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Rotational atherectomy with cutting balloon to optimize stent expansion in calcified lesions: The ROTACUT randomized trial

Samin K Sharma, MD[1]*, Roxana Mehran, MD[1], Birgit Vogel, MD[1], Amit Hooda, MD[1], Samantha Sartori, PhD[1], Regina Hanstein, PhD[1], Yihan Feng, MS[1], Richard A. Shlofmitz, MD[2], Allen Jeremias, MD[2], Alessandro Spirito, MD[1], Davide Cao, MD[1], Evan Shlofmitz, DO[2], Ziad A. Ali, MD, DPhil[2], Keisuke Yasumura, MD[1], Shingo Minatoguchi, MD[1], Yuliya Vengrenyuk, PhD[1], Annapoorna Kini, MD[1], Jeffrey W. Moses MD[2]

1. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA. 2. St. Francis Hospital & Heart Center, Roslyn, New York, USA

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KEYWORDS

- Stable angina
- Calcified stenosis
- Cutting Balloon

Abstract

Background: Percutaneous coronary intervention (PCI) of calcific lesions remains challenging for interventionalists.

Aims: To investigate whether combining rotational atherectomy (RA) with cutting balloon angioplasty (RA+CBA) results in more optimal stent expansion compared with RA followed by non-compliant balloon post-dilatation (RA+NCBA).

Methods: ROTACUT is a prospective multicenter randomized trial of 60 patients with coronary artery disease undergoing PCI of moderately or severely calcified lesions with drug-eluting stent implantation. Patients were randomized 1:1 to either RA+CBA or RA+NCBA. The primary endpoint was the minimum stent area on intravascular ultrasound (IVUS). Secondary endpoints included minimum lumen area and stent expansion assessed by IVUS and acute lumen gain, final residual diameter stenosis and minimum lumen diameter assessed by angiography. Clinical endpoints were obtained at 30 days.

Results: The mean age was 71.1±9.4 years and 22% were women. Procedural details of RA were similar between groups, as were procedure duration and contrast used. Minimum stent area was similar with RA+CBA versus RA+NCBA (6.7±1.7 mm^2 versus 6.9±1.8 mm^2; p=0.685). Furthermore, there were no significant differences regarding the other IVUS and angiographic endpoints. Procedural complications were rare and 30-day clinical events included 2 myocardial infarctions and 1 target vessel revascularization in the RA+CBA and 1 myocardial infarction in the RA+NCBA group.

Conclusions: Combining RA with CBA resulted in similar minimum stent area compared with RA followed by NCBA in patients undergoing PCI of moderately or severely calcified lesions. RA followed by CBA was safe with rare procedural complications and few clinical adverse events at 30 days.

**Corresponding author: The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York, USA. Email: samin.sharma@mountsinai.org*

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[1]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[2]St. Francis Hospital & Heart Center, Roslyn, New York, USA

Running title: RA with cutting balloon for calcified lesions

Corresponding author:

Samin K. Sharma, MD

The Zena and Michael A. Wiener Cardiovascular Institute,

Icahn School of Medicine at Mount Sinai

One Gustave L. Levy Place, Box 1030, New York, New York, USA

Email: samin.sharma@mountsinai.org

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To investigate whether combining rotational atherectomy (RA) with cutting balloon angioplasty (RA+CBA) results in more optimal stent expansion compared with RA followed by non-compliant balloon post-dilatation (RA+NCBA).

Methods:

ROTACUT is a prospective multicenter randomized trial of 60 patients with coronary artery disease undergoing PCI of moderately or severely calcified lesions with drug-eluting stent implantation. Patients were randomized 1:1 to either RA+CBA or RA+NCBA. The primary endpoint was the minimum stent area on intravascular ultrasound (IVUS). Secondary endpoints included minimum lumen area and stent expansion assessed by IVUS and acute lumen gain, final residual diameter stenosis and minimum lumen diameter assessed by angiography. Clinical endpoints were obtained at 30 days.

Results:

The mean age was 71.1±9.4 years and 22% were women. Procedural details of RA were similar between groups, as were procedure duration and contrast used. Minimum stent area was similar with RA+CBA versus RA+NCBA (6.7±1.7 mm^2 versus 6.9±1.8 mm^2; p=0.685). Furthermore, there were no significant differences regarding the other IVUS and angiographic endpoints. Procedural complications were rare and 30-day clinical events included 2 myocardial infarctions and 1 target vessel revascularization in the RA+CBA and 1 myocardial infarction in the RA+NCBA group.

Conclusion:

Combining RA with CBA resulted in similar minimum stent area compared with RA followed by NCBA in patients undergoing PCI of moderately or severely calcified lesions. RA followed by CBA was safe with rare procedural complications and few clinical adverse events at 30 days.

Condensed abstract

Percutaneous coronary intervention (PCI) of calcific lesions remains challenging for interventionalists. Combining rotational atherectomy (RA) with cutting balloon angioplasty (RA+CBA) may result in more optimal stent expansion compared with RA followed by non-compliant balloon post-dilatation (RA+NCBA). In the ROTACUT trial, 60 patients with stable coronary artery disease undergoing PCI of moderately or severely calcified lesions were randomized to either RA+CBA or RA+NCBA. The primary endpoint, minimum stent area, was similar between groups. Importantly, RA followed by CBA for the preparation of moderately or

severely calcified lesions was safe with rare procedural complications and few clinical adverse events at 30 days.

Abbreviations

CBA: cutting balloon angioplasty

IVUS: intravascular ultrasound

NCBA: non-compliant balloon post-dilatation

PCI: percutaneous coronary intervention

RA: rotational atherectomy

Introduction

Moderate to severe coronary calcification in patients undergoing percutaneous coronary intervention (PCI) is common, with some studies reporting a prevalence of >30%.[1, 2] This high prevalence is likely to increase further, considering the aging of the population and the steady increase of comorbidities such as diabetes and chronic kidney disease.[3, 4] Patients undergoing PCI of calcified lesions experience a high rate of major adverse cardiovascular events (MACE), including in the contemporary drug-eluting stent era.[5, 6] Rotational atherectomy (RA) is an established tool to facilitate PCI of calcified coronary lesions.[7] More specifically, RA can modify physical attributes of calcified plaque and thereby facilitate balloon angioplasty and stent deployment. Despite higher strategy success with versus without RA, restenosis rates and MACE were observed to remain high after PCI of calcified lesions regardless of the use of RA.[8] Combining RA with other types of lesion preparation may improve acute procedural outcomes

and, thus, longer-term outcomes. We designed the ROTACUT trial based on the hypothesis that a strategy of calcified lesion preparation with RA followed by cutting balloon angioplasty (RA+CBA) compared with RA followed by non-compliant balloon post-dilatation (RA+NCBA) will result in more optimal stent expansion.

Methods

Trial design

The ROTACUT trial (FDA IDE# G210030; ClinicalTrials.gov Identifier: NCT04865588) is a prospective randomized study of 60 patients undergoing PCI with drug-eluting stent implantation for moderately or severely calcified lesions. The study was conducted at Mount Sinai Hospital, New York, New York and St. Francis Hospital & Heart Center, Roslyn, New York. The Icahn School of Medicine at Mount Sinai designed and sponsored the trial supported by an investigator-initiated grant from Boston Scientific. The institutional review boards of the two participating centers approved the trial protocol. Follow-up for clinical endpoints was obtained by telephone at 30 and is ongoing for 270 days.

Study population

Patients undergoing PCI for a de novo calcified lesion with planned RA and planned drug-eluting stent implantation of a lesion with a target vessel reference diameter ≥2.5 mm and ≤4.0 mm, a lesion length ≥5 mm and moderate or severe calcification by angiography were eligible for enrollment in the trial. Severe calcification was defined as the presence of radiopacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least one location, and a total length of calcium (including segmented) of at least 15 mm

extending partially into the target lesion area. Moderate calcium was defined as the presence of radiopacities only during the cardiac cycle before contrast injection with calcium extending partially into the target lesion.[6, 9] Clinical exclusion criteria included cardiogenic shock, PCI for ST-segment elevation myocardial infarction, planned surgery within 6 months after the index PCI unless dual antiplatelet therapy can be maintained throughout the peri-surgical period, life expectancy less than 12 months and referral to coronary artery bypass grafting after heart team discussion. Angiographic exclusion criteria included lesions with angulation >45 degrees by visual estimate, lesion stenoses through which a guidewire will not pass, lesions in last remaining vessel with left ventricular ejection fraction <30%, lesions in saphenous vein grafts, angiographic evidence of thrombus or significant dissection at the treatment site, and lesions within 10 mm of a previously placed stent. A full list of inclusion and exclusion criteria is provided in the supplementary material (Supplementary Table 1).

Study treatment

Patients who met all inclusion and no exclusion criteria and who had signed an informed consent before proceeding to the catheterization laboratory were randomized before planned use of RA but after the guidewire had successfully passed the lesion. Randomization was an integrated functionality of the electronic data capture system and was conducted 1:1 to either RA+CBA or RA+NCBA (Central Illustration). RA with the ROTAPRO^{tm} device (Boston Scientific, Marlborough, MA, USA) was performed using a maximum burr-to-artery ratio of 0.4-0.6, a burr speed of 140,000–160,000 rotations per minute (rpm), and a maximum run duration of 20 seconds. Burr upsizing during the procedure was allowed, but the maximum burr-to-artery ratio was not to exceed the recommended ratio of 0.6. In patients randomized to RA+CBA, cutting

balloon atherotomy using a Wolverine^{tm} cutting balloon (Boston Scientific, Marlborough, MA, USA) was performed after RA. The Wolverine cutting balloon had to be sized 1:1 relative to the reference vessel diameter and the inflation pressure was recommended at 6 atm and was expected not to exceed the device rated burst pressure of 12 atm. The choice of drug-eluting stent and the use of post-dilatation was at the operator's discretion.

Study endpoints

The primary endpoint was post-procedural minimum stent area (in mm^2) as assessed on final post-procedure IVUS. As there was limited data available to estimate the expected minimum stent area after the rotational atherectomy plus cutting balloon angioplasty strategy, no formal sample size calculation was performed. The pre-defined total sample size of 60 patients was powered to detect effect sizes as listed in Supplementary Table 2, given an estimated minimum stent area of 5.50±2.36 mm^2, an equal variance, and a two-sided alpha of 0.05.

Secondary IVUS endpoints included in-segment minimum lumen area (in mm^2), minimum and mean stent expansion (in %), any dissection and malapposition on final IVUS. Furthermore, assessment of calcium fracture and any dissection were evaluated on IVUS post-CBA/NCBA before stent implantation. Secondary angiographic endpoints included in-segment and in-stent acute lumen gain (in mm), in-segment and in-stent final residual diameter stenosis (in %), and baseline, pre-stent and final in-segment and in-stent minimum lumen diameter (in mm). In addition, pre-stent and final dissections type B or greater, final perforations (Ellis type ≥2), and final side branch closures (≥1.5 mm) were collected. Device-related endpoints included any problems related to the devices, including but not limited to balloon rupture, blade

detachments, difficulty in withdrawing/advancing the device, or other device-related problems as identified by the investigator. Clinical endpoints at 30 days were all-cause death (further classified as cardiac and non-cardiac), myocardial infarction (as defined by the SCAI definition[10] and 4th universal definition[11] including peri-procedural myocardial infarction), target lesion revascularization, target vessel revascularization, stent thrombosis (definite/probable), major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5), and vascular complications. An independent core lab evaluated all IVUS and angiographic endpoints and an independent clinical events committee blinded to the study treatment adjudicated all major clinical events.

Quantitative coronary angiography

Coronary angiography for off-line quantitative coronary angiography (QCA) was performed at baseline, after RA, after CBA/NCBA, and at the end of the procedure (Central Figure).

IVUS analysis

The 60Mhz OptiCross^{tm} catheter (Boston Scientific, Marlborough, MA, USA) was used for IVUS with automated pull-back at 1mm/s. The catheter had to be advanced at least 5 mm distal to the target lesion. IVUS runs were performed at baseline, if possible (optional), after lesion preparation defined as RA+CBA or RA+NCBA, and at the end of the procedure (Central Figure). Any additional IVUS runs and assessments deemed clinically indicated by the operator to guide the procedure were allowed during the procedure. Only after the operator deemed the procedure to be finished, the final post-angioplasty IVUS run was performed for endpoint assessment. In order to reduce bias, operators were blinded to the final IVUS run pull-back

images and no additional stent placement or post-dilatation was allowed after the final IVUS run.

Statistical analysis

Summary statistics are presented according to treatment allocation. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations. Categorical variables were compared using a Chi-square test or Fisher's exact test if Chi-square assumptions were violated. Normally distributed continuous variables were compared using a Student's t-test, while non-normally distributed variables were assessed using a Mann-Whitney U test/Wilcoxon rank sum test. Procedural outcomes are presented by treatment allocation. Procedural outcomes were compared between treatment groups using a Chi-square test or Fisher's exact test if Chi-square assumptions were violated. The probability of the occurrence of clinical outcomes up to 30 days was estimated using the Kaplan-Meier method. The hazard ratio (RA+CBA compared to RA+NCBA [reference]), p-values and the corresponding 95% confidence interval (CI) were estimated from the Cox proportional hazard model. All statistical tests were two-sided with an α=0.05 and a 95% confidence interval.

Results

Baseline clinical characteristics

There were no significant differences in baseline characteristics between the RA+CBA and the RA+NCBA groups (Table 1). The mean age was 69.2±10.0 years in the RA+CBA group and 72.8±8.7 years in the RA+NCBA group (p=0.140), and the rate of female participants was overall about 22%. The burden of cardiovascular disease risk factors was high in both groups (Table 1).

Lesion and procedural characteristics

All patients had one lesion treated during the index procedure. A total of 10 patients (3 of the RA+CBA and 7 of the RA+NCBA group) underwent staged PCI for additional coronary lesions after the index procedure.

Procedural details of RA were similar between groups, including burr size, burr-to-artery ratio, number of burrs used and maximum burr rpm (Table 2). In the RA+CBA group, the maximum balloon length was shorter, the maximum balloon inflation pressure lower and the number of inflations greater compared with the RA+NCBA group. Maximum balloon diameter and balloon-to-artery ratio of the cutting balloon and non-compliant balloon did not significantly differ. Procedure duration time and contrast use were also similar regardless of treatment strategy. Post-stenting dilatation was performed in 96.6% of the RA+CBA group and in 83.9% of the RA+NCBA group (p=0.196). One patient assigned to the RA+CBA group underwent RA+NCBA.

Pre-procedure characteristics and procedural outcomes by QCA

QCA at baseline did not show significant differences in target lesion characteristics between groups (Table 3 and Supplementary Table 3). Severe calcification was present in 72.4% of the RA+CBA group and 74.2% of the RA+NCBA group (p=0.876). Procedural complications were rare and related to RA rather than CBA/NCBA angioplasty (Table 3 and Supplementary Table 3). Post-CBA/NCBA dissections type B or greater were present in 21.4% and 44.8% of patients assigned to RA+CBA and RA+NCBA, respectively (p=0.058). One dissection was present in the RA+NCBA and none in the RA+CBA group post procedure (after stenting +/- post-dilatation).

With regards to angiographic endpoints, no differences in acute lumen gain, final residual diameter stenosis and final minimum lumen diameter were found between groups in the final post-procedure assessment (Table 3).

Pre-procedure characteristics and procedural outcomes on IVUS

In 45 patients, IVUS was performed at baseline, with no significant differences in pre-procedure characteristics between groups (Table 4). Severe calcification was documented in 80.0% of the RA+CBA group and in 85.0% of the RA+NCBA group (p=0.519). The rate of calcium fractures was significantly higher in the RA+CBA compared with the RA+NCBA group (50.0% versus 22.6%; p=0.028). Dissections after CBA/NCBA were present in 96.4% of RA+CBA and 96.7% of RA+NCBA patients, with the majority limited to the intima and none beyond the media. In the final IVUS assessment post procedure (after stenting +/- post-dilatation), dissections were present in 3.4% of the RA+CBA versus 9.7% of the RA+NCBA group (p=0.613). Furthermore, stent malapposition was documented in 17.2% of the RA+CBA and 29.0% of the RA+NCBA group (p=0.281).

With regards to IVUS endpoints, no significant differences between groups were found for the primary endpoint of minimum stent area (6.7±1.7 mm^2 in RA+CBA versus 6.9±1.8 mm^2 in RA+NCBA; p=0.685) (Central Figure and Table 4). There was also no significant difference in the minimum stent area when medians (interquartile ranges) were compared (6.5 [5.3-7.8] mm^2 in RA+CBA versus 6.9 [5.5-8.0] mm^2 in RA+NCBA; p=0.636) (Central Figure). Furthermore, no significant difference was noted for in-segment minimum lumen area between groups. Final minimum and mean stent expansion tended to be larger in RA+CBA versus RA+NCBA (86.1±17.5% versus 78.6±14.7% and 112.5±19.4% versus 104.2±13.5%, respectively), however, the differences did not reach statistical significance (p=0.076 and p=0.058, respectively).

Device-related complications

No device-related complications, including balloon rupture, blade detachment, difficulty in withdrawing/advancing the device, or other device related problems as identified by the investigator, occurred in either of the groups (Supplementary Table 4).

Clinical outcomes at 30 days

In the intention-to-treat population, two myocardial infarctions occurred in the RA+CBA group and one in the RA+NCBA group (6.9% versus 3.2%; hazard ratio 2.14, 95% confidence interval 0.19-23.6; p=0.535) (Table 5). All of the myocardial infarctions were type 4a myocardial infarctions based on the 4th universal definition[11] associated with the index procedure. One of the patients with myocardial infarction and the only patient with a target vessel revascularization was the cross-over patient that received RA+NCBA instead of the assigned RA+CBA, and therefore, the clinical endpoint analyses in the per-protocol and as-treated populations found slightly different results (Supplementary Tables 5 and 6), however, with no significant differences between groups.

Discussion

ROTACUT is a randomized controlled trial to evaluate the safety and efficacy of lesion preparation with a combination of RA+CBA versus RA+NCBA in patients undergoing PCI with drug-eluting stent implantation of moderately or severely calcified lesions. The primary endpoint minimum stent area assessed on IVUS was not significantly different between groups. Similarly, secondary IVUS outcomes, including in-segment minimum lumen area and stent expansion, did not significantly differ between groups. With respect to secondary angiographic

endpoints, acute lumen gain, final residual diameter stenosis, and final minimum lumen diameter were also similar between groups. Overall, a strategy of RA followed by CBA was safe with rare procedural complications related to RA rather than CBA. No device-related complications occurred, and clinical endpoints were few at 30 days, with no significant differences between groups.

Lesion preparation for PCI of moderately or severely calcified coronary lesions remains a challenge for interventionalists despite continuous development of new devices and techniques and multiple investigations on the efficacy and safety of different strategies to facilitate stent deployment and expansion.[12-14] With regard to atheroablative strategies, RA can effectively modify calcified plaque and smoothen the vessel lumen to enable subsequent balloon dilatation and stent implantation.[7, 15] The ROTAXUS trial investigated lesion preparation with RA compared to standard balloon dilatation in patients with moderately or severely calcified coronary lesions.[8] Despite higher strategy success and initially higher acute lumen gain with RA, late lumen loss was higher with RA and MACE rates similar between groups at 9 months. In the PREPARE-CALC trial, RA was compared with atherotomy using scoring or cutting balloons in patients with severe calcification.[16] RA was associated with a significantly higher strategy success rate than atherotomy with comparable late lumen loss at 9 months. The ROTACUT trial is a randomized comparison (under FDA IDE) of combining an atherectomy with an atherotomy strategy by applying RA followed by CBA versus RA followed by NCBA. Our results support the feasibility and safety of such a strategy with only one cross-over to the RA+NCBA group and low complication rates related to RA rather than CBA. In the RA+CBA group, slow flow (7.1%), no reflow (3.6%) and distal embolization (7.1%) was present after RA, but none of these

complications occurred after CBA. A high prevalence of dissections was present on IVUS after RA+CBA as well as RA+NCBA, but most dissections were limited to the intima, and no dissection was noted beyond the media in either of the groups. On final IVUS, only one dissection was present in the RA+CBA group. The significantly higher rate of calcium fractures in the RA+CBA group compared with the RA+NCBA group did not translate into greater minimum stent area or acute lumen gain on final IVUS and QCA, respectively. In addition to an earlier pilot study,[17] the more recently published PREPARE-CALC-COMBO study investigated the combination of RA and CBA for lesion preparation in patients with severely calcified lesions.[18] The two primary endpoints of the PREPARE-CALC-COMBO study were in-stent acute lumen gain by QCA and stent expansion on optical coherence tomography (OCT). In contrast to our results, the PREPARE-CALC-COMBO investigators found higher acute lumen gain and larger minimum stent area with the RA+CBA strategy compared with RA or scoring/cutting balloon angioplasty alone. Stent expansion on OCT was comparable between the 3 groups. Interestingly, stent expansion with the RA+CBA strategy was numerically higher in ROTACUT compared to PREPARE-CALC-COMBO (86.1±17.5% versus 75.1±13.8%) and more favorable compared to the RA+NCBA group within the study, although the latter difference did not reach statistical significance. Noticeable differences between ROTACUT and PREPARE-CALC-COMBO should be acknowledged when comparing the results of both studies. First, ROTACUT was a randomized controlled trial and PREPARE-CALC-COMBO was a prospective single-arm study comparing results with a historical cohort (the randomized PREPARE-CALC trial) and thereby introducing potential operator bias. Second, the primary endpoints differed between studies. Several previous studies suggested minimum stent area on IVUS as the most powerful predictor for future adverse events.[19-21]

However, a recent study investigating alternative models to assess stent expansion on IVUS (Supplementary Table 7; not included in the results section) suggests the ratio of minimum stent area to vessel area as the most powerful predictor for target lesion revascularization and stent thrombosis, especially with an excellent overall final minimum stent area.[22] Cutoff values to predict stent failure have been suggested to be 5 to 5.5 mm^2.[23, 24] Third, in ROTACUT, CBA was performed according to the instructions of use (IFU) with an average maximum cutting balloon inflation pressure of 12.3±3.9 atm compared with 16.9±2.7 atm in PREPARE-CALC-COMBO. Lastly, ROTACUT used IVUS imaging for endpoint assessment, while PREPARE-CALC-COMBO used OCT. Final IVUS imaging was available in all patients in the ROTACUT trial, while OCT assessment in PREPARE-CALC-COMBO was missing in about 30%. Importantly, the final IVUS in ROTACUT was blinded to the operator so that the operator had to rely on the angiographic result for completion of the procedure. Previous data suggested IVUS-optimized stent implantation in complex coronary lesions, compared to angiographic guidance, resulting in a larger minimum lumen diameter.[25] More recent data added to the evidence supporting the important role of intravascular imaging guidance throughout complex coronary interventions, including data suggesting larger minimum stent area with OCT versus angiography guidance.[26] Nevertheless, whether access to the final IVUS run for operators would have impacted the study results remains uncertain.

The findings of the present study have important implications. The use of a combination of RA and CBA appears safe in clinical practice and is associated with high procedural success. These findings may be useful to the operator if RA alone has not resulted in the desired plaque modification. In addition, the evidence provided by ROTACUT set the stage for larger trials to

evaluate a strategy of RA followed by CBA for improvement of stent expansion in patients undergoing PCI for moderately or severely calcified coronary lesions.

Limitations

Certain limitations of the present trial have to be acknowledged when interpreting the results. First, ROTACUT was conducted in 2 high-volume tertiary PCI centers with a high prevalence of calcific coronary artery disease patients and highly experienced operators. The high procedural success rate may not be replicated in less experienced centers. Second, the sample size was small and definitive conclusions based on the results may be limited considering the possibility of a type 2 error. However, the findings of ROTACUT based on serial IVUS and angiographic assessments will inform the design and conduct of larger trials on strategies to improve stent expansion in patients undergoing PCI for moderately or severely calcified coronary lesions. Third, in addition to lesions with severe calcification, lesions with moderate calcification have been included in the ROTACUT trial. The advantage of using a cutting balloon in addition to RA might, however, only become apparent in a population with severely calcified lesions. This may be a consideration for the design of future trials. Fourth, post-stent dilatation was optional and more often performed in the RA+CBA group (96.6%) compared with the RA+NCBA group (83.9%). Although this difference was not statistically significant (p=0.196), its impact on the study results remains uncertain. Lastly, although follow-up for clinical outcomes at 270 days is ongoing, no further angiographic follow-up will occur and evaluating the impact of treatment strategy on late lumen loss will not be possible.

Conclusion

A strategy of combining RA with cutting balloon angioplasty resulted in similar minimum stent area compared with RA followed by non-compliant balloon post-dilatation in patients undergoing PCI of moderately or severely calcified lesions. RA followed by cutting balloon angioplasty for the preparation of moderately or severely calcified lesions was safe with rare procedural complications and few clinical adverse events at 30 days.

Impact on daily practice

The significantly higher rate of calcium fractures in patients undergoing rotational atherectomy (RA) and cutting balloon angioplasty (CBA) compared with patients undergoing RA followed by non-compliant balloon post-dilatation (NCBA) did not translate into greater minimum stent area or acute lumen gain. However, RA followed by cutting balloon angioplasty for the preparation of moderately or severely calcified lesions was safe with rare procedural complications and few clinical adverse events at 30 days. Also, final minimum and mean stent expansion tended to be larger in RA+CBA versus RA+NCBA, although the differences did not reach statistical significance. These findings may be useful to the operator if RA alone has not resulted in the desired plaque modification.

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Conflict of interest statement

Dr. Mehran reports institutional research payments from Abbott, Abiomed, Affluent Medical, Alleviant Medical, Amgen, AM-Pharma, Applied Therapeutics, Arena, AstraZeneca, AtriCure Inc., Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi Sankyo, Duke, Element Science, Faraday, Humacyte, Idorsia, I-Laser, Janssen, Magenta, MedAlliance, Medscape, Mediasphere, Medtelligence, Medtronic, MJH Healthcare, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Protembis, RenalPro, RM Global, Shockwave, Transverse Medical, Inc., Vivasure, Zoll; personal fees from Affluent Medical, Cardiovascular Research Foundation (CRF), Daiichi Sankyo Brasil, E.R. Squibb & Sons, Esperion Science/Innovative Biopharma, Europa Group/Boston Scientific, Gaffney Events, Educational Trust, Ionis Pharmaceuticals, J-CalC, Novartis, NovoNordisk, Vectura, VoxMedia, IQVIA, McVeigh Global, Overcome, Primer Healthcare of New Jersey, Radcliffe, SL Solutions, TARSUS Cardiology, WebMD; Equity <1% in Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse); no Fees from AMA (Scientific Advisory Board), SCAI (Women in Innovations Committee Member); Faculty CRF; and honoraria from JAMA Cardiology (Associate Editor), ACC (BOT Member, SC Member CTR Program). Dr. Ali reports institutional grant support from Abbott, Abiomed, Acist, Amgen, Boston Scientific, Cathworks, Canon, Conavi, Heartflow, Inari, Medtronic Inc, National Institute of Health, Nipro, Opsens Medical, Medis, Philips, Shockwave, Siemens, Spectrawave, Teleflex; consulting fees from Abiomed, Astra Zeneca, Boston Scientific, Cathworks, Opsens, Philips, Shockwave; and equity in Elucid, Lifelink, Spectrawave, Shockwave, VitalConnect. The other authors did not report any conflict of interest.

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Figure legend

Central Illustration: Design and primary outcome of the ROTACUT trial

A total of 60 patients were randomized to either rotational atherectomy (RA) followed by cutting balloon angioplasty (RA+CBA) or RA followed by non-compliant balloon post-dilatation (RA+NCBA). Coronary angiography for off-line quantitative coronary angiography (QCA) was performed at baseline, after RA, after RA+CBA/RA+NCBA, and at the end of the procedure. Intravascular ultrasound (IVUS) runs were performed at baseline if possible (optional), after lesion preparation defined as RA+CBA or RA+NCBA, and at the end of the procedure. The primary endpoint of the study was minimum stent area (in mm^2) on IVUS. Clinical endpoints were collected at 30 days.

Angio: angiography, CBA: cutting balloon angioplasty, DES: drug-eluting stent, IVUS: intravascular ultrasound, IQR: interquartile range, MACE: major adverse cardiac events, NCBA: non-compliant balloon post-dilatation, PCI: percutaneous coronary intervention, RA: rotational atherectomy, SD: standard deviation

** p-value for comparison of means (±SD)*

†p -value for comparison of medians (IQR)

Table 1. Baseline clinical characteristics

	RA+CBA N=29 (48.3%)	RA+NCBA N=31 (51.7%)	P-Value
Age, years, mean±SD	69.2±10.0	72.8±8.7	0.140
Sex, female, n (%)	8 (27.6)	5 (16.1)	0.282
Hispanic/Latino, n (%)	4 (13.8)	4 (12.9)	1.000
Race, n (%)			
White	12 (41.4)	20 (64.5)	0.073
Black	3 (10.3)	1 (3.2)	0.346
Asian	10 (34.5)	5 (16.1)	0.101
Pacific Islander	0 (0.0)	1 (3.2)	1.000
Other	5 (17.2)	5 (16.1)	1.000
Hypertension, n (%)	28 (96.6)	29 (93.5)	1.000
Hyperlipidemia, n (%)	28 (96.6)	29 (93.5)	1.000
Diabetes mellitus, n (%)	12 (41.4)	13 (41.9)	0.965
Insulin, n (%)	6 (50.0)	5 (38.5)	
Current smoker, n (%)	3 (11.1)	6 (19.4)	0.477
Family history of CAD, n (%)	15 (75.0)	18 (81.8)	0.714
Peripheral arterial disease, n (%)	4 (13.8)	3 (9.7)	0.702
Cerebrovascular, n (%) disease	3 (10.3)	5 (16.1)	0.708
Chronic renal insufficiency, n (%)	5 (17.2)	2 (6.5)	0.247
LVEF, %, mean±SD	55.6±9.8	57.3±7.6	0.453
Prior CABG, n (%)	2 (6.9)	2 (6.5)	1.000
Prior PCI, n (%)	20 (69.0)	20 (64.5)	0.715
Prior MI, n (%)	4 (13.8)	7 (22.6)	0.379
Prior stroke, n (%)	1 (3.4)	2 (6.5)	1.000

CABG: coronary artery bypass grafting, CAD: coronary artery disease, CBA: cutting balloon angioplasty, LVEF: left ventricular ejection fraction, MI: myocardial infarction, NCBA: non-compliant balloon post-dilatation, PCI: percutaneous coronary intervention, RA: rotational atherectomy, SD: standard deviation

Table 2. Lesion and procedural characteristics

	RA+CBA N=29 (48.3%)	RA+NCBA N=31 (51.7%)	P-Value
Number of diseased vessels, n (%)			0.866
1	19 (65.5)	20 (64.5)	
2	4 (13.8)	6 (19.4)	
3	6 (20.7)	5 (16.1)	
Target vessel, n (%)			0.895
LAD	18 (62.1)	16 (51.6)	
CX	4 (13.8)	3 (9.7)	
RCA	7 (24.1)	12 (38.7)	
Target vessel reference vessel diameter, mm	3.2±0.4	3.3±0.5	0.770
Procedure duration, min	75.6±29.4	70.9±22.4	0.483
Total amount of contrast used, cc	143.4±48.0	146.4±38.5	0.792
Rotational atherectomy			
Burr size, mm	1.6±0.1	1.6±0.2	0.674
Burr-to-artery ratio	0.5±0.1	0.5±0.1	0.612
Number of burrs used	1.1±0.3	1.0±0.0	0.161
Number of passes over calcification	6.2±3.4	6.0±3.1	0.775
Total duration of rotational atherectomy, sec	56.4±29.0	52.2±25.0	0.553
Maximum burr, rpm	151,931±6,058	151,935±3,802	0.997
CBA/POBA			
Maximum balloon diameter, mm	3.2±0.4	3.3±0.5	0.416
Balloon-to-artery ratio	1.0±0.1	1.0±0.2	0.633
Maximum balloon length, mm	8.7±5.1	20.0±6.5	<.001
Maximum balloon inflation pressure, atm	12.3±3.9	15.8±3.9	<.001
Number of inflation	4.2±2.5	2.3±0.8	<.001
Stent			
Number of stents, n (%)			0.155
1	21 (72.4)	27 (87.1)	
2	8 (27.6)	4 (12.9)	
Maximum stent diameter, mm	3.3±0.4	3.4±0.5	0.349
Minimum stent diameter, mm	3.2±0.4	3.3±0.5	0.203
Total stent length, mm	39.4±16.4	37.7±13.0	0.661
Maximum stent inflation pressure, atm	14.4±1.9	14.6±1.8	0.578
Post-stent dilatation			
Post-stent dilatation, n (%)	28 (96.6)	26 (83.9)	0.196
Maximum balloon diameter, mm	3.5±0.4	4.0±2.2	0.247
Maximum inflation pressure, atm	17.1±2.3	17.1±2.9	0.927
Number of inflations	3.3±2.6	3.0±1.7	0.675

Values are mean±standard deviation unless stated otherwise; atm: atmosphere, CBA: cutting balloon angioplasty, cc: cubic centimeters, min: minutes, NCBA: non-compliant balloon post-dilatation, RA: rotational atherectomy, rpm: rotations per minute, sec: seconds

Table 3. Pre-procedure characteristics and procedural outcomes by QCA

	RA+CBA N=29 (48.3%)	RA+NCBA N=31 (51.7%)	P-Value
Pre-procedure			
Lesion location, n (%)			0.895
Proximal	13 (44.8)	14 (45.2)	
Mid	15 (51.7)	17 (54.8)	
Distal	1 (3.4)	0 (0.0)	
Target lesion length, mm	31.3±11.9	32.8±11.2	0.633
Minimum lumen diameter, mm	1.1±0.4	1.0±0.4	0.348
Angulation, degree	28.8±10.9	29.7±8.3	0.725
Calcification, n (%)			0.876
Moderate	8 (27.6)	8 (25.8)	
Severe	21 (72.4)	23 (74.2)	
Calcium length, mm	19.1±11.8	18.5±7.0	0.788
Diameter stenosis, %	62.4±11.8	66.8±12.5	0.165
Post rotational atherectomy			
Dissection Type B or greater, n (%)	0 (0.0)	4 (14.6)	N/A
Staining, n (%)	N/A	0 (0.0)	N/A
Minimum lumen diameter, mm	1.4±0.3	1.4±0.4	0.438
Post CBA/NCBA before stent			
TIMI <3, n (%)	0 (0.0)	0 (0.0)	N/A
Slow flow, n (%)	0 (0.0)	0 (0.0)	N/A
No reflow, n (%)	0 (0.0)	0 (0.0)	N/A
Abrupt closure, n (%)	0 (0.0)	0 (0.0)	N/A
Distal Embolization, n (%)	0 (0.0)	0 (0.0)	N/A
New thrombus, n (%)	0 (0.0)	0 (0.0)	N/A
Perforation, n (%)	0 (0.0)	0 (0.0)	N/A
Spasm, n (%)	0 (0.0)	0 (0.0)	N/A
Dissection Type B or greater, n (%)	6 (21.4)	13 (44.8)	0.058
Staining, n (%)	0 (0.0)	2 (15.4)	N/A
Minimum lumen diameter, mm	1.8±0.4	1.7±0.3	0.387
Final post procedure			
Acute lumen gain, in-segment, mm	1.0±0.4	1.1±0.3	0.370
Acute lumen gain, in-stent, mm	1.5±0.3	1.6±0.4	0.269
Final residual diameter stenosis, in-segment, %	25.8±8.6	28.4±6.8	0.203
Final residual diameter stenosis, in-stent, %	13.8±6.5	14.8±6.1	0.564
Final minimum lumen diameter, in-segment, mm	2.1±0.3	2.1±0.4	0.910
Final minimum lumen diameter, in-stent, mm	2.5±0.3	2.5±0.4	0.890
Final dissection type B or greater, n (%)	0 (0.0)	1 (3.2)	N/A
Final perforation (Ellis type ≥2), n (%)	0 (0.0)	0 (0.0)	N/A
Final side branch closure, n (%)	0 (0.0)	0 (0.0)	N/A

Values are mean±standard deviation unless stated otherwise. CBA: cutting balloon angioplasty, NCBA: non-compliant balloon post-dilatation, TIMI: Thrombolysis in Myocardial Infarction, RA: rotational atherectomy

Table 4. Pre-procedure characteristics and procedural outcomes on IVUS

	RA+CBA N=29 (48.3%)	RA+NCBA N=31 (51.7%)	P-Value
Pre-procedure			
Target lesion length, mm	32.2±9.6	36.0±10.8	0.286
Minimum lumen area, mm^2	2.4±0.8	2.5±0.6	0.612
Eccentricity, n (%)	15 (100.0)	20 (100.0)	N/A
Thrombus, n (%)	0 (0.0)	0 (0.0)	N/A
Calcification, n (%)			0.519
Moderate	3 (20.0)	3 (15.0)	
Severe	12 (80.0)	17 (85.0)	
Calcium length, n (%)	26.0±7.6	29.4±9.6	0.256
Calcium arc max, degrees	319.3±61.2	303.5±63.7	0.467
Post CBA/NCBA before stent			
Calcium fracture, n (%)	14 (50.0)	7 (22.6)	0.028
Dissection, n (%)	27 (96.4)	30 (96.7)	1.000
Length, mm	7.8±5.3	8.5±6.3	0.514
Depth, n (%)			0.172
Intimal	25 (86.2)	24 (77.4)	
Medial	2 (6.9)	6 (19.3)	
Adventitial	0 (0.0)	0 (0.0)	
Final post procedure			
Minimum stent area, mm^2	6.7±1.7	6.9±1.8	0.685
In-segment minimum lumen area, mm^2	5.9±1.4	6.4±1.9	0.291
Final minimum stent expansion, %	86.1±17.5	78.6±14.7	0.076
Final mean stent expansion, %	112.5±19.4	104.2±13.5	0.058
Dissection, n (%)	1 (3.4)	3 (9.7)	0.613
Length	N/A	1.6±0.2	N/A
Depth, n (%)			1.000
Intimal	1 (3.4%)	2 (6.4%)	
Medial	0 (0.0%)	1 (3.2%)	
Adventitial	0 (0.0%)	0 (0.0%)	
Stent malapposition, n (%)	5 (17.2)	9 (29.0)	0.281

Values are mean±standard deviation unless stated otherwise. CBA: cutting balloon angioplasty, IVUS: intravascular ultrasound, NCBA: non-compliant balloon post-dilatation, RA: rotational atherectomy

Table 5. 30-day clinical outcomes (Intention-to-treat population)

Outcomes	RA+CBA N=29 (48.3%)	RA+NCBA N=31 (51.7%)	Hazard ratio (95% CI)	p-value
	no. of events (%)			
All-cause death	0 (0.0%)	0 (0.0%)	N/A	N/A
MI	2 (6.9%)	1 (3.2%)	2.14 (0.19-23.6)	0.535
TVR	1 (3.4%)	0 (0.0%)	N/A	N/A
TLR	0 (0.0%)	0 (0.0%)	N/A	N/A
Stent thrombosis	0 (0.0%)	0 (0.0%)	N/A	N/A
Major bleeding (BARC 3 or 5)	0 (0.0%)	0 (0.0%)	N/A	N/A
Vascular complications	0 (0.0%)	0 (0.0%)	N/A	N/A

The percentages mentioned above represent Kaplan-Meier rates at 30 days after index procedure.
BARC: Bleeding Academic Research Consortium, CBA: cutting balloon angioplasty, CI: confidence interval, MI: myocardial infarction, NCBA: non-compliant balloon post-dilatation, TVR: target vessel revascularization, TLR: target lesion revascularization, RA: rotational atherectomy

ROTACUT TRIAL

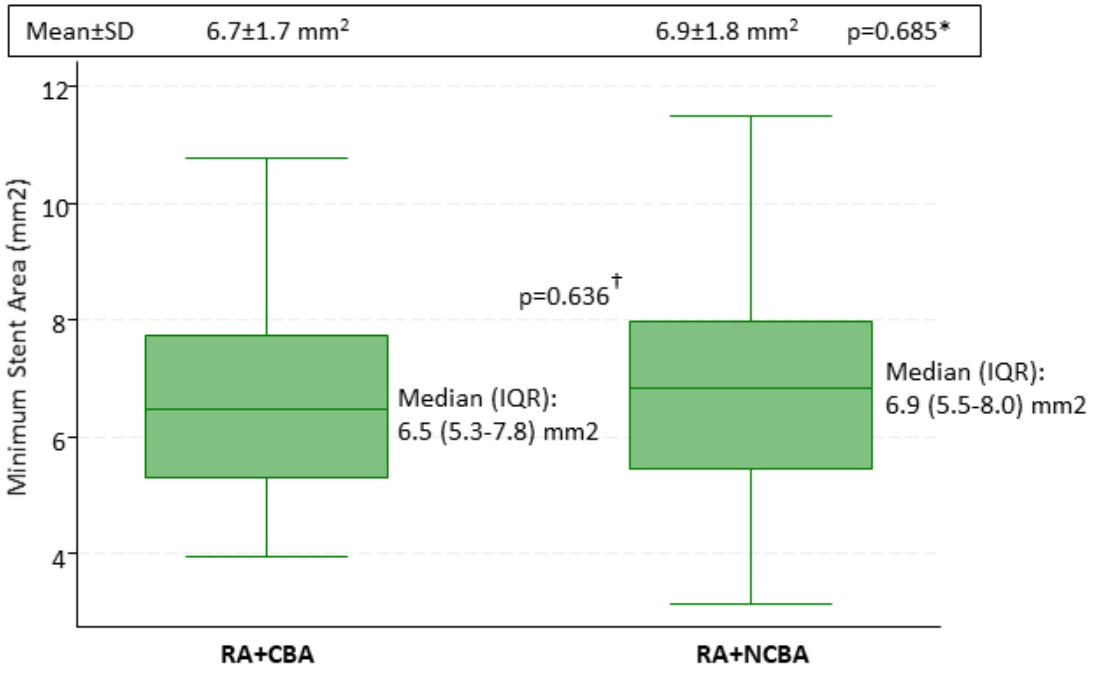
Patients with indication for PCI of a moderately or severely calcified lesion for which rotational atherectomy (RA) is deemed indicated

60 Patients randomized (1:1)

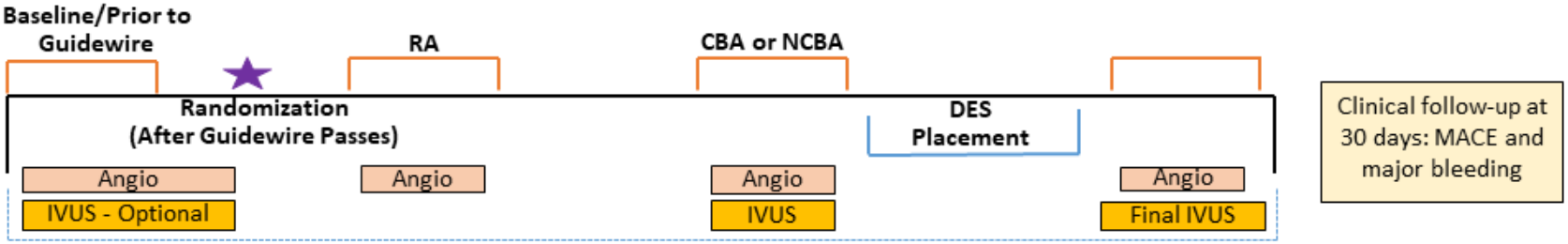
29 patients assigned to lesion preparation with RA and **cutting balloon angioplasty (CBA)** followed by DES implantation (+/- post-stent dilatation)

31 patients assigned to lesion preparation with RA and **non-compliant balloon post-dilatation (NCBA)** followed by DES implantation (+/- post-stent dilatation)

Primary Endpoint: Post Procedure Minimum Stent Area on IVUS



Procedural time line and imaging time points



Clinical follow-up at 30 days: MACE and major bleeding

Supplementary Material

Supplementary Table 1. Inclusion and exclusion criteria

Inclusion Criteria
1) Patient (or legal guardian) is ≥18 years if age and understands the trial requirements and the treatment procedures and provides written informed consent 2) Patient undergoing PCI for a de novo calcified lesion with planned rotational atherectomy and planned drug-eluting stent implantation of a lesion with target vessel reference diameter ≥2.5mm and ≤4.0mm, lesion length ≥5mm and moderate to severe calcification by angiography 3) Patient is eligible for PCI 4) Patient is willing and able to comply with all protocol-required follow-up evaluations
Exclusion Criteria
1) Patient in cardiogenic shock 2) Planned surgery (cardiac and non-cardiac) within 6 months after the index procedure unless the dual-antiplatelet therapy can be maintained throughout the perisurgical period 3) Patient undergoing primary PCI for ST-segment elevation myocardial infarction 4) Subject is pregnant, nursing, or is a woman of child-bearing potential who is not surgically sterile, <2 years postmenopausal, or does not consistently use effective methods of contraception 5) Patient has any other serious medical illness (e.g., cancer, end-stage congestive heart failure) that may reduce life expectancy to less than 12 months 6) Currently participating in another investigational drug or device study 7) Patient referred to coronary artery bypass grafting after heart team discussion
Angiographic Specific Exclusion Criteria
1) Lesion(s) with angulation > 45 degrees by visual estimate 2) Lesion(s) stenosis through which a guidewire will not pass. 3) Last remaining vessel with compromised left ventricular function (defined as left ventricular ejection fraction <30%) 4) Saphenous vein grafts 5) Angiographic evidence of thrombus 6) Angiographic evidence of significant dissection at the treatment site 7)Lesion(s) with previously placed stent within 10 mm (visual estimate)

PCI; percutaneous coronary intervention

Supplementary Table 2. Sample size rationale

Sample Size	Effect Size (mean difference in minimum stent area, mm^2)	Power
60	1.6	0.733
60	1.7	0.783
60	1.8	0.828
60	1.9	0.866

Supplementary Table 3. Additional QCA analysis

	RA+CBA N=29 (48.3%)	RA+NCBA N=31 (51.7%)	P-Value
Pre-procedure			
Eccentricity, n (%)	26 (89.7)	28 (90.3)	0.632
Tortuosity, n (%)	0 (0.0)	0 (0.0)	N/A
Ectasia, n (%)	0 (0.0)	1 (3.2)	N/A
Aneurysm, n (%)	0 (0.0)	1 (3.2)	N/A
Ulceration, n (%)	0 (0.0)	1 (3.2)	N/A
Thrombus, n (%)	0 (0.0)	0 (0.0)	N/A
Post rotational atherectomy			
TIMI<3, n (%)	0 (0.0)	1 (3.6)	N/A
Slow flow, n (%)	2 (7.1)	0 (0.0)	N/A
No reflow, n (%)	1 (3.6)	0 (0.0)	N/A
Abrupt closure, n (%)	0 (0.0)	0 (0.0)	N/A
Distal Embolization, n (%)	2 (7.1)	0 (0.0)	N/A
New thrombus, n (%)	0 (0.0)	0 (0.0)	N/A
Perforation, n (%)	0 (0.0)	0 (0.0)	N/A
Spasm, n (%)	0 (0.0)	0 (0.0)	N/A

Supplementary Table 4. Device-related complications

	ROTA+CBA N=29 (48.3%)	ROTA+NCBA N=31 (51.7%)	P-Value
Device deficiency, n (%)	0 (0.0)	0 (0.0)	N/A
Catheter difficult to cross lesion, n (%)	0 (0.0)	0 (0.0)	N/A
Balloon material rupture, n (%)	0 (0.0)	0 (0.0)	N/A
Catheter difficult to advance, n (%)	0 (0.0)	0 (0.0)	N/A
Catheter difficult to remove, n (%)	0 (0.0)	0 (0.0)	N/A
Balloon difficult to remove/withdraw from lesion, n (%)	0 (0.0)	0 (0.0)	N/A
Blade detachment of device or detachment of device component, n (%)	0 (0.0)	0 (0.0)	N/A

Supplementary Table 5. 30-days clinical outcomes (Per-protocol population)

Outcomes	**RA+CBA N=28 (47.5%)**	**RA+NCBA N=31 (52.5%)**	**Hazard ratio (95% CI)**	**p-value**
	no. of events (%)			
All-cause death	0 (0.0%)	0 (0.0%)	N/A	N/A
MI	1 (3.6%)	1 (3.2%)	1.11 (0.0 -17.7)	0.943
TVR	0 (0.0%)	0 (0.0%)	N/A	N/A
TLR	0 (0.0%)	0 (0.0%)	N/A	N/A
Stent thrombosis	0 (0.0%)	0 (0.0%)	N/A	N/A
Major bleeding (BARC 3 or 5)	0 (0.0%)	0 (0.0%)	N/A	N/A
Vascular complications	0 (0.0%)	0 (0.0%)	N/A	N/A

The percentages mentioned above represent Kaplan-Meier rates at 30 days after index procedure.

BARC: Bleeding Academic Research Consortium, CBA: cutting balloon angioplasty, CI: confidence interval, MI: myocardial infarction, NCBA: non-compliant balloon post-dilatation, TVR: target vessel revascularization, TLR: target lesion revascularization, RA: rotational atherectomy

Supplementary Table 6. 30-days clinical outcomes (As-treated populations)

Outcomes	**ROTA+CBA N=28 (46.7%)**	**ROTA+NCBA N=32 (53.3%)**	**Hazard ratio (95% CI)**	**p-value**
	no. of events (%)			
All-cause death	0 (0.0%)	0 (0.0%)	N/A	N/A
MI	1 (3.6%)	2 (6.3%)	0.57 (0.05-6.30)	0.648
TVR	0 (0.0%)	1 (3.1%)	N/A	N/A
TLR	0 (0.0%)	0 (0.0%)	N/A	N/A
Stent thrombosis	0 (0.0%)	0 (0.0%)	N/A	N/A
Major bleeding (BARC 3 or 5)	0 (0.0%)	0 (0.0%)	N/A	N/A
Vascular complications	0 (0.0%)	0 (0.0%)	N/A	N/A

The percentages mentioned above represent Kaplan-Meier rates at 30 days after index procedure.

BARC: Bleeding Academic Research Consortium, CBA: cutting balloon angioplasty, CI: confidence interval, MI: myocardial infarction, NCBA: non-compliant balloon post-dilatation, TVR: target vessel revascularization, TLR: target lesion revascularization, RA: rotational atherectomy

Supplemental Table 7. Alternative models of stent expansion

	ROTA+CBA N=29 (48.3%)	ROTA+NCBA N=31 (51.7%)	P-Value
Minimum stent area, mm2*	6.7±1.7	6.9±1.8	0.685
Final minimum stent expansion, %*,†	86.1±17.5	78.6±14.7	0.076
Final mean stent expansion, %*,‡	112.5±19.4	104.2±13.5	0.058
Minimum stent area/Vessel area stent§,‖	48.7±9.4	50.4±10.0	0.498
Minimum stent expansion by Linear Model, %§,¶	85.5±17.3	76.8±15.5	0.045
ILUMIEN IV stent expansion criteria, n (%)§,#	7 (24.1%)	4 (12.9%)	0.261

* Pre-defined study endpoints

† defined as minimum stent area divided by the reference lumen area x 100

‡ defined as mean stent area divided by the reference lumen area x 100

§ models proposed in Fujimura T, Matsumura M, Witzenbichler B, et al. JACC Cardiovasc Interv 2021;14:1639-50.

‖ defined as minimum stent area (MSA) divided by reference lumen area at the MSA x 100

¶ defined as minimum stent area divided by the ideal lumen area; the ideal luminal area without a stenosis was computed for each analyzed slice assuming uniform vessel tapering

defined as minimum stent area (MSA) of the proximal segment ≥90% of proximal reference luminal area and MSA of the distal segment ≥90% of distal reference luminal area