.71)	.23
Definite stent thrombosis	12 (0.7)	11 (0.8)	1 (0.3)	2.47 (0.32-19.15)	.37

Abbreviations: HR, hazard ratio; MI, myocardial infarction; TWENTE, Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente.

[a] Five-year follow-up information was obtained from 1370 of 1391 participants (98.5%) in the TWENTE trial and 308 of 318 (96.9%) nonenrolled eligible patients. Data were analyzed using the Kaplan-Meier method, which implies that patients who could not be followed up for the entire 5 years because of death, consent withdrawal, or loss to follow-up were censored at the exact moment of dropout. Please note that the percentages provided in the Table may therefore differ slightly from the results of straightforward calculations of nominator divided by denominator.

theless, data on the clinical outcome of eligible nonenrolled patients or of all nonparticipants (ie, nonenrolled eligible plus per-protocol excluded patients) are scarce. High-quality clinical trials occasionally report the clinical characteristics of the nonparticipating patients to provide insight into the degree (or the absence) of selection.[4] A single high-volume PCI center reported baseline characteristics and 12-month all-cause mortality of 579 patients who participated in 2 randomized all-comer trials[12] and compared these data with the mortality of 663 nonparticipants. Baseline characteristics differed significantly between trial participants and nonparticipants, with the latter being older and having more heart failure and unstable clinical syndromes, and finally a significantly higher 1-year all-cause mortality (6.9% vs 3.1%).[12] Because the nonparticipants included patients with exclusion criteria (eg, cardiogenic shock) and the outcome was focused on 12-month all-cause mortality,[12] a meaningful comparison with the 5-year outcome of the Nonenrolled TWENTE registry cannot be made. Nevertheless, in our study, 5-year all-cause mortality also tended to be higher in nonenrolled eligible patients than in trial participants (43 [13.8%] vs 142 [10.3%]).

Previous Randomized Studies With 5-Year Follow-up Comparing Newer-Generation DESs

Newer-generation durable polymer DESs have previously been assessed in randomized trials with long-term follow-up. In patients with low to moderate procedural risk in the SPIRIT III (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System) trial, the 5-year rate of TVF was lower in patients using the EES than in those using early-generation paclitaxel-eluting stents (19.3% vs 24.5%).[26] At the 5-year follow-up of the COMPARE (Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) trial, all comers treated with the EES (Xience V) showed significantly lower rates of various composite end points than patients treated with paclitaxel-eluting stents, including TVF (12.6% vs 17.8%) and definite or probable stent thrombosis (3.1% vs 5.9%).[27] In the 5-year results of the SORT OUT IV (Danish Organization of Randomized Trials with Clinical Outcome) trial, the composite end point of major adverse cardiac events and definite stent thrombosis was significantly lower in all-comer patients treated with the EES (Xience V) than in patients treated with early-generation sirolimus-eluting stents (14.0% vs 17.4% and 0.4% vs 2.0%, respectively).[28] Moreover, in the EXAMINATION (Clinical Evaluation of the Xience V Stent in Acute Myocardial Infarction) trial, the use of EES in patients with acute ST-segment elevation MI resulted in a lower 5-year mortality than treatment with bare-metal stents (8.7% vs 11.8%).[29] The randomized RESOLUTE AC trial has reported 5-year outcome data, showing similar efficacy and safety of ZES (Resolute) and EES in an all-comer population (rate of TVF, 20.0% vs 19.1%).[15] The outcome of the randomized TWENTE trial supports these findings in general. The exploratory subgroup analysis for the main end point of TVF also showed consistent results, with single-vessel treatment being the only exception (favoring ZES), which may most likely reflect a play of chance.

Limitations

Scientific evidence from multicenter trials is generally considered higher ranking than that from single-center trials. Our conclusions do not apply to patients with acute ST-segment elevation MI undergoing primary PCI because such patients were not studied. Patients with acute ST-segment elevation MI are of considerable interest for the assessment of novel stents,[30] whereas their enrollment may be challenging. The subgroup analysis was not prespecified but assessed the same sub-

groups as the RESOLUTE AC trial.[3] Results of comparisons between nonenrolled eligible patients and the trial population are hypothesis generating.

Conclusions

At the 5-year follow-up, the second-generation DESs used in the RCT showed favorable and similar long-term results in a broad patient population, most of whom were treated for non–ST-segment elevation acute coronary syndromes and complex coronary lesions. Outcome data from nonenrolled eligible patients support the validity of the randomized TWENTE trial and present, with the results of the randomized trial, a strong case for the long-term safety and efficacy of both devices. Moreover, these data underline the importance of aiming at high study enrollment.

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