Risk of target lesion failure in relationship to vessel angiographic geometry and stent conformability using the second generation of drug-eluting stents

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Background Vessel angulation and large changes in vessel geometry after stent implantation have been associated with an increased risk of target lesion failure (TLF) using bare-metal stents. Second-generation drug-eluting stents (DES)offer superior conformability and inhibition of neointima. The aim of the study is to investigate the relationship between pre and post-implant vessel geometry and the occurrence of TLF at 1 year after treatment with second-generation DES; and to compare the conformability of Resolute and Xience stents.

Methods The RESOLUTE All-Comers trial randomized 2292 patients (3366 lesions) to Resolute zotarolimus-DES (Medtronic CardioVascular) or Xience everolimus-DES (Abbott Vascular). At 1 year, 176 lesions (121 patients)presented with TLF; a composite of cardiac death, acute myocardial infarction (AMI) and target lesion revascularization (TLR). Lesions with TLF were matched with 176 lesions (168 patients) without TLF adjusting for clinical and procedural characteristics. The number of bends, vessel curvature and angulation were assessed with quantitative coronary angiography pre and post-implantation. The absolute difference post minus pre-implantation was used as a surrogate of stent conformability.

Results At pre-implantation, lesions without and with TLF had similar numbers of bends/lesion (1.81 vs 1.74; $P = .35$), vessel curvature (0.295 cm^{-1} vs 0.363 cm^{-1}; $P = .13$) and vessel angulation (46.3° vs 43.5°; $P = .80$), respectively. Lesions without and with TLR also had similar numbers of bends/lesion (1.39 vs 1.39; $P = .83$), vessel curvature (0.368 cm^{-1} vs 0.325 cm^{-1}; $P = .33$) and angulation (40.2° vs 37.2°; $P = .19$). Lesions without and with in-hospital AMI also presented with similar number of bends/lesion (1.69 vs 1.81; $P = .48$), vessel curvature (0.349 cm^{-1} vs 0.345 cm^{-1}; $P = .91$) and vessel angulation (43.53° vs 48.45°; $P = .38$). The absolute difference post- – pre-implantation was similar in lesions without and with TLF, TLR and In-hospital AMI. The absolute difference post- – pre-implantation was similar with both Resolute and Xience in vessel curvature (–0.046 cm^{-1} vs –0.047 cm^{-1}; $P = .66$) and was smaller in number of bends/lesion (–0.08 vs –0.16; $P = .13$) and in vessel angulation (–6.0° vs –10.1°; $P = .03$) with the Resolute.

Conclusions Bended, curved, and angulated lesions and changes in the number of bends/lesion, vessel curvature, and angulation from pre to post-implantation have no relation with TLF and TLR at 1 year and have no relation with In-hospital AMI using second-generation of DES. Resolute appears to be more conformable than Xience. (Am Heart J 2011;162:1069-1079.e2.)

Coronary stent implantation represented a substantial quantum leap in percutaneous coronary interventions (PCI). Compared to simple balloon angioplasty, metallic stents minimized the occurrence of several acute complications and expanded the indication of PCI to a more complex spectrum of lesions. However, coronary stenoses located in extremely angulated segments (>90°) are classified as type C lesions according to the American College of Cardiology/American Heart Association lesion type classification.[1] Type C lesions have been associated with poor acute angiographic results and with the occurrence of major adverse cardiac events with the

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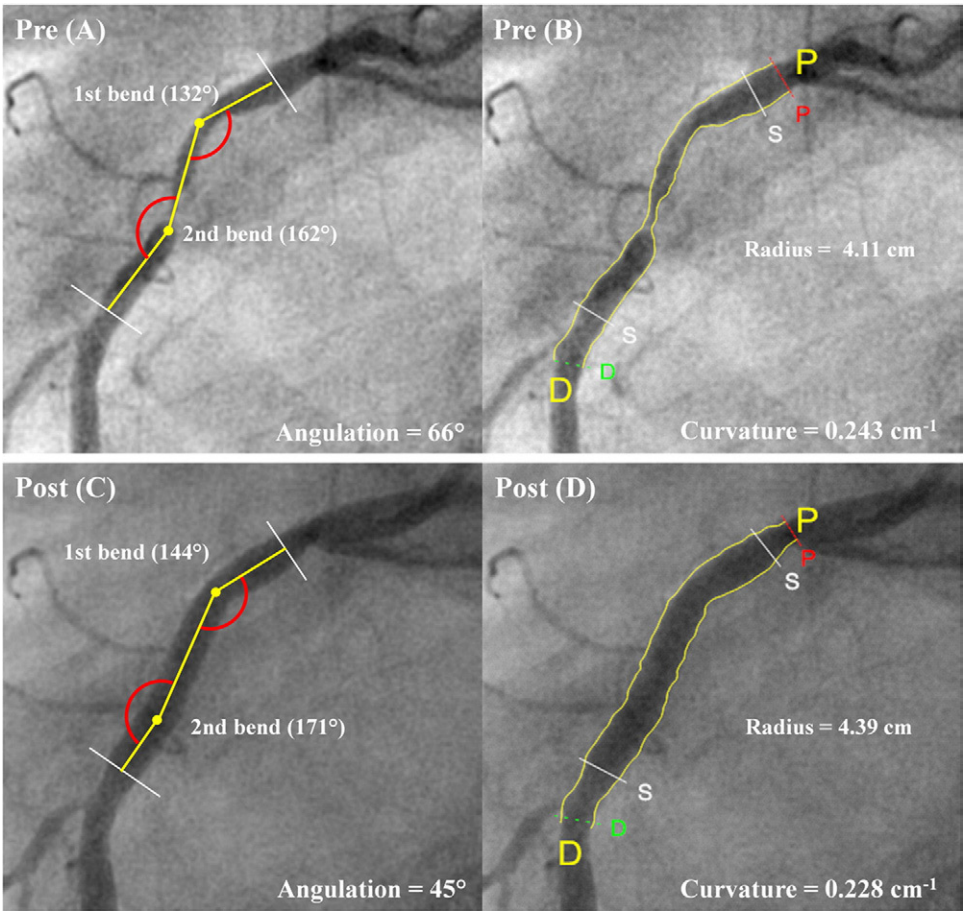
Figure 1



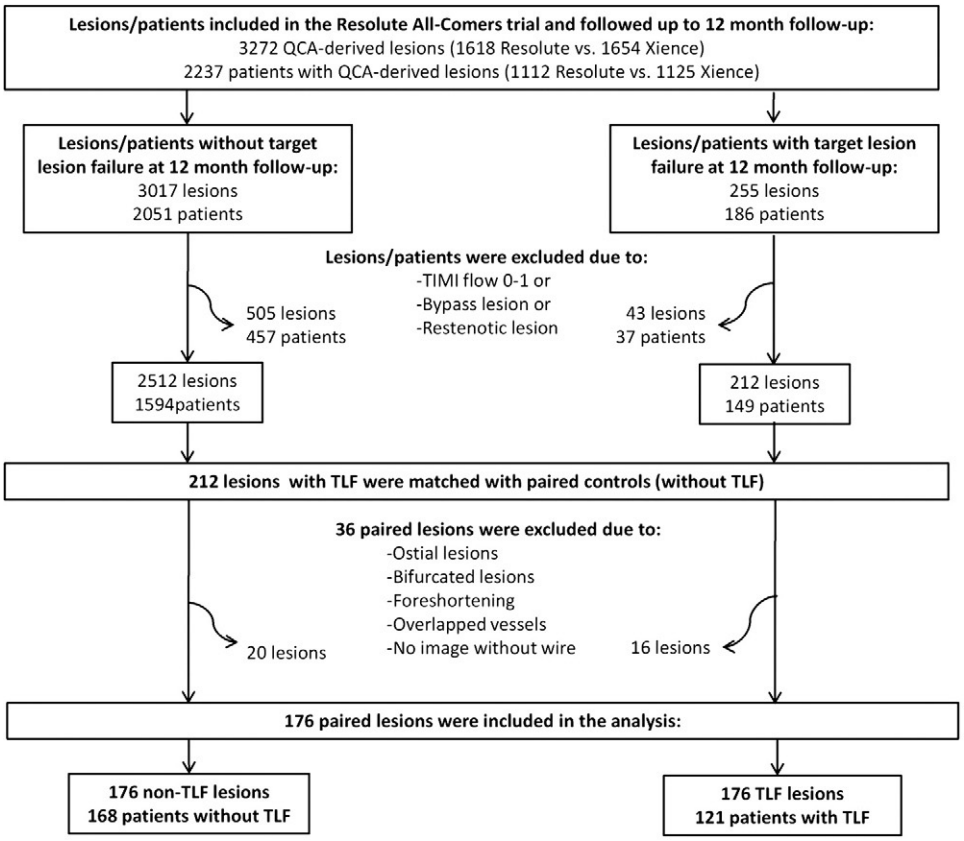
Curvature and angulation assessment using quantitative coronary angiography. Angiographic views of a severe lesion treated with a DES3.5x24 mm. *Angulation* is defined as the angle needed by the tip of the wire to cross the treated region. At pre-implantation (A), angulation is 66° (48°+18°): the first bend is 48° (180°-132°) and the second bend is 18° (180°-162°). The absolute difference between pre (A) and post-implantation (C) is 21°.*Curvature* is defined as the inverse of the radius of a perfect circle defined by the tangent of the center-line. The absolute difference in curvature between pre (B) and post-implantation (D) is 0.015 cm^{-1}.

use of bare-metal stents (BMS).[2,3] A potential explanation of these findings is that placement of rigid metallic stents in curved segments, with the consequential straightening of the vessel, has been associated with higher rates of peri-procedural acute myocardial infarction (AMI) and with a larger neointimal response (and restenosis) compared to straight segments.[4] The straightening of curved segments (due to stent implantation)can cause more disruption of the plaque and promote distal embolization and; modifies the flow dynamics and wall shear stress within the stented segment triggering an exacerbated neointimal response.[5]

The first generation of drug-eluting stents (DES) used the same stent platforms as previous BMS. However, the metallic platforms were coated with different co-polymers and anti-proliferative drugs that inhibited the neointimal response. Therefore, the first generation of DES decreased the risk of adverse events by mainly reducing the need for repeat target lesion revascularization (TLR).[6]There are few data regarding the relationship between vessel geometrical parameters and stent conformability and the occurrence of clinical events using first-generation DES. Similar to BMS, low shear stress has also been associated with a larger neointimal response after implantation of paclitaxel-eluting stents.[7] In contrast, no relationship between the shear stress and neointimal hyperplasia was seen after use of sirolimus-eluting stents.[7] Currently is unknown whether the inhibition of the neointimal response inflicted by the different anti-proliferative drugs can potentially overcome the higher risk of restenosis in curved stenotic segments.

The second generation of DES uses different metal alloys that enable stent struts to be thinner and has

Figure 2



Flow-chart of the patient selection.

different platform designs intended to provide better deliverability and conformability of the stent to the vessel wall.[8] It has been shown an important reduction in peri-procedural AMI with the second-generation DES compared to the first-generation DES.[9,10] Currently, it is unknown whether the improved conformability of second-generation DES leads to lower rates of adverse cardiac events.

The aims of the present study are: (1) to investigate if bended, curved and angulated lesions treated with second-generation DES are related to target lesion failure (TLF) and clinically-driven TLR at 1 year; (2) to investigate if bended, curved, and angulated lesions treated with second-generation DES are related to in-hospital AMI; (3) to investigate if changes in vessel bends, curvature, and angulation from pre- to post-implantation are related to TLF and clinically-driven TLR at 1 year and to in-hospital AMI using second-generation DES; (4) to compare the conformability in vivo of the Resolute and the Xience V stents in an all-comers, randomized trial.

Materials and methods

Population and study design

The present study is a post hoc analysis of the RESOLUTE All-Comers trial (ClinicalTrials.gov number, NCT00617084); a multicenter, randomized, all-comers trial comparing the Resolute zotarolimus-DES with the Xience V everolimus-DES.[11] The inclusion criteria and clinical and angiographic results at 1-year follow-up have been previously reported.[11] In brief, 2,292 patients (Resolute = 1,140 vs Xience = 1152) with 3366 lesions (Resolute = 1,661 vs Xience = 1,705) were enrolled, with a primary end-point of TLF, a composite of cardiac death, AMI not attributable to a non-target vessel, and clinically-driven TLR. The online Appendix contains detailed information about the stent devices and the clinical endpoints definitions. At 1 year of clinical follow-up, resolute was shown to be non-inferior to EES for the primary end point (Resolute = 92 [8.2%] versus Xience = 94 [8.3%], $P_{\text{non-inferiority}} < .001$).

The present study selected all lesions included in the RESOLUTE All-Comers trial with available baseline angiography and with clinical follow-up at 12 months. Lesions were defined by the core-laboratory (Cardialysis, Rotterdam, Netherlands) using quantitative coronary angiography (QCA). Lesions located

in venous or arterial by-pass grafts, restenotic lesions, stent thrombosis, and lesions with TIMI flow 0 to 1 (ie, due to chronic total occlusions or AMI) were also excluded from the present analysis. In order to compare the angiographic vessel bending, curvature and angulation of lesions with and without TLF at 1 year with similar risk factors for lesion failure, a propensity score matching was performed to select matched non-TLF lesions and TLF lesions. The propensity score was performed using clinical, procedural and angiographic factors as covariates.

Quantitative Coronary Angiography

Quantitative Coronary Angiography-derived lesions were defined as entire coronary segments treated with single or multiple overlapping stents. All angiographic measurements, pre and post-implantation, of the target lesion were obtained in the "in-stent" zone and within 5 mm proximal and distal to each stent edge.[11,12] Vessel geometrical parameters were assessed as the number of bends, curvature and angulation of the "in-stent" segment. Both curvature and angulation were assessed using the CASS 5.9 QCA software (Pie Medical Imaging) as previously reported.[13,14] Figure 1 shows the basic principles of the number of bends, curvature and angulation assessment. The online Appendix contains more detailed information about the QCA analysis.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality assumptions of all continuous variables. Since curvature and angulation are not normally distributed, both parameters are expressed as medians (inter-quartile range). The rest of continuous variables are expressed as means ± 1 SD. Categorical variables are presented as counts (%).Comparisons between groups were estimated using the respective Student *t* test or Mann-Whitney *U* test when variables were normally or not-normally distributed. Comparisons of categorical variables were estimated with the Chi-square test. All statistical tests were carried out at the two-sided 5% level of significance. All measures were obtained with SPSS 15.0 (SPSS Inc, Chicago IL). Clinical outcomes are presented non-hierarchically. Propensity score matching was performed using a proprietary macro developed and tested for SPSS (www.unc.edu/~painter). The online Appendix contains the used methodology of the propensity score matching.

Medtronic CardioVascular (Santa Rosa, CA) funded the RESOLUTE all-comers trial and has supported the present study. However, the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Population

The RESOLUTE all-comers trial included 3272 QCA-derived lesions in 2237 patients which were followed up to 1 year of clinical follow-up. A total of 255QCA-derived lesions in 186 patients experienced TLF at 1 year. After exclusion of 43 lesions which had either TIMI 0-1 flow, or were located in a by-pass graft or a previous stent, 212 lesions with TLF at 1 year were matched with 212 paired lesions without TLF at 1 year according to clinical and angiographic factors. Curvature and angulation analysis of 36 out of 212 paired matched lesions was not feasible and were excluded from the analysis. Therefore, 176 lesions in 168 patients without TLF at 1 year and 176 lesions in 121 patients with TLF at 1 year were included in the present study. A flow chart summarizing the patient selection is shown in Figure 2.

Table I. Clinical event responsible for the target lesion failure at 12 months

	Patients (n = 121) n (%)	Lesions (n = 176) n (%)
Cardiac death	23 (19.0)	26 (14.8)
AMI not clearly attributed to a non-target vessel (ARC)	80 (66.1)	136 (77.3)
Non-Q wave AMI	70 (57.9)	124 (70.5)
Q-wave AMI	10 (8.3)	12 (6.8)
In-hospital AMI not clearly attributed to a non-target vessel (ARC)	61 (50.4)	94 (53.4)
Clinically-driven TLR	40 (33.1)	42 (23.9)*
PCI	37 (30.6)	39 (22.2)
CABG	3 (2.5)	5 (2.8)
Stent thrombosis (ARC)	31 (25.6)	34 (19.3)
Definite	11 (9.1)	11 (6.3)
Probable	7 (5.8)	8 (4.5)
Possible	13 (10.7)	15 (8.5)
Stent thrombosis (all ARC types)		
Early (0-30 days)	13 (10.7)	14 (8.0)
Late (31-360 days)	16 (13.2)	20 (11.4)

AMI, Acute myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery by-pass graft; *TLR*, target lesion revascularization.
* 2TLR treated with PCI received a second TLR treated with PCI and CABG.

Table I shows the clinical event responsible for TLF in the group of patients/lesions with TLF at 1 year (n = 121). A total of 80 patients (66.1%) experienced a myocardial infarction (76.3% of them were observed in-hospital). Cardiac death was observed in 23 (19%) patients. A total of 42 lesions in 40 patients (33.1%) underwent a clinically-driven TLR.

Baseline clinical and non-geometrical angiographic characteristics

Table II shows the baseline clinical and angiographic characteristics of patients with paired-matched lesions according to the occurrence of TLF and clinically-driven TLR at 1 year and the occurrence of in-hospital AMI. All groups had with similar baseline clinical characteristics for demographic and cardiovascular risk factors. The clinical indication for the index procedure, number of vessels diseased and SYNTAX score were also similar in all groups. Only hypercholesterolemia was more frequently observed in the group with TLF (74%) than without TLF (62%), $P = .03$.

Table III shows the angiographic and procedural characteristics of the paired-matched lesions according

Table II. Clinical and angiographic characteristics of patients with matched lesions according to the occurrence of target lesion failure and target lesion revascularization at 1 year and the occurrence of in-hospital acute myocardial infarction

	Target lesion failure			Target lesion revascularization			In-hospital myocardial infarction		
Patient level (n = 289)	**No TLF (n = 168)**	**TLF (n = 121)**	***P***	**No TLR (n = 41)**	**TLR (n = 40)**	***P***	**No AMI (n = 89)**	**AMI (n = 61)**	***P***
Age, mean ± SD	66.6 ± 11.3	66.4 ± 11.6	.89	64.5 ± 11.3	62.8 ± 9.6	.40	66.6 ± 11.8	67.4 ± 10.7	.67
Males, n (%)	112 (66.7)	85 (70.2)	.52	31 (75.6)	33 (80.5)	.59	60 (67.4)	45 (73.8)	.40
Hypertension, n (%)	123 (73.2)	90 (74.4)	.82	31 (75.6)	31 (75.6)	1.00	69 (77.5)	44 (72.1)	.45
Hypercholesterolemia, n (%)	104 (61.9)	90 (74.4)	.03	26 (63.4)	31 (75.6)	.23	59 (66.3)	47 (77.0)	.16
Diabetes mellitus, n (%)	35 (20.8)	35 (28.9)	.11	11 (26.8)	14 (34.1)	.47	18 (20.2)	13 (21.3)	.87
Non-insulin dependent	22 (13.1)	20 (16.5)	.41	8 (19.5)	10 (24.4)	.59	12 (13.5)	9 (14.8)	.83
Insulin dependent	13 (7.7)	15 (12.4)	.19	3 (7.3)	4 (9.8)	.69	6 (6.7)	4 (6.6)	.97
Smoking history, n (%)	89 (53.0)	64 (52.9)	.99	26 (63.4)	25 (61.0)	.82	53 (59.6)	29 (47.5)	.15
Prior myocardial infarction, n (%)	47 (28.7)	39 (33.1)	.43	10 (25.0)	13 (32.5)	.46	21 (24.1)	16 (26.7)	.73
Prior coronary revascularization	59 (35.1)	41 (33.9)	.83	10 (24.4)	15 (36.6)	.23	26 (29.2)	17 (27.9)	.86
Prior PCI, n (%)	53 (31.5)	39 (32.2)	.90	9 (22.0)	15 (36.6)	.15	24 (27.0)	15 (24.6)	.75
Prior CABG, n (%)	14 (8.3)	11 (9.1)	.82	3 (7.3)	3 (7.3)	1.00	8 (9.0)	5 (8.2)	.87
BMI, mean ± SD	27.3 ± 4.0	28.0 ± 5.2	.21	28.6 ± 5.8	28.8 ± 4.8	.41	27.5 ± 4.9	27.5 ± 4.8	.97
Clinical indication, n (%):			.75			.27			.54
Stable angina	99 (58.9)	69 (57.0)		25 (61.0)	20 (48.8)		51 (57.3)	38 (62.3)	
Acute coronary syndrome	69 (41.1)	52 (43.0)		16 (39.0)	21 (51.2)		38 (42.7)	23 (37.7)	
Treated lesions per patient, n (%)	1.7 ± 0.9	1.7 ± 0.8	.58	1.9 ± 1.1	2.0 ± 0.9	.91	1.7 ± 0.8	1.9 ± 1.1	.30
Number of vessel disease, n (%):			.83			.33			.97
One	49 (29.2)	33 (27.3)		10 (24.4)	7 (17.1)		23 (25.8)	17 (27.9)	
Two	65 (38.7)	49 (40.5)		22 (53.7)	18 (43.9)		37 (41.6)	24 (39.3)	
Three	51 (30.4)	35 (28.9)		9 (22.0)	15 (36.6)		26 (29.2)	18 (29.5)	
Four	3 (1.8)	4 (3.3)		0 (0.0)	1 (2.4)		3 (3.4)	2 (3.3)	
Syntax score, mean ± SD	16.0 ± 9.9	17.9 ± 9.8	.13	16.8 ± 8.6	17.6 ± 9.2	.21	17.7 ± 10.5	17.2 ± 9.8	.80

CABG, Coronary artery by-pass graft; *BMI*, body mass index.

to the occurrence of TLF and clinically-driven TLR at 1 year and the occurrence of in-hospital AMI. Paired-matched lesions had a similar number of stents per lesion, total stent length and treated vessel. A similar number of Resolute and Xience stents were implanted in both paired lesions. QCA was also similar between groups at pre- and post-implantation.

Relationship between pre-implantation angiographic geometrical parameters and TLF and clinically-driven TLR at 1 year and in-hospital AMI.

Table IV shows the geometrical angiographic characteristics according to the occurrence of TLF and clinically-driven TLR at 1 year and according to the occurrence of in-hospital AMI. Lesions without and with TLF had a similar Pre-implantation number of bends/lesion (1.81 vs 1.74; P = .35), vessel curvature (0.295 cm^{-1} vs 0.363 cm^{-1}; P = .13) and vessel angulation (46.3° vs 43.5°; P = .80). Similarly, lesions without and with clinically-driven TLR had a comparable number of pre-implantation bends/lesion (1.39 vs 1.39; P = .83), vessel curvature (0.368 cm^{-1} vs 0.325 cm^{-1}; P = .33), and vessel angulation (40.2° vs 37.2°; P = .19). Lesions without and with in-hospital AMI also presented with similar number of bends/lesion (1.69 vs 1.81; P = .48), vessel curvature (0.349 cm^{-1} vs 0.345 cm^{-1}; P = .91), and vessel angulation (43.53° vs 48.45°; P = .38) at pre-implantation. Figure 3 shows the box plot distribution of the Pre-implantation curvature and angulation values in the global population and according to the total stent length.

Relationship between absolute changes from post- to pre-implantation angiographic geometrical parameters and TLF and clinically-driven TLR at 1 year

Table IV shows the geometrical angiographic characteristics according to the occurrence of TLF and clinically-driven TLR at 1 year and according to the occurrence of in-hospital AMI. Lesions without and with TLF had a similar absolute difference from post- to pre-implantation of number of bends/lesion (−0.11 vs −0.13; P = .86), vessel curvature (−0.039 cm^{-1} vs −0.054 cm^{-1}; P = .25) and vessel angulation (−7.9° vs −8.0°; P = .51). Lesions without and with clinically-driven TLR also had a similar absolute difference from post to pre-implantation of number of bends/lesion (−0.08 vs −0.03; P = .28), vessel curvature (−0.063 cm^{-1} vs −0.027 cm^{-1}; P = .49), and vessel angulation (−8.8° vs −4.9°; P = .62). Lesions without and with in-hospital AMI had also similar difference from post to pre-implantation of number of bends/lesion (−0.12 vs −0.12; P = .76), vessel curvature (−0.041 vs −0.054; P = .64), and vessel angulation

Table III. Procedural and angiographic characteristics

Lesion level (n = 352)		Target lesion failure			Target lesion revascularization			In-hospital myocardial infarction		
		No TLF (n = 176)	TLF (n = 176)	*P*	No TLR (n = 42)	TLR (n = 42)	*P*	No AMI (n = 94)	AMI (n = 94)	*P*
Procedural characteristics	Stents per lesion (n), mean ± SD	1.5 ± 0.8	1.5 ± 1.0	.81	1.3 ± 0.7	1.3 ± 0.9	.89	1.4 ± 0.7	1.6 ± 1.1	.25
	Total nominal stent length (mm), mean ± SD	27.57 ± 16.66	27.95 ± 21.00	.85	23.0 ± 15.4	24.4 ± 20.8	.74	25.76 ± 15.83	30.34 ± 24.05	.12
	Minimal nominal stent diameter (mm), mean ± SD	2.85 ± 0.41	2.86 ± 0.48	.72	3.0 ± 0.4	2.8 ± 0.5	.27	2.86 ± 0.41	2.89 ± 0.55	.63
	Treated artery			.57			.39			.98
	LAD	83 (47.2)	74 (42.0)		16 (38.1)	19 (45.2)		38 (40.4)	37 (39.4)	
	LCX	39 (22.2)	46 (26.1)		7 (16.7)	10 (23.8)		21 (22.3)	22 (23.4)	
	RCA	54 (30.7)	56 (31.8)		19 (45.2)	13 (31.0)		35 (37.2)	35 (37.2)	
	Lesion type, n (%):			.37			.66			.17
	A	2 (1.2)	0		0	0		1 (1.1)	0	
	B1	49 (27.8)	42 (23.9)		11 (26.2)	13 (31.0)		32 (34.0)	20 (21.3)	
	B2	54 (30.7)	58 (32.9)		15 (35.7)	13 (31.0)		25 (26.6)	30 (31.9)	
	C	71 (40.3)	76 (43.2)		16 (38.1)	16 (38.1)		36 (38.3)	44 (46.8)	
	Stent type, n (%):			.59			.66			.38
	Resolute	89 (50.6)	84 (47.7)		21 (50.0)	23 (54.8)		49 (52.1)	43 (45.7)	
	Xience	87 (49.4)	92 (52.3)		21 (50.0)	19 (45.2)		45 (47.9)	51 (54.3)	
	Bifurcated lesions, n (%)	24 (13.6)	23 (13.1)	.88	6 (14.6)	6 (14.6)	1.00	11 (11.7)	13 (13.8)	.66
Angiographic characteristics (pre-implantation)	Lesion length (mm), mean ± SD	12.69 ± 7.39	13.75 ± 8.93	.24	12.74 ± 6.16	12.21 ± 9.16	.77	13.94 ± 10.48	15.32 ± 11.08	.22
	Reference vessel diameter (mm), mean ± SD	2.49 ± 0.47	2.57 ± 0.63	.19	2.65 ± 0.68	2.50 ± 0.62	.31	2.57 ± 0.50	2.65 ± 0.70	.31
	Maximal lumen diameter (mm), mean ± SD	3.20 ± 0.62	3.24 ± 0.75	.63	3.32 ± 0.78	3.17 ± 0.80	.40	3.22 ± 0.63	3.31 ± 0.82	.39
	Minimal lumen diameter (mm), mean ± SD	0.98 ± 0.37	1.04 ± 0.39	.14	1.02 ± 0.39	1.02 ± 0.44	.96	1.05 ± 0.38	1.07 ± 0.43	.80
	Diameter stenosis (%), mean ± SD	60.12 ± 13.80	59.19 ± 11.86	.51	60.99 ± 13.33	59.46 ± 14.04	.62	58.53 ± 12.35	59.18 ± 12.66	.73
Angiographic characteristics (post-implantation)	Stent length (mm), mean ± SD	22.53 ± 13.08	23.56 ± 17.41	.53	19.14 ± 10.95	19.73 ± 15.08	.84	21.52 ± 12.50	25.57 ± 20.16	.10
	Reference vessel diameter (mm), mean ± SD	2.68 ± 0.44	2.69 ± 0.56	.83	2.81 ± 0.62	2.60 ± 0.51	.09	2.70 ± 0.46	2.80 ± 0.65	.25
	Maximal lumen diameter (mm), mean ± SD	3.25 ± 0.49	3.30 ± 0.60	.40	3.35 ± 0.67	3.16 ± 0.53	.16	3.24 ± 0.46	3.41 ± 0.68	.04
	Minimal lumen diameter (mm), mean ± SD	2.30 ± 0.39	2.33 ± 0.52	.59	2.44 ± 0.55	2.28 ± 0.50	.18	2.33 ± 0.39	2.42 ± 0.59	.22
	Diameter stenosis (%), mean ± SD	13.91 ± 6.90	13.38 ± 6.95	.47	13.12 ± 6.94	12.33 ± 6.66	.61	13.54 ± 6.45	13.47 ± 6.87	.94
	Absolute gain (mm), mean ± SD	1.32 ± 0.44	1.30 ± 0.46	.69	1.42 ± 0.56	1.27 ± 0.42	.19	1.29 ± 0.41	1.38 ± 0.50	.20

Table IV. Geometrical angiographic characteristics according to the occurrence of TLF and TLR at 1 year

Lesion level			Pre-implantation	Post-implantation	Absolute difference (post – pre-implantation)	P*	P†
TLF at 12 m (n = 176 paired matched lesions)	Bends, n	Non-TLF	1.81 ± 1.11	1.68 ± 0.96	−0.11 ± 0.44	.35	.86
		TLF	1.74 ± 1.11	1.56 ± 0.95	−0.13 ± 0.46		
	Curvature (cm^{-1})	Non-TLF	0.295 (0.161 to 0.523)	0.259 (0.116 to 0.397)	−0.039 (−0.136 to 0.002)	.13	.25
		TLF	0.363 (0.195 to 0.554)	0.268 (0.140 to 0.438)	−0.054 (−0.194 to −0.001)		
	Angulation (degrees)	Non-TLF	46.30 (24.72 to 70.63)	31.14 (17.17 to 56.67)	−7.85 (−20.00 to −0.94)	.80	.51
		TLF	43.53 (24.16 to 82.51)	30.69 (14.34 to 59.83)	−7.98 (−21.26 to −1.88)		
TLR at 12 m (n = 42 paired matched lesions)	Bends, n	Non-TLR	1.39 ± 0.70	1.31 ± 0.58	−0.08 ± 0.28	.83	.28
		TLR	1.39 ± 0.80	1.39 ± 0.82	−0.03 ± 0.16		
	Curvature (cm^{-1})	Non-TLR	0.368 (0.187 to 0.708)	0.296 (0.179 to 0.418)	−0.063 (−0.239 to 0.002)	.33	.49
		TLR	0.325 (0.180 to 0.470)	0.231 (0.103 to 0.438)	−0.027 (−0.182 to −0.003)		
	Angulation (degrees)	Non-TLR	40.20 (24.11 to 59.53)	26.89 (17.30 to 44.61)	−8.84 (−17.72 to −0.87)	.19	.62
		TLR	37.23 (10.05 to 50.58)	25.41 (7.50 to 45.06)	−4.85 (−15.68 to −2.42)		
In-hospital AMI (n = 94 paired matched lesions)	Bends, n	Non-AMI	1.69 ± 1.06	1.49 ± 0.83	−0.12 ± 0.45	.48	.76
		AMI	1.81 ± 1.18	1.59 ± 0.98	−0.12 ± 0.43		
	Curvature (cm^{-1})	Non-AMI	0.349 (0.178 to 0.645)	0.252 (0.115 to 0.445)	−0.041 (−0.165 to 0.002)	.91	.64
		AMI	0.345 (0.193 to 0.598)	0.276 (0.157 to 0.455)	−0.054 (−0.194 to −0.002)		
	Angulation (degrees)	Non-AMI	43.53 (25.35 to 64.52)	26.98 (15.19 to 44.90)	−7.84 (−21.13 to −1.68)	.38	.79
		AMI	48.45 (24.66 to 94.41)	34.07 (18.47 to 72.24)	−8.23 (−20.81 to −0.97)		

* *P* = comparison at pre-implantation of TLF vs non-TLF/TLR vs non-TLR/in-hospital AMI vs non-in-hospital AMI.
† *P* = comparison of the absolute difference TLF vs non-TLF/TLR vs non-TLR/in-hospital AMI vs non-in-hospital AMI.

(−7.84 vs −8.23; *P* = .79). Figure 4 shows the box plot distribution of the absolute difference from post to pre-implantation of vessel curvature and angulation in the global population and according to the total stent length.

Comparison of the stent conformability between Resolute and Xience V stents

In total, 173 lesions in 141 patients were treated with the Resolute stent and 179 lesions in 148 patients were treated with the Xience V. Table V shows the vessel geometrical parameters according to stent type. Both groups had similar pre-implantation geometrical parameters (number of bends/lesion, vessel curvature and angulation). The absolute difference from post- to pre-implantation of number of bends/lesion trended to be lower with the Resolute than with the Xience V (−0.08 vs −0.16; *P* = .13). The absolute difference in vessel curvature was similar in both stents (−0.046 cm^{-1} with Resolute and −0.047 cm^{-1} with Xience; *P* = .66). The absolute difference in vessel angulation from post- to pre-implantation was significantly lower with the Resolute than with the Xience (−6.0° vs −10.1°; *P* = .03). Figure 5 shows the box plot distribution of the absolute difference between post- to pre-implantation of vessel curvature and angulation for the Resolute and Xience stents.

Discussion

The main results of the present study are the following: (1) with the use of second-generation DES, vessel bend, curvature and angulation are not related with TLF and clinically-driven TLR at 1-year follow-up, and vessel geometrical parameters are neither related with inhospital AMI; (2) with the use of second-generation DES, changes in vessel geometry from pre to post-implantation are not related with TLF and clinically-driven TLR and with inhospital AMI; (3) resolute stent seems to demonstrate better conformability to adapt to the vessel wall than the Xience.

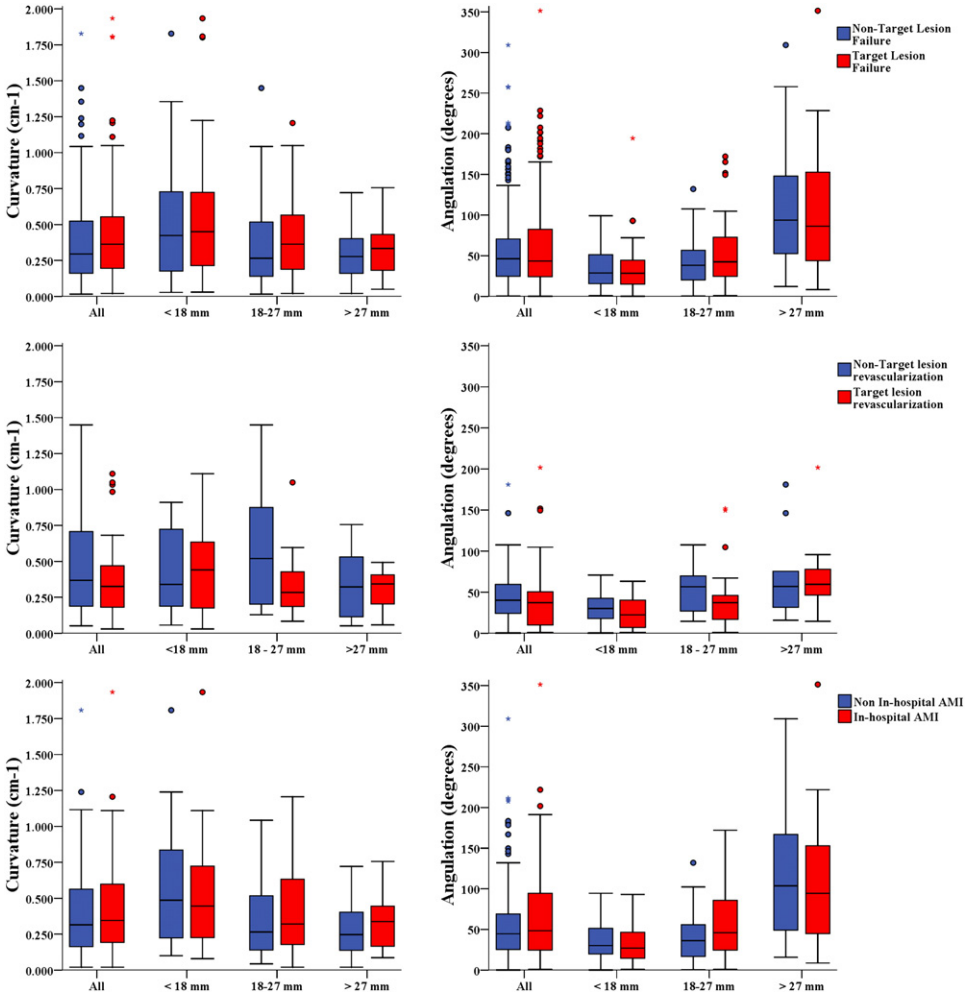
Vessel geometrical parameters and clinical outcomes

The present study did not show any relationship between bended, curved, and angulated lesions, and the occurrence of TLF at 1-year follow-up using second-generation DES. It is noteworthy that most of the lesions presenting with TLF at 1 year were caused by the occurrence of In-hospital AMI (53.4%) and a relatively low percentage of cases were caused by clinically driven TLR (23.9%).

Periprocedural myocardial infarction is mainly attributed to two principal causes: occlusion of a side-branch and/or distal embolization due to plaque disruption or local vessel trauma.[15] In cases of bended, curved, and angulated lesions, distal embolization is the most plausible explanation for the occurrence of peri-procedural myocardial infarction. Using first-generation DES (excluding patients with stent restenosis or by-pass lesions), van Gaal et al showed thatcomplex lesions (B2/C) and diffuse coronary disease with a high SYNTAX score were related to peri-procedural myocardial infarction.[16] It is noteworthy that both American Heart Association lesion type and SYNTAX score include vessel angulation and tortuosity to estimate the respective scores.[1,16]

The crimped stent profile, pushability, trackability, crossability, and bending stiffness of the stent delivery

Figure 3

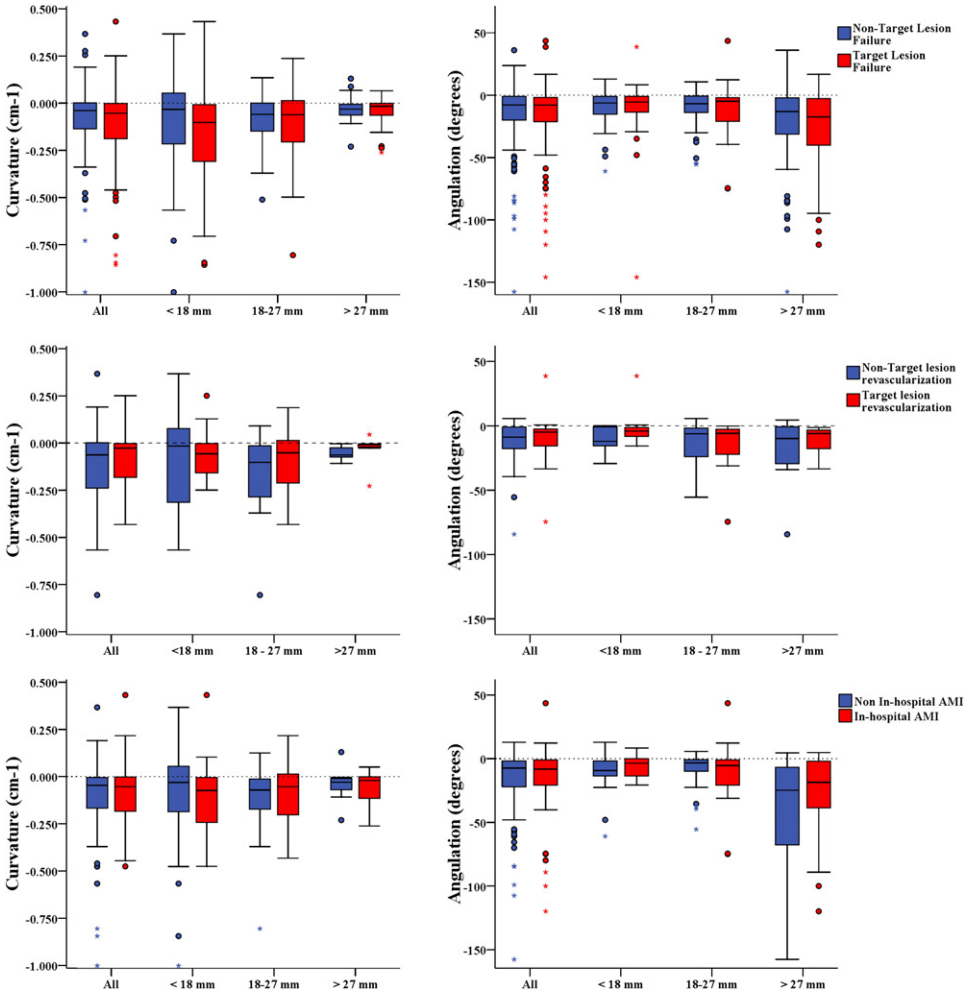


Vessel curvature and angulation at pre-implantation in non-TLF and TLF lesions, in non-TLR and TLR lesions and in non In-hospital AMI and In-hospital AMI. Box plot distribution of vessel curvature and angulation values at pre-implantation according to total stent length (tertiles) and presence of components of TLF.

system are the most important features of stent design capable of preventing plaque disruption or local vessel trauma and therefore minimizing distal embolization of material responsible for myocardial injury. Bench studies have shown better stent delivery properties with second-generation DES compared to BMS or first-generation DES.[17] Large randomized trials have shown a trend for fewer myocardial infarctions at 30 days with the second-generation everolimus-DES than with the first-generation paclitaxel-DES.[9] Similarly, the Endeavor zotarolimus-DES (Medtronic CardioVascular, Santa Rosa, CA), with the same metallic platform as the Resolute zotarolimus-DES, also had lower peri-procedural myocardial infarction rate in comparison to the first-generation sirolimus-DES[10] and paclitaxel-DES.[18] The better stent deliverability of second-generation DES may partially explain the absence of a relationship between vessel bending, curvature, and angulation with In-hospital AMI observed in the present study.

A potential relationship between pre-implantation vessel bend, curvature, and angulation and clinically-driven TLR has not been demonstrated in the present study. Previous studies using BMS showed that a pre-stent vessel angulation ≥33.5° and an absolute difference between pre and post-implantation ≥9.1° were independent predictors of angiographic restenosis.[4] The most plausible mechanisms involved in the higher restenosis rate of highly angulated vessel were probably the changes

Figure 4



Absolute difference post – pre-implantation of vessel curvature and angulation in non-TLF and TLF lesions, in non-TLR and TLR lesions and in non In-hospital and In-hospital AMI lesions. Box plot distribution of absolute differences post – pre-implantation vessel curvature and angulation according to total stent length (tertiles) and presence of components of TLF.

in wall shear stress and the occurrence of stent fractures at hinging points.

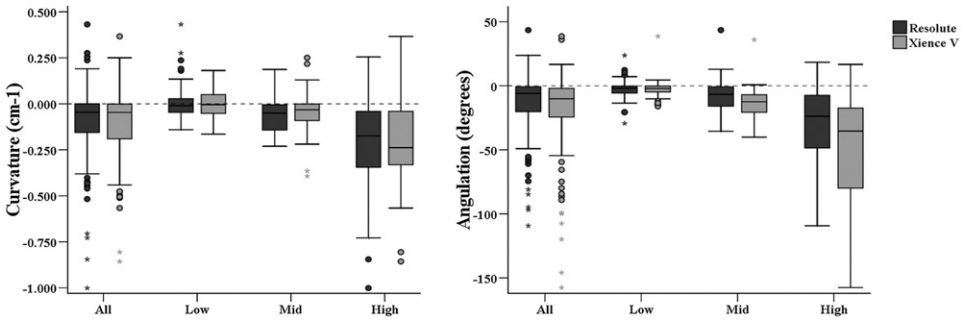
Coronary stenting of curved vessels decreases the average wall shear stress throughout the stented segment and creates neoangulations at the stent edges submit to low shear stress.[19] Regions with low shear stress show a larger neointimal response than those regions with physiologic shear stress.[5] Therefore, straightening of curved coronary arteries may create artificial conditions of low shear stress leading to a higher neointimal response.[4,7] Of note, this relationship has not been seen after implantation of sirolimus-DES.[7] Moreover, clinical studies using first-generation sirolimus-DES showed no relationship between angulated lesions and angiographic restenosis at 9 months of follow-up.[20,21] It is still unknown if the late catch-up phenomenon, defined as a progressive loss of angiographic minimal lumen diameter, can modify the relationship between vessel bend, curvature, and angulation with stent restenosis at longer follow-up.[22]

Stent fracture is the second potential explanation of the larger neointimal response related to bended, curved, and angulated vessels. The prevalence of metallic stent fracture ranges from 2.4% to 29.0% in different registries.[23] Stent fracture have been mainly associated to a specific first-generation DES with closed cell design, long stents, overlapped stents, stent implantation in hinging points, and angulated lesions.[23] No stent fractures were seen in the analysis of the 42 lesions with clinically driven TLR reported in the present study. It is still not known if the different material and design of the Resolute and

Table V. Geometrical angiographic characteristics according to the stent type

Lesion level (n = 352) Resolute = 173, Xience = 179		**Pre-implantation**	**Post-implantation**	**Absolute difference**	***P****	***P**†*
Bends, n	Resolute	1.76 ± 1.09	1.64 ± 0.92	–0.08 ± 0.39	.70	.13
	Xience	1.80 ± 1.13	1.59 ± 1.00	–0.16 ± 0.51		
Curvature (cm^{-1})	Resolute	0.348 (0.175 to 0.571)	0.252 (0.116 to 0.415)	–0.046 (–0.155 to 0.000)	.86	.66
	Xience	0.344 (0.183 to 0.510)	0.276 (0.133 to 0.433)	–0.047 (–0.194 to 0.000)		
Angulation (degrees)	Resolute	46.89 (24.91 to 85.93)	34.90 (15.69 to 62.06)	–5.99 (–20.15 to –0.74)	.93	.03
	Xience	43.82 (24.24 to 74.75)	26.98 (15.77 to 49.38)	–10.12 (–24.41 to –1.98)		

Figure 5



Absolute difference post – pre-implantation of vessel curvature and angulation according to stent type (stent conformability). Box plot distribution of absolute differences post – pre-implantation vessel curvature and angulation according to stent type and vessel geometry tertiles.

Xience stent platforms will result in lower rates of stent fracture at follow-up compared with first-generation DES. Stent fractures are usually caused by fatigue of the material and, therefore, are usually found at longer term follow-up than 1 year.[23]

Stent conformability

Stent conformability is defined as the ability of a expanded stent to adapt to the natural shape of the vessel hence minimizing trauma to the vessel wall.[24] A stent's conformability is dependent on the stent's material, strut thickness and platform design; and is therefore different between the commercial devices that are currently available.[17] The present study found a slightly better conformability of Resolute compared to Xience. However, the better conformability of the Resolute stent does not seem to have any clinical implication at 1 year follow-up. However, further investigations with longer follow-up are required to evaluate these findings.

Limitations

The first limitation of the present study is the lack of 3-dimensional QCA analysis of vessel geometrical parameters. Coronary vessels have complex 3-dimensional anatomy in continuous movement. Although the two analysts were requested to select the 2-dimensional angiographic end-diastolic view with the least foreshortening, we have to acknowledge that in 2-dimensions, geometrical parameters are simple planar projections of complex structures and cannot reflect the real vessel shape. Moreover, the angiographic vessel geometry analysis has been performed in a single angiographic view due to the lack of valid orthogonal angiographic views in the vast majority of cases. The second limitation of the present study is the short clinical follow-up. The neointimal response associated with low shear stress regions can potentially be involved with the late "catch-up" phenomenon at longer follow-up. It is not known if the lack of relationship of vessel geometry and changes in vessel bend, curvature, and angulation post implantation with stent restenosis will be seen after 1 year.

Conclusion

Using second-generation DES, number of bends/lesions, vessel curvature and vessel angulation are not related with TLF and clinically driven TLR at 1 year and with the occurrence of Inhospital AMI. Changes in the

number of bends/lesion, vessel curvature and vessel angulation from pre to post-implantation (stent conformability) are also not associated with TLF and clinically driven TLR at 1 year and are not associated with the occurrence of In-hospital AMI using second-generation DES. The Resolute stent seems to be more conformable to the actual vessel shape than the Xience V, although it does not appear to have any clinical significance at 1 year follow-up. Further investigations with longer follow-up are required to ensure the absence of late events in patients with large curved vessels and large changes in vessel geometry.

Disclosures

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Appendix

Study devices

Resolute zotarolimus-DES (Medtronic CardioVascular, Santa Rosa, CA) consists of the Driver cobalt chromium (CoCr) platform coated with a mixture of 3 durable polymers that contain and release the anti-proliferative-drug zotarolimus. At 60 days, 85% of the zotarolimus has eluted. The metallic platform is constructed using a modular design using short modules of 1 mm length compounded of round and edgeless struts of 91 μm thickness. The modules are joined together using proprietary laser-fusion patterns (3 links per module) intended to provide high flexibility.

Xience V everolimus-DES (Abbott Vascular Devices, Santa Clara, CA) consists of the Multilink Vision CoCr platform coated with a non-erodible biocompatible polymer that contains and releases the anti-proliferative drug (everolimus). Around 80% of the drug is released within the first 30 days, with nearly all the drug released within 4 months. The platform consists of serpentine rings connected by long links fabricated from a single slotted tube. The strut thickness is 81 μm.

Procedure technique

Balloon angioplasty and stent implantation were performed according to standard techniques and current anticoagulation and anti-platelet therapy.[11] Direct stenting and post-dilatation were left to the operator's discretion. No mixture of stent types was allowed unless the operator was unsuccessful in implanting the study device. In this case, implantation of a non-study stent was permitted. The study protocol recommended treatment with dual anti-platelet therapy for at least 6 months after stent implantation.

Quantitative coronary angiography

All quantitative non-geometrical parameters were measured by the core-laboratory (Cardialysis, Rotterdam, Netherlands) using the Cardiovascular Angiography Analysis System (CASS) II software (Pie Medical Imaging, Maastricht, Netherlands). The following QCA parameters were calculated: maximal lumen diameter, minimal lumen diameter, interpolated reference vessel diameter, percent diameter stenosis (difference between the reference vessel diameter and minimal lumen diameter/reference vessel diameter ×100).

Vessel curvature and angulation were assessed by two independent analysts (Cardialysis, Rotterdam, Netherlands) blinded to clinical outcomes and stent type. Both analysts were requested to select the angiographic view with least foreshortening of the culprit lesion and least overlap with other coronary vessels. Curvature and angulation were measured pre and post-implantation in the end-diastolic frame using the same angiographic view (maximal difference between pre and post-implantation of 10°). The absolute difference pre – post-implantation was assessed to show changes in vessel geometry and was used as surrogate of stent conformability (larger changes mean poorer stent conformability). The number of bends was assessed as the number of angles measured within the "in stent" segment.

Lesions excluded from the present study included aorto-ostial coronary lesions, bifurcated lesions with stenting of the main-branch and side-branch, important foreshortening of the culprit lesion, and overlap of multiple vessels in all angiographic views. Intracoronary guide-wires straighten the coronary arteries; therefore, all lesions without any angiographic view (pre- and/or post-implantation) without the intracoronary wire were also excluded.

Clinical outcomes

Clinical outcomes were adjudicated by an independent clinical events committee. TLF was defined as a composite end-point including death from cardiac causes, any AMI not clearly attributed to a non-target vessel and the occurrence of clinically-driven TLR. All deaths were considered cardiac unless an undisputed non-cardiac cause was present. AMI was defined according to an extended historical protocol definition and according to Academic Research Consortium definitions.[25,26] TLR was considered clinically indicated if the QCA at follow-up showed a diameter stenosis greater than 50% plus one of the following: a positive history of recurrent angina pectoris, objective signs of ischemia, abnormal results of any invasive functional diagnostic test, or diameter stenosis greater than 70% as assessed by QCA.

Statistical methods

Propensity score matching was performed using a proprietary macro developed and tested for SPSS 11.5 or later versions (www.unc.edu/~painter). First, the program performed a logistic regression to score all QCA-derived lesions according to the occurrence of TLF at 12 months (dependent variable). Logistic regression was performed using as covariates clinical and procedural parameters that were clinically relevant for the occurrence of TLF and/or potentially related to coronary tortuosity: age, sex, diabetes mellitus, hypertension, acute coronary syndrome, total stent length, minimal stent size, and number of stents/lesion. Secondly, the macro searched the best match case of the non-TLF lesions for every TLF lesion according to the propensity score. Matching was performed using the nearest available neighbor method. Using the nearest available neighbor method, both TLF and non-TLF lesions were randomly sorted. Then the first TLF lesion was selected to find its closest control match based on the absolute value of the difference between

the propensity score of the TLF and non-TLF lesions under consideration (delta). The closest non-TLF lesion was selected as a match. This procedure was repeated for all the TLF lesions. This method guarantees that a match is always found for all the TLF lesions. Moreover, the program removed the selected control matched non-TLF lesion that was not reconsidered for subsequent matches.

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