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Women Treated with Second-Generation Zotarolimus-Eluting Resolute Stents and Everolimus-Eluting Xience V Stents: Insights from the Gender-Stratified, Randomized, Controlled TWENTE Trial

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Background: Women are underrepresented in clinical research, and few data are available from randomized head-to-head comparisons of second-generation drug-eluting stents (DES) in *female* patients. Aim of this study was to assess safety and efficacy of two second-generation DES in women. In TWENTE—a prospective, randomized, comparative DES trial—"real-world" patients were stratified for gender before randomization for Resolute or Xience V stents. Methods: Target vessel failure (TVF; cardiac death, target vessel-related myocardial infarction, and clinically indicated target vessel revascularization) after 1 year was the predefined endpoint. Results: Among 1,391 patients, 382 (27.5%) women were randomized to Resolute ($n = 192$) and Xience V ($n = 190$). Baseline and procedural characteristics were similar for females in both study arms, except for smaller vessel and stent diameters in Resolute-treated lesions. After 1 year, TVF (8.9 vs. 8.4%; adjusted odds ratio [OR]: 0.95, 95% confidence interval [CI]: 0.41–2.20, $P = 0.91$) and a patient-oriented composite endpoint (13.0 vs. 12.1%, $P = 0.79$) did not differ significantly between women in both arms. Women were older than men ($P < 0.01$) and had more often diabetes mellitus (26.4 vs. 19.8%, $P = 0.01$) and hypertension (63.6 vs. 52.5%, $P < 0.01$), but there was no significant gender difference in TVF (adjusted OR: 1.18, 95% CI: 0.73–1.92, $P = 0.50$). Conclusions: This gender-stratified TWENTE trial analysis resulted in no significant difference in safety and efficacy outcomes between Resolute- and Xience V-treated females.

Key words: drug-eluting stent(s); gender; Xience V; Resolute; women; percutaneous coronary intervention

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INTRODUCTION

In many countries with a Western lifestyle, cardiovascular disease is a leading cause of death for both genders. However, women are often underrepresented in cardiovascular research [1–3]. Less than one-third of all cardiovascular clinical trials report sex-specific results, and most trials include fewer women [4,5]. Percutaneous coronary intervention (PCI) trials previously demonstrated an improvement in clinical outcome in women with first-generation drug-eluting stents (DES) as compared to bare metal stents [6–8]. Second-generation DES were developed, such as the Resolute zotarolimus-eluting stent and the Xience V everolimus-eluting stent, which aimed at enhanced biocompatibility and an improved clinical outcome [9–12]. To date, gender-specific data have only been published for Xience V, which showed prolonged clinical benefit compared to Taxus [13,14].

This study reports gender-specific data of Resolute and Xience V from the randomized TWENTE trial, which recently compared these DES in 1,391 "real-world" PCI patients and applied a gender stratification prior to randomization [12,15]. The aim of this analysis of the TWENTE trial was to assess potential differences in procedural and clinical outcome between women treated with Resolute versus Xience V stents. In addition, we assessed between-gender differences in outcome within this population of contemporary practice PCI patients treated with second-generation DES.

METHODS

Study Design and Patient Population

The TWENTE trial (ClinicalTrials.gov NCT01066650) has been previously described in detail [12]. In brief, TWENTE was an investigator-initiated, patient-blinded, randomized noninferiority study with limited exclusion criteria in a "real-world" study population with a majority of complex lesions and "off-label" indications for DES. The study was performed between June 2008 and August 2010 at Thoraxcentrum Twente, Enschede, The Netherlands. Patients capable of providing informed consent with an indication for PCI with DES were randomized for treatment with Resolute (Medtronic, Santa Rosa, CA) or Xience V stents (Abbott Vascular, Santa Clara, CA) in a ratio of 1:1 after stratification for gender. There was no limit for lesion length, reference vessel size, and number of target lesions or vessels. The most important exclusion criterion was a recent stent thrombosis (ST)-elevation myocardial infarction (STEMI) [12]. The TWENTE trial was approved by the institutional ethics committee and complied with the Declaration of Helsinki.

Intervention, Medication, and In-hospital Course

Lesion predilatation, direct stenting, stent postdilatation, and/or use of glycoprotein IIb/IIIa antagonists were permitted at the operators' discretion. Operators were encouraged to make liberal use of postdilatation. All patients were pretreated with acetylsalicylic acid and clopidogrel. At discharge, the combination of 100 mg of acetylsalicylic acid once daily indefinitely and clopidogrel 75 mg once daily for 1 year was prescribed. Cardiac biomarkers and electrocardiograms were systematically assessed in all patients before and after PCI to identify periprocedural myocardial infarction [12].

Definitions of Clinical Endpoints

Definitions of all clinical endpoints have been described previously in detail [12]. In brief, the prespecified primary clinical endpoint was the incidence of target vessel failure (TVF) within 1 year, a composite endpoint that was defined as cardiac death, target-vessel-related myocardial infarction (or not attributable to a nontarget vessel), or clinically driven target-vessel revascularization.

Prespecified secondary endpoints included the individual components of the primary endpoint as well as target lesion failure, defined as composite of cardiac death, target-vessel-related myocardial infarction, and clinically indicated target-lesion revascularization; Major Adverse Cardiac Events (MACE), a composite of all-cause death, any myocardial infarction, emergent coronary-artery bypass surgery or clinically indicated target-lesion revascularization; and a patient-oriented composite endpoint, consisting of all-cause mortality, any myocardial infarction, and any repeat revascularization. All clinical endpoints were defined according to the Academic Research Consortium [16,17].

Acquisition and Analysis of Clinical Data

Clinical follow-up data were obtained at visits at outpatient clinics, or, if not feasible, by telephone follow-up and/or medical questionnaire. For any potential event trigger, members of the study team gathered all clinical information from the referring cardiologist, general practitioner, and/or hospital involved (100% follow-up data available). 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 based on the principle of intention-to-treat.

Statistical Analysis

Statistical analyses were performed with SPSS vers.15.0 (SPSS, Chicago, IL). Categorical variables were assessed with use of χ^2 or Fisher's exact tests, as appropriate, whereas continuous variables were assessed with the Wilcoxon rank-sum test or Student's *t*-test, as appropriate. The primary endpoint TVF was assessed in both genders by χ^2, and also differences between treatment groups with 95% CIs are reported. The time to the primary endpoint and to the components thereof was assessed according to the method of Kaplan–Meier, and the log-rank test was applied to compare the two groups. Logistic regression was performed to test for interaction between gender and stent type with regard to TVF. In addition, multivariate logistic regression analyses were performed to adjust for baseline variables showing differences ($P \leq 0.15$) between the comparators in each stratum (between Resolute and Xience V in women stratum, or between Resolute and Xience V in men stratum, or between women and men stratum), that is age, diabetes, renal failure, smoking status, hypertension, peripheral artery disease, previous coronary bypass surgery, acute coronary syndrome, bifurcation treatment, in-stent restenosis lesion, small vessels, long lesions, use of glycoprotein IIb/IIIa antagonist, off-label indication, left main lesion, lesion in right coronary artery or right circumflex, graft lesions, chronic total occlusion, aorta-ostial lesion, severe calcified lesion, the presence of thrombus, preprocedural reference vessel diameter, baseline stenosis, direct stenting, maximal stent diameter, postdilatation, number of stents placed, and total stent length. Unless otherwise specified, *P*-values and confidence intervals were two-sided. A *P*-value ≤ 0.05 was considered significant.

RESULTS

Gender Populations

Among the 1,391 patients enrolled in the TWENTE trial, there were 382 women (27.5%) of whom 192 were treated with Resolute and 190 with Xience V. The trial also comprised 1,009 men (72.5%) of whom 505 were treated with Resolute and 504 with Xience V. All women and all but four men completed the study (there were four withdrawals of consent).

Women Treated with Resolute Versus Xience V

Demographics, angiographic details, and procedural characteristics were similar for women treated with Resolute versus Xience V. However, in the Resolute arm there was more small vessel disease ($P = 0.04$) with smaller lumen dimensions in the target lesion and the reference segment ($P = 0.02$ for both), resulting in a smaller maximum stent diameter ($P = 0.04$; Tables I). There was no significant difference in clinical outcome at 1-year follow-up between women treated with Resolute versus Xience V. The primary outcome measure TVF (8.9 vs. 8.4%, $P = 0.88$) (log-rank test, $P = 0.87$, Fig. 1) and the patient-oriented composite endpoint were similar between groups (13.0 vs. 12.1%, $P = 0.79$). There was a nonsignificant trend for less definite-or-probable stent thrombosis in women treated with Resolute versus Xience V (0 vs. 2.1%, $P = 0.06$), whereas there was no definite stent thrombosis in women.

Men Treated with Resolute Versus Xience V

Male patients treated with Resolute were slightly younger ($P = 0.05$) and had longer target lesions ($P = 0.02$; Table I) than males treated with Xience V. No significant difference in angiographic or procedural characteristics was observed between both arms (Tables II and III). Clinical outcome measures at 1-year follow-up were similar for males in both treatment arms (Table IV). The primary outcome measure TVF occurred in 8.0% of the males in both treatment arms ($P = 0.99$) (log-rank test, $P = 0.99$, Fig. 2). Definite stent thrombosis occurred in none of the male patients treated with Xience V and in four males treated with Resolute stents ($P = 0.12$).

Women Versus Men

Women were almost 5 years older than men ($P < 0.01$) and had a higher prevalence of diabetes mellitus (26.4 vs. 19.8%, $P = 0.01$) and hypertension (63.6 vs. 52.5%, $P < 0.01$). In addition, women had less often a history of previous coronary bypass surgery (7.6 vs. 11.8%, $P = 0.02$), suffered less often from peripheral artery disease (5.1 vs. 8.6%, $P = 0.03$), and their target lesions involved less often bifurcations with side-branch treatment (11.0 vs. 16.9%, $P < 0.01$). Aorta-ostial lesions (10.4 vs. 6.1%, $P < 0.01$) and right coronary lesions (36.0 vs. 28.9%, $P < 0.01$) were more common in women than in men, whereas bypass lesions were less common (1.0 vs. 2.7%, $P = 0.02$, Table II). Women had somewhat smaller target vessels, resulting in smaller lumen dimensions after PCI ($P = 0.04$) and less acute gain ($P = 0.03$, Table III). The primary outcome measure TVF was similar for women and men (8.6 vs. 8.0%, $P = 0.68$) (log-rank test, $P = 0.66$, Fig. 3). Various other clinical outcome parameters showed no significant difference between women and men, but in women there was a trend toward a higher cardiac (2.1 vs. 0.9%, $P = 0.09$) and all-cause mortality at 1-year follow-up (3.1 vs. 1.7%, $P = 0.09$) (Table IV). Definite stent thrombosis only occurred in four male patients.

TABLE I. Baseline Characteristics of Patients

	Total population ($N=1,391$)			Women ($N=382$)			Men ($N=1,009$)		
	Women ($N=382$)	Men ($N=1,009$)	*P*-value	Resolute ($N=192$)	Xience V ($N=190$)	*P*-value	Resolute ($N=505$)	Xience V ($N=504$)	*P*-value
Age (years)	67.6 (10.3)	62.9 (10.7)	<0.01	68.3 (9.9)	66.8 (10.6)	0.18	62.2 (10.8)	63.6 (10.6)	0.05
Body mass index (kg/m^2)	27.8 (4.8)	27.7 (3.6)	0.72	27.5 (4.5)	28.1 (5.1)	0.30	27.7 (3.7)	27.7 (3.5)	0.91
Diabetes mellitus (any)	101 (26.4)	200 (19.8)	0.01	56 (29.2)	45 (23.7)	0.22	102 (20.2)	98 (19.4)	0.76
Diabetes mellitus requiring insulin	41 (10.7)	74 (7.3)	0.04	25 (13.0)	16 (8.4)	0.15	34 (6.7)	40 (7.9)	0.46
Chronic renal failure[a]	6 (1.6)	32 (3.2)	0.10	1 (0.5)	5 (2.6)	0.12	18 (3.6)	14 (2.8)	0.48
Arterial hypertension	243 (63.6)	530 (52.5)	<0.01	120 (62.5)	123 (64.7)	0.65	266 (52.7)	264 (52.4)	0.93
Hypercholesterolaemia	223/373 (59.8)	580/984 (58.9)	0.78	109/192 (56.8)	114/181 (63.0)	0.22	283/496 (57.1)	297/488 (60.9)	0.23
Current smoker	83 (21.7)	257 (25.5)	0.15	42 (21.9)	41 (21.6)	0.94	134 (26.5)	123 (24.4)	0.44
Family history of CAD	211 (59.6)	529 (55.4)	0.17	102 (53.1)	109 (57.4)	0.40	268 (53.1)	261 (51.8)	0.68
Peripheral artery disease	19/984 (5.1)	85/369 (8.6)	0.03	8/187 (4.3)	11/182 (6.0)	0.44	43/496 (8.7)	42/488 (8.6)	0.97
Myocardinfarction (any)	105 (27.5)	345 (34.2)	0.17	50 (26.0)	55 (28.9)	0.53	163 (32.3)	182 (36.1)	0.20
Previous PCI	72 (18.8)	216 (21.4)	0.29	36 (18.8)	36 (18.9)	0.96	103 (20.4)	113 (22.4)	0.43
Previous CABG	29 (7.6)	119 (11.8)	0.02	11 (5.7)	18 (9.5)	0.17	57 (11.3)	62 (12.3)	0.62
Clinical indication			0.08			0.88			0.52
Stable angina pectoris	178 (46.6)	496 (49.2)		88 (45.8)	90 (47.4)		247 (48.9)	249 (49.4)	
Unstable angina	105 (27.5)	325 (23.4)		55 (28.6)	50 (26.3)		117 (23.2)	103 (20.4)	
Non-ST-elevation MI	99 (25.9)	293 (29.0)		49 (25.5)	50 (26.3)		141 (27.9)	152 (30.2)	
Clinical indication: acute coronary syndrome	204 (53.4)	178 (50.8)	0.39	104 (54.2)	100 (52.6)	0.76	258 (51.1)	255 (50.6)	0.88
Left ventricular ejection fraction < 30%[b]	10 (3.3)	22 (2.9)	0.75	4 (2.6)	6 (4.1)	0.47	15/374 (4.0)	7/375 (1.9)	0.08
Multivessel treatment	84 (22.0)	252 (25.0)	0.25	47 (24.5)	37 (19.5)	0.24	127 (25.1)	125 (24.8)	0.90
Total no lesions treated per patient			0.33			0.57			0.60
One lesion treated	243 (63.6)	614 (60.9)		122 (63.5)	121 (63.7)		300 (59.4)	314 (62.3)	
Two lesions treated	97 (25.4)	296 (29.3)		46 (24.0)	51 (29.3)		152 (30.1)	144 (28.6)	
Three of more lesions treated	42 (11.0)	99 (9.8)		24 (12.5)	18 (9.5)		53 (10.5)	46 (9.1)	
De novo coronary lesions only[c]	352 (92.1)	935 (92.7)	0.74	179 (93.2)	173 (91.1)	0.43	465 (92.1)	470 (93.3)	0.47
At least one CTO	32 (8.4)	63 (6.2)	0.16	17 (8.9)	15 (7.9)	0.74	34 (6.7)	29 (5.8)	0.52
At least one bifurcation	89 (23.3)	273 (27.1)	0.15	44 (22.9)	45 (23.7)	0.86	135 (26.7)	138 (27.4)	0.82
At least one bifurcation with side-branch treatment	42 (11.0)	171 (16.9)	0.01	18 (9.4)	24 (12.6)	0.31	80 (15.8)	91 (18.1)	0.35
At least one in-stent restenosis	26 (6.8)	43 (4.3)	0.05	11 (5.7)	15 (7.9)	0.40	25 (5.0)	18 (3.6)	0.28
At least one small-vessel (RVD, <2.75 mm)	250 (65.4)	624 (61.8)	0.22	135 (70.3)	115 (60.5)	0.04	310 (61.4)	314 (62.3)	0.77
At least one lesion length >27 mm	75 (19.6)	218 (21.6)	0.42	31 (16.1)	44 (23.2)	0.09	125 (24.8)	93 (18.5)	0.02
Glycoprotein IIb/IIIa antagonist	44 (11.5)	149 (14.8)	0.12	18 (9.4)	26 (13.7)	0.19	72 (14.3)	77 (15.3)	0.65
At least one off label indication[d]	289 (75.7)	788 (78.1)	0.33	141 (73.4)	148 (77.9)	0.31	406 (80.4)	382 (75.8)	0.08

Data are number (%) or mean (SD).

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

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

[c]Including chronic total occlusion, but not grafts and in-stent restenosis.

[d]Off-label stent use includes renal insufficiency, an ejection fraction of <30%, the occurrence of acute myocardial infarction within the previous 72 hr, more than one lesion per vessel, at least two vessels with stents, a lesion measuring more than 27 mm, bifurcation, bypass grafts, in-stent restenosis, unprotected left main artery, lesions with thrombus, or total occlusion.

Abbreviations: CABG: coronary artery bypass grafting, CAD: coronary artery disease, CTO: chronic total occlusion, MI: myocardial infarction, PCI: percutaneous coronary intervention, and RVD, reference vessel diameter.

After adjustment for differences in baseline variables, stent type was not a significant predictor of TVF in both women (adjusted OR: 0.95, 95% CI: 0.41–2.20, $P=0.91$), and men (adjusted OR: 0.92, 95% CI: 0.58–1.46, $P=0.72$), comparing Resolute versus Xience V. When analyzing all patients in a multivariate model,

TABLE II. Baseline Lesion Characteristics

	Total lesions ($N=2,116$)			Women ($N=578$)			Men ($N=1,568$)		
	Female ($N=578$)	Male ($N=1,538$)	P-value	Resolute ($N=295$)	Xience V ($N=283$)	P-value	Resolute ($N=785$)	Xience V ($N=783$)	P-value
Target lesion coronary artery									
Left main	12 (2.1)	42 (2.7)	0.40	9 (3.1)	3 (1.1)	0.09	17 (2.2)	25 (3.3)	0.17
Left anterior descendens	228 (39.4)	650 (42.3)	0.24	112 (38.0)	116 (41.0)	0.46	329 (41.9)	321 (42.6)	0.78
Left circumflex	124 (21.5)	359 (23.3)	0.36	72 (24.4)	52 (18.4)	0.08	171 (21.8)	188 (25.0)	0.14
Right coronary artery	208 (36.0)	445 (28.9)	<0.01	99 (33.6)	109 (38.5)	0.22	250 (31.8)	195 (25.9)	0.01
Bypass graft	6 (1.0)	42 (2.7)	0.02	3 (1.0)	3 (1.1)	0.96	18 (2.3)	24 (3.2)	0.28
ACC-AHA lesion class			0.77			0.98			0.72
A	40 (6.9)	114 (7.4)		21 (7.1)	19 (6.7)		56 (7.1)	58 (7.7)	
B1	129 (22.3)	349 (22.7)		67 (22.7)	62 (21.9)		174 (22.2)	175 (23.2)	
B2	195 (33.7)	483 (31.4)		100 (33.9)	95 (33.6)		242 (30.8)	241 (32.0)	
C	214 (37.0)	592 (38.5)		107 (36.3)	107 (37.8)		313 (39.9)	279 (37.1)	
De novo lesions[a]	545 (94.3)	1454 (94.5)	0.82	280 (94.9)	265 (93.6)	0.51	744 (94.8)	710 (94.3)	0.67
Chronic total occlusion	34 (5.9)	66 (4.3)	0.12	18 (6.1)	16 (5.7)	0.82	35 (4.5)	31 (4.1)	0.74
In stent restenosis	29 (5.0)	46 (3.0)	0.03	13 (4.4)	16 (5.7)	0.49	25 (3.2)	21 (2.8)	0.65
Aorta ostial lesion	60 (10.4)	94 (6.1)	<0.01	24 (8.1)	36 (12.7)	0.07	52 (6.6)	42 (5.6)	0.39
Severe calcification	112 (19.4)	252 (16.4)	0.10	64 (21.7)	48 (17.0)	0.15	128 (16.3)	124 (16.5)	0.93
Bifurcated lesion	117 (20.2)	401 (26.1)	<0.01	57 (19.3)	60 (21.2)	0.57	201 (25.6)	200 (26.6)	0.67
Thrombus present[b]	14 (2.4)	57 (3.7)	0.14	9 (3.1)	5 (1.8)	0.32	24 (3.1)	33 (4.4)	0.17
Total occlusion	59 (10.2)	144 (9.1)	0.56	32 (10.8)	27 (9.5)	0.60	77 (9.8)	67 (8.9)	0.54
Preprocedural TIMI flow (grade)			0.42			0.71			0.89
0	35 (6.1)	85 (5.5)		19 (6.4)	16 (5.7)		44 (5.6)	41 (5.4)	
1	24 (4.2)	59 (3.8)		13 (4.4)	11 (3.9)		33 (4.2)	26 (3.5)	
2	30 (5.2)	110 (7.2)		18 (6.1)	12 (4.2)		55 (7.0)	55 (7.3)	
3	489 (84.6)	1284 (83.5)		245 (83.1)	244 (86.2)		653 (83.2)	631 (83.8)	

Data are number (%).

[a]Including chronic total occlusion, but not grafts and in-stent restenosis.

[b]Thrombus triggering use of thrombus aspiration catheters.

Abbreviations: ACC: American College of Cardiology, AHA: American Heart Association, TIMI: thrombolysis in myocardial infarction.

female gender was not associated with TVF (adjusted OR: 1.18, 95% CI: 0.73–1.92, $P=0.50$) or other clinical outcome measures. In addition, logistic regression analysis showed no significant interaction between stent type and gender with regard to TVF ($P=0.90$) or other clinical endpoints.

DISCUSSION

There has recently been a call for more gender-specific analyses in clinical trials, which should improve our knowledge about potential gender differences and may ultimately improve cardiovascular health of the female patients [1]. The study design of the randomized TWENTE trial recognized the value of gender-specific data by employing a gender stratification step prior to randomization for type of DES [15]. Gender stratification ensured a randomization between DES types that was balanced within both women and men. This prespecified gender analysis of the TWENTE trial data demonstrated that there was no significant difference in clinical safety and efficacy between female patients treated with Resolute or Xience V stents.

Female Populations of Previous DES Studies

In the present gender analysis, both Resolute and Xience V showed high procedural success and relatively low clinical event rates in women, despite a relatively high patient and lesion complexity in TWENTE.

The female population of several major DES trials in all comer populations ranged from 23.1 to 29.3% [9,10,18]. The TWENTE trial, which enrolled patients between 2008 and 2010, comprised 27.5% women. This proportion of female patients in TWENTE matches the routine clinical practice in the Netherlands (28% in 2009) [19] as well as a trend that was observed from the analysis of 33 prospective European stent trials: the proportion of women gradually increased from 22% (in 1995–1997) to 26% (in 2003–2006) [20]. The increase in female patients during that period reflected daily clinical practice as more women suffered from obstructive coronary disease. In addition, it paralleled a progress in stent

TABLE III. Quantitative Coronary Angiography and Procedural Results

	Total lesions ($N = 2,116$)			Women ($N = 578$)			Men ($N = 1,568$)		
	Female ($N = 578$)	Male ($N = 1,538$)	P-value	Zotarolimus-eluting Resolute stent ($N = 295$)	Everolimus-eluting Xience V stent ($N = 283$)	P-value	Zotarolimus-eluting Resolute stent ($N = 785$)	Everolimus-eluting Xience V stent ($N = 783$)	P-value
Lesion length (mm)	14.61 (10.05–21.86)	14.31 (9.61–22.15)	0.70	14.94 (10.04–21.67)	14.39 (10.05–22.19)	0.63	14.40 (9.81–22.80)	14.26 (9.43–21.63)	0.16
Diameter of reference vessel (mm)	2.60 (2.23–2.99)	2.68 (2.31–3.09)	0.01	2.58 (2.17–2.95)	2.64 (2.26–3.05)	0.02	2.69 (2.36–3.09)	2.66 (2.28–3.09)	0.33
Baseline minimum lumen diameter (mm)	0.99 (0.75–1.33)	0.98 (0.72–1.27)	0.25	0.95 (0.70–1.29)	1.05 (0.78–1.37)	0.02	0.97 (0.72–1.28)	0.99 (0.71–1.27)	0.70
Baseline stenosis (lumen diameter, %)	60.66 (51.60–70.26)	62.36 (53.13–71.49)	0.13	61.5 (52.1–70.66)	60.23 (50.84–69.3)	0.14	63.15 (53.08–71.54)	61.76 (53.36–71.49)	0.77
Post procedure stenosis (lumen diameter, %)	12.13 (8.97–15.34)	11.72 (9.07–15.33)	0.78	12.08 (8.97–15.26)	12.17 (8.94–15.39)	0.84	11.52 (8.90–14.81)	11.95 (9.26–15.74)	0.05
Postprocedure minimum lumen diameter (mm)	2.23 (1.83–2.64)	2.25 (1.92–2.68)	0.05	2.21 (1.80–2.61)	2.27 (1.88–2.66)	0.18	2.30 (1.94–2.70)	2.25 (1.88–2.65)	0.06
Acute gain in segment (mm)	1.22 (0.85–1.59)	1.27 (0.88–1.72)	0.03	1.21 (0.85–1.65)	1.22 (0.85–1.55)	0.60	1.27 (0.91–1.72)	1.27 (0.82–1.69)	0.26
Number of stents implanted (mean, SD)									
Per patient	2.04 (1.24)	2.08 (1.16)	0.78	1.99 (1.23)	2.08 (1.25)	0.46	2.04 (1.18)	1.99 (1.15)	0.53
Per lesion	1.35 (0.67)	1.32 (0.60)	0.45	1.29 (0.59)	1.40 (0.74)	0.06	1.31 (0.59)	1.33 (0.61)	0.46
Total stent length (mm) (mean, SD)									
Per patient	40.78 (27.36)	41.04 (26.68)	0.55	39.98 (26.82)	41.58 (27.95)	0.57	42.54 (27.96)	39.52 (25.26)	0.07
Per lesion	27.0 (16.5)	26.9 (15.4)	0.97	26.0 (15.1)	27.9 (17.8)	0.82	27.4 (15.5)	26.5 (15.3)	0.24
Direct stenting	206 (35.6)	618 (40.2)	0.06	101 (34.2)	105 (37.1)	0.47	315 (40.1)	303 (40.2)	0.96
Postdilatation	483 (83.6)	1244 (80.9)	0.16	239 (81.0)	244 (86.2)	0.09	637 (81.1)	607 (80.6)	0.79
Maximal stent diameter per lesion (mm) (mean, SD)	2.94 (0.46)	2.99 (0.46)	0.04	2.90 (0.45)	2.98 (0.47)	0.04	2.99 (0.45)	2.98 (0.47)	0.82
Implantation of study stent only	573 (99.1)	1521 (98.9)	0.63	294 (99.7)	279 (98.6)	0.21	774 (98.6)	747 (99.2)	0.26
Device success[a]	566 (97.9)	1508 (98.0)	0.85	292 (99.0)	274 (96.8)	0.07	771 (98.2)	737 (97.9)	0.63
Lesion success[b]	577 (99.8)	1535 (99.8)	0.92	295 (100)	282 (99.6)	0.49	783 (99.7)	752 (99.9)	0.59
Procedure success[c]	362/382 (94.8)	970/1009 (96.1)	0.26	183/192 (95.3)	179/190 (94.2)	0.63	484/505 (95.8)	486/504 (96.4)	0.63

Data are median (IQR) or number (%), unless otherwise stated.

[a]Device success is defined as the attainment at the target site of a final residual diameter stenosis of <50% using only the assigned study device.

[b]Lesion success is defined as the attainment at the target site of a final residual diameter stenosis of <50% using any percutaneous method.

[c]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.

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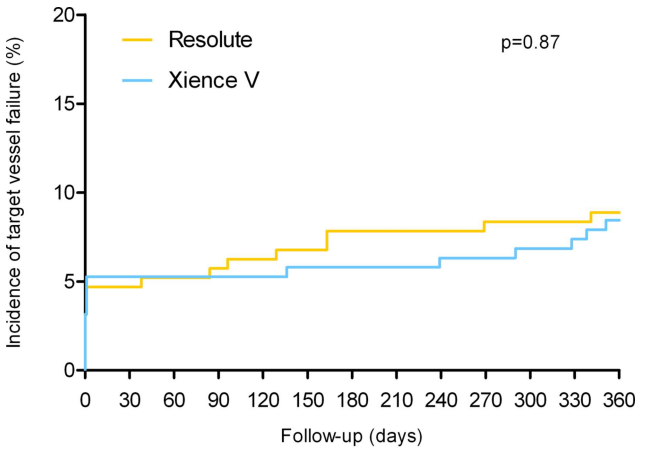
technology (e.g., improved stent material, stent design, delivery system, and development of DES), which facilitated stent implantation in coronary vessels with small lumen dimensions that are more frequent in women [13,21].

Previous studies established an angiographic [22] and clinical benefit [8,21,23,24] of first-generation DES over bare metal stents in women. Endeavor, the first-generation zotarolimus-eluting stent that had a polymer-based coating that differed significantly from that of the second-generation Resolute, was recently shown to be particularly efficient in women in suppressing neointimal ingrowth and preventing binary restenosis [22].

Recent studies demonstrated in patient populations that also comprised women the superiority of second-generation Xience V over first-generation paclitaxel-eluting stents [9,11]. Pooled data analysis of SPIRIT II and III, studies in well-defined patient and lesion populations, found fewer MACE and TVF at 2-year follow-up in women treated with Xience V as compared to women treated with paclitaxel-eluting stents. Also, women treated with Xience V had after 8 months a somewhat higher binary restenosis rate compared to male patients. However, that difference was statistically nonsignificant [25].



Days	0	90	180	270	360
Number at risk					
Resolute	192	180	176	175	173
Xience V	190	180	178	177	173

Fig. 1. Cumulative incidence of TVF in women. TVF was a composite of cardiovascular death, target vessel myocardial infarction, or target vessel revascularization. *P*-value is calculated by log-rank test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Gender and PCI Outcome

In the present era, female gender was associated with an inferior outcome after PCI [26–28], which has been partly related to the often higher cardiovascular risk profile and on average smaller vessel size [14,29]. On the contrary, studies with first-generation DES show no clear relationship between gender and outcome [7,8,23,30]. Only in one DES study, female gender was associated with less favorable clinical outcome as a result of more repeat revascularization procedures [13,14]. In the "real-world" study population of TWENTE, there was also no relationship between gender and clinical outcome after treatment with one of the second-generation DES. Although target vessel size was significantly smaller in women, outcome measures did not differ between women and men. This was despite the fact that women were on average 5 years older than men ($P < 0.01$), which matches exactly a difference of 5 years in age (63 vs. 68 years) that was recently reported for the Netherlands, based on the data from all PCI in 2009 [19]. In addition, women had a higher incidence of diabetes mellitus and hypertension ($P \leq 0.01$), and a lower incidence of previous bypass surgery ($P = 0.02$). Only all-cause and cardiac mortality rates tended to be slightly higher in women ($P = 0.09$). Although women had a higher cardiovascular risk profile and smaller target vessels, no significant gender difference in clinical outcome was observed in this study.

Gender and Stent Thrombosis in DES

Stent thrombosis is a potentially lethal complication of coronary stenting that is relatively rare in second-generation DES [9–12,31]. The incidence of stent thrombosis is assumed to be similar for both genders [7,23,32–34]. In TWENTE, stent thrombosis was rare both in the overall study population and in the female subpopulation.

Limitations of the Study

Despite gender-stratification, this study was statistically not powered to confirm noninferiority of the study stents in women. The results cannot be applied to women receiving DES in the setting of an acute STEMI, as this clinical syndrome was an exclusion criterion.

CONCLUSIONS

In this prespecified analysis of the gender-stratified TWENTE trial, there was no significant difference in safety and efficacy between female patients treated with Resolute and Xience V stents. Despite a higher cardiovascular risk profile and smaller target vessels in women, no significant gender difference in clinical outcome was observed.

TABLE IV. One-Year Clinical Outcomes

	Women (*N*= 382)	Men (*N*= 1,005)	Difference (95% CI)	*P*-value	Zotarolimus-eluting Resolute stent (*N*=192)	Everolimus-eluting Xience V stent (*N*=190)	Difference (95% CI)	*P*-value	Zotarolimus-eluting Resolute stent (*N*=503)	Everolimus-eluting Xience V stent (*N*=502)	Difference (95% CI)	*P*-value
Target vessel failure	33 (8.6)	80 (8.0)	0.7 (−2.5 to 3.9)	0.68	17 (8.9)	16 (8.4)	0.4 (−5.2 to 6.1)	0.88	40 (8.0)	40 (8.0)	0.0 (−3.3 to 3.3)	0.99
Death												
Any cause	12 (3.1)	17 (1.7)	1.4 (−0.2 to 3.1)	0.09	6 (3.1)	6 (3.2)	0.0 (−3.6 to 3.5)	0.99	9 (1.8)	8 (1.6)	0.2 (−1.4 to 1.8)	0.81
Cardiac cause	8 (2.1)	9 (0.9)	1.2 (−0.1 to 2.5)	0.09	3 (1.6)	5 (2.6)	−1.1 (−4.0 to 1.8)	0.50	4 (0.8)	5 (1.0)	−0.2 (−1.4 to 1.0)	0.75
Target vessel related MI												
Any	20 (5.2)	44 (4.4)	0.9 (−1.6 to 3.3)	0.50	9 (4.7)	11 (5.8)	−1.1 (−5.6 to 3.4)	0.63	23 (4.6)	21 (4.2)	0.4 (−2.1 to 2.9)	0.76
Q-wave	3 (0.8)	8 (0.8)	0.0 (−1.1 to 1.0)	1.00	0 (0.0)	3 (1.6)	−1.5 (−3.4 to 0.2)	0.12	5 (1.0)	3 (0.6)	0.4 (−0.7 to 1.5)	0.48
Non-Q-wave	17 (4.5)	36 (3.6)	0.9 (−1.4 to 3.1)	0.45	9 (4.7)	8 (4.2)	0.5 (−3.7 to 4.6)	0.82	18 (3.6)	18 (3.6)	0.0 (−2.3 to 2.3)	1.00
Periprocedural MI	19 (5.0)	38 (3.8)	1.2 (−1.1 to 3.5)	0.32	9 (4.7)	10 (5.3)	−0.6 (−5.0 to 3.8)	0.80	20 (4.0)	18 (3.6)	0.4 (−2.0 to 2.8)	0.75
Clinically indicated TVR												
Any	10 (2.6)	32 (3.2)	−0.6 (−2.6 to 1.4)	0.58	6 (3.1)	4 (2.1)	1.0 (−2.2 to 4.2)	0.75	17 (3.4)	15 (3.0)	0.4 (−1.8 to 2.6)	0.72
Percutaneous	7 (1.8)	26 (2.6)	−0.8 (1.0 to −2.6)	0.41	5 (2.6)	2 (1.1)	1.5 (−1.2 to 4.3)	0.45	14 (2.8)	12 (2.4)	0.4 (−1.6 to 2.4)	0.70
Surgical	3 (0.8)	6 (0.6)	0.2 (−0.8 to 1.1)	0.70	1 (0.5)	2 (1.1)	−0.5 (−2.3 to 1.2)	0.62	3 (0.6)	3 (0.6)	0.0 (−1.0 to 1.0)	1.00
Target lesion failure	31 (8.1)	71 (7.1)	1.1 (−2.0 to 4.1)	0.50	17 (8.9)	14 (7.4)	1.5 (−4.0 to 7.0)	0.60	38 (7.6)	33 (6.6)	1.0 (−2.2 to 4.2)	0.54
Clinically indicated TLR												
Any	7 (1.8)	22 (2.2)	−0.4 (−2.0 to 1.3)	0.68	5 (2.6)	2 (1.1)	1.6 (−1.2 to 4.3)	0.45	14 (2.8)	8 (1.6)	1.2 (−0.6 to 3.0)	0.20
Percutaneous	5 (1.3)	17 (1.7)	−0.4 (−1.9 to 1.1)	0.61	4 (2.1)	1 (0.5)	1.6 (−0.7 to 3.8)	0.37	11 (2.2)	6 (1.2)	1.0 (−0.6 to 2.6)	0.22
Surgical	2 (0.5)	5 (0.5)	0.0 (−0.8 to 0.9)	1.00	1 (0.5)	1 (0.5)	0.0 (−1.5 to 1.5)	1.00	3 (0.6)	2 (0.4)	0.2 (−0.7 to 1.1)	1.00
Death from cardiac causes or target-vessel MI	22 (5.8)	45 (4.5)	1.3 (−1.2 to 3.8)	0.32	12 (6.3)	10 (5.3)	1.0 (−3.7 to 5.7)	0.68	22 (4.4)	23 (4.6)	−0.2 (−2.8 to 2.4)	0.87
Major adverse cardiac events	39 (10.2)	93 (9.3)	1.0 (−2.5 to 4.4)	0.59	21 (10.9)	18 (9.5)	1.5 (−4.6 to 7.6)	0.64	49 (9.7)	44 (8.8)	1.0 (−2.6 to 4.6)	0.59
Patient-oriented composite end-point	48 (12.6)	103 (10.2)	2.3 (−1.4 to 6.0)	0.22	25 (13.0)	23 (12.1)	0.9 (−5.8 to 7.6)	0.79	53 (10.5)	50 (10.0)	0.6 (−3.2 to 4.3)	0.76
Definite ST (0–360 days)												
All patients	0 (0)	4 (0.4)	−0.4 (−1.0 to 0.2)	0.58	0 (0)	0 (0)	–	–	4 (0.8)	0 (0)	0.8 (−0.0 to 1.6)	0.12
Acute (0–1 day)	0 (0)	0 (0)	–	–	0 (0)	0 (0)	–	-	0 (0)	0 (0)	–	–
Subacute (2–30 days)	0 (0)	1 (0.1)	−0.1 (−0.4 to 0.2)	1.00	0 (0)	0 (0)	–	–	1 (0.2)	0 (0)	0.2 (−0.2 to 0.6)	1.00
Late (31–360 days)	0 (0)	3 (0.3)	−0.3 (−0.8 to 0.2)	0.56	0 (0)	0 (0)	–	–	3 (0.6)	0 (0)	0.6 (−0.0 to 1.2)	0.25
Probable ST (0–360 days)												
All patients	4 (1.0)	6 (0.6)	0.5 (−0.5 to 1.4)	0.48	0 (0)	4 (2.1)	−2.1 (−4.1 to 0.0)	0.06	2 (0.4)	4 (0.8)	−0.4 (−1.4 to 0.6)	0.45
Acute (0–1 day)	1 (0.3)	3 (0.3)	0.0 (−0.7 to 0.6)	1.00	0 (0)	1 (0.5)	−0.5 (−1.6 to 0.5)	0.50	1 (0.2)	2 (0.4)	−0.2 (−0.9 to 0.5)	0.62
Subacute (2–30 days)	2 (0.5)	2 (0.2)	0.3 (−0.3 to 1.0)	0.31	0 (0)	2 (1.1)	−1.0 (−2.5 to 0.4)	0.25	0 (0)	2 (0.4)	−0.4 (−1.0 to 0.2)	0.25
Late (31–360 days)	1 (0.3)	1 (0.1)	0.2 (−0.3 to 0.6)	0.48	0 (0)	1 (0.5)	−0.5 (−1.6 to 0.5)	0.50	1 (0.2)	0 (0)	0.2 (−0.2 to 0.6)	1.00
ST (0–360 days)												
Possible	2 (0.5)	4 (0.4)	0.1 (−0.6 to 0.9)	0.67	1 (0.5)	1 (0.5)	0.0 (−1.5 to 1.5)	1.00	3 (0.6)	1 (0.2)	0.4 (−0.4 to 1.2)	0.62
Definite or probable	4 (1.0)	10 (1.0)	0.0 (−1.1 to 1.2)	1.00	0 (0)	4 (2.1)	−2.1 (−4.1 to 0.0)	0.06	6 (1.2)	4 (0.8)	0.4 (−0.8 to 1.6)	0.75
Definite, probable or possible	6 (1.6)	14 (1.4)	0.2 (−1.2 to 1.6)	0.80	1 (0.5)	5 (2.6)	−2.1 (−4.6 to 0.4)	0.12	9 (1.8)	5 (1.0)	0.8 (−0.7 to 2.2)	0.28

Data are number of patients (%).

MI: myocardial infarction. ST: stent thrombosis. TLR: target lesion revascularization. TVR: target vessel revascularization. Major adverse cardiac event is a composite of all-cause death, any myocardial infarction, emergent coronary-artery bypass surgery or clinically indicated target lesion revascularization. Patient-oriented composite endpoint is a composite of endpoint of all-cause death, any myocardial infarction or any revascularization.

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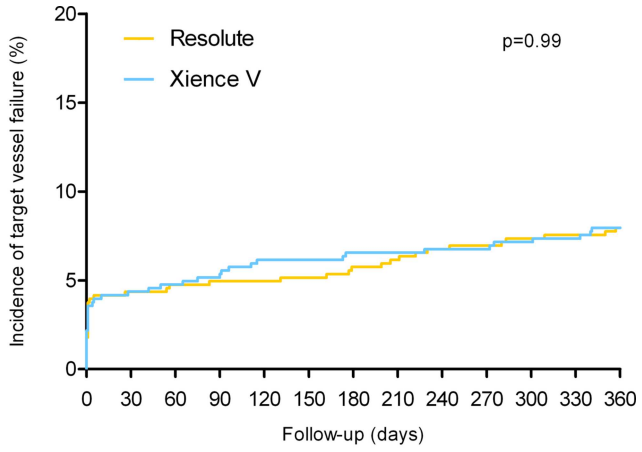
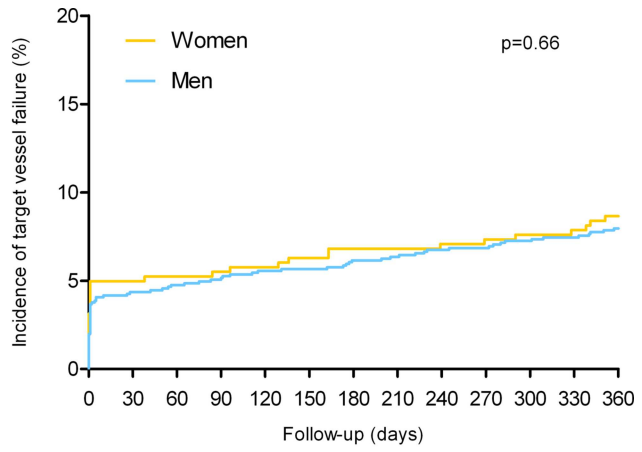


Days	0	90	180	270	360
Number at risk					
Resolute	505	478	471	465	458
Xience V	504	477	468	466	459

Fig. 2. Cumulative incidence of TVF in men. TVF was a composite of cardiovascular death, target vessel myocardial infarction, or target vessel revascularization. *P*-value is calculated by log-rank test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Days	0	90	180	270	360
Number at risk					
Men	1009	955	939	931	917
Women	382	360	354	352	346

Fig. 3. Cumulative incidence of TVF stratified for gender. TVF was a composite of cardiovascular death, target vessel myocardial infarction, or target vessel revascularization. *P*-value is calculated by log-rank test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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