Three-year clinical outcome of patients with bifurcation treatment with second-generation Resolute and Xience V stents in the randomized TWENTE trial

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Background Only limited data from large randomized clinical trials have been published on the long-term performance of second-generation drug-eluting stents in bifurcation lesions.

Methods We investigated in patients in the randomized TWENTE trial the long-term safety and efficacy of treating bifurcation lesions with 2 widely applied second-generation drug-eluting stents, the zotarolimus-eluting Resolute stent (Medtronic Inc, Santa Rosa, CA) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA). Three-year follow-up was available in 99.3%. Patients were categorized into treatment for ≥1 bifurcation lesion versus treatment for nonbifurcation lesions only.

Results Among the 1,391 patients of the TWENTE trial, 362 (26%) were treated for bifurcation lesions. At 3-year follow-up, target-vessel failure did not differ between patients treated for bifurcation versus nonbifurcation lesions (13.1% vs 12.6%; $P = .84$), whereas the periprocedural myocardial infarction rate was higher in patients with bifurcation lesions (6.9% vs 3.1%; $P < .01$). Of the 362 patients with bifurcation lesion treatment, 179 (49.4%) were treated with Resolute and 183 (50.6%) with Xience V. There was no significant difference in target-vessel failure between the Resolute and Xience V groups with bifurcation treatment (13.6% vs 12.6%; $P = .78$), and their incidence of definite-or-probable stent thrombosis was low and similar (1.1% vs 0.5%, respectively; $P = .62$).

Conclusion Despite a significant difference in periprocedural myocardial infarction, 3-year clinical outcome after implantation of second-generation stents was favorable and similar for patients with and without bifurcation lesions. In addition, we observed no difference in long-term clinical outcome after bifurcation lesion treatment with Resolute and Xience V stents. (Am Heart J 2015;169:69-77.)

Percutaneous coronary interventions (PCIs) of bifurcation lesions have been associated with an increased procedural risk and a higher restenosis rate.[1] The introduction of the first generation of drug-eluting stents (DES) reduced the incidence of restenosis.[2-4] Meanwhile, second-generation DES with more biocompatible, durable polymer-based coatings have been developed, such as the zotarolimus-eluting Resolute stent (Medtronic Inc, Santa Rosa, CA) and everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA). Both DES are widely applied, and they have shown favorable clinical results in a large population of all-comer patients[5,6] and in the broad patient population of the TWENTE trial.[7-9] In bifurcation lesions, second-generation DES reduced the risk of restenosis and the need for repeat revascularization, as compared with first-generation DES.[10-12] In addition, a randomized trial that exclusively used second-generation DES recently reported very favorable 2-year outcome data after treatment of bifurcation lesions in an all-comer patient population.[13]

Nevertheless, so far, only limited data from large randomized clinical trials have been published on the long-term performance of second-generation DES in bifurcation lesions.[13-15] Therefore, in the present sub-study of the TWENTE trial,[7,8,16] we performed an analysis of the 3-year follow-up data of TWENTE to compare long-

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Table I. Characteristics of all study patients with and without bifurcated target lesions and of both stent arms in patients with bifurcated target lesions

	All patients (n = 1391)			Patients with bifurcated target lesions (n = 362)		
	Bifurcated target lesion	Nonbifurcated target lesion		Resolute	Xience V	
Patient characteristics	**(n = 362)**	**(n = 1029)**	***P***	**(n = 179)**	**(n = 183)**	***P***
Age (y)	64.3 (10.5)	64.3 (10.6)	.98	64.5 (11.1)	64.0 (10.0)	.68
Female	89 (24.6)	293 (28.5)	.15	44 (24.6)	45 (24.6)	1.00
BMI (kilograms per square meter)	27.5 (3.8)/317	27.8 (4.0)/872	.25	27.1 (3.4)/156	27.9 (4.1)/161	.05
Diabetes mellitus	75 (20.7)	226 (22.0)	.62	37 (20.7)	38 (20.8)	.98
Arterial hypertension	198 (54.7)	575 (55.9)	.70	95 (53.1)	103 (56.3)	.54
Hypercholesterolemia	194 (55.1)	609 (60.6)	.07	93 (52.2)/178	101 (58.0)/174	.27
Current smoker	95 (26.2)	245 (23.8)	.35	45 (25.1)	50 (27.3)	.64
Family history of CAD	188 (51.9)	552 (53.6)	.58	90 (50.3)	98 (53.6)	.53
Previous MI	114 (31.5)	336 (32.7)	.69	55 (30.7)	59 (32.2)	.76
Previous PCI	66 (18.2)	222 (21.6)	.18	33 (18.4)	33 (18.0)	.92
Previous CABG	25 (6.9)	123 (12.0)	<.01	11 (6.1)	14 (7.7)	.57
Clinical syndrome			.65			.47
Stable angina pectoris	171 (47.2)	503 (48.9)		82 (45.8)	89 (48.6)	
Unstable angina	91 (25.1)	234 (22.7)		50 (27.9)	41 (22.4)	
Non–ST-elevation MI	100 (27.6)	292 (28.4)		47 (26.3)	53 (29.0)	
Lesion/procedural characteristics						
Medina classification						.54
0.0.1	30 (8.3%)			17 (9.5)	13 (7.1)	
0.1.0	63 (17.5)			30 (16.8)	33 (18.0)	
0.1.1	43 (11.9)			16 (8.9)	27 (14.8)	
1.0.0	59 (16.3)			27 (15.1)	32 (17.5)	
1.0.1	21 (5.8)			11 (6.1)	10 (5.5)	
1.1.0	62 (17.2)			35 (19.6)	27 (14.8)	
1.1.1	84 (23.1)			43 (24.0)	41 (22.4)	
Multivessel treatment	127 (35.1)	209 (20.3)	<.01	65 (36.3)	62 (33.9)	.63
Total no. of lesions treated per patient			<.01			.75
1 lesion treated	179 (49.4)	678 (65.9)		90 (50.3)	89 (48.6)	
≥2 lesions treated	183 (50.6)	351 (34.1)		89 (49.7)	94 (51.4)	
Treated coronary vessels						
Right coronary artery	70 (19.3)	435 (42.3)	<.01	34 (19.2)	36 (19.7)	.91
Left anterior artery	269 (74.3)	455 (44.2)	<.01	136 (76.8)	132 (72.1)	.31
Circumflex artery	135 (37.3)	304 (29.5)	<.01	64 (36.2)	70 (38.3)	.68
De novo lesions	320 (88.4)	874 (84.9)	.10	156 (88.1)	162 (88.5)	.33
Severe calcification	78 (21.5)	197 (19.1)	.32	38 (21.5)	40 (21.9)	.93
≥1 Chronic total occlusion	26 (7.2)	69 (6.7)	.76	15 (8.4)	11 (6.0)	.38
≥1 In-stent restenosis	14 (3.9)	55 (5.3)	.27	6 (3.4)	8 (4.4)	.62
≥1 Aorto-ostial lesion	25 (6.9)	127 (12.3)	<.01	10 (5.6)	15 (8.2)	.34
≥1 Small vessel†	257 (71.0)	617 (60.0)	<.01	121 (67.6)	136 (74.3)	.16
≥1 Lesion length, >27 mm	72 (19.9)	221 (21.5)	.52	39 (21.8)	33 (18.0)	.37
Longest lesion length (millimeters)	22.3 (11.6)	20.4 (13.0)	.87	20.7 (12.2)	20.0 (11.1)	.61
Degree of stenosis (pre-PCI)*	67.3 (13.7)	68.0 (14.4)	.43	68.6 (13.5)	66.1 (13.8)	.08
Residual in-stent stenosis (post-PCI)*	14.8 (6.1)	13.6 (7.9)	<.01	14.8 (6.1)	14.8 (6.2)	.90
Total stent length per patient (millimeters)	40 (24-60)	30 (18-51)	<.01	42 (24-63)	40 (28-56)	.98
No. of stents per patient	2.0 (1.0-3.0)	2.0 (1.0-2.0)	<.01	2.0 (1.0-3.0)	2.0 (1.0-3.0)	.73
Postdilation	343 (94.8)	879 (85.4)	<.01	170 (96.0)	171 (93.4)	.27

Abbreviation: *BMI*, body mass index; *CAD*, coronary artery disease; *MI*, Myocardial infarction; *PCI*, percutaneous coronary interventions; *CABG*, coronary artery bypass graft.
Values are mean (±SD), n (%), or median (interquartile range; IQR).
* In case of multiple target lesions, the most severe diameter stenosis is presented.
† A reference vessel diameter <2.75 mm defined a small vessel.

Table II. Techniques applied with Xience V and Resolute stents in both single-stent and 2-stent approaches among 362 patients with bifurcated target lesions

Single-stent approach (n = 280)	Resolute (n = 145)	Xience V (n = 135)	P
Main vessel stenting only	137 (94.5)	126 (93.3)	.69
Side-branch stenting only	8 (5.5)	8 (6.7)	
Use of final kissing balloon inflation	48 (33.1)	55 (40.7)	.19

2-stent approach (n = 82)	Resolute (n = 34)	Xience V (n = 48)	P
T stenting	22 (64.7)	26 (54.2)	.61
Culotte stenting	2 (5.9)	7 (14.6)	
Mini-crush technique	4 (11.8)	7 (14.6)	
Crush technique	4 (11.8)	3 (6.3)	
V stenting	2 (5.9)	5 (10.4)	
Use of final kissing balloon inflation	27 (79.4)	33 (68.8)	.28

term clinical outcome in patients with and without treatment of a bifurcated target lesion. In addition, to evaluate potential between-stent differences, we compared the outcome of patients with bifurcation treatment with Resolute versus Xience V stents.

Methods

Patient population, interventional procedures, and angiographic analysis

We assessed 1,391 patients in the randomized TWENTE trial (ClinicalTrials.gov NCT01066650), which was performed between June 2008 and August 2010 at the Thoraxcentrum Twente, the Netherlands, and has previously been described in detail.[7,9] In brief, a broad and heterogeneous population of PCI patients (but no ST-elevation myocardial infarction within 48 hours) were randomized for treatment with Resolute or Xience V stents. Interventional procedures and the application of concomitant medication were performed according to institutional protocols and current guidelines. In bifurcations, provisional T stenting was the generally preferred approach. Nevertheless, the treatment strategy, technique of stenting, and decision to perform a final kissing balloon inflation were left at the operator's discretion. The TWENTE trial was approved by the institutional ethics committee and complied with the Declaration of Helsinki, and all patients provided written informed consent.[7]

For the purpose of the present analysis, patients were categorized into treatment of ≥1 bifurcation lesion versus treatment of nonbifurcation lesions only. In accordance with the definition of a relevant side branch in the SYNTAX score,[17] a relevant bifurcation was defined as a junction of a main vessel and a side branch with minimum lumen diameter ≥1.5 mm (after administration of intracoronary nitrates, before PCI) as measured by quantitative coronary angiography (QCA). Angiographic analyses were performed offline by experienced angiographic analysts of the Thoraxcentrum Twente (blinded for stent arm) with the use of edge-detection software (QAngio XA version 7.1; Medis, Leiden, the Netherlands).[7] In the bifurcation group, a further thorough analysis was performed, comparing the single-stent and the 2-stent strategies for bifurcation treatment, the 2 allocated DES, and the application or omission of a final kissing-balloon inflation.

Follow-up and definition of clinical end points

Details of the 3-year clinical follow-up have been reported.[16] Clinical event adjudication was performed by an independent, external clinical event committee, organized by independent clinical research organizations (Cardialysis, Rotterdam, the Netherlands; and Diagram, Zwolle, the Netherlands). Clinical end points were defined according to the Academic Research Consortium (ARC).[18,19] *Cardiac death* was defined as any death due to proximate cardiac cause (eg, myocardial infarction [MI], low-output failure, and fatal arrhythmia). *Myocardial infarction* was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker (creatine kinase–MB fraction or troponin), based on the updated ARC definition of MI. *Periprocedural MI* (*PMI*) was defined as target-vessel–related MI within 48 hours after PCI.[18,19] Cardiac markers were systematically assessed with subsequent serial measurements in the case of relevant biomarker elevation or complaints. *Stent thrombosis* was defined according to ARC as definite or probable.

The composite end point *target-vessel failure* (*TVF*) was defined as cardiac death, target-vessel–related MI, or clinically driven target-vessel revascularization (TVR). *Target-lesion failure* (TLF) was defined as a composite of cardiac death, target-vessel–related MI, and clinically indicated target-lesion revascularization; and a *patient-oriented composite end point* (POCE) as a composite of all-cause mortality, any MI, and any repeat (target- and nontarget vessel) revascularization.[7]

Statistics and data analysis

Categorical data were presented as numbers and percentages, whereas continuous variables were expressed as mean ± SD. Baseline characteristics were compared using χ^2 test or Fisher exact test for categorical variables and using one-way analyses of variance for continuous variables. Kruskal-Wallis rank sum test (nonparametric data) was used to compare total number of stents and stent length between treatment for a bifurcation or nonbifurcation target lesion, and results were presented as median and interquartile range. The time to clinical end point was assessed according to the Kaplan-Meier method, and the log-rank test was applied to compare patients with bifurcation treatment versus patients with

Table III. Three-year clinical outcome in patients with or without treatment of bifurcation lesions

	All patients (n = 1381)			Stenting strategy in patients with bifurcated lesion (n = 360)		
	Bifurcation	Nonbifurcation		1-stent	2-stent	
	(n = 360)	(n = 1021)	*P*	(n = 278)	(n = 82)	*P*
Death						
All-cause mortality	18 (5.0)	61 (6.0)	.49	14 (5.0)	4 (4.9)	1.00
Cardiac death	7 (1.9)	30 (2.9)	.32	5 (1.8)	2 (2.4)	.66
MI						
Target-vessel MI	29 (8.1)	51 (5.0)	.03	21 (7.6)	8 (9.8)	.52
PMI	25 (6.9)	32 (3.1)	<.01	18 (6.5)	7 (8.5)	.52
Revascularization						
TVR	16 (4.4)	73 (7.1)	.07	14 (5.0)	2 (2.4)	.54
Target lesion revascularization	12 (3.3)	52 (5.1)	.17	10 (3.6)	2 (2.4)	1.00
Stent thrombosis						
Definite-or-probable (0-1080)	3 (0.8)	18 (1.8)	.22	1 (0.4)	2 (2.4)	.13
Very late definite or probable (361-1080)	2 (0.6)	5 (0.5)	1.00	1 (0.4)	1 (1.2)	.40
Composite end points						
TVF	47 (13.1)	129 (12.6)	.84	36 (12.9)	11 (13.4)	.91
Target lesion failure	44 (12.2)	116 (11.4)	.66	33 (11.9)	11 (13.4)	.71
Major adverse cardiac events	52 (14.4)	147 (14.4)	.98	40 (14.4)	12 (14.6)	.96
Patient-oriented composite end point	59 (16.4)	175 (17.1)	.74	47 (16.9)	12 (14.6)	.63

Abbreviation: *SB*, side-branch.
Values are n (%). During 3-year follow-up, 2 patients with bifurcated target lesions and 8 patients without bifurcated target lesions withdrew their consent, which explains the minor differences in number of patients as compared with baseline.

treatment of nonbifurcation lesions only. Confidence intervals and *P* values were 2 sided. *P* values < .05 were considered significant. Parameters were considered as potential confounders, if in univariate analyses associations were found with a *P* value < .10. A multivariate Cox regression model was then used to adjust for potential confounders. Analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, IL). The TWENTE trial is an investigator-initiated study, supported by equal unrestricted grants from Abbott Vascular and Medtronic. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Baseline characteristics of patients, lesions, and procedures

Of the 1,391 patients in the TWENTE trial, 362 (26.0%) patients were treated for bifurcation lesions and 1,029 (74.0%) for nonbifurcation lesions only. Within the bifurcation group, 179 (49.4%) patients were treated with Resolute and 183 (50.6%) with Xience V stents. In bifurcated target lesions, the side-branch lumen measured 2.27 ± 0.41 mm with a lesion length of 10.1 ± 6.8 mm and a side-branch stenose 62.5% ± 13.6% before PCI. A total of 79.0% of these side branches had lumen diameters ≥2.0 mm by QCA. During follow-up, 10 (0.7%) patients withdrew consent or refused further participation (2 in the bifurcation group). In all remaining 1,381 patients (99.3%), follow-up was obtained.

Baseline characteristics of patients, lesions, and procedures are shown in Table I. Patients with bifurcation treatment had aortoostial lesions and a history of previous coronary artery bypass graft (CABG) less often, and they were more often treated in the left anterior descending artery and by postdilation of the implanted stents (Table I). Among patients of the bifurcation group treated with Resolute versus Xience V, there was no difference in the technique of stenting and the rate of final kissing balloon inflation (Table II).

Clinical outcome

At 3-year follow-up, patients in the bifurcation group showed a higher incidence of target-vessel MI (8.1% vs 5.0%; *P* = .03) but no difference in TVF compared with the nonbifurcation group (Table III). Among patients with bifurcation lesions, there was no difference in TVF between patients with side branches ≥2.0 mm vs <2.0 mm (13.3% vs

Table III. *(continued)*

Kissing balloon in patients with bifurcated lesions (n = 360)			Allocated stent in patients with bifurcated lesions (n = 360)			Maximum SB diameter in patients with bifurcated lesions (n = 360)		
Kissing Balloon (n = 162)	**No Kissing Balloon (n = 198)**	***P***	**Resolute (n = 177)**	**Xience V (n = 183)**	***P***	**SB ≥2.0 mm (n = 286)**	**SB <2.0 mm (n = 74)**	***P***
Death								
10 (6.2)	8 (4.0)	.36	10 (5.6)	8 (4.4)	.58	16 (5.6)	2 (2.7)	.55
4 (2.5)	3 (1.5)	.71	4 (2.3)	3 (1.6)	.72	6 (2.1)	1 (1.4)	1.00
MI								
13 (8.0)	16 (8.1)	.98	15 (8.5)	14 (7.7)	.77	22 (7.7)	7 (9.5)	.62
13 (8.0)	12 (6.1)	.47	13 (7.3)	12 (6.6)	.77	19 (6.6)	6 (8.1)	.66
Revascularization								
9 (5.6)	7 (3.5)	.36	7 (4.0)	9 (4.9)	.66	13 (4.5)	3 (4.1)	1.00
5 (3.1)	7 (3.5)	.81	6 (3.4)	6 (3.3)	.95	10 (3.5)	2 (2.7)	1.00
Stent thrombosis								
0 (0.0)	3 (1.5)	.26	2 (1.1)	1 (0.5)	.62	1 (0.3)	2 (2.7)	.11
0 (0.0)	2 (1.0)	.50	1 (0.6)	1 (0.5)	1.00	1 (0.3)	1 (1.4)	.37
Composite end points								
25 (15.4)	22 (11.1)	.23	24 (13.6)	23 (12.6)	.78	38 (13.3)	9 (12.2)	.80
22 (13.6)	22 (11.1)	.48	24 (13.6)	20 (10.9)	.45	35 (12.2)	9 (12.2)	.99
26 (16.0)	26 (13.1)	.43	28 (15.8)	24 (13.1)	.47	43 (15.0)	9 (12.2)	.53
30 (18.5)	29 (14.6)	.32	31 (17.5)	28 (15.3)	.57	49 (17.1)	10 (13.5)	.45

12.2%; $P = .80$; Table III). The rates of definite-or-probable stent thrombosis were low and similar for both patients with bifurcation lesions and patients with nonbifurcated lesions (0.8% vs 1.8%; $P = .22$). Dual antiplatelet therapy use at 3-year follow-up was slightly lower than after 2 years (70/1302 [5.4%] vs 91/1312 [6.9%])[9] and was similar between the bifurcation and nonbifurcation groups (5.0% vs 5.5%; $P = .70$). Among patients with bifurcation lesions, use of a single-stent or a 2-stent approach (independent of the allocated stent) and the use or omission of a final kissing balloon inflation were not associated with differences in clinical outcome (Table III). In patients with bifurcation lesions, there was no difference in TVF and other clinical end points between the Resolute and Xience V stent arm (13.6% vs 12.6%; $P = .78$).

Figure 1 presents the Kaplan-Meier curves for TVF (Figure 1A) and the components thereof (Figure 1B-D). The abrupt early rise in TVF was numerically higher in patients of the bifurcation group, mainly as the result of a higher incidence of PMI (Figure 1C). A landmark analysis (Figure 2) showed that after >48 hours, there was no difference between the bifurcation and nonbifurcation group ($P = .37$). In addition, the Kaplan-Meier curves of TVR for the 2 study groups showed a somewhat diverging course in favor of patients with bifurcation treatment (Figure 1D; $P = .06$).

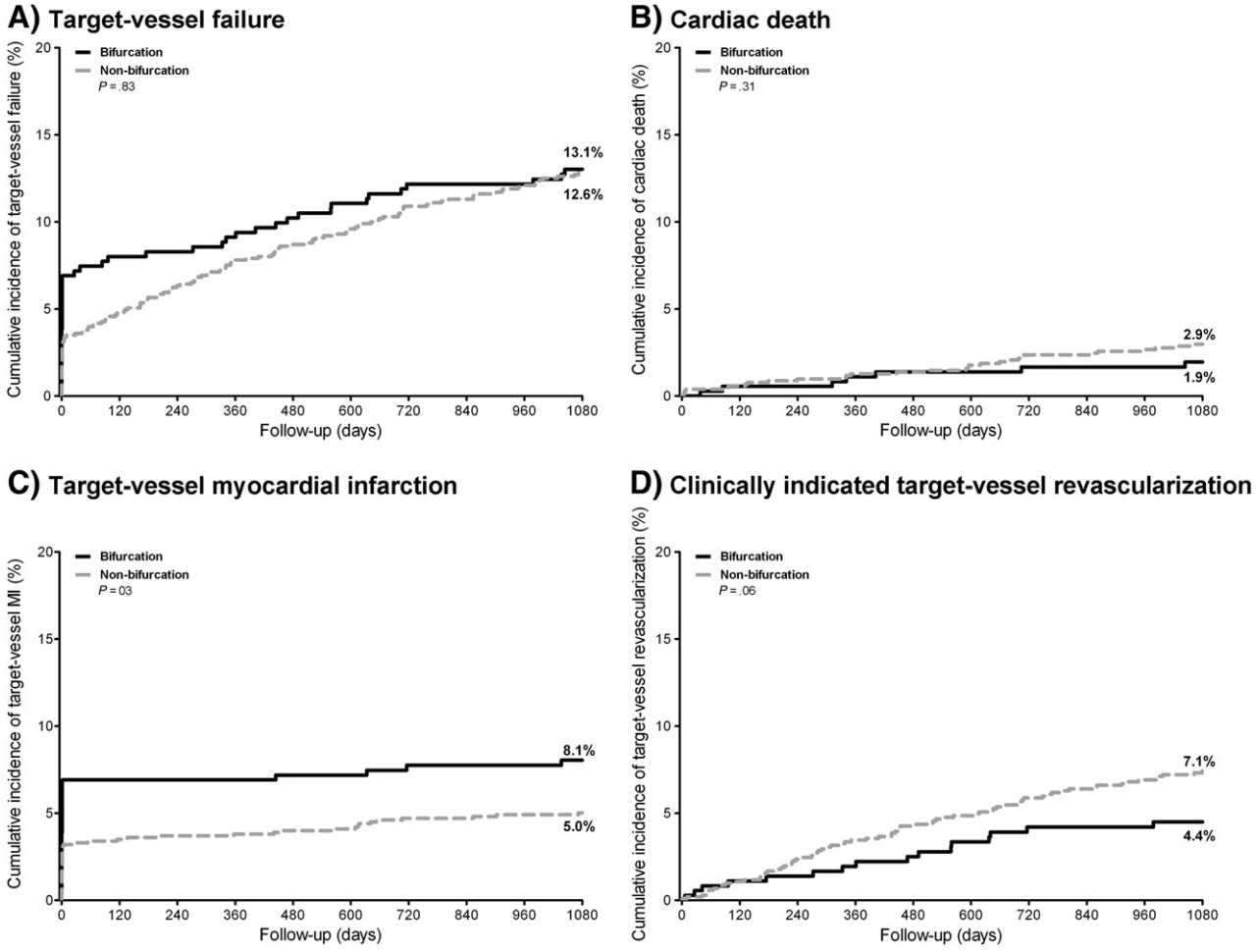
Risk factors of target-vessel MI

Cox regression analysis suggested that bifurcation treatment may be associated with an increased risk of target-vessel MI (HR 1.64; 95% CI 1.04-2.58; $P = .03$); but after adjustment for potential confounders (multivessel treatment, total stent length, number of stents, postdilation, treatment of circumflex artery, no. of lesions treated, and residual in-stent stenosis after stent implantation) in a multivariate Cox regression model, bifurcation treatment turned out to be no independent predictor of target-vessel MI (adjusted HR 1.29; 95% CI 0.80-2.06; $P = .30$). With an increasing degree of residual in-stent lumen diameter stenosis, there was an increase in the risk of target-vessel MI that was no more than slight (adjusted HR 1.03; 95% CI 1.01-1.05; $P < .01$).

Risk factors of repeat revascularization

Although statistically nonsignificant, there was a higher risk of TVR in patients with nonbifurcated lesions (HR 1.7 95% CI 0.97-2.86; $P = .06$). Previous CABG and treatment of (≥1) aortoostial lesion were identified as potential confounder and therefore tested in a multivariate Cox regression model, which showed that both parameters were predictors of TVR (adjusted HR 2.31; 95% CI 1.40-3.82, $P < .01$; adjusted

Figure 1



Kaplan-Meier curves of the composite clinical end point target-vessel failure (A) and its individual components (B-D).

HR 2.00; 95% CI 1.18-3.34; P = .01, respectively). After adjustment for these confounders, treatment of nonbifurcated lesions did not independently predict TVR (adjusted HR 1.52; 95% CI 0.89-2.62; P = .13).

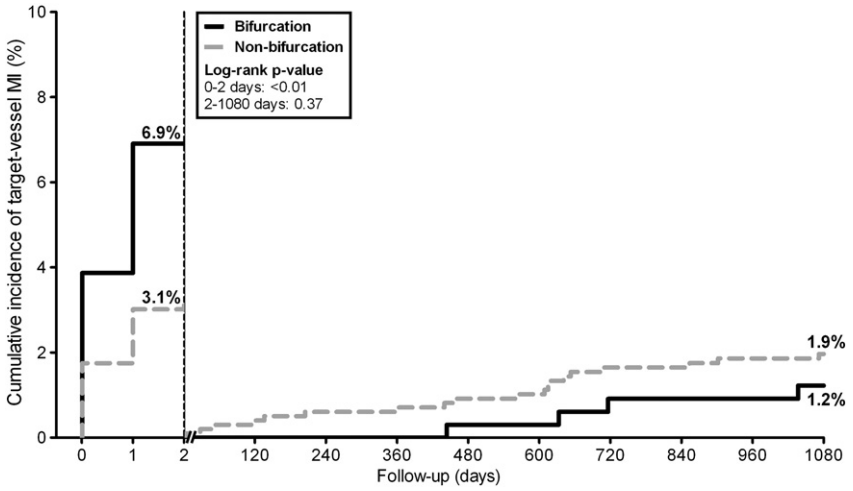
Discussion

Despite a higher incidence of PMI, patients treated for bifurcation lesions with second-generation DES had a favorable long-term clinical outcome that was similar to the outcome of patients with nonbifurcation lesions. In patients with treatment of bifurcated target lesions, different treatment strategies (ie, single-stent or 2-stent approach) and the use of final kissing balloon inflation did not affect long-term outcome. In patients treated with a 2-stent approach, the rate of final kissing balloon inflation was numerically higher in the Resolute group as compared with Xience V group (79.4% vs 68.8%; P = .28), which may be related to the more open cell design of the Resolute stent.[20] Nevertheless, there was no difference in clinical outcome between patients treated for bifurcated lesions with Resolute versus Xience V stents.

The numerically higher incidence of TVR in the nonbifurcation group (P = .06) was attributed to the presence of a more advanced atherosclerotic burden as shown by the multivariate analysis that demonstrated a significantly higher prevalence of previous CABG and aortoostial target lesions in that group. The importance of these 2 parameters as risk factors of repeat revascularization has previously been shown.[21,22]

The definite-or-probable stent thrombosis rate was numerically higher in the nonbifurcation group versus the bifurcation group (1.8% vs 0.8%; P = .22) and in patients with bifurcation treatment with a 2-stent approach versus a single stent (2.4% vs 0.4%; P = .13). Although the latter is in line with the substudy of the Resolute All Comers,[13] the stent thrombosis data should

Figure 2



Landmark analysis of target-vessel MI at 2 days.

be interpreted with caution due to the limited number of events.

Previous bifurcation studies with DES

The introduction of DES has substantially reduced the rate of repeat revascularization after treatment of bifurcation lesions.[2-4] Because of differences in stent design, clinical outcome of bifurcation stenting may differ between DES.[20] The randomized CORpal and SEAside studies compared Xience V and the first-generation sirolimus-eluting Cypher stent (Cordis, Waren, NJ) in bifurcation lesions and found after 12 and 18 months, respectively, no difference in clinical outcome between the 2 DES.[11,12] However, in a recently reported pooled analysis of both trials, the rate of major adverse cardiac events (MACE) beyond 1 year was significantly lower (P = .03) after treatment with Xience V as compared with Cypher,[14] underlining the importance of long-term clinical assessment of DES.[15]

There are somewhat less data available on the Resolute stent in bifurcation lesions. A multicenter registry, comprising 180 patients treated with Resolute, showed a low MACE rate at 9-month follow-up.[23] In the Z-SEAside study, use of the Resolute stent in bifurcated lesions of 75 patients resulted in a lower procedure-related composite end point (as compared with Cypher). Nevertheless, at 2-year follow-up, there was no difference in a composite clinical and angiographic end point.[24]

Overall, Xience V and Resolute have shown favorable results in various patient populations that included patients with bifurcation lesions.[5-7,16,21,25,26] A recent analysis that pooled both stent arms of the RESOLUTE All Comers trial, which used the same DES as the TWENTE trial (and thus our present substudy), showed similar clinical outcomes for patients treated for bifurcated versus nonbifurcated lesions at 2-year follow-up.[13] In the study reported by Diletti et al[13] as well as in our present study, there was a higher incidence of PMI in patients with bifurcation lesions. In the absence of an unequivocal cause of PMI in patients with bifurcated target lesions, we speculate that (stent-induced) closures of side branches may have resulted in PMI. Although PMI may be considered a marker of PCI procedure complexity (eg, treatment of a bifurcated lesion), the clinical impact of PMI remains partly unclear.[27] In addition, in the present study, there was no evidence of a relationship between the occurrence of PMI after bifurcation treatment and an adverse clinical outcome. However, in the presence of larger side branches and an increased risk of side-branch occlusion, one may consider the use of an additional guide wire in the side branch, a more aggressive pharmacologic (antiplatelet) therapy, and, occasionally, the upfront use of a 2-stent approach to protect the patency of the side branch.

In both studies, the number of patients treated with a 2-stent approach was reasonable (81[13] and 82 patients in the present study), representing 20.7% and 22.7% of all patients with bifurcation treatment. In the TWENTE trial population, final kissing balloon inflation was performed in 73.2% of patients treated with the 2-stent approach. In the absence of data on the use of final kissing balloon inflation in the RESOLUTE All Comers trial, we can only speculate that potential differences in the frequency of kissing balloon inflation might have played a role.

A randomized bifurcation study with first-generation DES has previously shown a lower restenosis rate of the side branch in lesions that had been treated with kissing balloon inflation (7.9% vs 15.4%; P = .04).[28] In our present clinical study, in the absence of a routine angiographic follow-up, clinical outcome was similar in

patients treated for bifurcation lesions with and without final kissing balloon inflation.

Bifurcation analyses should focus on target lesions with side branches of a relevant size. However, through the various bifurcation studies, there was no general consensus on the minimum lumen diameter of side branches that should be addressed and on the method of assessment (ie, visually determined or measured by QCA).[11-13,24,28] Compared with visual assessment, QCA is more objective and may be stricter in preventing the inclusion of too small side branches.[29] In the TWENTE trial and the present bifurcation substudy, a minimum side-branch diameter ≥1.5 mm by QCA was applied, which is in line with the definition of relevant bifurcations for the SYNTAX score.[17] In addition, almost 80% of our patients with bifurcated target lesions had side branches ≥2.0 mm by QCA, and their TVF rate did not differ from patients with smaller side branches ($P = .80$). Bifurcations with side branches ≥2.0 mm were also addressed by previous bifurcation studies such as the SEASIDE trial and Z-SEASIDE registry, which included patients based on a visual assessment of the side-branch lumen diameter.[11,24]

Study limitations

Because of the relatively limited sample size and the low event rates, no definite conclusion can be drawn from the present post hoc analysis, and findings should be considered hypothesis generating. Nevertheless, because of the low event rates with the study stents used, the analysis was based on the 3-year clinical outcome data (which increased the overall no. of adverse events). In addition, the comparison between the outcome of patients treated with 2-stent versus single-stent approach and of patients treated with kissing balloon inflation versus the omission thereof are limited by the small size of these patient subgroups. Similar to previous bifurcation studies that used several different definitions of bifurcated target lesion and relevant side branch, the comparability of our findings with data of trials that used different definitions and/or addressed dissimilar patient populations may be limited. We did not measure the bifurcation angle; a dedicated 3-dimensional reconstruction and analysis software for bifurcations may be a promising tool to obtain reliable data on true lesion geometry.[30] The TWENTE trial did not comprise a routine angiographic follow-up; as such, no angiography-based subanalyses of side-branch patency could be performed.

Clinical implications

The present analysis of the randomized TWENTE trial, which enrolled a broad study population of patients with advanced coronary disease and complex coronary lesions in most patients, reassures that use of the study stents for the treatment of bifurcated coronary lesions is safe and effective. These findings are relevant, as in most patients with bifurcation lesions a simple approach with provisional T-stenting was applied, which is currently the recommended approach.[31,32] The favorable outcome of various subgroups of patients suggest that, with the use of second-generation DES, long-term clinical outcome is favorable and similar for bifurcation treatment with a single-stent or 2-stent approach and with or without kissing balloon inflation.

Conclusions

Despite a significant difference in PMI, 3-year clinical outcome after implantation of second-generation stents was favorable and similar for patients with and without bifurcation lesions. In addition, we observed no difference in long-term clinical outcome after bifurcation lesion treatment with Resolute and Xience V stents.

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Disclosures

Conflict of interest: Clemens von Birgelen is or has been consultant to and has received lecture fees or travel expenses from Abbott Vascular, Boston Scientific, and Medtronic; he received travel expenses from Biotronik and lecture fees from MSD; the institution has received research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. All other authors declare that they have no conflict of interest. The TWENTE trial is an investigator-initiated study, supported by equal unrestricted grants from Abbott Vascular and Medtronic.

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