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Combined rotational atherectomy and cutting balloon angioplasty prior to drug-eluting stent implantation in severely calcified coronary lesions: The PREPARE-CALC-COMBO study

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Abstract

Objectives: To evaluate the safety and efficacy of lesion preparation using rotational atherectomy (RA) with consecutive cutting balloon angioplasty (Rota-Cut).

Background: Whether the Rota-Cut combination improves stent performance in severely calcified coronary lesions is unknown.

Methods: PREPARE-CALC-COMBO is a single-arm prospective trial in which 110 patients were treated with a Rota-Cut strategy before implantation of sirolimus-eluting stents and compared with patients treated with modified balloon (MB, scoring or cutting) or RA from a historical cohort (the randomized PREPARE-CALC trial). The study had two primary endpoints: in-stent acute lumen gain (ALG) by quantitative angiographic analysis and stent expansion (SE) on optical coherence tomography.

Results: In-stent ALG was significantly higher with Rota-Cut compared to RA or MB alone (1.92 ± 0.45 mm vs. 1.74 ± 0.45 mm with MB vs. 1.70 ± 0.42 mm with RA; $p = 0.001$ and $p < 0.001$, respectively). SE was comparable between groups (75.1 ± 13.8% vs. 73.5 ± 13.3 with MB vs. 73.1 ± 12.2 with RA; $p = 0.19$ and $p = 0.39$, respectively). The Rota-Cut combination resulted in higher minimal stent area (MSA) (7.1 ± 2.2mm^2 vs. 6.1 ± 1.7mm^2 with MB vs. 6.2 ± 1.9mm^2 with RA; $p = 0.003$ and $p = 0.004$, respectively). In-hospital death occurred in one patient. Target vessel failure at 9 months was low and comparable between groups (8.2% vs. 8% with MB vs. 6% with RA; $p = 1$ and $p = 0.79$, respectively).

Abbreviations: ALG, acute lumen gain; CB, cutting balloon; MB, modified balloon; RA, rotational atherectomy; Rota-Cut, combined lesion preparation using rotational atherectomy followed by cutting balloon angioplasty; SE, stent expansion.

Conclusion: Rota-Cut combination resulted in higher ALG and larger MSA compared with historical control of RA or MB alone, but was not associated with higher SE. Despite extensive lesion preparation, this strategy is safe, feasible, and associated with favorable clinical outcome at 9 months.

KEYWORDS
complex percutaneous coronary intervention, coronary calcification, cutting balloon, rotational atherectomy, Rota-Cut

1 | INTRODUCTION

Percutaneous coronary intervention (PCI) of severely calcified lesions remains challenging despite the constantly improving tools and techniques. Severe coronary calcifications form resistant hard plaques that may hinder delivery of stents or limit their expansion, raising the risk of stent thrombosis and restenosis. This is particularly relevant for drug-eluting stents (DES); as heavily calcified lesions can damage their polymer coating during vigorous advancement leading to inadequate diffusion of antiproliferative drugs into the subintima. Consequently, the presence of extensive calcium arcs could impair the long-term effectiveness of DES.[1–3] In this context, proper lesion preparation is crucial for a successful stent implantation with good long-term outcomes.[1–4]

In contemporary practice, several tools for calcified lesion preparation are available with different mechanisms of action. Some depend on static barometric pressure like high pressure balloons and others depend on mechanical methods to crack calcium. Scoring and cutting balloons (CBs) are special modified balloons (MB) with either a nitinol spiral cage or cutting blades that enable fracturing calcified plaques. Ultrasound shock waves for fracturing is a novel technique applied by intravascular lithoplasty balloons. Rotational atherectomy (RA), on the other hand, is an atheroablative method. It utilizes a rotating diamond tipped burr with a constant, circular orbit that ablates in the forward direction creating a pathway in the calcified plaque.

In the randomized PREPARE-CALC (High-speed rotational atherectomy vs. modified balloons before drug-eluting stent implantation in severely calcified coronary lesions) trial, strategy success with RA was more common compared with MB strategy (98% vs. 81%; $p = 0.03$),[5] which was attributed to more crossover and stent failure in patients treated with a primary MB-based strategy. Nevertheless, in-stent acute gain was not significantly different between both techniques. Similarly, stent expansion (SE) as assessed by optical coherence tomography (OCT) was similar in both strategies.[6]

The combination of two techniques with different mechanisms of calcium modification could have a synergic effect and might improve stents results. Recently, a small pilot study revealed larger acute gain of cross-sectional area as assessed with intravascular ultrasound, when RA was combined with CB angioplasty as compared with RA followed by conventional balloon dilatation before DES implantation.[7] However, there are concerns about the safety of such an extensive lesion preparation approach.

In the present study we sought to evaluate the safety and the efficacy on both angiographic and OCT level of RA followed by CB angioplasty before implantation of DES in severely calcified lesions.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

The Evaluation of a Strategy to PREPARE severely CALCified Coronary Lesions with a Combination Of rotational atherectomy and Modified BallOons Trial (PREPARE-CALC-COMBO) is a single-arm prospective trial performed among patients with documented myocardial ischemia and severely calcified native coronary lesions. The MB ($n = 100$) and RA ($n = 100$) cohorts of the randomized PREPARE-CALC trial served as historical controls. The trial was performed at a single high-volume, experienced center in Germany (Heart Center Segeberger Kliniken), with fully trained operators with several years of interventional cardiology and especially RA experience.

Between January 2019 and June 2020, 110 eligible patients who met all clinical and angiographic inclusion criteria after written informed consent were treated with a strategy of lesion preparation using RA followed by CB angioplasty (Rota-Cut) before final DES implantation. The main inclusion criteria were angiographically proven coronary artery disease in the presence of anginal symptoms or reproducible ischemia in the target area; reduction in luminal diameter of 50%–100% with target reference vessel diameter between 2.25 and 4.0 mm; and severe calcification of the target lesion as defined by cineangiography (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).[8] Inclusion and exclusion criteria were the same as for the PREPARE-CALC trial and are shown in the Supporting Information: Table 1. The study flow chart is presented in Figure 1. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices and was approved by the local ethic committee. All patients provided written informed consent.

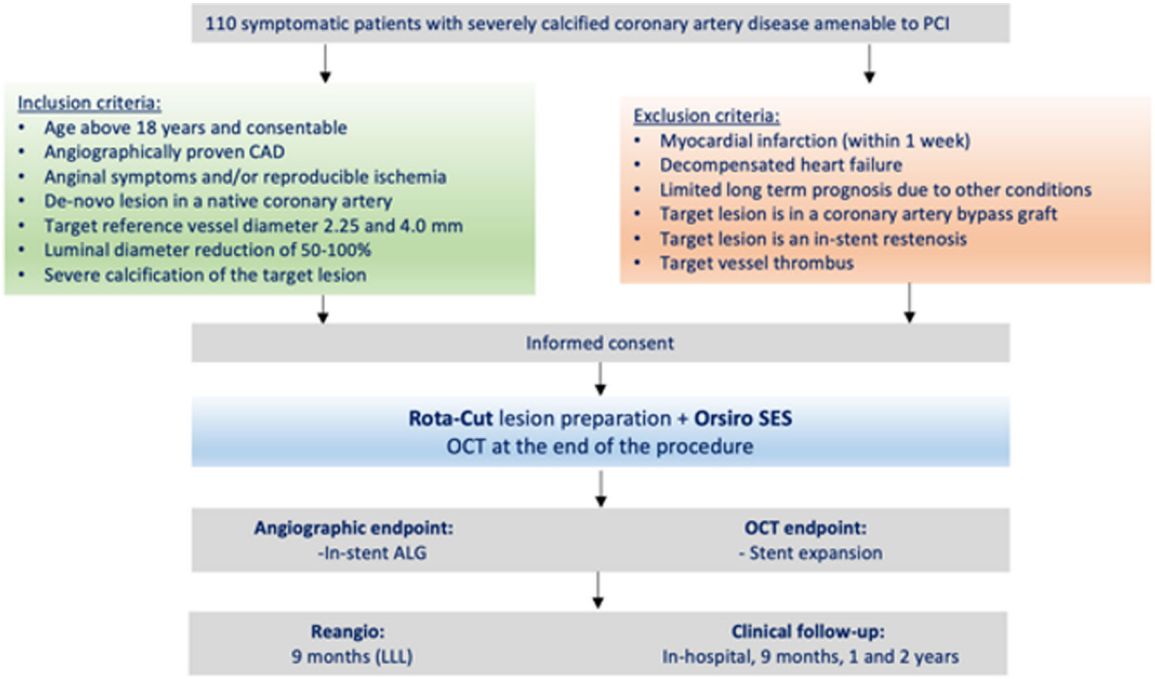

FIGURE 1 Study flow chart. Study flow chart of the PREPARE-CALC COMBO trial. ALG, acute lumen gain; CAD, coronary artery disease; LLL, late lumen loss; PCI, percutaneous coronary intervention; OCT, optical coherence tomography; RA, rotational atherectomy; Rota-Cut, rotational atherectomy in combination with cutting balloon; SES, sirolimus-eluting stent. [Color figure can be viewed at wileyonlinelibrary.com]

2.2 | Procedures

RA was performed by the Rotablator or RotaPro systems (Boston Scientific Corporation). The burr size was selected to reach a burr/vessel ratio of 0.5 (max. 0.7 if needed). In all patients, additional balloon dilatation using CB (Wolverine™ Cutting Balloon, Boston Scientific Corporation) was performed after RA. Further predilatation with a standard balloon before or after the use of the CB was left to the discretion of the operator. The use of more than one CB or multiple standard balloons was allowed. The size of the final balloon was chosen in a 1:1 ratio according to the reference vessel diameter.

Stenting was performed using a current generation bioabsorbable polymer sirolimus-eluting stent (BP-SES) (Orsiro, Biotronik AG). Postdilatation was performed at the operator's discretion. OCT imaging was performed once an optimal angiographic result was achieved after DES implantation as per operators' visual assessment. Stent optimization after OCT imaging was allowed at the operator's discretion.

2.3 | Quantitative angiographic analysis

Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core (QCA) laboratory (ISAResearch Centre) with an automated edge-detection system (Qangio XA version 7.3, Medis Medical Imaging Systems) by independent personnel 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. In-stent acute lumen gain (ALG) was defined as the in-stent minimal lumen diameter (MLD) at the end of the index procedure minus baseline MLD. Detailed description of the protocols for acquisition and analysis of angiographic data is provided in the online Appendix (Supporting Information: II).

2.4 | OCT analysis

Image acquisition was performed with the ILUMIEN OPTIS console and the Dragonfly™ intravascular imaging catheter (St. Jude Medical) according to predefined standard operating procedure of the imaging core laboratory (Zentrum für Klinische Studien). All OCT data were stored offline and analyzed with the windows based QIvus 3.1.12.0 software (Medis Medical Imaging Systems) using the methods recommended in the expert consensus report for OCT.[9] Reference lumen area was estimated as the mean lumen area of the most proximal and the most distal cross-sectional areas of the analyzed segment. SE was calculated as the minimum stent area (MSA) divided by the reference lumen area × 100.[6,10] Detailed description of the protocols for acquisition and analysis of OCT data is provided in the online Appendix (Supporting information: III).

2.5 | Follow-up and endpoints

In-hospital monitoring was similar to the PREPARE-CALC trial.[5] At 9 months, a clinical visit and a follow-up coronary angiography were performed. Further clinical follow-up is planned at 1 and 2 years.

The primary endpoint of the trial is in-stent ALG on QCA. The co-primary endpoint is the SE on quantitative OCT analysis. TVF was defined as a composite of cardiac death, target vessel related MI and clinically driven target vessel revascularization (TVR). Stent thrombosis was defined as proposed by the Academic Research Consortium.[11] Detailed endpoint definitions are provided in the Supporting Information: I. Results at 1 and 2 years will be reported later. Relevant data were collected and entered into a dedicated electronic database. All major cardiac events were adjudicated by the clinical event adjudication committee.

2.6 | Statistical analysis

The aim of this study was to assess whether the preparation of severely calcified coronary lesions with a combination of RA and CB improves ALG compared to RA or MB alone.

In the PREPARE-CALC trial, ALG was similar in patients treated with either MB (1.74 ± 0.45 mm) or RA (1.70 ± 0.42 mm).[5] In a pilot trial, the Rota-Cut lesion preparation resulted in a trend toward larger minimal stent diameter compared to RA alone (2.7 ± 0.4 mm vs. 2.5 ± 0.4 mm; $p = 0.097$).[7] Data about ALG with the Rota-Cut combination are lacking. We assumed an ALG in the Rota-Cut strategy to be 1.85 mm. Based on superiority hypothesis testing, 134 lesions were needed to detect superiority with a power of 80% at a two-sided α-level of 0.05 in comparison with historical data on isolated RA or MB strategies form the PREPARE-CALC trial.

With regard to the co-primary endpoint, SE was 73.5 ± 13.3% in the MB group and 73.1 ± 12.2% in the RA group in the OCT sub-analysis of the PREPARE-CALC trial.[6] Assuming a SE of 80% in the Rota-Cut treatment group and a standard deviation of 13%, a superiority sample size of 54 patients was calculated given a power of 80% at an α level of 0.05.[6] With an expected attrition rate of 7% in angiographic data and 20% of OCT data, and with 1.3 lesions/patient expected, we designed the study to include a total of 110 patients.

All statistical analyses were performed by an independent statistician. Categorical measures were represented as numbers and percentages and were compared with historical data using a χ^2 test or Fisher's exact test as appropriate. Continuous variables were represented as mean ± standard deviation and comparison with historical data was done using a two-sided unpaired t-test or a Mann–Whitney test, according to data distribution. For lesion-level data, differences between groups were checked for significance with generalized estimating equations to address intrapatient correlation in patients who underwent multi-lesion intervention. The estimated relative risk is the ratio of the risk probabilities, and a confidence interval was constructed based on a logarithmic transformation.

All tests were two-sided and a p value of 0.05 was considered statistically significant. No adjustment was made for the primary and secondary endpoint comparisons. The steering committee had full access to all the data in the study and takes full responsibility for its integrity and the data analysis.

3 | RESULTS

3.1 | Baseline clinical and angiographic characteristics

The mean age of the Rota-Cut study population was 74.9 ± 8.2 years and 78.2% were males. Compared to the historical control groups, dyslipidemia was less frequent compared to both arms of the PREPARE-CALC trial. There were no significant differences between the study population and both control groups with respect to other cardiovascular risk factors. Baseline characteristics are summarized in Table 1.

Overall, 160 lesions were treated (1.45 lesion/patient). Left main location was present in 11.3%, and 93.1% of lesions were classified as type B2/C according to the American College of Cardiology/American Heart Association (ACC/AHA) classification. Patients were comparable to the historical control groups with respect to lesion location and morphology (Table 2).

3.2 | Procedural details

Procedural characteristics are listed in Table 2.

Concerning CB angioplasty, smaller CBs with higher inflation pressure were used in PREPARE-CALC COBMO compared to the historical MB peer (2.8 ± 0.36 mm vs. 2.94 ± 0.34 mm; $p = 0.001$ and 16.9 ± 2.7 atm vs. 15.6 ± 3 atm; $p = 0.002$). Regarding the RA technique, higher rotational speed was applied as compared to the RA arm of the control group, while other technical aspects (burr size, burr to artery ratio and use of more than one burr) were similar. Additional standard balloon predilatation was less frequently performed in PREPARE-CALC COMBO but with a larger mean balloon size and higher inflation pressure as compared to both control arms.

More stents per lesion were implanted and inflation pressure was higher in the PREPARE-CALC COMBO population compared to both historical comparison groups. Nevertheless, total stent length and stent diameter did not differ significantly. After stenting, balloon postdilatation was performed for the vast majority (87.5%) of treated lesions, with a similar balloon size and postdilatation pressure compared to the control arms.

3.3 | Procedural and in-hospital outcome

Procedural complications and in-hospital outcome are represented in Table 3. Strategy success was achieved in all but four patients

TABLE 1 Baseline characteristics

	RA + CB (n = 110)	MB (n = 100)	RA (n = 100)	p Value MB vs. RA + CB	p Value RA vs. RA + CB
Age (years)	74.9 ± 8.2	75.0 ± 6.9	74.8 ± 7.1	0.70	0.57
Males	86 (78.2%)	75 (75%)	77 (77%)	0.63	0.87
Height (cm)	172.5 ± 8.3	172.3 ± 9.5	172.0 ± 8.7	0.90	0.71
Weight (kg)	83.6 ± 16.4	84.2 ± 15.8	83.1 ± 17.0	0.77	0.86
Diabetes mellitus	34 (30.9%)	34 (34%)	33 (33%)	0.66	0.77
Hypertension	96 (87.3%)	93 (93%)	93 (93%)	0.25	0.25
Dyslipidemia	49 (44.5%)	69 (69%)	68 (68%)	<0.001	<0.001
Current smokers	19 (17.3%)	9 (9%)	15 (15%)	0.08	0.66
Chronic kidney disease[a]	22 (20%)	21 (21%)	26 (26%)	0.86	0.30
Previous MI	20 (18.2%)	22 (22%)	21 (21%)	0.50	0.73
Previous PCI	40 (36.4%)	55 (55%)	47 (47%)	0.008	0.13
Previous CABG	16 (14.5)	13 (13%)	6 (6%)	0.84	0.07
Unstable angina	10 (9.1%)	9 (9%)	8 (8%)	0.59	0.89
Atrial fibrillation	11 (10%)	11 (11%)	18 (18%)	0.82	0.16
Left main disease	30 (27.2%)	37 (37%)	23 (23%)	0.14	0.53
Multivessel disease	91 (82.7%)	70 (70%)	74 (74%)	0.08	0.39
LV ejection fraction (%)	55.2 ± 10.2	56.9 ± 10.6	55.7 ± 11.7	0.23	0.74
Multilesion PCI	40 (36.4%)	42 (42%)	35 (35%)	0.48	0.89
Unfractionated heparin	110 (100%)	98 (98%)	99 (99%)	0.22	0.48
Bivalirudin	0 (0%)	2 (1%)	1 (1%)	0.22	0.48
GP IIb/IIIa antagonists	3 (2.7%)	0 (0%)	2 (2%)	0.25	1.00

Note: Values are n (%) or mean ± SD.

Abbreviations: CABG, coronary artery bypass graft; CB, cutting balloon; GP, glycoprotein; LV, left ventricle; MB, modified balloon; MI, myocardial infarction; PCI, percutaneous coronary intervention; RA, rotational atherectomy.

[a]Defined as glomerular filtration rate <60 ml/min/1.73 m^2.

(96.4%). In three cases, stents were damaged during advancement and a strategy failure was documented. In one patient, due to the occurrence of coronary perforation covered stents were implanted and the lesion was not totally covered with DES. Large coronary dissections occurred in 10.9% of patients (vs. 7% with MB vs. 3% with RA; $p = 0.97$ and $p = 0.003$, respectively). Coronary perforation, pericardial effusion and no/slow flow phenomena were not significantly different between the PREPARE-CALC COMBO group and the PREPARE-CALC treatment arms. In hospital death occurred in one patient treated for an ostial RCA lesion due to acute type A aortic dissection.

3.4 | Quantitative angiographic analysis

Results of baseline and postprocedural QCA are listed in Table 4. In PREPARE-CALC COMBO, treated lesions were longer (24.05 ± 11.63 mm vs. 20.16 ± 11.88 mm in MB group; $p = 0.005$ and 20.86 ± 12.30 mm in RA group; $p = 0.023$) with higher diameter stenosis (Rota-Cut: 70.47 ± 10.23% vs. MB: 65.18 ± 9.53% and vs. RA: 63.43 ± 9.80; $p < 0.001$ for both comparisons). Of interest, concerning coronary calcification, which was the main angiographic inclusion criterion for the study, the angiographic core laboratory adjudicated only 10 of treated lesions as moderately calcified (6.7%), with a significant difference compared to both control arms of the PREPARE-CALC trial (27% with moderate calcification in MB group and 23.5% in RA group; both $p < 0.001$).

In-stent ALG, the primary endpoint of the study, was significantly higher in the Rota-Cut group (1.92 ± 0.45 mm) compared the control group of MB (1.74 ± 0.45 mm; $p = 0.001$) and RA (1.70 ± 0.42 mm; $p < 0.001$). Cumulative frequency distribution curves are shown in Figure 2.

The 9-month angiographic follow-up was available in 71% of the study population (79 patients, 113 lesions). Details of the follow-up QCA are summarized in Supporting Information: Table 2. In-stent LLL was 0.26 ± 0.6 mm and was not significantly different compared to

TABLE 2 Angiographic and procedural characteristics

	RA + CB (*n* = 160)	MB (*n* = 137)	RA (*n* = 141)	*p* Value MB vs. RA + CB	*p* Value RA vs. RA + CB
Location				0.78	0.30
Left main	18 (11.3%)	20 (14.6%)	15 (10.6%)		
Left anterior descending	69 (43.1%)	61 (44.5%)	78 (55.3%)		
Left circumflex	20 (12.5%)	16 (11.7%)	16 (11.3%)		
Right coronary artery	53 (33.1%)	40 (29.2%)	32 (22.7%)		
Reference vessel diameter (mm)	3.43 ± 0.56	3.31 ± 0.44	3.25 ± 0.47	0.038	0.002
Lesion length (mm)	26.99 ± 13.82	30.07 ± 18.30	29.81 ± 15.23	0.11	0.096
Diameter stenosis (%)	85.30 ± 9.7	83.54 ± 8.76	83.02 ± 10.35	0.11	0.052
Ostial location	47 (29.4%)	35 (25.5%)	40 (28.4%)	0.52	0.90
Bifurcation	79 (49.4%)	61 (44.5%)	55 (39.0%)	0.42	0.08
Moderate/severe tortuosity	48 (30%)	44 (32.1%)	49 (34.7%)	0.82	0.51
Chronic total occlusion	6 (3.8%)	4 (2.9%)	4 (2.8%)	0.75	1.00
B2/C lesion	149 (93.1%)	129 (94.2%)	137 (97.2%)	0.53	0.09
7 Fr guiding catheter	116 (72.5%)	111 (81.0%)	130 (92.2%)	0.21	<0.001
Cutting/scoring balloon diameter (mm)	2.80 ± 0.36	2.94 ± 0.34	—	0.001	—
Cutting/scoring balloon pressure (atm)	16.9 ± 2.7	15.6 ± 3.0	—	0.002	—
Use of >1 cutting/scoring balloon	11 (6.9%)	12 (8.7%)	—	0.37	—
Cutting/scoring to artery ratio	0.85 ± 0.12	0.90 ± 0.11	—	0.015	—
Starting burr size (mm)	1.49 ± 0.16	—	1.52 ± 0.17	—	0.05
Max. burr size (mm)	1.51 ± 0.15	—	1.53 ± 0.18	—	0.32
Use of >1 burr	13 (8.1%)	—	7 (4.9%)	—	
Rotational speed (RPM)	172,537 ± 7,327	—	164,224 ± 23,827	—	<0.001
Burr to artery ratio	0.46 ± 0.1		0.47 ± 01	—	0.17
Balloon predilatation	105 (65.6%)	103 (75.2%)	119 (84.4%)	0.077	<0.001
Number of predilatation balloons	1.44 ± 0.74	1.70 ± 0.93	1.54 ± 0.87	0.026	0.36
Max. predil. balloon diameter (mm)	3.13 ± 0.51	2.88 ± 0.43	2.97 ± 0.42	<0.001	0.009
Max. predil. balloon pressure (atm)	22.09 ± 4.49	19.48 ± 4.83	18.83 ± 3.73	<0.001	<0.001
No. of stents/lesion	2.0 ± 1.07	1.71 ± 0.85	1.51 ± 0.62	0.011	<0.001
Total stent length/lesion (mm)	37.02 ± 17.02	35.41 ± 18.00	35.63 ± 15.69	0.42	0.45
Min. stent diameter (mm)	3.03 ± 0.48	3.14 ± 0.44	3.13 ± 0.47	0.042	0.067
Max. stent diameter (mm)	3.35 ± 0.45	3.37 ± 0.45	3.31 ± 0.41	0.69	0.42
Max. stent implantation pressure (atm)	18.68 ± 3.05	17.47 ± 3.54	16.47 ± 2.87	0.002	<0.001
Balloon postdilatation	140 (87.5%)	117 (83.0%)	111 (81.0%)	0.15	0.35
Max. postdil. balloon diameter (mm)	3.73 ± 0.59	3.70 ± 0.54	3.68 ± 0.49	0.64	0.46
Max. postdil. balloon pressure (atm)	21.22 ± 3.29	21.86 ± 4.65	20.95 ± 4.88	0.31	0.48

Note: Values are *n* (%) or mean ± SD.

Abbreviations: CB, cutting balloon; MB, modified balloon; RA, rotational atherectomy; RPM, rotations per minute.

TABLE 3 Procedural and in-hospital outcome

	RA + CB (*n* = 110)	MB (*n* = 100)	RA (*n* = 100)	*p* Value MB vs. RA + CB	*p* Value RA vs. RA + CB
Procedural duration (min)	85.34 ± 33.7	78.5 ± 40.6	88.2 ± 34.9	0.09	0.52
Fluoroscopy time (min)	24.0 ± 13.0	19.6 ± 13.4	23.9 ± 12.2	0.015	0.78
Contrast amount (ml)	260.2 ± 92.6	230.0 ± 93.8	233.0 ± 109.1	0.03	0.03
Large dissection (>5 mm)	12 (10.9%)	7 (7%)	3 (3%)	0.97	0.03
Perforation	4 (3.6%)	2 (2%)	4 (4%)	0.69	1.00
Pericardial effusion	5 (4.5%)	0 (0%)	3 (3%)	0.06	0.73
No/slow flow	1 (0.9%)	0 (0%)	2 (2%)	1.00	0.61
Final TIMI flow <III	1 (0.9%)	0 (0%)	1 (1%)	1.00	1.00
Residual stenosis >20%	0 (0%)	2 (2%)	0 (0%)	0.22	1.00
Stent failure	3 (2.7%)	4 (4%)	1 (1%)	0.70	0.62
Crossover	0 (0%)	16 (16%)	0 (0%)	<0.001	1.00
Strategy success[a]	106 (96.4%)	81 (81%)	98 (98%)	0.0006	0.68
Death	1 (0.9%)	0 (0%)	0 (0%)	1.00	1.00
Myocardial infarction	3 (2.7%)	1 (1%)	2 (2%)	0.62	1.00
Target vessel re-PCI	0 (0%)	0 (0%)	0 (0%)	1.00	1.00
CABG	1 (0.9%)	0 (0%)	0 (0%)	1.00	1.00
Stent thrombosis	0 (0%)	0 (0%)	0 (0%)	1.00	1.00
Access site complications	5 (4.5%)	5 (5%)	3 (3%)	1.00	0.72

Note: Values are *n* (%) or mean ± SD.

Abbreviations: CABG, coronary artery bypass graft; CB, cutting balloon; MB, modified balloon; PCI, percutaneous coronary intervention; RA, rotational atherectomy; TIMI, Thrombolysis in Myocardial Infarction.

[a]See text for definition.

both control arms. Binary restenosis was present in 8% of cases and tended to be higher compared to the RA control group (2.1%; $p = 0.07$).

3.5 | OCT

OCT data after DES implantation were available in 76 (69.1%) patients and are displayed in Table 5. OCT was not performed in eight patients due to chronic kidney disease or history of contrast induced nephropathy, in 10 cases due to long procedure and high contrast volume use and in one case due to the occurrence of a procedural complication. In seven patients the OCT was technically not possible (advancement of the catheter not possible, or catheter damage) and in eight patients the OCT imaging quality was insufficient for core lab analysis.

SE, the co-primary endpoint, was comparable between the Rota-Cut population and the historical control groups (75.1 ± 13.8% vs. 73.5 ± 13.3 with MB vs. 73.1 ± 12.2 with RA; $p = 0.19$ and $p = 0.39$, respectively). Cumulative frequency distribution curves are represented in Figure 3. SE ≥ 80% was reached in 35.5% of cases (vs. 38.9% with MB; $p = 0.85$% and 27.5% with RA; $p = 0.14$). However, the Rota-Cut combination resulted in higher MSA (7.1 ± 2.2 vs. 6.1 ± 1.7 $mm^{2.}$ in MB group; $p = 0.003$ and 6.2 ± 1.9 mm^2 in RA group; $p = 0.004$).

3.6 | Nine-month clinical outcome

Clinical outcomes at 9-month are represented in Supporting Information: Table 3. Complete follow-up over 9 months was available for all patients (100%). At 9-month, overall mortality was 4.5% with 1.8% of cardiac mortality. Clinically indicated TVR occurred in three patients (2.7%) and target lesion revascularization in 6.3%. No case of spontaneous MI or stent thrombosis was documented during the follow-up period. TVF occurred in nine patients (8.2% vs. 8% in MB group; $p = 1.00$% and 6% in RA group; $p = 0.79$).

4 | DISCUSSION

The aim of the PREPARE-CALC COMBO trial was to assess the safety of the Rota-Cut strategy and its efficacy in improving the angiographic result as assessed by ALG and OCT derived SE

TABLE 4 Baseline and postprocedural quantitative coronary angiography data

	RA + CB (*n* = 160)	MB (*n* = 136)	RA (*n* = 137)	*p* Value MB vs. RA + CB	*p* Value RA vs. RA + CB
Before procedure					
Lesion length (mm)	24.05 ± 11.63	20.16 ± 11.88	20.86 ± 12.30	0.005	0.023
Reference vessel diameter (mm)	3.08 ± 0.47	3.08 ± 0.47	3.10 ± 0.49	0.95	0.68
Minimal lumen diameter (mm)	0.90 ± 0.34	1.07 ± 0.34	1.15 ± 0.35	<0.001	<0.001
Diameter stenosis (%)	70.47 ± 10.23	65.18 ± 9.53	63.43 ± 9.80	<0.001	<0.001
Severe calcification[a]	150 (94.3%)	100 (73.0%)	104 (76.5%)	<0.001	<0.001
Immediately after procedure					
Minimal lumen diameter (mm)					
In-stent	2.83 ± 0.43	2.81 ± 0.47	2.85 ± 0.43	0.89	0.66
In-segment	2.47 ± 0.55	2.58 ± 0.53	2.62 ± 0.67	0.079	0.072
Diameter stenosis (%)					
In-stent	12.87 ± 4.89	12.34 ± 5.14	12.62 ± 5.36	0.37	0.63
In-segment	20.38 ± 8.2	17.12 ± 7.39	17.58 ± 7.31	<0.001	0.002
Acute lumen gain (mm)					
In-stent	1.92 ± 0.45	1.74 ± 0.45	1.70 ± 0.42	0.001	<0.001
In-segment	1.56 ± 0.57	1.50 ± 0.51	1.47 ± 0.64	0.34	0.034

Note: Values are *n* (%) or mean ± SD.

Abbreviations: CB, cutting balloon; MB, modified balloon; RA, rotational atherectomy.

[a]As adjudicated by the angiographic core laboratory.

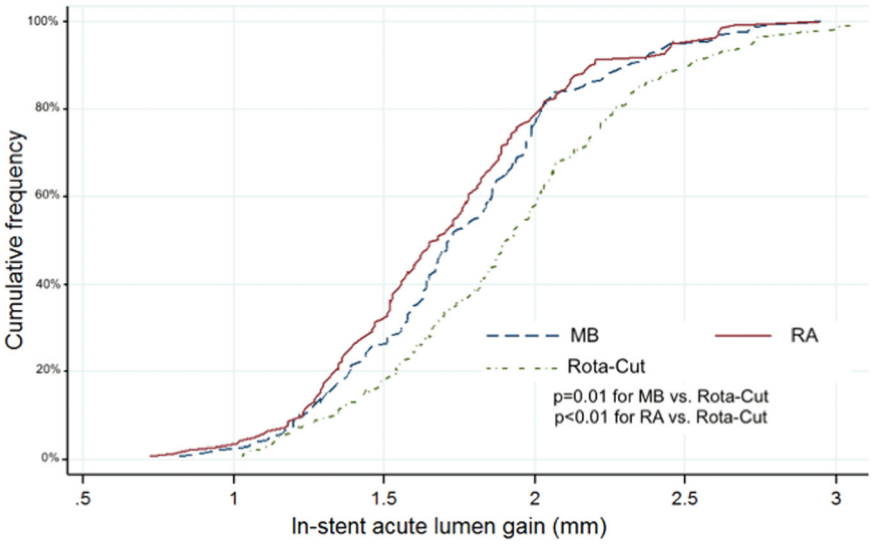

FIGURE 2 Acute lumen gain Cumulative frequency curves of the primary endpoint of in-stent acute lumen gain of the PREPARE-CALC COMBO trial and both arms of the PREPARE-CALC trial. MB, modified balloon; RA, rotational atherectomy Rota-Cut, rotational atherectomy in combination with cutting balloon. [Color figure can be viewed at wileyonlinelibrary.com]

compared to historical data of RA or MB from the PREPARE-CALC trial.

The principal findings of this study are as follows:

1. The primary endpoint of ALG on QCA analysis was higher with the Rota-Cut combination as compared to RA or MB alone.
2. Rota-Cut resulted in a significantly increased MSA as compared with both RA or MB alone. The co-primary endpoint SE was comparable with the historical data of the PREPARE-CALC arms and remained under the recommended cut-off of 80% in two thirds of cases.
3. Although large coronary dissections occurred more frequently in the Rota-Cut group compared with RA alone, the rates of procedural complications were generally low with excellent clinical outcome at 9 months.

Stent underexpansion has been established as a major predictor of stent failure.[12,13] Higher SE is associated with better clinical

TABLE 5 Optical coherence tomography measurement

Poststenting OCT	RA + CB (*n* = 76)	MB (*n* = 54)	RA (*n* = 51)	*p* Value MB vs. RA + CB	*p* Value RA vs. RA + CB
Length, mm	32.2 ± 12.7	32.6 ± 13.1	37.70 ± 12.4	0.52	0.005
Max. lumen area, mm^2	12.9 ± 4.1	12.0 ± 2.80	12.6 ± 3.9	0.16	0.44
Max. stent area, mm^2	12.2 ± 3.4	11.3 ± 2.7	11.6 ± 3.5	0.13	0.18
Min. lumen area, mm^2	6.9 ± 2.2	6.3 ± 1.7	6.3 ± 2.1	0.065	0.044
Min. stent area, mm^2	7.1 ± 2.2	6.1 ± 1.7	6.2 ± 1.9	0.003	0.004
Min. stent area <4.5 mm^2	8 (10%)	10 (18.5%)	11 (21.6%)	0.19	0.08
Avg. lumen area, mm^2	9.4 ± 2.6	8.9 ± 1.8	8.8 ± 2.4	0.13	0.072
Avg. stent area, mm^2	9.5 ± 2.5	8.7 ± 1.7	8.6 ± 2.3	0.021	0.010
Stent expansion (%)	75.1 ± 13.8	73.5 ± 13.3	73.1 ± 12.2	0.19	0.39
Stent expansion ≥80%	27 (35.5%)	21 (38.9%)	14 (27.5%)	0.87	0.14
Presence of malapposition	65 (85.5%)	51 (94.4%)	47 (92.2%)	0.16	0.40

Note: Values are *n* (%) or mean ± SD.

Abbreviations: CB, cutting balloon; MB, modified balloon; OCT, optical coherence tomography; RA, rotational atherectomy.

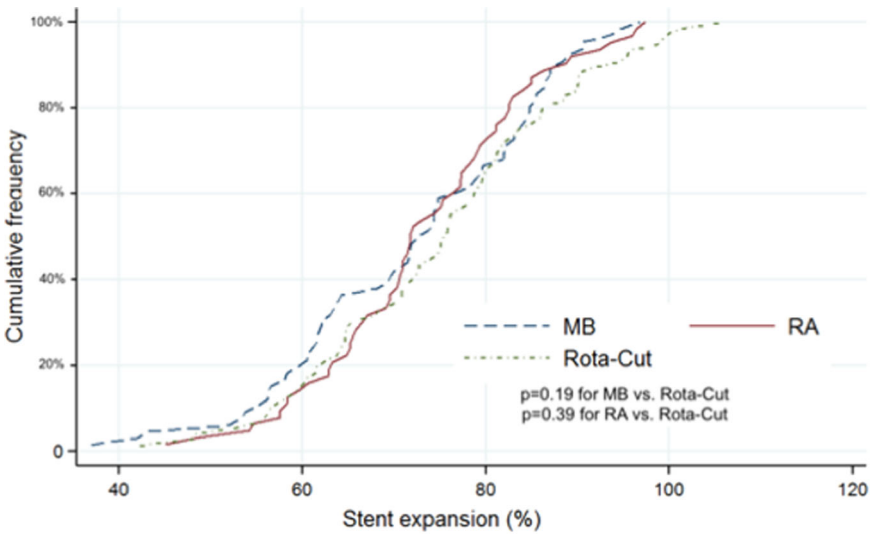

FIGURE 3 Stent expansion cumulative frequency curves of the co-primary endpoint of stent expansion in optical coherence tomography of the PREPARE-CALC COMBO trial and both arms of the PREPARE-CALC trial. MB, modified balloon; RA, rotational atherectomy; Rota-Cut, rotational atherectomy in combination with cutting balloon. [Color figure can be viewed at wileyonlinelibrary.com]

outcomes and lower risk of stent failure.[13–16] In the ROTAXUS trial, lesion preparation with RA improved angiographic stent results as compared with standard balloon dilatation (ALG: 1.56 ± 0.43 vs. 1.44 ± 0.49; $p = 0.01$). Several other trials reported angiographic stent performance after application of special methods for aggressive lesion preparation. In the randomized ISAR-CALC trial, although super high-pressure balloon increased minimum lumen diameter (2.83 ± 0.34 mm vs. 2.65 ± 0.36 mm; $p = 0.03$) and reduced diameter stenosis (11.6 ± 4.8% vs. 14.4 ± 5.6%; $p = 0.02$) compared to scoring balloon, there was no significant difference in terms of ALG between both techniques (1.89 ± 0.42 mm vs. 1.83 ± 0.45 mm; $p = 0.60$).[17] The Disrupt CAD III trial was a prospective single arm multicenter trial designed for regulatory approval of intravascular lithotripsy. In terms of angiographic performance ALG was 1.7 ± 0.5 mm.[18] In the PREPARE-CALC trial, ALG did not differ between MB and RA.[5]

In the PREPARE-CALC COMBO study, the higher ALG reached with the implementation of the Rota-Cut combination can be explained by the synergistic effect of the two different mechanisms of lesion preparation. On one hand, RA is feasible in nearly every calcified lesion, ablates superficial calcium and facilitates the advancement of bulky material but is limited by the burr size which usually does not exceed 1.75 mm and might have limited efficacy on large vessels and deep calcifications. On the other hand, CB creates focal concentrations of dilating force and thereby assists in luminal expansion of coronary lesions. The expanded balloon configuration provides a linear cutting surface that efficiently scores the fragilized plaque. Interestingly, according to independent core laboratory analysis lesions with higher degree of calcification and higher stenosis grade were included in the PREPARE-CALC COMBO trial which underlines the efficacy of the Rota-Cut in terms of angiographic stent results.

Adequate angiographic results do not preclude certain abnormalities in intravascular imaging.[19,20] Due to its higher resolution, OCT is more accurate for detecting lumen or stent-related morphologies with potential clinical impact such as stent malapposition or underexpansion immediately after stenting. Furthermore, stent-related findings are easier to interpret with OCT.[21] In our trial, post-procedural OCT data were available in a considerable number of patients (69%). The magnitude of treatment effect for SE with the Rota-Cut combination in our study was modest and the co-primary endpoint was not reached. Although current recommendations for intracoronary imaging suggest a value of >80% to indicate optimal SE,[21] it is worth mentioning that in other studies including severe calcified lesions the results were below this cut-off as well (Disrupt CAD III trial: 78.4 ± 25.8% with intravascular lithotripsy; ISAR-CALC trial: 72 ± 12% with super-high pressure balloon and 68 ± 13% with scoring balloon).

Absolute SE appears to be a better predictor of future stent patency than relative expansion.[13,14,16,21] In our trial, MSA was significantly higher with the Rota-Cut combination compared to RA or MB alone. Furthermore, MSA < 4.5 mm^2 was two-fold higher in the both PREPARE-CALC arms compared to the Rota-Cut group (10% vs. 18.5% in MB group; $p = 0.19\%$ and 21.6% in RA group; $p = 0.08$). Our results are in line with the trial done by Li and colleagues who found that cross-sectional stent area on intravascular ultrasound with the Rota-Cut group (5.9 ± 1.7 mm^2) was significantly larger than that of RA alone (5.0 ± 1.4 mm^2; $p = 0.021$).

Improved stent results using extensive lesion preparation in the PREPARE-CALC COMBO trial was at the expense of increased contrast consumption and longer procedures compared to MB alone. Large coronary dissections were, as expected, more frequent as compared to RA group. However, in general, we observed a low rate of serious peri-procedural complications and in-hospital events were rare which underscores the safety of the Rota-Cut strategy taking into consideration the complexity of treated patients and lesions. Interestingly the burr-to-artery ratio in our trial (0.46 ± 0.1) was near to the lower limit recommended by experts.[22] Regarding CB lesion preparation, the CB-to-artery ratio was in the one hand significantly lower compared to the historical comparison MB arm, and on the other hand higher pressure was applied. This may explain the relatively low rate of peri-procedural complications despite higher acute lumen gain, because a moderate atheroablation and an improved technique of plaque laceration were combined instead of aggressively performing each technique alone. The low complication rate could also be attributed to the operators' and center expertize in the treatment of complex coronary lesions. Thus, we believe that a well-equipped setting is required to achieve similar results.

Our trial has some important limitations. First, although baseline clinical characteristics of the treated population ware comparable and angiographic characteristics less favorable compared to the historic control cohort, the nonrandomized design with potential operator bias and the presence of unmeasured confounders remain a limitation of this study, and findings can only be considered hypothesis-generating. Second, most cases in the MB arm of the PREPARE-CALC trial were treated using scoring balloons whereas only CB were used in this study. Third, the impact of the lower burr-to-artery ratio on the results of our trial cannot be excluded. Fourth, our trial included patients with mostly stable coronary disease and preserved left ventricular function and therefore our findings cannot be applied to patients with reduced ejection fraction presenting with acute coronary syndromes. Finally, OCT data were not available in 30.1% of patients.

5 | CONCLUSION

In conclusion, in an elderly population with complex calcified coronary lesions a strategy of lesion preparation using the combination of RA and CB is feasible and safe, and may improve ALG and MSA as compared to each strategy alone. Even with an extensive lesion preparation strategy, the cut-off of 80% SE could only be reached in one-third of the treated population, though clinical outcome at 9 months remained favorable.

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CONFLICTS OF INTEREST

Dr. Allali is a consultant and proctor for Boston Scientific. Dr. Abdel-Wahab is a consultant and proctor for Boston Scientific and Medtronic. Dr. Hemetsberger is an honorary speaker for Boston Scientific. Dr. Richardt has received institutional research grants from St. Jude Medical, Biotronik and Medtronic. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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