Two-Year Clinical Outcomes of Newer-Generation Drug-Eluting Stent Implantation Following Rotational Atherectomy for Heavily Calcified Lesions

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Background: Clinical outcomes of implantation of the newer-generation drug-eluting stent (DES) following rotational atherectomy for heavily calcified lesions remain unclear in the real-world setting.

Methods and Results: We enrolled 252 consecutive patients (273 lesions) treated with newer-generation DES following rotational atherectomy. The primary endpoint was the cumulative 2-year incidence of major adverse cardiovascular events (MACE), defined as cardiac death, myocardial infarction, clinically-driven target lesion revascularization, and definite stent thrombosis. Complete clinical follow-up information at 2-year was obtained for all patients. The mean age was 73.2±9.0 years and 155 patients (61.5%) were male. Cumulative 2-year incidence of MACE (cardiac death, myocardial infarction, clinically-driven target lesion revascularization and definite stent thrombosis) was 20.3% (7.0%, 2.1%, 18.1% and 2.1%, respectively). Predictors of MACE were presenting with acute coronary syndrome (hazard ratio [HR]: 3.80, 95% confidence interval [CI]: 1.29–11.2, P=0.02), hemodialysis (HR: 1.93, 95% CI: 1.04–3.56, P=0.04) and previous coronary artery bypass graft (HR: 2.26, 95% CI: 1.02–5.00, P=0.045).

Conclusions: PCI for calcified lesions requiring rotational atherectomy is still challenging even in the era of newer-generation DES.

Key Words: Newer-generation drug-eluting stents; Percutaneous coronary intervention; Rotational atherectomy

Drug-eluting stents (DES) have greatly reduced the rates of in-stent restenosis and subsequent target lesion revascularization (TLR) compared with bare-metal stents (BMS).1-2 However, percutaneous coronary intervention (PCI) for heavy calcified lesions is challenging, because of the low procedural success and high complication rate as compared with non-calcified lesions.3,4 Rotational atherectomy (RA; Rotablator™ Boston Scientific, Maple Grove, MN, USA) is useful for modifying calcified lesions, leading to improved stent deliverability and procedural success rate.5-8 The 1st-generation DES following RA reduced the rate of TLR as compared with BMS, but the TLR rate remained high at 6.8–21.2%.9-13 Recent pivotal clinical trials showed that newer-generation DES have improved safety and similar efficacy compared with 1st-generation DES.14,15 However, the effect of these DES following RA on clinical outcomes has not been fully evaluated, so we sought to investigate the clinical outcomes of newer-generation DES following RA for heavily calcified lesions.

Methods

Study Population and Procedural Protocol

From February 2010 to September 2012, a total of 2,701 consecutive patients underwent PCI with DES implantation at Kokura Memorial Hospital, and 2,605 patients were treated only with a newer-generation DES (biolimus-eluting stent [BES; Nobori™, Terumo, Tokyo, Japan], cobalt chromium everolimus-eluting stent [CoCr-EES; Xience V™/Xience Prime™, Abbott Vascular, Santa Clara, CA; Promus™, Boston Scientific, Natick, MA, USA] or platinum chromium everolimus-eluting stent [PtCr-EES; Promus Element™, Boston Scientific, Natick]). Of these, 252 with 273 lesions underwent RA and were enrolled in the study (Figure 1).
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The procedural details of RA have been reviewed elsewhere. In brief, procedures began with the smallest possible rotation burr (1.25, 1.5 or 1.75 mm). Rotational speed was between 180,000 and 210,000 rpm. A continuous intracoronary infusion containing verapamil, nitroglycerin and unfractionated heparin and pausing the rotablation were used to avoid slow flow. Care was taken to avoid any decrease in rotational speed exceeding 5,000 rpm. After the procedure, all patients were advised to continue on aspirin (81–162 mg/day) for life unless there were contraindications. Either ticlopidine (200 mg/day) or clopidogrel (75 mg/day) was also prescribed for at least one year after stent implantation. All study patients gave written informed consent for the procedure and the follow-up protocol, which was approved by the Review Board of Kokura Memorial Hospital. Follow-up data until September 2014 were obtained either from a review of the hospital records by clinic visit or scripted telephone interview with the patient, family member, or primary care physician.

Quantitative Coronary Angiographic Analysis

Coronary angiography (CAG) was performed after intracoronary administration of 0.2 mg nitroglycerin. Quantitative CAG (QCA) was performed before and after stenting and at 6–12 month follow-up, using a guiding catheter to calibrate the magnification and a validated automated edge detection algorithm (CASS 5.7, Pie Medical Imaging, Eindhoven, The Netherlands). Follow-up CAG was scheduled 6–12 months after the initial procedure, regardless of clinical symptoms. Patients who underwent unscheduled follow-up CAG within 12 months for clinical reasons were included in the angiographic analysis. The analyses were performed independently by 2 experienced observers at the Angiographic Core Laboratory, Kokura Memorial Hospital, who were blinded to the clinical information. Procedural success was defined as a final residual stenosis <30% and grade 3 Thrombolysis in Myocardial Infarction (TIMI) flow. The target lesion for measurement of the minimal luminal diameter included 5 mm margins proximal and distal to the stent as well as the stent itself. In-stent restenosis was defined as a percent diameter stenosis of >50% within the stent at the time of follow-up. Late lumen loss was defined as the difference between the immediate post-procedural minimal lumen diameter and the lumen diameter at follow-up CAG.

Study Endpoint and Definition

The primary endpoint was the cumulative 2-year incidence of major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction (MI), clinically-driven TLR (CD-TLR), and definite stent thrombosis. Cardiac death was defined as any death from a proximate cardiac cause, unwit-
nessed death and death of unknown cause, and all procedure-related deaths.\textsuperscript{17} MI was defined according to the Academic Research Consortium.\textsuperscript{17} TLR was defined as a repeat revascularization inside the stent or within 5 mm proximal or distal to the stent. Target vessel revascularization (TVR) was defined as a repeat PCI or repeat coronary artery bypass graft (CABG) on the target vessel. TLR or TVR was considered clinically indicated if the angiographic percentage diameter stenosis of the then-treated lesion was ≥50% in the presence of ischemic signs or symptoms or if the diameter stenosis was ≥70%, irrespective of ischemic signs or symptoms.\textsuperscript{17} Stent thrombosis was defined as proposed by the Academic Research Consortium.\textsuperscript{17} Clinical events were adjudicated by the consensus of 2 interventional cardiologists (H.J. and S.K.) in the hospital.

### Statistical Analysis

Data are presented as values and percentages, mean±SD or median and interquartile range. For baseline data, categorical variables were compared between groups with the chi-square test or Fisher’s exact test, as appropriate; continuous variables were compared between groups with the t-test or the Mann-Whitney U test, based on the distribution.

For each endpoint, cumulative incidence probability through 2 years was estimated by the Kaplan-Meier method. Hazard ratios (HR) of prognostic variables for MACE incidence were estimated by unadjusted and multivariable-adjusted Cox regression models. Because of the limited numbers of events, covariates to be adjusted for the multivariable model were screened by the estimates of univariable Cox model (P<0.10). If clinically similar variables remained, we selected a variable that we considered most clinically relevant from among them. Multivariable models were constructed using DES type and the variable with P<0.10 in the univariate analysis: presenting with acute coronary syndrome (ACS), previous CABG, previous PCI, hemodialysis (HD) and ejection fraction (EF) <40%.

### Results

#### Clinical Characteristics

The baseline patient characteristics are shown in Table 1. The mean age of the patients was 73.2±9.0 years (61.5% male) and there were high prevalences of diabetes mellitus (50.8%), HD (23.0%) and multivessel disease (52.0%). Most patients were treated with BES (57.9%) or CoCr-EES (36.5%).

#### Angiographic and Procedural Characteristics and Results

Angiographic and procedural characteristics are shown in
Table 2. There was a high frequency of left anterior descending artery (55.3%) and type B2/C (83.1%) lesions. In the QCA data, reference diameter was 2.47 mm and lesion length was 31.9 mm. Procedural details and interventional strategy data are listed in Table 3. The procedural success rate was 98.9%. The median bur size was 1.5 mm and median total stent length was 32.0 mm. The incidence of periprocedural complications such as slow flow and MI was relatively low.

Follow-up CAG Results
Follow-up CAG data are listed in Table 3. At 6–12 months, follow-up data were obtained for 80.3% (203 patients with 220 lesions). Mean number of follow-up angiographic days was 225 ± 60. Late lumen loss was 0.46 ± 0.57 mm and binary restenosis was 18.9%.

Clinical Outcome at 2 Years
The 2-year clinical outcomes are shown in Table 4 and Figure 2. Complete clinical follow-up information at 2 years was obtained for all patients. The cumulative 2-year incidence estimate of

<table>
<thead>
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<th>1 year</th>
<th>2 years</th>
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<tr>
<td>All-cause death</td>
<td>17 (6.7)</td>
<td>34 (13.5)</td>
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<tr>
<td>Cardiac death</td>
<td>7 (2.8)</td>
<td>17 (7.0)</td>
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<tr>
<td>Non-cardiac death</td>
<td>10 (4.0)</td>
<td>17 (7.0)</td>
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<tr>
<td>MI</td>
<td>3 (1.2)</td>
<td>5 (2.1)</td>
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<td>Definite stent thrombosis</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
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<tr>
<td>Probable stent thrombosis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Any TLR</td>
<td>45 (18.8)</td>
<td>52 (21.9)</td>
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<tr>
<td>CD-TLR</td>
<td>36 (15.1)</td>
<td>43 (18.1)</td>
</tr>
<tr>
<td>Any TVR</td>
<td>57 (21.3)</td>
<td>59 (24.8)</td>
</tr>
<tr>
<td>CD-TVR</td>
<td>36 (15.1)</td>
<td>44 (18.6)</td>
</tr>
<tr>
<td>Total MACE</td>
<td>40 (16.4)</td>
<td>49 (20.3)</td>
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Values are expressed as n (%). CD, clinically-driven; MACE, major adverse cardiovascular events; TLR, target lesion revascularization; TVR, target vessel revascularization. Other abbreviations as in Table 1.

Figure 2. Kaplan-Meier curves for 2-year incidence of clinical outcome: (A) major adverse cardiovascular events (MACE), (B) cardiac death, (C) myocardial infarction (MI), and (D) clinically-driven target lesion revascularization (CD-TLR).
Although the cause of stent thrombosis is multifactorial, a lesion with severe calcification requiring RA is a risk factor for stent thrombosis because of inadequate stent expansion and incomplete stent apposition. Recently, Furuichi et al reported that definite stent thrombosis occurred in 2.1% of patients treated with 1st-generation DES following RA. As compared with that, the newer-generation DES have thinner stent struts and biocompatible or biodegradable polymers, resulting in a lower rate of stent thrombosis (0.19–0.60% at 2 years). To date, however, there has been no report investigating the incidence of stent thrombosis in patients with newer-generation DES following RA. In the present study, the cumulative incidence of definite stent thrombosis was 2.1% at 2 years, which was similar to that reported previously. Therefore, we have to recognize that severe calcified lesions requiring RA remain a risk factor for stent thrombosis even with the newer-generation DES.

Although there was scant data regarding the predictors of clinical outcome in patients after DES implantation following RA, EF <40%, diabetes mellitus and lower age are reportedly predictors of MACE or TLR after DES implantation following RA. Rathore et al reported that previous CABG, non-aorta ostial lesion, chronic total occlusion lesion and HD were predictors of binary restenosis in patients after implanting DES or BMS following RA. In addition, Sakakura et al reported that off-label use of RA including MI had a higher rate of procedural complications than on-label use. In the present study, presenting ACS, HD and previous CABG were predictors of MACE in patients treated with newer-generation DES implantation following RA, findings that were consistent with previous studies. Therefore, clinicians should recognize that patients presenting with ACS or a history previous CABG have poor clinical outcomes, even if undergoing PCI with newer-generation DES following RA.

Some differences in terms of stent design, metallic alloy, and polymer are found among the newer-generation DES, which may lead to different clinical outcomes according to lesion characteristics. MACE (MI, CD-TLR, and definite stent thrombosis) was 20.3% (2.1%, 18.1% and 2.1% respectively).

**Predictors of MACE for Newer-Generation DES Following RA**

The predictors of MACE at 2 years by Cox proportional hazards models were: presenting with ACS (HR: 3.80, 95% confidence interval [CI]: 1.29–11.2, P=0.02), HD (HR: 1.93, 95% CI: 1.04–3.56, P=0.04) and previous CABG (HR: 2.26, 95% CI: 1.02–5.00, P=0.045) (Figure 3). The main findings of this study are: (1) the cumulative 2-year incidence of MACE after newer-generation DES implantation following RA was 20.3%; (2) predictors of MACE after newer-generation DES implantation following RA were presenting ACS, HD and previous CABG.

Several previous studies have reported that 1st-generation DES following RA led to better clinical outcomes than with BMS, which was driven mainly by a lower TLR rate, because the TLR rate was still high (6.8–21.2%). Although the newer-generation DES have improved safety and all have similar efficacy as compared with 1st-generation DES, there are no data regarding clinical outcomes of using newer-generation DES following RA. In the present study, the overall cumulative 2-year incidence of CD-TLR was 18.1% despite using newer-generation DES, which was higher than reported previously. This might be explained by the fact that the present study population had more complex patient and lesion characteristics, including a high prevalence of diabetes (50.8%), HD (23.0%), small reference diameter (2.47 mm) and long lesion length (31.9 mm) compared with previous studies. Taken together, the results suggest that PCI for severe calcified lesions requiring RA was still challenging even in the era of newer-generation DES.

Stent thrombosis is a rare, but potentially life-threatening complication that has raised intriguing issues in the DES era. Although the cause of stent thrombosis is multifactorial, a lesion with severe calcification requiring RA is a risk factor for stent thrombosis because of inadequate stent expansion and incomplete stent apposition. Recently, Furuichi et al reported that definite stent thrombosis occurred in 2.1% of patients treated with 1st-generation DES following RA. As compared with that, the newer-generation DES have thinner stent struts and biocompatible or biodegradable polymers, resulting in a lower rate of stent thrombosis (0.19–0.60% at 2 years). To date, however, there has been no report investigating the incidence of stent thrombosis in patients with newer-generation DES following RA. In the present study, the cumulative incidence of definite stent thrombosis was 2.1% at 2 years, which was similar to that reported previously. Therefore, we have to recognize that severe calcified lesions requiring RA remain a risk factor for stent thrombosis even with the newer-generation DES.

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**Discussion**

The predictors of MACE for Newer-Generation DES Following RA

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**Figure 3.** Predictors for major adverse cardiovascular events. ACS, acute coronary syndrome; BES, biolimus-eluting stent; CABG, coronary artery bypass graft; CI, confidence interval; EES, everolimus-eluting stent; EF, ejection fraction; HR, hazard ratio; PCI, percutaneous coronary intervention.
acteristics. Indeed, Lee et al reported that stent strut thickness was associated with the TLR rate after DES following RA. To date, however, the optimal DES for severe calcified lesions requiring RA remains unclear. With respect to strut thickness, the BES might have a worse clinical outcome than either the CoCr-EES or PtCr-EES because of its thicker struts (120 μm vs. 81 μm). Nevertheless, the present study demonstrated that the BES was comparable to the EES in terms of MACE at 2 years. These findings suggest that stent strut thickness is not associated with MACE with the newer-generation DES. Further studies are needed to assess the clinical outcomes of the different newer-generation DES in patients with severe calcified lesions requiring RA.

Study Limitations
First, this study was a retrospective and observational study in a single center, so selection bias may have occurred, which could have affected the outcome. Second, angiographic follow-up was not performed in all patients, which could influence the QCA data. Third, routine follow-up CAG might have biased the incidence of TLR. Finally, the long-term clinical outcomes in patients undergoing PCI with newer-generation DES following RA remain unclear until further studies provide additional results.

Conclusions
PCI for calcified lesions requiring RA is still challenging even in the newer-generation DES era, especially in patients presenting with ACS, HD or previous CABG.

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Disclosures
No conflict of interest.

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