Original Studies

Clinical Outcome of Patients With Implantation of Second-Generation Drug-Eluting Stents in the Right Coronary Ostium: Insights From 2-Year Follow-up of the TWENTE Trial

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Objectives: The aim of the present study was to assess the impact on clinical outcome of right coronary artery (RCA) ostial coverage with second-generation drug-eluting stents (DES). Background: Treatment of the aorta-ostial (AO) region of the RCA with bare metal stents and first-generation DES has been associated with a higher risk of target-lesion revascularization (TLR). Methods: Of the 1,391 patients of the prospective TWENTE trial, we identified 321 (23%) with single-vessel RCA treatment, who were categorized into stenting with AO stent coverage (AOC) versus stenting without AOC. The AO region was defined as 3 mm from the aortic orifice. Results: The 67 (20.9%) patients with AOC showed more severe lesion calcifications than the 254 patients without AOC (31.3% vs. 12.6%; $P < 0.01$). In the AOC group, there was a higher prevalence of hypercholesterolemia and family history of coronary disease (75.4% vs. 61.6%, and 68.7% vs. 53.5%, respectively; $P = 0.03$). During 2-year follow-up, patients in the AOC group had a higher incidence of TLR (7.5% vs. 1.6%; $P = 0.02$). Following adjustment for confounders, AOC independently predicted TLR with an adjusted hazard ratio of 4.1 (95% CI: 1.17–14.39; $P = 0.03$). Conclusion: AO treatment of the RCA with second-generation DES is feasible, but our data suggest that stent coverage of the right AO segment remains a predictor of TLR.

Key words: right coronary artery; aorta-ostial lesion; revascularization; ostium; drug-eluting stent

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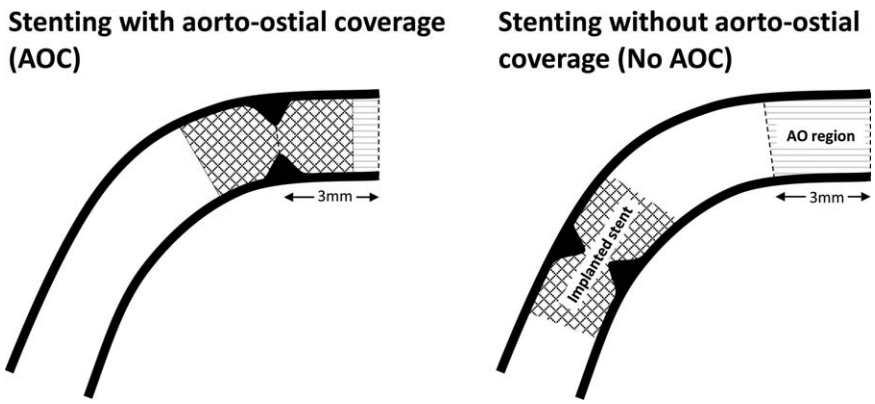

Fig. 1. Scheme explaining the definition of the compared patient groups. Patients with AOC were compared with patients without AOC (no AOC).

INTRODUCTION

Percutaneous coronary interventions (PCI) of the aorto-ostial (AO) region are known to be technically challenging as interventional location and guiding catheter engagement share the same space [1]. While balloon angioplasty often led to suboptimal results in ostial lesions [2,3], use of bare metal stents [4,5] and first-generation drug-eluting stents (DES) [6] increased both early procedural success and safety of PCI in the AO region. However, stenting was associated with a higher incidence of in-stent restenosis in the most proximal coronary segments [6,7], which has been attributed to stent recoil due to the rigid nature of the vessel wall [2]. To date, most DES studies that have addressed AO disease have been performed with bare metal stents and first-generation DES [6,8–11].

Implantation of bare metal stents and predominantly early generation DES in AO lesions of the right coronary artery (RCA) has been associated with a 10 times higher risk of repeat revascularization procedures than treatment of left main ostial lesions [8]. For that reason, a focused evaluation of PCI procedures that involve the RCA ostium is of interest. Meanwhile, second-generation DES with more biocompatible durable polymer-based coatings have been developed, such as the zotarolimus-eluting Resolute stent (Medtronic, Santa Rosa, CA) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA), which showed favorable clinical results [12–14].

Currently, there is only limited knowledge about the outcome of PCI with second-generation DES involving the AO region of the RCA. We therefore assessed patients with RCA single-vessel treatment with second-generation DES in the prospective TWENTE trial [12,13,15], and compared the 2-year clinical outcome of patients with versus without ostial stent coverage.

METHODS

Study Population

We assessed patients with single-vessel RCA treatment within the randomized TWENTE trial (ClinicalTrials.gov *NCT*01066650), which was performed between June 2008 and August 2010 at Thoraxcentrum Twente, Enschede, the Netherlands, and has previously been described in detail [12,13]. In brief, in a broad and heterogeneous patient population with many complex lesions [15], patients with an indication for PCI with DES, who were capable of providing informed consent, were randomized for treatment with either the Resolute or Xience V stent. The study was approved by the institutional ethics committee and complied with the Declaration of Helsinki, and all patients provided written informed consent.

Angiographic Assessment

Angiographic data were categorized into stenting with AO stent coverage (AOC) versus stenting without AO stent coverage (No AOC). A patient was allocated to the AOC group if any part of the stent covers the AO region, the area arising within 3 mm of the aortic orifice (Fig. 1). Classification was performed by two experienced angiographic analysts; in the case of disagreement, two interventional cardiologists were consulted to achieve consensus. Quantitative coronary angiographic analyses were performed offline with the use of edge-detection software (QAngio XA version 7.1, Medis, Leiden, the Netherlands) [12].

Follow-up and Definition of Clinical Endpoints

Details of the 2-year clinical follow-up have been reported previously [13] and were used to assess clinical outcome of stenting with and without AOC. In

TABLE I. Characteristics of Study Patients Undergoing Single-Vessel PCI of the RCA

	AOC ($n=67$)	No AOC ($n=254$)	P-value
Age (years)	63.2 ± 9.6	64.4 ± 10.6	0.42
Gender (male)	40 (59.7)	177 (69.7)	0.12
Clinical risk factor			
Diabetes mellitus	24 (35.8)	62 (24.4)	0.06
Hypercholesterolemia	49/65 (75.4)	151/247 (61.1)	0.03
Arterial hypertension	35 (52.2)	150 (59.1)	0.32
Family history of CAD	46 (68.7)	136 (53.5)	0.03
Current smoking	13 (19.4)	65 (25.6)	0.29
Obesity (BMI ≥ 30 kg/m^3)	28.2 ± 4.4	28.0 ± 4.1	0.82
Cardiovascular history			
Previous myocardial infarction (any)	24 (35.8)	88 (34.6)	0.86
Previous PCI	15 (22.4)	67 (26.4)	0.51
Previous CABG	10 (14.9)	30 (11.8)	0.49
Clinical syndrome at presentation			
Stable angina pectoris	35 (52.2)	118 (46.5)	0.02
Unstable angina pectoris	21 (31.3)	52 (20.5)	
Non-ST-elevation MI	11 (16.4)	84 (33.1)	
Lesion characteristics			
De novo lesions only	58 (86.6)	241 (94.9)	0.03
Aorta-ostial lesion[a]	36 (53.7)		
At least one chronic total occlusion	9 (13.4)	20 (7.9)	0.16
At least one in-stent restenosis	9 (13.4)	13 (5.1)	0.03
At least one bifurcation lesion	0 (0.0)	7 (2.8)	0.35
At least one severe calcification	21 (31.3)	32 (12.6)	<0.01
At least one thrombus present	2 (3.0)	16 (6.3)	0.38
At least one total occlusion	55 (82.1)	210 (82.7)	0.91
Number of lesions treated			
One lesion treated	44 (65.7)	194 (76.4)	0.07
Two lesions treated	19 (28.4)	55 (21.7)	
Three or more lesions treated	4 (6.0)	5 (2.0)	
Procedure-related characteristics			
Reference diameter (mm)	3.3 ± 0.7	2.8 ± 0.6	<0.01
MLD pre (mm)[b]	1.2 ± 0.6	0.9 ± 0.5	<0.01
MLD post (mm)[b]	2.8 ± 0.6	2.5 ± 0.6	<0.01
Δ Prepost MLD (mm)	−1.6 ± 0.8	−1.6 ± 0.6	0.63
Lumen diameter stenosis pre (%)[b]	63.5 ± 17.3	68,9 ± 14.7	0.11
Lumen diameter stenosis post (%)[b]	11,4 ± 6.2	12.9 ± 8.4	0.15
Δ Prepost stenosis (%)	52.2 ± 16.6	56.0 ± 16.8	0.10
Total number of stents	2.0 (1.0–3.0)	1.0 (1.0–2.0)	<0.01
Total stent length (mm)	53 (18.0–74.0)	30 (18.0–48.0)	<0.01
At least one direct stenting	25 (37.3)	103 (40.6)	0.63
At least one stent postdilation	65 (97.0)	218 (85.8)	0.01
Overlapping stents	35 (52.2)	86 (33.9)	<0.01

Data are n (%), mean ± SD or median (IQR); CAD, coronary artery disease; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; MLD, Minimum lumen diameter post.

[a]An AO lesion was defined as any lesion with a luminal stenosis of ≥ 50% by visual estimation, arising within 3 mm of the aortic orifice.

[b]In case of more than one lesion, data of the most sever lesion (i.e., lesion with the highest diameter stenosis pre PCI) are presented.

addition, we compared the outcome of patients of the AOC group treated with Resolute versus Xience V. Clinical event adjudication (follow-up data were available in all patients of this study) was performed by the independent, external research organization Cardialysis (Rotterdam, the Netherlands). Clinical endpoints were defined according to the Academic Research Consortium (ARC) [16,17]. Cardiac death was defined as any death due to proximate cardiac cause (e.g., Myocardial infarction (MI), low-output failure, and fatal arrhythmia). MI 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 myocardial band fraction or troponin), based on the updated ARC definition of MI and periprocedural MI was defined as MI within 48 hr after PCI [16,17]. Cardiac markers were systematically assessed with subsequent serial measurements in the case of relevant biomarker elevation or complaints (97% of the cases had at least one blood sampling

TABLE II. Two-Year Clinical Outcome in Patients with Single-Vessel PCI of the RCA

				AOC population ($n=67$)		
	AOC ($n=67$)	No AOC ($n=254$)	P-value	Resolute ($n=29$)	Xience V ($n=38$)	P-value
Death						
All-cause mortality	5 (7.5)	6 (2.4)	0.06	2 (6.9)	3 (7.9)	1.00
Cardiac death	3 (4.5)	3 (1.2)	0.11	1 (3.4)	2 (5.3)	1.00
Myocardial infarction						
Target-vessel MI	2 (3.0)	12 (4.7)	0.74	1 (3.4)	1 (2.6)	1.00
Revascularization						
Target-vessel revascularization	6 (9.0)	9 (3.5)	0.10	3 (10.3)	3 (7.9)	1.00
Target-lesion revascularization[a]	5 (7.5)	4 (1.6)	0.02	3 (10.3)	2 (5.3)	0.65
Stent thrombosis						
Definite or probable stent thrombosis	1 (1.5)	4 (1.6)	1.00	0 (0.0)	1 (2.6)	1.00
Composite endpoints						
Target-vessel failure	11 (16.4)	19 (7.5)	0.03	5 (17.2)	6 (15.8)	1.00
Target-lesion failure	10 (14.9)	17 (6.7)	0.03	5 (17.2)	5 (13.2)	0.74
Major adverse cardiac events	12 (17.9)	20 (7.9)	0.02	6 (20.7)	6 (15.8)	0.60
Patient-oriented composite endpoint	18 (26.9)	31 (12.2)	<0.01	8 (27.6)	10 (26.3)	0.90

Data are n (%).
[a]Two of the five TLR were related to the ostial stent and three to a stent other than the ostial stent.

performed between 12 and 18 hr after PCI). Stent thrombosis was defined according to ARC as definite or probable.

The composite endpoint target-vessel failure (TVF) was defined as cardiac death, target-vessel-related MI, or clinically driven target-vessel revascularization. Target-lesion failure (TLF) was defined as composite of cardiac death, target-vessel-related MI, and clinically indicated target-lesion revascularization (TLR); and a patient-oriented composite endpoint (POCE) as a composite of all-cause mortality, any MI, and any repeat (target-vessel and nontarget vessel) revascularization [12].

Statistical Analysis

Categorical data were presented as numbers and percentages whereas continuous variables were expressed as mean ± standard deviation (SD). Baseline characteristics were compared using chi-square test or Fisher's exact test for categorical variables and using one-way analyses of variance for continuous variables including age, body-mass index, minimum reference diameter, and maximal stenosis as data were normally distributed. Kruskal–Wallis rank-sum test (nonparametric data) was used to compare total number of stents and stent length between AOC, and presented as median and interquartile range. The time to the individual endpoint was assessed according to the Kaplan–Meier method, and the log-rank test was applied to compare stenting with versus without AOC. Univariate and Cox regression analyses were performed to assess the event risk for stenting with versus without AOC. A potential confounder was identified if P-values were <0.10 at univariate analysis. A multivariate Cox regression analysis was then performed to adjust for potential confounders. Confidence intervals and P-values were two-sided and a P-value <0.05 was considered statistically significant. Analyses were performed using SPSS 15.0 (SPSS, Chicago, Illinois).

RESULTS

Patient and Lesion Characteristics

A total of 321 patients with single-vessel RCA treatment were analyzed, of whom 67 (20.9%) underwent stenting with AOC and 254 (79.9%) stenting without AOC. Patients with AOC had a higher prevalence of hypercholesterolemia compared to patients without AOC (75.4% vs. 61.1%; $P=0.03$) and more frequently a family history of coronary artery disease (68.7% vs. 53.5%; $P=0.03$; Table I). The prevalence of diabetes mellitus tended to be higher in patients of the AOC group (35.8% vs. 24.4%; $P=0.06$).

In patients of the AOC group, lesions were more often severely calcified (31.3% vs. 12.6%; $P<0.01$) and restenotic (13.4% vs. 5.1%; $P=0.03$). As may be expected, based on the definitions of both groups, patients with AOC had a larger vessel diameter (minimum reference 3.3 ± 0.7 mm vs. 2.8 ± 0.6 mm; $P<0.01$), and a higher number [2.0 (1.0–3.0) vs. 1.0 (1.0–2.0); $P<0.01$] and total length of stents implanted [53 (18.0–74.0) mm vs. 30 (18.0–48.0) mm; $P<0.01$]. In addition, lesions in the AOC group were more frequently postdilated (97.0% vs. 85.8%; $P=0.01$) and stents were more often overlapping (52.2% vs. 33.9%; $P<0.01$). Residual stenosis and minimal lumen diameter (MLD) were substantially improved after stent implantation for both the groups. Nevertheless difference

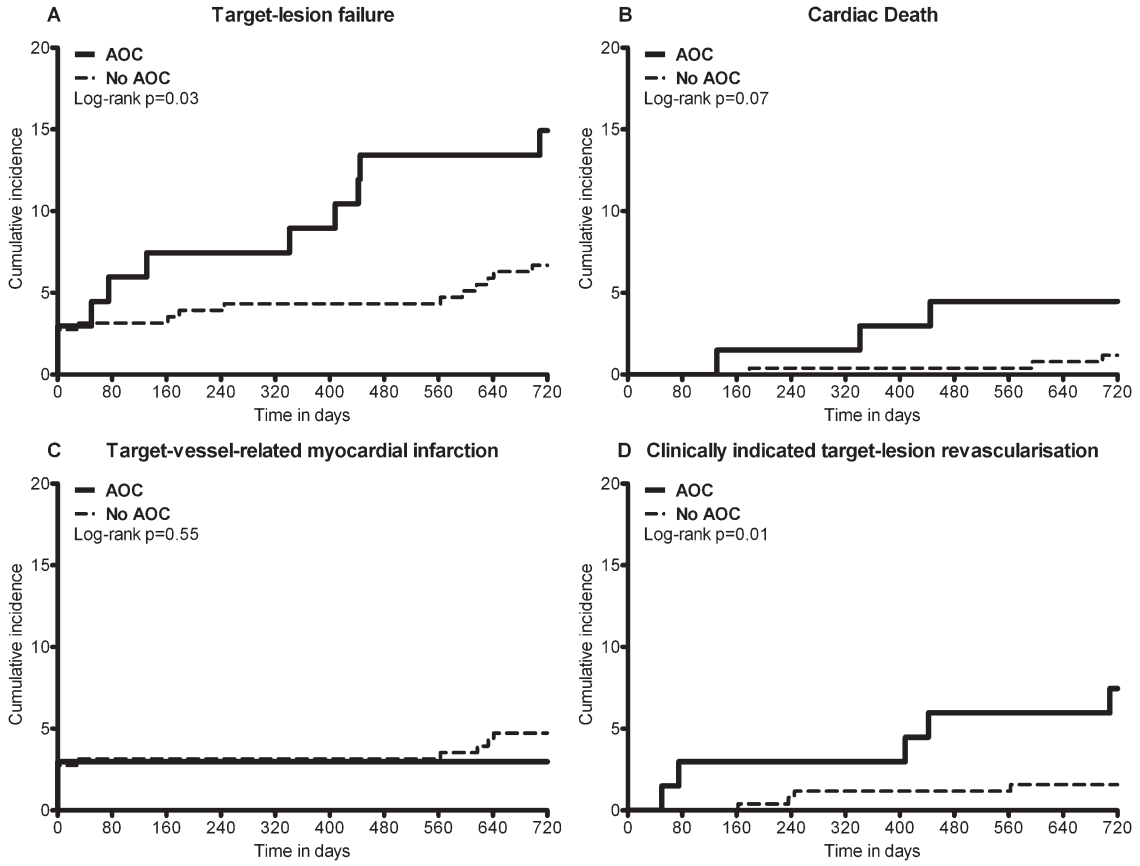

Fig. 2. Two-year clinical outcome in patients with versus without RCA AOC. Kaplan–Meier curves of AOC ($n = 67$) versus No AOC ($n = 254$) of the composite endpoint target-lesion failure (A) and its components: cardiac death (B), target-vessel-related MI (C), and clinical indicated target-lesion revascularization (D).

(pre PCI and post PCI) in MLD and maximal diameter stensosis did not differ between the AOC and No AOC group (MLD: -1.6 ± 0.8 mm vs. -1.6 ± 0.6 mm; $P < 0.63$ and $52.2 \pm 16.6\%$ vs. $56.0 \pm 16.8\%$; $P = 0.10$, respectively).

Clinical Follow-Up

Patients with AOC had a higher incidence of TVF (16.4% vs. 7.5%; $P = 0.03$) and TLF (14.9% vs. 6.7%; $P = 0.03$) as compared to patients without AOC (Table II). The composite endpoint POCE was also significantly higher in patients of the AOC group (26.9% vs. 12.2%; $P < 0.01$), which was mainly attributed to a higher rate of TLR (7.5% vs. 1.6%; $P = 0.02$). Of the AOC group, 5/67 patients required TLR, which was in two patients related to the ostial stent (and in three related to a stent other than the ostial stent). Definite stent thrombosis was noted in none of the patients with AOC and in two (0.8%) of the patients without AOC.

The TVF rates of all patients treated with Resolute versus Xience V stent showed no significant difference [13/162 (8.0%) vs. 17/159 (10.7%); $P = 0.41$]. Within patients of the AOC group, there was no statistically significant difference in clinical outcome between both stents groups (Table II).

Figure 2 presents the Kaplan–Meier curves for TLF (and the components thereof) for patients with versus without AOC, showing a diverging course of TLF ($P = 0.03$) after 2 months, which was mainly based on a significant difference in TLR ($P = 0.01$), while the time-to-event curves of target-vessel MI were very similar. A Cox regression analysis revealed that AOC was associated with the composite endpoint TLF (hazard ratio 2.32, 95% confidence interval: 1.10–5.10; $P = 0.04$). After adjustment for potential confounders (only adjustment for overlapping stents was required), AOC was independently associated with TLR (adjusted hazard ratio 4.07 95% confidence interval: 1.07–15.48; $P = 0.04$).

DISCUSSION

The present substudy of the TWENTE trial in patients with single-vessel treatment of the RCA demonstrates

that treatment of the AO region with second-generation DES is feasible but associated with a higher risk of repeat revascularization procedures. This may be partly attributed to the rigid nature of the vessel wall in the coronary ostium [2]. In addition, we found that only two of the five TLR events were related to the ostial stent. This suggests that the need for stenting of the RCA ostium may indicate the presence of extensive and advanced coronary atherosclerosis that is associated with a higher risk of repeat revascularizations within the various stented coronary segments.

An increased risk of TLR following AO stenting has also been observed by a French group in a retrospective analysis of 181 patients, treated for AO coronary disease in the RCA and left main stem [8]. They found that in RCA AO lesions, the risk of TLR was 10 times higher than in AO lesions of the left main stem [8]. Therefore, a focused assessment of RCA ostial treatment, as performed in our present study, is of interest. In addition, we report data on the use of second-generation DES in AO disease, which is currently scarce. Only a single retrospective study by a Japanese group focused on the treatment of RCA lesions in a study population of 135 patients and compared the implantation of first-generation sirolimus-eluting Cypher stents (Cordis/Johnson & Johnson, New Brunswick, NJ) and bare metal stents in ostial ($n = 73$) and proximal RCA lesions ($n = 62$) [6]. In this study, the TLR rate of ostial RCA lesions was 13.5% after 8 months in the Cypher stent group and 36.1% months after 6.5 months in the bare metal stent group ($P < 0.05$) [6]. Despite the longer follow-up of 24 months, we found in our present study a lower TLR rate of 8.3% in RCA AO lesions, which suggests a rather favorable performance of the second-generation DES in this setting.

Thus far, more attention has been paid to stenting of AO left main lesions [7], but many studies have not reported outcome separately for ostial and other target-lesion locations. The introduction of DES for the treatment of left main disease has reduced the need for repeat revascularization (from 15–30% in bare metal stents) to 10–19%, making PCI of the left main stem a reasonable alternative to bypass surgery [18]. Mehilli et al. [19] recently compared second-generation zotarolimus-eluting Resolute stents and everolimus-eluting Xience V stents in a randomized study of unprotected left main PCI with routine follow-up and reported 1 year after stenting similar TLR rates of 11.7% and 9.4% ($P = 0.35$). The SYNTAX Score regards the AO lesion location as an adverse feature since percutaneous treatment is technically more challenging, but the score adds the extra point for the AO lesion location irrespective of whether this lesion is located in the RCA or in the left main stem [20].

A high radial strength in combination with a high visibility and longitudinal stability of the device may be characteristics of an "ideal" stent for the treatment of AO lesions. The radial strength of the implanted devices can sometimes be increased by the so-called double stenting technique (i.e., stent in stent implantation), which has improved angiographic outcome in selected cases with acute stent recoil [21]. Most recently, third-generation DES (also called novel generation DES) have been introduced to meet the demand for more flexible and highly deliverable devices, which has been achieved by novel designs and/or materials of bare-metal stent platforms [22]. To date, no comprehensive data are available on the outcome of PCI with such DES in the subgroup of AO lesions. However, as the high flexibility and thin-strut design of third-generation DES may be associated with reduced longitudinal device stability [23,24], it is uncertain whether these novel devices may improve the outcome of PCI in AO lesions.

In the present study, the rate of definite–or–probable stent thrombosis following DES implantation in the AO region (1.5%) was not higher than in patients without ostial stent coverage (1.6%; i.e., No AOC group). Thrombotic occlusion of a stent in the most proximal coronary segment may result in a particularly large myocardial necrosis with a high clinical risk [25]. Besides a delayed endothelial coverage of DES struts, both vessel wall inflammation and premature occurrence of neoatherosclerosis have been identified as triggers of stent-thrombosis in durable-polymer based DES [26–30]. The two latter factors may be greatly avoided by the use of DES with biodegradable coatings [31,32], of which—after degradation of the coating material—only a bare metal stent remains in the coronary artery [29,33].

Implications

The findings of the present study show that treatment of the right coronary ostium with second-generation DES is feasible and associated with relatively favorable clinical outcome in a study population that resembles routine clinical practice. The higher risk of repeat revascularization procedures in patients with AO stent coverage (i.e., AOC group) did not result from an excess in ostial instent restenosis but may most likely be related to the greater extent of atherosclerotic disease burden in patients who require stenting of the most proximal segment of the RCA. Our data suggest that the need to cover the ostium of the RCA with a stent may be considered as an indicator of a generally increased risk of repeat revascularization that should be taken into account when

planning the initial revascularization therapy in a heart team discussion.

Limitations

This study was limited by its posthoc nature and should be considered as hypothesis generating. The low number of AO-lesion within the AOC group (36/67) did not permit further meaningful subanalyses. Nevertheless, our data suggest that the increased risk of TLR in the AOC group is not related to problems that occur in the AO segment, but that the need for stenting the RCA ostium is an indicator of extended atherosclerotic disease burden with an inherent risk of more TLR events. Our study adds novel information on the performance of second-generation DES in the AO segment of the RCA. Nevertheless, the regular use of intravascular ultrasound (IVUS) could have further improved our understanding of true ostial involvement in the lesion and the presence and extent of calcium [34]. Although patients with very recent ST-segment elevation MI were not studied in the TWENTE trial, a total of 52% of the patient population presented with acute coronary syndromes, and the vast majority of patients had complex lesions and met the criteria of so-called off-label DES use.

CONCLUSIONS

Treatment of the AO region of the RCA with second-generation DES is feasible, but our data suggest that stent coverage of the right AO segment remains a predictor of TLR in the RCA.

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