JACC: CARDIOVASCULAR INTERVENTIONS VOL. 6, NO. 1, 2013

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2012.07.017

High-Speed Rotational Atherectomy Before Paclitaxel-Eluting Stent Implantation in Complex Calcified Coronary Lesions

The Randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) Trial

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Objectives This study sought to determine the effect of rotational atherectomy (RA) on drug-eluting stent (DES) effectiveness.

Background DES are frequently used in complex lesions, including calcified stenoses, which may challenge DES delivery, expansion, and effectiveness. RA can adequately modify calcified plaques and facilitate stent delivery and expansion. Its impact on DES effectiveness is widely unknown.

Methods The ROTAXUS (Rotational Atherectomy Prior to TAXUS Stent Treatment for Complex Native Coronary Artery Disease) study randomly assigned 240 patients with complex calcified native coronary lesions to RA followed by stenting (n = 120) or stenting without RA (n = 120, standard therapy group). Stenting was performed using a polymer-based slow-release paclitaxel-eluting stent. The primary endpoint was in-stent late lumen loss at 9 months. Secondary endpoints included angiographic and strategy success, binary restenosis, definite stent thrombosis, and major adverse cardiac events at 9 months.

Results Despite similar baseline characteristics, significantly more patients in the standard therapy group were crossed over (12.5% vs. 4.2%, p = 0.02), resulting in higher strategy success in the rotablation group (92.5% vs. 83.3%, p = 0.03). At 9 months, in-stent late lumen loss was higher in the rotablation group (0.44 ± 0.58 vs. 0.31 ± 0.52, p = 0.04), despite an initially higher acute lumen gain (1.56 ± 0.43 vs. 1.44 ± 0.49 mm, p = 0.01). In-stent binary restenosis (11.4% vs. 10.6%, p = 0.71), target lesion revascularization (11.7% vs. 12.5%, p = 0.84), definite stent thrombosis (0.8% vs. 0%, p = 1.0), and major adverse cardiac events (24.2% vs. 28.3%, p = 0.46) were similar in both groups.

Conclusions Routine lesion preparation using RA did not reduce late lumen loss of DES at 9 months. Balloon dilation with only provisional rotablation remains the default strategy for complex calcified lesions before DES implantation. (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease. A Multicenter, Prospective, Randomized Controlled Trial [ROTAXUS]; NCT00380809) (J Am Coll Cardiol Intv 2013;6:10–9) © 2013 by the American College of Cardiology Foundation

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Manuscript received June 21, 2012, accepted July 4, 2012.

Drug-eluting stents (DES) have substantially reduced restenosis rates in randomized clinical trials evaluating simple de novo coronary artery lesions (1–5). DES have also shown favorable results when implanted in complex lesions and patients (6), but higher event rates are observed when treating such subsets compared with simple patients even with newer generation DES (7). To obtain the desired long-term effectiveness of DES, successful initial implantation must be accomplished, which occasionally makes aggressive lesion preparation essential in patients with complex anatomy (8). Heavily calcified lesions present a special challenge due to their resistant plaque burden, which may lead to failure of stent delivery or expansion and, therefore, may increase the likelihood of stent thrombosis and/or restenosis. Moreover, heavily calcified lesions may form a particular threat to DES; both damage to the polymer/drug coating during vigorous advancement and inadequate diffusion of the drug to the subintima through extensive calcium arcs could contribute to ineffectiveness of DES when implanted into such lesions.

Rotational atherectomy (RA) can effectively ablate calcified plaques, facilitating in many cases stent delivery and expansion. However, late restenosis remains high when it is used as a stand-alone therapy or when combined with bare-metal stents (9,10). Recently, some observational studies suggested a favorable long-term outcome of RA followed by DES implantation (11–15). Theoretically, RA and DES could act synergistically in complex lesions as RA could avert stent coating damage and DES could effectively suppress neointimal proliferation. Therefore, RA of heavily calcified lesions may improve the efficacy of DES, but this concept is not supported by randomized controlled studies.

Methods

Patients and study design. ROTAXUS (Rotational Atherectomy Prior to TAXUS Stent Treatment for Complex Native Coronary Artery Disease) is a randomized active-controlled superiority trial in patients with documented myocardial ischemia and complex calcified native coronary artery lesions. The trial was performed at 3 high-volume, experienced interventional study sites in Germany. The participating centers and investigators were selected on the basis of experience with percutaneous coronary intervention (PCI) and RA. Procedures were performed by fully trained operators with at least 50 prior rotablation procedures and several years of interventional experience.

Between August 2006 and March 2010, 240 eligible patients who gave written informed consent were randomized 1:1 to a strategy of rotablation followed by stenting or stenting without prior rotablation (standard therapy). Stenting was performed using the polymer-based slow-release paclitaxel-eluting Taxus Liberté stent (paclitaxel-eluting stents [PES]; Boston Scientific, Boston, Massachusetts). Inclusion and exclusion criteria are shown in Tables 1 and 2 (16). The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocol was approved by the institutional ethics committee of the 3 participating centers.

Randomization and procedures. Randomization was carried out through computer-generated block randomization forms for each participating center. After the patient provided a written informed consent, a numbered envelope was opened, assigning the patient to either RA and stenting or stenting without rotablation in a 1:1 randomization fashion. The date of randomization marked the patient's entry into the study, and the assigned interventional technique had to be performed as soon as possible.

After the decision to perform intervention, patients received 325 to 500 mg of aspirin intravenously or orally (if they did not receive it within the prior 12 h) and an oral loading dose of 600 mg of clopidogrel. Immediately before intervention, intra-arterial or intravenous heparin was given to maintain an activated clotting time ≥250 s, or 200 to 250 s if a glycoprotein IIb/IIIa receptor blocker had been administered. The use of glycoprotein IIb/IIIa antagonists, other antithrombotics (e.g., bivalirudin), and further cardiac medications was left to the discretion of the treating physician.

Abbreviations and Acronyms

CK = creatine kinase
DES = drug-eluting stent(s)
LLL = late lumen loss
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RA = rotational atherectomy
TIMI = Thrombolysis In Myocardial Infarction
TLR = target lesion revascularization
TVR = target vessel revascularization

Coronary angiography was performed according to the conventional and local standards. Percutaneous intervention was either performed in the same setting, if the patient had consented to the study before the procedure and angiographic eligibility had been determined, or performed in a separate setting. In case of multivessel disease, all other vessels should have been successfully treated before the assigned treatment is applied to the target vessel(s). This was done either in the same setting or in a previous setting.

Rotablation was performed by the Rotablator (Boston Scientific Scimed, Maple Grove, Minnesota). The burr size was selected to reach a burr/vessel ratio of 0.5 (maximum: 0.7 if needed). Rotablation speed ranged between 140,000 and 180,000 rotations per minute. The burr was platformed immediately proximal to the lesion to avoid injury to the healthy vessel segment. Heparin, verapamil, and nitroglycerin were administered during rotablation as an intracoro-

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Table 1. Inclusion Criteria

Clinical Inclusion Criteria
1. Age above 18 years
2. Angiographically proven coronary artery disease
3. Angina II to IV following the Canadian Cardiovascular Society classification criteria and/or reproducible ischemia in the target area by ECG or scintigraphy
4. The patient signing an informed written consent
Angiographic Inclusion Criteria*
First-degree criteria
1. De-novo lesion in a native coronary artery
2. Target reference vessel diameter between 2.5 and 4.0 mm by visual estimation
3. Luminal diameter reduction of 70% to 99% by visual estimation
4. Moderate to severe calcification of the target lesion†
Second-degree criteria
1. Ostial location
2. Bifurcational lesions
3. Long lesions (≥15 mm)

*Lesions had to fulfill all first-degree criteria and at least 1 second-degree criterion to be eligible for inclusion. †Coronary calcium was angiographically graded as follows: none/mild; moderate (radiopacities noted only during the cardiac cycle before contrast injection); and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen) (16).

ECG = electrocardiogram.

nary infusion, and a temporary pacemaker wire was inserted during rotablation of the right coronary artery and the left circumflex artery in patients with a dominant left system.

Stent delivery was performed in all patients using exclusively PES. More than 1 study stent was permitted for treatment of the target lesion(s). The appropriate stent length for the target lesion should have been ≥4 mm longer than the lesion length to allow for coverage between healthy vessel segments, with adequate stent overlapping. Postdilation was performed at the operator's discretion. Upon procedure completion, intracoronary nitroglycerin was administered and final angiography of the vessel was performed in at least 2 orthogonal views that showed the target site to be free of foreshortening or vessel overlap.

Follow-up and endpoints. All patients received 100 mg of aspirin daily indefinitely and 75 mg of clopidogrel for at least 6 months. An electrocardiogram was performed 24 h after the procedure or before discharge, whichever occurred first. Additional 12-lead electrocardiograms were required to document any suspicious cardiac ischemic episodes. In addition, creatine kinase (CK) and creatine kinase-myocardial band (CK-MB) were measured after the procedure between 8 and 12 h. If any CK elevation was noted after the procedure, additional measurements were performed, as needed. During their hospital stays, patients were clinically monitored for the occurrence of any adverse events and any additional coronary interventional treatment. At 9 months, a clinic visit and a repeat coronary angiography were performed. Off-line quantitative and qualitative analyses of all angiographic parameters were performed by the angiographic core laboratory. All major cardiac events were adjudicated by the clinical event adjudication committee (see Online Appendix).

The primary endpoint of the trial was the in-stent late lumen loss (LLL) at 9 months, defined as the difference between the immediate post-procedure in-stent minimal lumen diameter and the in-stent minimal lumen diameter at 9-month follow-up angiography. Secondary endpoints included major adverse cardiac events defined as a composite of death, new myocardial infarction (MI) and target vessel revascularization (TVR) at 9 months, target lesion revascularization (TLR), stent thrombosis (definite), in-segment LLL (inside the stent or within 5 mm proximal or distal to the stent), binary restenosis (in-stent and in-segment), angiographic success, strategy success, procedural duration, and contrast amount. Death was defined as all-causes of mortality. MI was defined as elevated CK ≥3× the upper limit of normal with elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves (non–Q-wave MI), or as chest pain or other acute symptoms consistent with myocardial ischemia and/or new pathological Q waves in 2 or more contiguous electrocardiogram leads in the absence of timely cardiac enzyme data and/or new pathological Q waves in 2 or more contiguous leads and elevation of cardiac enzymes (Q-wave MI). TVR was defined as a repeated procedure, either PCI or bypass surgery, on the target vessel, and TLR was defined as any reintervention inside the stent implanted during the index procedure or within 5 mm proximal or distal to the stent. Stent thrombosis was defined as proposed by the Academic Research Consortium (17). Angiographic success was defined as successful stent delivery and expansion with attainment of <20% in-stent residual stenosis of the target lesion in the presence of TIMI (Thrombolysis In Myocardial Infarction) flow grade 3, whereas strategy success was defined as angiographic success without crossover or stent loss.

Quantitative angiographic analysis. Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISARESEARCH Center, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems,

Table 2. Exclusion Criteria

Clinical Exclusion Criteria
1. Myocardial infarction within 4 weeks
2. Left ventricular ejection fraction <30%
3. Limited long-term prognosis due to other conditions
Angiographic Exclusion Criteria
1. Unprotected left main lesions
2. Coronary artery bypass graft stenoses
3. In-stent restenoses
4. Chronic total occlusions
5. Target vessel thrombus
6. Target vessel dissection

Leiden, the Netherlands) by an independent experienced operator unaware of the treatment allocation. Measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerine using the same single worst-view projection at all times. The contrast-filled nontapered catheter tip was used for calibration. Quantitative analysis was performed on both the in-stent and in-segment areas (including the stented segment, as well as both 5-mm margins proximal and distal to the stent). Intraobserver variability was calculated at 0.09 ± 0.07 mm for the measurement of vessel size. Qualitative morphological lesion characteristics were characterized by standard criteria.

Statistical analysis. We assumed an LLL of 0.5 ± 0.5 mm in patients assigned to the group without RA and a 40% reduction (LLL of 0.3 mm) in patients assigned to RA according to results of initial observational studies (11). On this basis, 198 patients/lesions were needed to provide an 80% power to detect this reduction at a 2-sided alpha-error level of 0.05. To account for the expected dropouts at follow-up, the total patient number for the study was set at 240 patients.

All statistical analyses were performed by the statistical core institute in a blinded manner regarding the randomly assigned treatment and on an intention-to-treat basis. Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as counts and proportions (%). We tested data distribution for normality using the Kolmogorov-Smirnov test for goodness of fit. For patient-level data, differences between groups were checked for significance with Student *t* test or Wilcoxon rank-sum test (continuous data) or the chi-square or Fisher exact test when the expected cell value was less than 5 (categorical variables). For lesion-level data, differences between groups were checked for significance with generalized estimating equations to address intrapatient correlation in patients who underwent multilesion intervention. All tests were 2-sided and a p value of 0.05 was considered statistically significant. No adjustment was made for the primary and secondary endpoint comparisons. Event-free survival was assessed using Kaplan-Meier method. The study chair and principal investigators vouch for the accuracy and completeness of the reported data.

Results

Baseline clinical and angiographic characteristics. Of 240 patients enrolled in the study, 120 patients (86 men, 70.5 ± 8.2 years) were randomized to rotablation followed by PES (RA + PES group) and 120 patients (96 men, 71.8 ± 7.2 years) to PES without prior rotablation (standard therapy control group). The study flow chart is summarized in Figure 1. There were no clinically relevant differences between both groups with respect to clinical presentation (mostly stable angina), cardiovascular risk factors, prevalence of chronic renal failure, or history of myocardial infarction (Table 3). Multivessel disease was common and was present in 74% of either group. Overall, 322 lesions were treated: 146 in the RA + PES group and 172 in the standard therapy group. Patients were also well balanced according to lesion location and morphology (Table 4). The

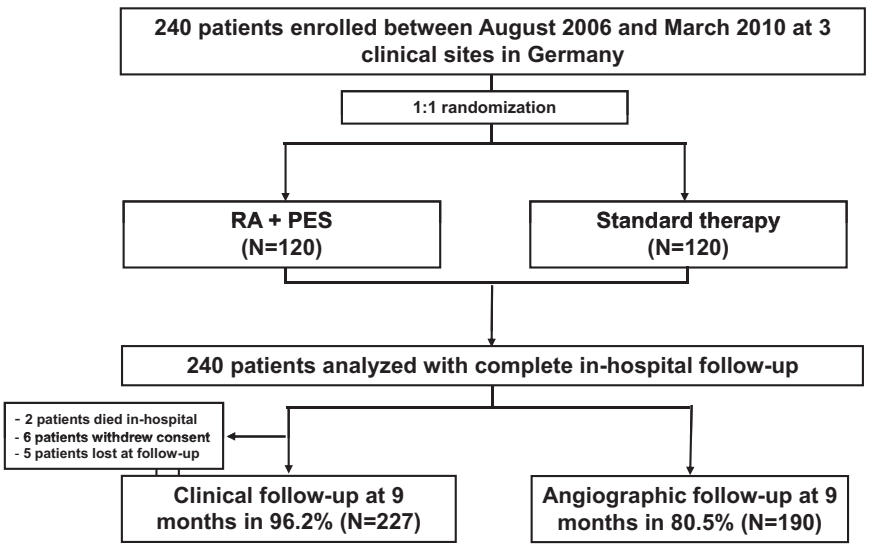

Figure 1. Study Flow Chart

PES = paclitaxel-eluting stent(s); RA = rotational atherectomy.

Table 3. Baseline Characteristics (N = 240 Patients)

	RA + PES (n = 120)	Standard Therapy (n = 120)	p Value
Age, yrs	70.5 ± 8.2	71.8 ± 7.2	0.20
Men	86 (72.3)	96 (81.7)	0.13
BMI, kg/m^2	27.9 ± 4.3	27.8 ± 4.0	0.68
Diabetes mellitus	33 (27.7)	32 (26.8)	0.88
Hypertension	106 (89.1)	95 (79.8)	0.05
Dyslipidemia	91 (76.5)	87 (73.1)	0.55
Current smokers	24 (20.2)	16 (13.5)	0.17
Family history of CAD	39 (32.8)	44 (37.0)	0.50
Chronic renal failure	5 (4.2)	8 (6.7)	0.40
Previous MI	38 (31.9)	29 (24.4)	0.20
Previous PCI	44 (37.0)	39 (32.8)	0.50
Previous CABG	9 (7.6)	15 (12.6)	0.20
Unstable angina	17 (14.3)	16 (13.4)	0.85
Left main disease	11 (9.2)	8 (6.7)	0.47
Multivessel disease	88 (74.0)	88 (74.0)	>0.99
LV ejection fraction, %	55.5 ± 10.6	53.0 ± 11.5	0.10
Ad hoc PCI	11 (9.3)	9 (7.6)	0.64
Multilesion PCI	23 (19.3)	32 (27.1)	0.16
Unfractionated heparin	49 (41.2)	70 (50.4)	0.15
Bivalirudin	70 (58.8)	59 (49.6)	0.15
GP IIb/IIIa antagonists	4 (3.4)	0	0.12

Values are n (%) or mean ± SD.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; GP = glycoprotein; LV = left ventricle; MI = myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); RA = rotational atherectomy.

target lesions were of high-grade stenosis (diameter stenosis by visual estimate 81.5 ± 10.2% in the RA + PES group and 80.0 ± 10.8% in the standard therapy group) and, in accordance with the angiographic inclusion criteria, were quite complex (46.9% with heavy calcifications, 46.6% with moderate or severe tortuosity, 47.8% at bifurcations, and 89.8% type B2/C lesions). Lesions treated in the RA + PES group were slightly longer by visual estimation (20.6 ± 9.3 mm vs. 18.5 ± 9.2 mm, p = 0.04) and were more commonly type B2/C lesions (93.8% vs. 86.3%, p = 0.15).

Procedural details and outcome. Procedural details are shown in Table 4. Only 20 procedures (8.3%) were performed as an ad hoc PCI. Most RA procedures (83.6%) were performed through a 7-F guiding catheter, whereas most standard procedures (71.6%) were performed through a 6-F guiding catheter. Balloon pre-dilation was performed in most lesions with a similar mean balloon size in both groups (2.6 ± 0.4 mm in the standard therapy group and 2.5 ± 0.3 mm in the RA + PES group), but the mean inflation pressure was higher in the standard therapy group (15.8 ± 4.9 atm vs. 13.6 ± 5.1 atm, respectively; p = 0.003). For rotablation, a single burr was used in most lesions (94.5%) with a mean burr size of 1.5 ± 0.2 mm. The mean stent length/lesion was well beyond the mean lesion length. After stenting, balloon post-dilation was performed for almost two-thirds of treated lesions in both groups (Table 4).

Procedural complications and outcome are shown in Table 5. Coronary dissections, perforations, and no-/slow-flow phenomena were rare and occurred equally in both groups, but procedural and fluoroscopy times were longer in the rotablation group. The intention-to-treat analysis revealed an identical angiographic success rate (96.7%) for both groups. Three cases of stent loss were recorded, all in the standard therapy group; 1 of these developed a periprocedural transient ischemic attack. In addition, there were 15 (12.5%) crossovers from standard therapy to rotablation because of failure of balloon or stent delivery or suboptimal balloon expansion despite the use of a noncompliant balloon. The reason for crossover of 5 (4.2%) patients from rotablation to standard PCI was a protocol deviation in 3 patients, failure of rotablation wire passage in 1 patient, and total occlusion of the target vessel at the time of PCI in 1 patient. As a result, overall strategy success was significantly higher in the rotablation group (92.5% vs. 83.3%, p = 0.03).

In-hospital outcome. There were 2 deaths during hospitalization, and both occurred in the RA + PES group. One patient died within 24 h during emergency surgery for a large coronary perforation, and the second patient died 5 days after PCI because of massive pulmonary embolism. Target vessel re-PCI during hospitalization became necessary in 1 patient in each group. The incidence of protocol-defined periprocedural MI was low in both groups (1.7% in the RA + PES group vs. 3.4% in the standard therapy group), but access site complications were numerically higher in the rotablation group (5.9% vs. 1.7%, respectively; p = 0.17) (Table 5). Post-procedural troponin T levels (8 to 24 h after PCI) were analyzed in 172 patients with normal baseline values and showed a similar incidence of any troponin T elevation (45.1% vs. 50%, p = 0.52) and troponin T elevation >3× above the upper limit of normal (24.4% vs. 32.2%, p = 0.26) in the RA and standard therapy groups, respectively.

Nine-month clinical outcome. Complete follow-up over 9 months was available for 227 of 240 patients (96.2%) (n = 113 of the RA + PES group and n = 114 of the standard therapy group); median follow-up duration was not different in both groups (279.5 vs. 301.0 days, respectively; p = 0.15). At 9 months, overall mortality was 5.0% versus 5.8% in the RA + PES versus standard therapy group, respectively (p = 0.78). MI occurred in 6.7% versus 5.8% (p = 0.79) and TVR in 16.7% versus 18.3% (p = 0.73) of patients, resulting in a cumulative major adverse cardiac events rate of 24.2% versus 28.3% in the RA + PES versus standard therapy group, respectively (p = 0.46). Cumulative incidence curves for death, MI, TVR, and major adverse cardiac events are shown in Figure 2. TLR occurred in 11.7% versus 12.5% (p = 0.84), and a single case of definite stent thrombosis was observed in the rotablation group.

Table 4. Angiographic and Procedural Characteristics (N = 322 Lesions)

	RA + PES (n = 146)	Standard Therapy (n = 176)	p Value
Location			0.06
Left main, protected	3 (2.1)	2 (1.1)	
Left anterior descending	101 (69.2)	111 (63.1)	
Left circumflex	7 (4.8)	22 (12.5)	
Right coronary artery	35 (24.0)	41 (23.3)	
Reference vessel diameter, mm	3.1 ± 0.4	3.1 ± 0.3	0.54
Lesion length, mm	20.6 ± 9.3	18.5 ± 9.2	0.04
Diameter stenosis, %	81.5 ± 10.2	80.0 ± 10.8	0.19
Ostial location	27 (18.5)	31 (17.6)	0.89
Bifurcation	72 (49.3)	82 (46.6)	0.79
Moderate/severe tortuosity	67 (46.2)	83 (47.2)	0.87
Severe calcification	65 (44.5)	86 (49.1)	0.61
B2/C lesion	137 (93.8)	152 (86.3)	0.15
7-F guiding catheter	122 (83.6)	50 (28.4)	<0.001
Balloon pre-dilation	130 (89.0)	160 (90.9)	0.48
Maximum pre-dilation balloon size, mm	2.5 ± 0.3	2.6 ± 0.4	0.41
Maximum pre-dilation balloon pressure, atm	13.6 ± 5.1	15.8 ± 4.9	0.003
Starting burr size, mm	1.5 ± 0.2	—	—
Maximum burr size, mm	1.5 ± 0.2	—	—
Use of >1 burr	8 (5.5)	—	—
Rotational speed, RPM	165,947 ± 8,919	—	—
No. of stents/lesions	1.3 ±0.6	1.3 ±0.6	0.38
Total stent length/lesions, mm	27.7 ± 12.2	25.2 ± 11.5	0.06
Balloon post-dilation	92 (63.0)	116 (65.9)	0.58
Maximum post-dilation balloon size, mm	3.3 ± 0.5	3.3 ± 0.4	0.84
Maximum post-dilation balloon pressure, atm	21.7 ± 5.8	21.5 ± 5.8	0.32

Values are n (%) or mean ± SD.
RPM = rotations per minute; other abbreviations as in Table 3.

Quantitative angiographic analysis. Details of baseline quantitative coronary angiographic analysis are listed in Table 6. Baseline minimal lumen diameter was slightly smaller in the rotablation group, but residual diameter stenosis of the stented segment was significantly less (10.79 ± 5.61% vs. 12.34 ± 7.85%, p = 0.04) and acute gain was significantly higher (1.56 ± 0.43 mm vs. 1.44 ± 0.49 mm, p = 0.01) in the rotablation group.

The 9-month angiographic follow-up is determined on the basis of 190 patients (80.5%); 98 patients (123 lesions) randomized to the RA + PES group and 92 patients (132 lesions) randomized to the standard therapy group. The only differences observed between patients with and those without angiographic follow-up is that the latter were older (75.3 ± 5.7 years vs. 70.0 ± 7.8 years, p < 0.001) and more commonly women (38.8% vs. 19.6%, p = 0.005). Details of the follow-up quantitative coronary angiographic analysis are shown in Table 7. At 9 months, in-stent LLL (the primary endpoint) was 0.44 ± 0.58 mm in the RA + PES group and 0.31 ± 0.52 mm in the standard therapy group (p = 0.04). In-segment LLL was numerically higher in the rotablation group (0.36 ± 0.57 mm vs. 0.25 ± 0.57 mm, p = 0.11). Binary restenosis (both in-stent and in-segment) was similar in both groups. The results of the primary endpoint were consistent in lesions with moderate calcification (LLL: 0.42 ± 0.55 mm in the RA + PES group vs. 0.33 ± 0.46 mm in the standard therapy group, p = 0.32) and in those with severe calcification (0.48 ± 0.62 mm in the RA + PES group vs. 0.28 ± 0.58 mm in the standard therapy group, p = 0.07).

Discussion

Practice guidelines recommend the use of RA for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting (bailout situations) (18,19). The aim of ROTAXUS was to explore a potentially new indication for RA by evaluating whether routine elective rotablation of complex calcified lesions could improve DES efficacy. The principal finding of the study is that RA before PES implantation was not superior to PES implantation without prior rotablation in reducing the primary endpoint of in-stent LLL at 9 months, indicating that rotablation does not increase the efficacy of DES in this complex group of patients.

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Table 5. Procedural and In-Hospital Outcome (N = 240 Patients)

	RA + PES (n = 120)	Standard Therapy (n = 120)	p Value
Procedural duration, min	66.4 ± 44.5	57.4 ± 34.5	0.05
Fluoroscopy time, min	22.8 ± 21.9	18.1 ± 16.7	0.04
Contrast amount, ml	201.0 ± 113.6	181.8 ± 93.6	0.11
Dissections	4 (3.3)	4 (3.3)	>0.99
Perforations	2 (1.7)	1 (0.8)	0.56
Cardiac tamponade	1 (0.8)	1 (0.8)	>0.99
No/slow flow	0 (0)	1 (0.8)	0.32
Persistent advanced AV block	1 (0.8)	0 (0)	>0.99
Angiographic success*	116 (96.7)	116 (96.7)	>0.99
Stent loss	0 (0)	3 (2.5)	0.08
Crossover	5 (4.2)	15 (12.5)	0.02
Strategy success*	111 (92.5)	100 (83.3)	0.03
Death	2 (1.7)	0 (0)	0.50
Myocardial infarction	2 (1.7)	4 (3.4)	0.68
Target vessel re-PCI	1 (0.8)	1 (0.8)	>0.99
CABG	1 (0.8)	0 (0)	>0.99
MACE*	5 (4.2)	5 (4.2)	>0.99
Stent thrombosis	0 (0)	0 (0)	>0.99
Access site complications	7 (5.9)	2 (1.7)	0.17

Values are n (%) or mean ± SD. *See text for definition.
AV = atrioventricular; MACE = major adverse cardiac events; other abbreviations as in Table 3.

RA is an essential technique with growing importance in the current PCI era as increasingly complex patients and lesions are considered for interventional therapy. Particularly in heavily calcified lesions, stent delivery and expansion are often difficult or even impossible without RA. Moreover, heavily calcified lesions may form a special threat to DES; both damage to the polymer/drug coating (20) and inadequate drug diffusion through extensive calcification may decrease DES effectiveness when implanted into such lesions. By contrast, RA causes additional vessel injury with increased neointimal growth. Restenosis rates after rotablation of calcified lesions are 2× to 3× higher than for noncalcified lesions and remain unacceptably high even after stenting in studies conducted in the pre-DES era (10,21–23). This could be prevented by an antiproliferative drug coating of the implanted stent; therefore, RA and DES may act synergistically in complex calcified lesions. In this context, Nakamura et al. (24) described an advantage of RA before implanting sirolimus-eluting stents in terms of long-term clinical and angiographic outcomes compared with implanting sirolimus-eluting stents without prior rotablation among long lesions, which may be interpreted as an add-on effect in the RA + DES arm.

ROTAXUS is the first randomized controlled trial to evaluate a strategy of routine RA before DES implantation in complex calcified coronary lesions, and we could not demonstrate superior effectiveness of the RA + DES strategy. The reasons for this finding were 2 unexpected observations: 1) the LLL in the control group was lower than assumed; and 2) the LLL in the RA group was higher than assumed. The 0.31-mm LLL in the control cohort was even below the LLL pattern known from various TAXUS trials (1–4). Obviously, lesion morphology did not impair PES effectiveness, which could be attributed to the fact that, although not demanded by the protocol, an aggressive lesion preparation with high-pressure balloon dilation was applied in more than 90% of the lesions before PES implantation. Pre-dilation with pressures higher than those in the RA group might have mitigated potential damage of the drug coating during stent placement and allowed sufficient stent expansion despite the presence of calcium. Nevertheless, a considerable number of patients could not be treated successfully by balloon dilation before stenting and had a stent loss and/or had to crossover to RA. By contrast, the LLL of 0.44 mm in the RA group is an acceptable value in terms of previous TAXUS trials (1–4). PES, however, did not obviate the additional RA associated vessel injury and neointimal formation, and all late angiographic outcome measures (minimal lumen diameter and percentage of diameter stenosis) were consistently poorer in the RA arm. From an angiographic perspective, the superior acute gain obtained by RA was counterbalanced by an increased late loss resulting in a neutral effect on restenosis. Ultimately, the angiographic and clinical restenosis rate is DES-like (i.e., near 10%), which is far below the numbers in the RA–bare-metal stent era (10) and is confirming several observational studies on RA and DES with positive acute and long-term outcomes (11–15).

One might speculate about potential factors within the study protocol that were unfavorable for RA. First, it is possible that a patient population with an even higher fraction of severely calcified lesions can obtain more benefit from the RA + DES concept. In ROTAXUS, more than 50% of the patients had angiographically moderate calcification, which might be a lesion quality not requiring RA. It is also possible that an intravascular ultrasound-guided intervention would have offered a more appropriate lesion selection. Nevertheless, according to the American College of Cardiology/American Heart Association lesion morphology classification, ROTAXUS comprised the most complex population ever included in a randomized stent study. Second, it might be argued that the RA strategy that was applied in ROTAXUS does not provide sufficient plaque ablation with a mean burr size of 1.5 mm and a burr-to-vessel ratio of 0.5. A previous study, however, has documented a more favorable long-term outcome with our less aggressive RA strategy (25). Third, it is conceivable that the ROTAXUS results could have differed if another DES system had been used. The Taxus stent was the workhorse DES at the time of study initiation with numerous published studies and registries, which allows us to evaluate our results within the framework of this large data pool. Fourth, it is possible that the observation period was too short to

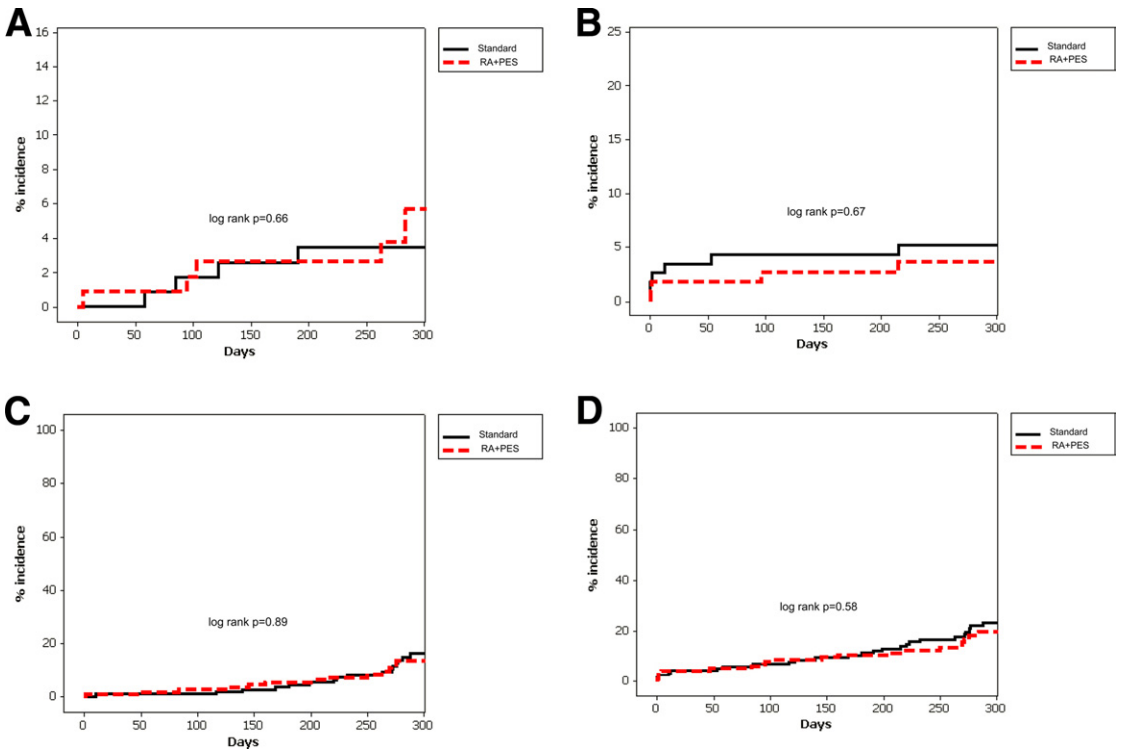

Figure 2. Clinical Outcome

Cumulative incidence curves for death **(A),** myocardial infarction **(B),** target vessel revascularization **(C),** and major adverse cardiac events **(D)** in the RA + PES and standard therapy groups. Abbreviations as in Figure 1.

detect an advantage of the RA + DES approach. In general, TLR rates continuously increase over time in patients who have received a DES (26). We recently reported that the TLR rate reached a plateau after 30 months with no further events thereafter in our RA + DES population (15), which could be either a play of chance or the result of a particular

Table 6. Baseline Quantitative Coronary Angiography Data (N = 322 Lesions)

	RA + PES (n = 146)	Standard Therapy (n = 176)	p Value
Before procedure			
Lesion length, mm	19.49 ± 9.66	17.99 ± 9.54	0.19
Reference vessel diameter, mm	2.68 ± 0.41	2.76 ± 0.39	0.11
Minimal lumen diameter, mm	1.01 ± 0.36	1.10 ± 0.41	0.05
Diameter stenosis, %	62.23 ± 12.01	60.19 ± 12.91	0.14
Immediately after procedure			
Minimal lumen diameter, mm			
In-stent	2.57 ± 0.38	2.55 ± 0.45	0.53
In-segment	2.26 ± 0.49	2.29 ± 0.53	0.58
Diameter stenosis, %			
In-stent	10.79 ± 5.61	12.34 ± 7.85	0.04
In-segment	18.21 ± 8.77	19.09 ± 10.69	0.38
Acute gain, mm			
In-stent	1.56 ± 0.43	1.44 ± 0.49	0.01
In-segment	1.24 ± 0.54	1.19 ± 0.55	0.26

Values are mean ± SD.
Abbreviations as in Table 3.

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Table 7. Nine-Month Follow-Up Quantitative Coronary Angiography Data (N = 255 Lesions)

	RA + PES (n = 123)	Standard Therapy (n = 132)	p Value
Minimal lumen diameter, mm			
In-stent	2.14 ± 0.63	2.25 ± 0.62	0.17
In-segment	1.91 ± 0.57	2.02 ± 0.65	0.17
Diameter stenosis, %			
In-stent	22.01 ± 19.92	19.86 ± 19.64	0.35
In-segment	27.92 ± 18.97	26.99 ± 1.73	0.62
Late lumen loss, mm			
In-stent	0.44 ± 0.58	0.31 ± 0.52	0.04
In-segment	0.36 ± 0.57	0.25 ± 0.57	0.11
Binary restenosis, %			
In-stent	14 (11.4)	14 (10.6)	0.71
In-segment	15 (12.2)	17 (12.9)	0.89

Values are n (%) or mean ± SD.
Abbreviations as in Table 3.

vessel biology after RA + DES. Long-term follow-up of the ROTAXUS population may provide further insights into this phenomenon.

Clinical implications. This study emphasizes the importance of careful lesion preparation in complex calcified coronary lesions to ensure stent delivery and complete expansion. Although routine RA did not improve DES efficacy, RA remains an important tool for uncrossable or undilatable lesions and improves overall procedural success in this setting. A strategy of balloon dilation with provisional rotablation before stenting should remain the default strategy for complex calcified lesions in the DES era.

Study limitations. It should be noted that in using a primary angiographic endpoint, the conclusions of our trial are determined on the basis of incomplete observations (80.5% angiographic follow-up in the current study). This is an inherent feature of all DES trials using such an angiographic endpoint. In this regard, concordance of the results of the secondary endpoint analyses (including TLR), for which data were available on over 95% of patients, is noteworthy. We acknowledge that routine angiographic follow-up increases the incidence of TLR in a manner that may not reflect real-life practice. However, this increases the sensitivity of a study to detect differences in restenosis between various devices or strategies. This trial was not powered to detect differences in clinical events, and clinical outcome data must be interpreted with this in mind. The rather slow enrollment rate for 3 high-volume centers remains a possible source of bias.

Conclusions

In this randomized controlled trial, routine rotablation before PES implantation in complex calcified coronary lesions was not superior to PES implantation without rotablation in reducing the primary endpoint of LLL at 9 months, indicating that rotablation does not increase the efficacy of DES in calcified lesions. The superior acute gain obtained by rotablation was counterbalanced by an increased late loss resulting in a neutral effect on restenosis. Therefore, balloon dilation with provisional rotablation before stenting remains the default strategy for complex calcified lesions in the DES era.

Acknowledgments

The authors are grateful for the clinical research group at the Herzzentrum Segeberger Kliniken GmbH, especially Mrs. Daniela Schürmann-Kuchenbrandt, Mr. Marcus Ring, and Mr. Guido Kassner.

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Key Words: calcified lesions ■ drug-eluting stents ■ lesion preparation ■ rotablation ■ rotational atherectomy.

APPENDIX

For a list of investigators and their affiliations, please see the online version of this paper.