CLINICAL STUDY

Comparison of Drug-Eluting Stent and Plain Old Balloon Angioplasty After Rotational Atherectomy in Severe Calcified and Large Coronary

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Summary
Drug-eluting stent (DES) is well known to be effective in severely calcified lesion after rotational atherectomy (ROTA). However, there are still some situations when stents should be avoided and plain old balloon angioplasty (POBA) should be the preferred option. The present study aims to explore whether POBA is comparably effective to DES in large and calcified coronary pretreated by ROTA in clinical outcomes.

Consecutive patients treated for severely calcified lesions in the large (≥ 3 mm) coronary using ROTA + DES or ROTA + POBA were retrospectively analyzed. The major adverse cardiac events (MACE), including all-cause/cardiac death and target lesion revascularization (TLR) at 1 year and 2 years posttreatment, were compared between groups using the Cox regression analysis to identify independent predictors of TLR and MACE.

The analysis included 285 cases in the ROTA + DES group and 47 cases in the ROTA + POBA group, without relevant differences in clinical baseline characteristics. Of note, lesion length was greater in the ROTA + DES group (37.2 versus 19.3 mm, P < 0.001); the ROTA + DES group had a higher rate of chronic total occlusion (CTO) lesions, with 8.4%, and the ROTA + POBA group had none. The inhospital/30-day mortality rate (5.3%, ROTA + DES; 6.4%, ROTA + POBA) and the 12- and 24-month all-cause/cardiac mortality rate (9.3%, ROTA + DES; 7.7%, ROTA + POBA) were not significantly different between the two groups. TLR rates were not significantly different between the two groups at 12 (4.6%, ROTA + DES; 4.3%, ROTA + POBA) and 24 (5.3%, ROTA + DES; 6.4%, ROTA + POBA) months.

Outcomes were comparable for ROTA + DES and ROTA + POBA in severely calcified large coronary artery intervention with respect to midterm death or TLR rate, especially for short lesion of < 20 mm.

(Int Heart J 2021; 62: 264-273)

Key words: De novo lesion, Stentless strategy, Percutaneous coronary intervention

Epidemiological data have shown a worsening of coronary calcification with aging, with a prevalence of coronary calcification of up to 50% among individuals 40-49 years of age and increasing to 80% among those 60-69 years of age.1,2 Coronary calcification is a strong and independent predictor of adverse coronary events, even after a percutaneous coronary intervention (PCI).3-9 Rotational atherectomy (ROTA), used to remove plaque and, thus, reduce the severity of calcification, can be effective in facilitating balloon dilation in modern cardiac catheterization settings.10 In agreement with previously published findings,11 we have previously reported the effectiveness of combining ROTA with drug-eluting stents (ROTA + DES) for the treatment of calcified lesions.12 However, some situations, such as adverse bleeding effects, medication nonadherence, or large side branch ostial lesion, remain, which may lead physicians to choose stentless strategy, and POBA emerges as the preferred option. By comparison, extremely poor outcomes have been reported for treatment of such lesions using the

*These authors contributed equally to this work.
This research was supported by grant 2016YFC1301202 from National Key Research and Development Program of China and DFJH201807 from High-level Hospital Construction Project of Guangdong Provincial People’s Hospital.
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Released in advance online on J-STAGE March 17, 2021.
doi: 10.1536/ihj.20-538
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DES VERSUS POBA FOR CALCIFIED CORONARY AFTER ROTA

To our knowledge, there is no available data comparing the safety, effectiveness, and clinical prognosis of ROTA + DES or ROTA + POBA for the treatment of de novo lesions in large calcified coronary arteries. As such, this study aims to compare the outcome of using ROTA + DES and ROTA + POBA for large vessel angioplasty on the occurrence of major adverse cardiac events (MACE) and clinically driven TLR in a relatively large sample of patients, evaluated at a midterm follow-up after treatment.

Methods

Study population: This is a retrospective cohort study of consecutive patients who underwent treatment for de novo severe calcified lesions using ROTA-facilitated PCI (either POBA or DES) at Sapporo Cardiovascular Clinic between January 2013 and November 2015. A large coronary artery was defined by a reference diameter ≥ 3.0 mm, measured using quantitative coronary angiography (QCA) or visually determined if QCA was not applicable. Severe calcification was defined by a linear calcium density, visible on both sides of the target lesion under detailed fluoroscopic imaging. Patients with the following factors were excluded: in-stent restenosis (ISR); treated using ROTA plus a drug-coated balloon, BMS, or cover stent; and lesions with visible thrombus. Patients lost to follow-up were also excluded (Figure 1). The decision to perform ROTA + POBA or ROTA + DES was left to the doctor’s discretion. The stentless treatment (ROTA + POBA) would be more prone to be performed if “stentlike” results were achieved, especially in cases such as the following: lesions length within 20 mm, ostial lesion in side branch but with normal main vessel, residual stenosis < 50% after ROTA, or intolerance of longtime dual antiplatelets. Follow-up was regularly and routinely done at least twice within two years, with patients interviewed by the doctors in the clinic. Coronary computed tomography angiography or interventional coronary angiography (CAG) examination was performed in cases of suspected ISR or to investigate clinically driven concerns (such as

Figure 1. Screening procedure to identify the study population from our patient database. BMS indicates bare-metal stent; DCB, drug-coated balloon; ISR, in-stent restenosis; and ROTA, rotational atherectomy.

classic stentless plain old balloon angioplasty (POBA) alone due to limited expansion of the lesion and risk of marked dissection. Meanwhile, it has been suggested that, with the preparation of the vessel by ROTA, POBA could provide a stentless alternative to ROTA + DES for the treatment of calcified lesions, which would reduce the risk associated with the long-term use of antiplatelet agents necessary after DES implantation.

Although several studies have evaluated the effectiveness of different ROTA-facilitated PCI strategies for the treatment of calcified lesions, the evidence remains limited because the number of reported cases is relatively small (about 203), the size of treated vessels is also relatively small (≤ 3 mm), and casual follow-up methods were used, such as telephone interview or office visit at 9 months after implantation. Specifically, with regard to ROTA + POBA, one study has reported on the safety and workability of this strategy for the management of complex cases, with a target lesion revascularization (TLR) rate of 22%-31% in relatively small vessels with an average diameter of 2.6 mm, compared with a rate of 11%-13% for the ROTA + DES strategy in vessels with an average diameter of 3.1 mm. However, there is a paucity of data regarding outcomes of using ROTA + POBA for the treatment of large calcified coronary arteries, with evidence for the ROTA + DES strategy for these cases similarly being limited. In fact, the BASKET-PROVE study reported a comparable rate of mortality or myocardial infarction for DES and bare-metal stents (BMS), when used for the treatment of nonselected lesions in large vessel (≥ 3 mm). This raises the important issue of a potential effect of vessel diameter on PCI outcomes.

We do know that stent implantation in large vessels provides only a small clinical benefit, as the early advantage of a decrease in rate of restenosis is outweighed by the rate of late stent thrombosis-related problems. Based on this information, we hypothesized that ROTA + POBA may not be inferior to ROTA + DES for the treatment of lesions in large calcified coronary arteries, with regard to the risk of a cardiac event.

To our knowledge, there is no available data comparing the safety, effectiveness, and clinical prognosis of ROTA + DES or ROTA + POBA for the treatment of de novo lesions in large calcified coronary arteries. As such, this study aims to compare the outcome of using ROTA + DES and ROTA + POBA for large vessel angioplasty on the occurrence of major adverse cardiac events (MACE) and clinically driven TLR in a relatively large sample of patients, evaluated at a midterm follow-up after treatment.

Methods

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new-onset symptoms, evidence of cardiac ischemia, or high index of clinical suspicion for significant coronary disease). The study was approved by the hospital ethic committee, and all subjects were given informed consent.

**Procedure:** CAG was performed according to conventional methods. Dual antiplatelet therapy, using aspirin and thienopyridine (ticlopidine, 100 mg, twice daily, or clopidogrel, 75 mg, once daily), was prescribed for at least 12 months after ROTA + DES treatment and 3 months after ROTA + POBA treatment. Aspirin (100 mg, daily) was prescribed for life.

ROTA was performed using a Rotablator™ (Boston Scientific, Natick, MA, USA). In accordance with Japanese insurance policy, a maximum of two burrs were used when required. A modified ROTA technique was used in all cases, as per the previously described clinical guidelines at our institution.6) The standard of a stent/lumen ratio 1:1-1:1.02 for DES implantation was used, with the target lesion pretreated using sufficient rotablation and balloon dilatation. Angiographic success of ROTA + DES was defined as successful stent delivery and expansion, with an in-stent residual stenosis of ≤ 20% and a thrombolysis in myocardial infarction (TIMI) flow grade of 3.5) The ROTA + POBA strategy included a maximum burr/artery ratio of ≤ 0.70, followed by relatively large balloon controlled angioplasty, with very low pressure (1-4 atm).3) Semi- and noncompliant balloons were both used in the study. Semi-compliant type was mainly used in ROTA + POBA strategy with balloon/artery ratio of 1.0:1.2, especially in the diffuse lesion, because the dilution effect of semi-compliant balloon would be concentric, homogenous, and powerful enough for plaque redistribution with low pressure. The expansion of semi-compliant balloon with low pressure would be controllable for dissection and avoidance of other complications. Angiographic success of ROTA + POBA was defined as a residual stenosis of < 50%, with a TIMI flow grade of 3, determined by QCA, and no major dissections visible on the final angiogram of the index artery, after the last balloon inflation. In case of a residual stenosis of ≥ 50%, a higher balloon inflation pressure or DES was used. DES would also be used in cases with severe dissection (types D-F) after POBA, with these cases included in the ROTA + DES group for the analysis. The strategy of ROTA followed by DES or POBA was based on the doctor’s clinical judgment. All clinical decisions, such as site of vascular access and burr size/speed/motion, were left to the doctor’s discretion.

**Quantitative coronary angiography:** QCA was performed according to standard methods and definitions using the quantitative angiographic analysis system CAAS (version 5.9.1; Pie Medical Imaging, Maastricht, the Netherlands).6) The images with the least amount of foreshortening and the highest degree of stenosis were selected for the analysis.

**Endpoints:** MACE was defined as an acute occlusion or unscheduled emergent revascularization in hospitalization, all-cause or cardiac death, hospitalization due to heart failure, definite stent thrombosis, and TLR. Cardiac death was defined as any death without a clear no cardiac cause. TLR was defined as a repeat intervention within 5 mm, proximal or distal, of the target lesion previously treated in the index procedure or a coronary artery bypass graft (CABG) surgery of a lesion in the same epicardial vessel treated in the index procedure.6) Statistical analyses: Data were analyzed using SAS (version 9.4; SAS Institute Inc., Cary, NC). Patients were divided into the ROTA + DES and ROTA + POBA groups for comparisons. Continuous variables with a non-normal distribution were presented as median [interquartile range (IQR)] and analyzed using the Wilcoxon-Mann-Whitney U test. Categorical variables were presented as proportions (%) and analyzed using the Pearson’s chi-squared (χ²) test or Fisher’s exact test, as appropriate for the data type. Collinearity was evaluated using the Spearman’s correlation and Belsley’s criterion. Clinical event rates were calculated using Kaplan-Meier analysis, with between-group comparisons using the log-rank test. Hazard ratios (HR) and their 95% confidence interval (CI) were calculated using the Cox proportional hazards model, with assumptions of proportional hazards confirmed based on Schoenfeld residuals. All P-values are two-sided, and P-values < 0.05 were regarded as significant.

**Results**

**Baseline characteristics of the patients:** During the 3-year period of the study, 1374 patients underwent ROTA-based PCI treatment, and 332 of these patients presenting with 380 de novo lesions met our inclusion criteria (Figure 1). Relevant characteristics of the study group are summarized in Table I. The median age was 76 years, with 38% of patients having diabetes and 86.7% hypertension. Of note, 47% had undergone a previous PCI and 11.1% a CABG. The ROTA + DES:ROTA + POBA distribution was 6:1, with 285 ROTA + DES cases and 47 ROTA + POBA cases. The clinical baseline characteristics were comparable between the two groups, with the exception of a higher rate of previous PCI in the ROTA + DES (43.9%) than the ROTA + POBA (66.0%; P = 0.005) and rate of dual antiplatelet treatment (93.7% and 72.4%, respectively; P < 0.001).

**Baseline angiographic characteristics:** Angiographic characteristics are reported in Table II. The main target vessel was the left anterior descending artery in both groups. The reference vessel diameter was 3.3 (3.1, 3.6) and 3.3 (3.2, 3.7) mm in the ROTA + DES and ROTA + POBA group, respectively (P = 0.271). The rate of American Heart Association/American College of Cardiology (AHA/ACC) type B2/C lesions was > 97% in both groups. However, the median lesion length was much greater in the ROTA + DES (37.2 mm) than in the ROTA + POBA (19.3 mm) group, with a higher rate of chronic total occlusion (CTO) lesions in the ROTA + DES group and none in the ROTA + POBA group (8.4% versus 0%, respectively). The ROTA + POBA group had a greater prevalence of ostial and bifurcation lesion.

**PCI procedure data and QCA comparison:** The angiographic success of both ROTA strategies was > 97.9%. As shown in Table III, more than half of the patients (57.4%) in the ROTA + POBA group required two burrs, a rate which was significantly higher than for the ROTA + DES.
group (27%). To achieve sufficient ablation, the maximum burr size was significantly larger in the ROTA + POBA (2.0 mm) than in the ROTA + DES (1.75 mm) group, resulting in a higher maximum burr/artery ratio (0.56 versus 0.52, respectively). The maximum balloon size, however, did not differ between the groups, although the maximum balloon pressure in the ROTA + DES group (24 atm) was much higher than that in the ROTA + POBA group (1 atm; \( P < 0.001 \)) for different ballooning purposes of full stent expansion and plaque redistribution, respectively. As a result, the acute gain (2.1 versus 1.3 mm) and minimum lumen diameter (MLD) after PCI (3.3 versus 2.5 mm) were significantly greater in the ROTA + DES than in the ROTA + POBA group. No severe residual dissection (type

### Table 1. Baseline Characteristics of Participants

| Characteristics          | Overall  | ROTA + DES (\( n = 285 \)) | ROTA + POBA (\( n = 47 \)) | \( P \)-value |
|--------------------------|----------|-----------------------------|-----------------------------|--------------|
| Age, years               | 76 (68,81) | 76 (69,82) | 74 (65,79) | 0.067 |
| BMI, kg/m\(^2\)          | 23.4 (20.8,26.4) | 23.4 (20.8,26.4) | 23.5 (21.7,27.0) | 0.388 |
| Men, n (%)               | 114 (34.3) | 100 (35.1) | 14 (29.8) | 0.478 |
| Current smoker, n (%)    | 62 (18.7) | 54 (18.9) | 8 (17.0) | 0.844 |
| Diabetes mellitus, n (%) | 126 (38.0) | 106 (37.2) | 20 (42.6) | 0.483 |
| Hypertension, n (%)      | 288 (86.7) | 246 (86.3) | 42 (89.4) | 0.568 |
| Hyperlipidemia, n (%)    | 248 (74.7) | 210 (73.7) | 38 (80.9) | 0.295 |
| Clinical diagnosis, n (%)| 320 (96.4) | 276 (96.8) | 44 (93.6) | 0.414 |
| Stable angina            | 175 (52.7) | 156 (53.4) | 24 (51.1) | 0.079 |
| Non-STEMI                | 1 (0.3) | 1 (0.4) | 0 (0.0) | 0.844 |
| STEMI                    | 11 (3.3) | 8 (2.8) | 3 (6.4) | 0.624 |
| Previous MI, n (%)       | 67 (20.2) | 58 (20.4) | 9 (19.1) | 0.849 |
| Previous PCI, n (%)      | 156 (47.0) | 125 (43.9) | 31 (66.0) | 0.005 |
| Previous CABG, n (%)     | 37 (11.1) | 35 (12.3) | 2 (4.3) | 0.105 |
| Hemodialysis, n (%)      | 35 (10.5) | 31 (10.9) | 4 (8.5) | 0.624 |
| eGFR                     | 50.5 (39.0,63.0) | 51 (39.62) | 50 (42.64) | 0.641 |
| LVEF                     | 66.0 (61.0,69.0) | 65.7 (61.0,69.0) | 66.0 (61.3,68.9) | 0.858 |
| Dual antiplatelet, n (%) | 301 (90.6) | 267 (93.7) | 34 (72.4) | <0.001 |
| ACEI/ARB, n (%)          | 175 (52.7) | 156 (54.7) | 19 (40.4) | 0.009 |
| Statin, n (%)            | 181 (54.5) | 151 (53.0) | 30 (63.8) | 0.166 |

Data are presented as medians (interquartile range) or absolute numbers (percentages). The Wilcoxon–Mann–Whitney \( U \)-test, Pearson \( \chi^2 \)-test, or Fisher exact test was used for between-group comparisons, as appropriate. BMI indicates body mass index; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

### Table 2. Baseline Characteristics of Involved Lesions

| Characteristics          | Overall  | ROTA + DES (\( n = 285 \)) | ROTA + POBA (\( n = 47 \)) | \( P \)-value |
|--------------------------|----------|-----------------------------|-----------------------------|--------------|
| Treated vessel, n (%)    | 20 (6.0) | 15 (5.3) | 5 (10.6) | 0.151 |
| Left main                | 168 (50.6) | 138 (48.4) | 30 (63.8) | 0.05 |
| LAD                      | 44 (13.3) | 28 (9.8) | 16 (34.0) | <0.001 |
| LCX                      | 114 (34.3) | 113 (39.6) | 1 (2.1) | <0.001 |
| RCA                      | 3.3 (3.1,3.6) | 3.3 (3.1,3.6) | 3.3 (3.2,3.7) | 0.271 |
| Reference diameter, mm   | 176 (53.0) | 152 (53.4) | 24 (51.1) | 0.079 |
| Angulation > 45°, n (%)  | 2 (0.6) | 1 (0.4) | 1 (2.1) | 0.263 |
| Lesion type, n (%)       | 330 (99.4) | 284 (99.6) | 46 (97.9) | 0.001 |
| A/B1                     | 31.0 (23.5,40.8) | 37.2 (25.6,41.8) | 19.3 (15.0,25.1) | <0.001 |
| CTO                      | 24 (7.2) | 24 (8.4) | 0 (0.0) | 0.033 |
| Ostial, n (%)            | 144 (43.4) | 109 (38.2) | 35 (74.5) | <0.001 |
| Aorto-ostial, n (%)      | 30 (20.8) | 30 (27.5) | 0 (0.0) | 0.012 |
| Non-aorto-ostial, n (%)  | 114 (79.2) | 79 (72.5) | 35 (100) | <0.001 |
| Bifurcation, n (%)       | 176 (53.0) | 144 (50.5) | 32 (68.1) | 0.025 |

Data are presented as medians (interquartile range) or absolute numbers (percentages). The Wilcoxon–Mann–Whitney \( U \)-test, Pearson \( \chi^2 \)-test, or Fisher exact test was used for between-group comparisons, as appropriate. LAD indicates left anterior descending coronary; LCX, left circumflex artery; RCA, right coronary artery; and CTO, chronic total occlusion.
Table III. Comparison of Percutaneous Coronary Intervention Procedure and Quantitative Coronary Angiography Between the Two Strategies

| Characteristics                  | Overall          | ROTA + DES (n = 285) | ROTA + POBA (n = 47) | P-value |
|----------------------------------|------------------|----------------------|----------------------|---------|
| Procedure                        |                  |                      |                      |         |
| Maximum stent size, mm           | 3.50 (3.00,3.50) | 3.50 (3.00,3.50)     | -                    | NA      |
| Maximum burr size, mm            | 1.75 (1.75,1.75) | 1.75 (1.50,1.75)     | 2.00 (1.75,2.15)     | < 0.001 |
| Maximum balloon size, mm         | 3.5 (3.0,3.5)    | 3.5 (3.0,3.8)        | 3.5 (3.0,4.0)        | 0.582   |
| Maximum balloon pressure         | 23 (18,24)       | 24 (20,24)           | 1 (1,14)             | < 0.001 |
| Maximum burr/artery ratio        | 0.53 (0.47,0.57) | 0.52 (0.47,0.56)     | 0.56 (0.53,0.61)     | < 0.001 |
| Maximum balloon/artery ratio     | 1.00 (0.93,1.09) | 1.00 (0.93,1.09)     | 1.01 (0.94,1.12)     | 0.976   |
| Maximum stent/artery ratio       | 0.94 (0.83,1.00) | 0.97 (0.89,1.01)     | NA                   |         |
| Minimum rotational speed         | 140000           | 140000               | 120000               | 0.009   |
| Total stent length               | 38 (24,38)       | 38 (24,38)           | -                    | NA      |
| Number of burrs used (≥ 2), n (%)| 104 (31.3)       | 77 (27.0)            | 27 (57.4)            | < 0.001 |
| Number of stents used            | 1 (1.1)          | 1 (1.1)              | -                    | NA      |
| Angiographic success, n (%)      | 325 (97.9)       | 279 (97.9)           | 46 (97.9)            | > 0.999 |
| Immediate QCA                    |                  |                      |                      |         |
| MLD before PCI, mm               | 1.24 (0.94,1.45) | 1.24 (0.95,1.45)     | 1.26 (0.92,1.44)     | 0.894   |
| % stenosis before PCI            | 63 (57,72)       | 63 (57,72)           | 63 (57,74)           | 0.490   |
| MLD after PCI, mm                | 3.3 (2.9,3.5)    | 3.3 (3.0,3.6)        | 2.5 (2.1,2.8)        | < 0.001 |
| % stenosis after PCI             | 4.0 (-4.0,14.8)  | 2.0 (-5.0,10.0)      | 28.0 (18.0,40.5)     | < 0.001 |
| Acute gain, mm                   | 1.99 (1.63,2.33) | 2.1 (1.7,2.4)        | 1.3 (0.9,1.5)        | < 0.001 |
| PCI complication, n (%)          | 7 (2.1)          | 6 (1.8)              | 1 (0.3)              | > 0.999 |
| Residual dissection type (≥ C)   | 0 (0.0)          | 0 (0.0)              | 0 (0.0)              | > 0.999 |
| Slow/no flow                     | 2 (0.6)          | 2 (0.7)              | 0 (0.0)              | > 0.999 |
| Perforation                      | 4 (1.2)          | 4 (1.4)              | 0 (0.0)              | > 0.999 |
| Burr stuck                       | 1 (0.3)          | 0 (0.0)              | 1 (2.1)              | 0.141   |

Data are presented as medians (interquartile range) or absolute numbers (percentages). The Wilcoxon–Mann–Whitney U-test, Pearson \( \chi^2 \) test, or Fisher exact test was used for between-group comparisons, as appropriate. QCA indicates quantitative coronary angiography; MLD, minimum lumen diameter; and PCI, percutaneous coronary intervention.

> C) and only 28% (18.0, 40.5) residual stenosis occurred in the ROTA + POBA group. As a typical case shown in Supplemental Figures 1-4, severe calcified de novo lesion at left circumflex artery (LCX) ostium but with normal LMT/LAD was found by CAG and IVUS. ROTA with 1.75-/2.15-mm burrs (140,000 rpm) and then POBA with 3.0 * 12 mm semi-compliant balloon (4 atm) were performed. There was no residual stenosis after treatment, and no complication occurred.

Inhospital and follow-up outcome: The 12- and 24-month follow-up rates were 100% and 57.5%, respectively, with a median follow-up of 15.3 months (IQR, 10.0-24 months). The inhospitlal/30-day mortality rate was < 1% in the ROTA + DES group, and the ROTA + POBA group had no occurrence of death (Table IV). There were no significant between-group differences in the rate of all-cause or cardiac death at 12 and 24 months. Only one definite stent thrombosis was identified in the ROTA + DES group. The Kaplan-Meier curves indicated a TLR rate of 4.6% and 4.3%, respectively, for the ROTA + DES and ROTA + POBA groups at 12 months and 5.3% and 6.4%, respectively, at 24 months (\( P = 0.398 \), Figure 2). The rate of MACE was 11.9% and 8.5% in the ROTA + DES and ROTA + POBA groups at 12 months and 14.7% and 12.8% at 24 months, respectively (\( P = 0.632 \), Figure 2).

Predictors of TLR and MACE in large calcified coronary: As shown in Table V, current smoker [adjusted HR (aHR), 1.81; 95% CI, 1.11-2.94] and hemodialysis (aHR, 8.33; 95% CI, 3.20-21.68) were associated with TLR. Meanwhile, impaired left ventricular ejection fraction (aHR, 0.97; 95% CI, 0.94-0.99) and hemodialysis were significantly related to the occurrence of MACE (Table VI). Of note, the choice of ROTA + DES or ROTA + POBA nor the maximum burr/artery ratio had no significant influence on prognosis.

Discussion

To the best of our knowledge, this is the first study to compare the effects of ROTA followed by DES or POBA for the treatment of de novo lesions in large calcified coronary arteries. The major findings of our study are as follows. First, ROTA + POBA was also safe and feasible in severely calcified large coronary intervention. Second, ROTA + POBA was not inferior to ROTA + DES on the midterm rate of freedom of cardiac death or TLR in large- and short-length calcified coronary lesions. Third, hemodialysis was an independent risk factor for TLR and MACE.

DES is widely used to treat patients with coronary artery disease, improving vessel patency after PCI due to its capability of preventing elastic recoil, residual arterial dissection, and ISR. However, compared with small coronary lesions, the benefit of DES (versus BMS) is relatively small in patients treated for larger coronary lesions. Specifically, the early advantage of DES in decreasing the rate of restenosis is outweighed by the longer-term risk...
Table IV. Clinical Outcomes at 12 and 24 Months Between the Two Strategies

| Characteristics                  | Overall | ROTA + DES (n = 285) | ROTA + POBA (n = 47) | P-value |
|----------------------------------|---------|----------------------|----------------------|---------|
| Inhospital/30-day outcomes, n (%)|         |                      |                      |         |
| TLR                              | 0 (0.0) | 0 (0.0)              | 0 (0.0)              | > 0.999 |
| Inhospital death                  | 2 (0.6) | 2 (0.7)              | 0 (0.0)              | > 0.999 |
| 30-day death                      | 2 (0.6) | 2 (0.7)              | 0 (0.0)              | > 0.999 |
| 12-month follow-up, n (%)         |         |                      |                      |         |
| MACE                             | 38 (11.4)| 34 (11.9)           | 4 (8.5)              | 0.495   |
| All-cause death                   | 18 (5.4) | 16 (5.6)            | 2 (4.3)              | > 0.999 |
| Cardiac death                     | 9 (2.7)  | 7 (2.5)              | 2 (4.3)              | 0.482   |
| Stent thrombosis (definite)       | 0 (0.0)  | 0 (0.0)              | 0 (0.0)              | > 0.999 |
| HF                               | 10 (3.0) | 8 (2.8)              | 2 (4.3)              | 0.638   |
| TLR                              | 15 (4.5) | 13 (4.6)            | 2 (4.3)              | > 0.999 |
| 24-month follow-up, n (%)         |         |                      |                      |         |
| MACE                             | 48 (14.5)| 42 (14.7)           | 6 (12.8)             | 0.722   |
| All-cause death                   | 21 (6.3) | 18 (6.3)            | 3 (6.4)              | > 0.999 |
| Cardiac death                     | 9 (2.7)  | 7 (2.5)              | 2 (4.3)              | 0.482   |
| Stent thrombosis (definite)       | 1 (0.3)  | 1 (0.4)              | 0 (0.0)              | > 0.999 |
| HF                               | 15 (4.5) | 13 (4.6)            | 2 (4.3)              | > 0.999 |
| TLR                              | 18 (5.4) | 15 (5.3)            | 3 (6.4)              | 0.728   |

Data are presented as absolute numbers (percentages). The Pearson χ² test or Fisher exact test was used, as appropriate. ROTA indicates rotational atherectomy; DES, drug-eluting stent; POBA, plain old balloon angioplasty; TLR, target lesion revascularization; and MACE, major adverse cardiac events.

...for adverse cardiac events due to late stent thrombosis, which may be greater for DES than for BMS.20-26 The necessity of using DES in large coronary lesions, therefore, is challenged by the emerging clinical practice. Although second-generation DES have been shown to significantly reduce the rate of target vessel revascularization in large coronary arteries, the BASKET-PROVE study did not, however, identify a significant difference between the rate of death or myocardial infarction between DES and BMS.20 Of note, while the efficacy and safety of DES have been demonstrated in small-diameter vessels with heavily calcified lesions following ROTA,22,23 our study further demonstrates an angiographic success rate of > 99% for the ROTA + DES strategy in heavily calcified large vessels, with the TLR rate also being acceptably low at 5.3%. Furthermore, hemorrhagic tendency or medication nonadherence may lead physicians to choose a stentless strategy, since DES requires a longer duration of dual antiplatelet therapy. In the meantime, metal stents should be avoided as they are unessential for some specific lesions such as ostial side branch alone or short length.

On the other hand, POBA as a classic stentless technique might offer an alternative choice for the large coronary intervention.22,23 The utility of POBA for the treatment of heavily calcified coronary lesions has been associated with a lower angiographic success and a higher rate of complications, because of the undilatable calcified ring and severe dissection or vessel perforation after high-pressure ballooning.24 However, the physical removal of plaque and reduction in plaque rigidity by ROTA have increased the feasibility of using the POBA strategy for the treatment of large calcified coronary lesions.11,25 Some lesions were bulky or nodular in the study, but most cases were more than 270 degree calcification, and we sufficiently used modification and debulking effects in ROTA. Since the vessel diameter was more than 3 mm and calcifications were extensive, aggressive ROTA strategy (relatively large burr and slow speed) was used for sufficient debulking and ablation effect. Controlled large ballooning was then performed for plaque redistribution to get enough lumen acute gain. Therefore, no severe residual dissection (type > C) has occurred. "Recoil" did happen in the ROTA + POBA group, but only 28% (18.0, 40.5) residual stenosis was relatively acceptable in stentless method. It is important to note, as well, that the patients in our ROTA + POBA group had significantly greater complex health issues than patients included in a previous study,11 which further underlines the possible clinical utility of the ROTA + POBA strategy. Comorbid health conditions in the ROTA + POBA group included older age (median, 74 years), diabetes (42.6%), hemodialysis (8.5%), previous PCI (66%) and CABG (4.3%), and a high prevalence rate of AHA/ACC type B2/C lesions (99.4%). Fortunately, the high procedural success rate (97.9%) of the ROTA + POBA strategy, with a low rate of early MACE, is favorably comparable to the clinical outcomes reported in previous studies.20,26 Importantly, no perforation or other complication, with the exception of one burr being stuck, and no abrupt vessel closure or 30-day MACE occurred in the ROTA + POBA group. In addition, no acute occlusion or major complication associated with the ROTA + POBA strategy occurred, which was consistent with the previous report,11 indicating the safety of leaving a large coronary vessel without a stent after ROTA.

The overall clinical outcome of ROTA + POBA was comparable to that of ROTA + DES in our study, which may be explained as follows. First, the STRATAS study implicated a greater effect of surgical technique, than burr...
Figure 2. Comparison of target lesion revascularization (TLR) and major adverse cardiac event (MACE) among different PCI strategies. DES indicates drug-eluting stent; POBA, plain old balloon angioplasty; and ROTA, rotational atherectomy.

size, of the rate of acute complications and restenosis after ROTA. In our study, all ROTA procedures were performed by skilled and experienced doctors to guarantee stable technique performance. Moreover, in the ROTA + POBA strategy, only a pressure of 1-4 atm was used to avoid intimal damage after ROTA. In addition, an important component of POBA was to debulk and stabilize the lesion by redistributing the plaque, a strategy known as
minimal traumatic ROTA (MTRA) in our institution. Although a previous study did not identify a benefit of MTRA for small-diameter vessels, the technique may be of specific benefit in large vessels. Second, as the reference diameter of vessels treated in our study was large, aggressive ROTA would yield a large acute gain in lumen diameter, with the relatively high blood flow achieved offering some protection against acute restenosis. Third, almost all patients adhered to our strict follow-up protocol, including good medical adherence. Lastly, there was a higher prevalence of CTO and aorto-ostial lesions in the ROTA + DES than in the ROTA + POBA group, with the lesions also being of greater length in this group. Consequently, the heavy calcification would increase the risk of incomplete stent expansion and, thus, of a higher rate of restenosis. Follow-up coronary angiogram was clinically driven, which might have led to an underestimation of the rate of restenosis and TLR, especially in the ROTA + DES group.

Despite the lack of a difference in clinical outcomes between the two groups, we consider that there still must be some underlying difference that would distinguish the optimal strategy for specific cases. Although the prevalence of AHA/ACC type B2/C lesions was not different between the ROTA + DES and ROTA + POBA groups, there was a greater prevalence of aorto-ostial and CTO lesions, as well as lesions of greater length, in the ROTA + DES than in the ROTA + POBA group, all of which are strong risk factors for restenosis. After high-pressure balloononing and provisional support to the vessel wall by the metal struts, MLD after PCI and the acute gain were significantly greater in the ROTA + DES than in the ROTA + POBA group. Therefore, the ROTA + DES strategy was deemed to provide excellent performance for the treatment of these specific types of lesion. By comparison, the ROTA + POBA strategy was used in our study for patients with shorter and bifurcation lesions, especially for LCX ostial bifurcation lesions. Accurate stenting of a bifurcation lesion (such as an LCX ostial lesion) is normally considered to be challenging as the lesion cannot be fully covered by the stent, as well as the possibility of having the plaque shift to main branch (e.g., left main truck/left main branches).

### Table V. Predictors of TLR in Large Calcified Coronary Arteries

| Variables | Univariate analysis HR (95% CI) | P-value | Multivariate analysis HR (95% CI) | P-value |
|-----------|--------------------------------|---------|----------------------------------|---------|
| LVEF      | 1.00 (0.94–1.05)                | 0.871   | 1.81 (1.11–2.94)                 | 0.017   |
| Current smoker | 1.67 (1.03–2.70)                | 0.037   | 0.90 (0.52–1.55)                 | 0.768   |
| Diabetes | 3.00 (0.40–22.44)                | 0.284   | 2.08 (0.53–8.13)                 | 0.341   |
| Hyperlipidemia | 2.01 (0.59–6.86)                | 0.265   | -                                | -       |
| Hemodialysis | 7.37 (2.86–19.03)               | < 0.001 | 8.33 (3.20–21.68)                | < 0.001 |
| ROTA + DES versus POBA | 1.60 (0.53–4.83)               | 0.403   | -                                | -       |
| Reference diameter | 1.64 (0.66–4.05)                | 0.288   | -                                | -       |
| Lesion length | 1.01 (0.99–1.03)                | 0.605   | -                                | -       |
| MLD after PCI | 1.09 (0.39–3.04)                | 0.863   | -                                | -       |
| %DS after PCI | 1.08 (0.97–1.04)                | 0.637   | -                                | -       |
| Maximum bur/artery ratio | 0.09 (0.00–28.03)          | 0.420   | -                                | -       |
| Statin    | 2.55 (0.93–7.04)                | 0.070   | -                                | -       |

TLR indicates target lesion revascularization; LVEF, left ventricular ejection fraction; ROTA, rotational atherectomy; DES, drug-eluting stent; POBA, plain old balloon angioplasty; MLD, minimum lumen diameter; and DS, diameter stenosis.

### Table VI. Predictors of MACE in Large Calcified Coronary Arteries

| Variables | Univariate analysis HR (95% CI) | P-value | Multivariate analysis HR (95% CI) | P-value |
|-----------|--------------------------------|---------|----------------------------------|---------|
| LVEF      | 0.96 (0.93–0.98)                | 0.001   | 0.97 (0.94–0.99)                 | 0.008   |
| Current smoker | 0.87 (0.61–1.23)                | 0.429   | -                                | -       |
| Diabetes | 2.02 (0.73–5.58)                | 0.177   | -                                | -       |
| Hyperlipidemia | 1.02 (0.56–1.88)                | 0.940   | -                                | -       |
| Hemodialysis | 6.49 (3.65–11.55)               | < 0.001 | 6.15 (3.30–11.46)                | < 0.001 |
| ROTA + DES versus POBA | 1.19 (0.58–2.44)               | 0.633   | -                                | -       |
| Reference diameter | 0.90 (0.45–1.79)                | 0.769   | -                                | -       |
| Lesion length | 1.00 (0.99–1.02)                | 0.739   | -                                | -       |
| MLD after PCI | 0.97 (0.53–1.78)                | 0.923   | -                                | -       |
| %DS after PCI | 1.00 (0.98–1.02)                | 0.961   | -                                | -       |
| Maximum bur/artery ratio | 0.60 (0.20–18.85)            | 0.768   | -                                | -       |
| Statin    | 1.11 (0.65–1.90)                | 0.700   | -                                | -       |

MACE indicates major adverse cardiac events; LVEF, left ventricular ejection fraction; ROTA, rotational atherectomy; DES, drug-eluting stent; POBA, plain old balloon angioplasty; MLD, minimum lumen diameter; and DS, diameter stenosis.
anterior descending coronary) during implantation, which would lead to an even more complex situation. In this study, all LCX ostial lesions were successfully treated using the ROTA + POBA strategy. Therefore, the ROTA + POBA strategy can provide an alternative method to DES implantation for the treatment of such challenging lesions. Because of the noted differences in the characteristics of the lesions between the two groups, the detailed procedure of ROTA and ballooning likely differed between the two groups. Specifically, a more aggressive ablation strategy was adopted in the ROTA + POBA group, with more burrs used, larger burr size, and higher burr/artery ratio, as well as a lower rotational speed. The “low” ablation speed would further lead to a larger and smoother lumen as a result of burr deflection motion. This could potentially explain the predominant concept of “debulking” in the POBA strategy, to achieve a greater lumen diameter, compared with the strategy of “facilitated expansion” with DES. The maximum balloon/artery ratio did not differ; however, the balloon pressure was significantly lower in ROTA + POBA, providing a sufficiently large lumen and plaque redistribution, without severe dissection as a conservative approach. Of note, a previous report that aggressive ROTA with adjunctive balloon inflation of < 1 atm did not provide an advantage over more routine burr sizing plus routine angioplasty was based on an analysis of small vessels only, with a reference diameter of only about 2.6 mm and a lumen diameter of < 2.0 mm after PCI. In our study, vessel diameters were ≥ 3 mm, with a lumen diameter after POBA of about 2.5 mm, which is much larger than previously reported. The favorable prognosis obtained in our case series indicates the feasibility of using an aggressive ROTA strategy, with controlled large ballooning, in large calcified arteries. We also believe that emphasizing the difference between plaque “debulking,” in POBA, from plaque “modification,” in DES, is important, which would differentially guide the doctor’s ROTA performance.

To our knowledge, this is the first and largest retrospective study to have compared the early and midterm safety and effectiveness of ROTA + POBA and ROTA + DES for de novo lesions in large calcified coronary arteries.

**Limitations:** The limitations of our study should be acknowledged here. The major concern is that the selection of the ROTA + DES or ROTA + POBA in each case was at the doctor’s discretion and not randomized, despite baseline characteristics being comparable between the two groups. Detail on severe calcification morphology was also insufficient; however, most lesions were more than 270 degree calcification as confirmed by IVUS or CAG. Most frequently, in this study, patients treated with POBA were at high risk of bleeding from DAPT or had recently undergone another surgical procedure recently. Therefore, we consider that our study provides pilot information on the ROTA practice for this subgroup of patients.

**Conclusions**

We did not identify a significant difference in the rate of early and midterm all-causes or cardiac death and TLR between ROTA + DES and + POBA for heavily calcified lesion in large coronary arteries. In selected cases, however, such as calcified coronary of ≥ 3 mm in diameter and < 20 mm in length, ROTA + POBA provides a clinically acceptable alternative to DES implantation.

**Acknowledgments**

The authors appreciate the contribution of Professor Jiyan Chen and the cooperation between Sapporo Cardiovascular Clinic and Guangdong Provincial People’s Hospital.

**Disclosure**

**Ethics approval and consent to participate:** The study was approved by the ethic committee of Sapporo Cardiovascular Clinic, and all subjects were given informed consent.

**Conflicts of interest:** The authors declare that there is no conflict of interest.

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**Supplemental Files**

Supplemental Figures 1-4
Please see supplemental files; https://doi.org/10.1536/ihj.20-538