Five-Year Clinical Outcomes After Drug-Eluting Stent Implantation Following Rotational Atherectomy for Heavily Calcified Lesions

Hiroyuki Jinnouchi, MD; Shoichi Kuramitsu, MD; Tomohiro Shinozaki; Takashi Hiromasa, MD; Yohei Kobayashi, MD; Yasuaki Takeji, MD; Mizuki Miura, MD; Hisaki Masuda, MD; Yukiko Matsumura, MD; Yuhei Yamaji, MD; Kenichi Sakakura, MD; Takenori Domei, MD; Yoshimitsu Soga, MD; Makoto Hyodo, MD; Shinichi Shirai, MD; Kenji Ando, MD

**Background:** Percutaneous coronary intervention for heavily calcified lesions requires rotational atherectomy (RA). Long-term clinical outcomes after drug-eluting stent (DES) implantation following RA for heavily calcified lesions remain unclear. We assessed 5-year clinical outcomes after DES implantation following RA.

**Methods and Results:** Between March 2006 and September 2011, 219 consecutive patients with 219 lesions treated with DES following RA, were retrospectively enrolled. The cumulative 5-year incidence of target-lesion revascularization (TLR) and definite stent thrombosis (ST) were assessed. The cumulative incidence of TLR within ≤ the first year was 18.6%. Late TLR beyond >1 year continued to occur at 1.9% per year without a decrease in the rate (5-year incidence, 26.0%). The cumulative incidence of definite ST at 30 days, 1 and 5 years was 0.9%, 2.3% and 2.9%, respectively. The annual rate of definite ST beyond 1 year was 0.15%. On multivariate analysis, the significant predictor of TLR within 1 year was use of first-generation DES (hazard ratio [HR], 2.09; 95% CI: 1.10–4.03, P=0.02) and that of TLR beyond 1 year was hemodialysis (HR, 3.29; 95% CI: 1.06–10.55, P=0.04).

**Conclusions:** Late TLR beyond 1 year continued to occur up to 5 years at a constant annual incidence, whereas very late ST was rare. Careful long-term clinical follow-up is continually needed in patients who have already received DES following RA for heavily calcified lesions.

**Key Words:** Calcification; Drug-eluting stent; Percutaneous coronary intervention; Rotational atherectomy
Quantitative Coronary Angiography (CAG)

CAG was performed after 0.2 mg i.c. nitroglycerin. Quantitative CAG (QCA) was performed before and after stenting, using a guiding catheter to calibrate the mag-

and then were treated only with DES were enrolled in this study, which included only the initial procedure (Figure 1). Heavy calcification was defined visually as the presence of calcium within the vessel wall at the site of the stenosis before contrast injection, which generally compromises both sides of the vessel wall.15,18 At Kokura Memorial Hospital, RA was indicated in patients who met the following criteria: (1) coronary artery disease with severe calcification on angiography and/or intravascular ultrasound (IVUS); (2) target lesion deemed undilatable by a balloon according to angiography and/or IVUS; (3) inability to fully expand the target lesion even after balloon dilatation; (4) inability to cross the stents even after balloon dilatation and with any devices. The procedural details of RA have been described elsewhere.19 In brief, the procedure began with the smallest possible rotablation burr (1.25, 1.5 or 1.75 mm). The rotational speed was between 180,000 and 210,000 r.p.m. Continuous i.c. infusion of verapamil, nitroglycerin and unfractionated heparin and pause of rotablation were used to avoid slow flow. Care was taken to avoid any full of rotational speed, which exceeded 5,000 rpm. After the procedure, all patients were advised to continue aspirin (81–162 mg daily) for life unless there were contraindications. Either ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was also prescribed for at least 1 year after stent implantation. Routine follow-up angiography 6–12 months after stent implantation was recommended to all patients regardless of clinical symptoms. All patients gave written informed consent for the procedure and the follow-up protocol, which was approved by the institutional review board of Kokura Memorial Hospital. Follow-up data until September 2016 were obtained either from a review of hospital records based on clinic visits or scripted telephone interviews with the patients, family members or primary care physicians.

Statistical Analysis

Data are presented as number (%) or mean ±SD. For each endpoint, the cumulative incidence probability through 5 years was estimated using the Kaplan-Meier method. To evaluate the incidence of late TLR and very late ST (VLST) beyond 1 year, landmark analysis at 1 year, which resets the risk set at a landmark point of 1 year, was applied to the Kaplan-Meier estimates. Similarly, Cox proportional hazards models were used to identify independent risk factors among 17 candidate variables for TLR within (≤) and beyond (>) the 1-year landmark point. The continuous variables were dichotomized by clinically meaningful reference values. Variables with P<0.10 in univariable Cox models were entered into a multivariable Cox model. If clinically similar variables remained, we selected the variable that we considered to be more clinically relevant. Finally, first- and second-generation DES were compared in terms of the 5-year incidence of TLR and ST, using log-rank test and hazard ratio (HR) estimates. For TLR, landmark analysis at the 1-year point and multivariable adjustment for the chosen variables were applied, and the directly adjusted (i.e., standardized to the total population) cumulative incidence probabilities were estimated.

All statistical analysis was performed by a statistician (S.T.) using JMP version 10.0.2 and SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-sided P<0.05 was considered to indicate statistical significance.
Long-Term Clinical Outcome of ROTA-DES

Results

Baseline Characteristics

Five-year clinical follow-up was 98.6% complete in all patients. The current group predominantly included patients with stable angina. The great majority of patients, however, had high-risk features such as advanced age, diabetes mellitus (DM), hemodialysis and multivessel disease (Table 1). In addition, the great majority of patients had American Heart Association/American College of Cardiology type B2/C lesions with complex lesion characteristics such as small reference diameter, long lesion length or severe calcification (Table 2). The procedural success rate was extremely high, and the complication rate was remarkably low (Table 2).

Clinical Outcomes

The cumulative 5-year incidence of all-cause death and cardiac death were 34.9% and 10.8%, respectively (Table 3; Figure 2A). Cardiac death comprised 30.9% of all-cause death. The cumulative 5-year incidence of MI was rela-
In this cohort, 79.4% of patients underwent follow-up angiography within 1 year. The cumulative incidence of TLR within the first year was high (18.6%; Figures 2B,3A). Late TLR beyond 1 year continued to occur at a constant rate up to 5 years (1.9%/year; Table 3, Figure 3B). ID-TLR within 1 year was relatively high (13.4%) and also continued to occur at a constant rate of 1.3%/year (Table 3, Figure 2B). Of 37 patients who received ID-TLR, 21 had positive functional ischemia (electrocardiographic changes at rest, n=10; positive stress test results, n=11), 28 had ischemic symptoms with angiographic diameter stenosis ≥50% (effort angina, n=16; symptom at rest, n=12), and 5 had angiographic diameter stenosis ≥70% without angina or positive functional study.

The cumulative incidence of definite ST within the first year was relatively high (30 days, 0.9%; 1 year, 2.3%; Table 3, Figure 3). VLST, however, occurred only in 1 patient up to 5 years (Table 3, Figure 3). ST was the cause of MI during follow-up in 40.0% of 15 MI events. All patients with early ST and VLST were on dual antiplatelet therapy (DAPT) at the time of ST, whereas DAPT was interrupted in 2 (66.6%) of 3 patients with late ST before the occurrence of ST, but continued in the remaining patient. Regarding the DES type associated with ST, 4 patients (1 early ST and 3 late ST) received paclitaxel-eluting stents (PES). The remaining 2 patients (1 early ST and 1 VLST) received biolimus-eluting stent and sirolimus-eluting stent (SES), respectively. The independent risk factor for TLR within 1 year was first-generation DES use (HR, 2.09; 95% CI: 1.10-4.03, P=0.02); DM and post-intervention MLD ≤2.25 mm tended to be...
Long-Term Clinical Outcome of ROTA-DES

In the present study, the main findings were as follows: (1) the cumulative incidence of TLR within the first year was very high, and late TLR beyond 1 year continued to occur at a constant rate; (2) the cumulative incidence of ST within the first year was high, but VLST was rare; (3) the risk factors for TLR within and beyond 1 year were first-generation DES use and hemodialysis, respectively; and (4) second-generation DES had a lower rate of TLR than first-generation DES.

In previous studies, patients with calcified lesions had a high TLR rate because they had predominantly unfavorable patient and lesion characteristics. Therefore, the TLR rate after PCI requiring RA due to calcified lesions remained high (6.8–21.2%). Recently, Furuichi et al showed that TLR at 13 months was 9.8% in patients treated with first-generation DES. More recently, the Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease (ROTAXUS) trial reported that the rates of TLR after PES implantation were 11.7% at 9 months and 13.8% at 2 years, respectively. In the present study, the TLR rate was 18.6% at 1 year, which was higher than previously reported. This

**Discussion**

First- and Second-Generation DES

In the present crude cohort, the second-generation DES group had a lower cumulative 5-year incidence of TLR than the first-generation DES group (HR, 0.48; 95% CI: 0.27–0.83, P<0.01; Figure 4A). Even after multivariable adjustment, there was a significant difference between first- and second-generation DES (HR, 0.48; 95% CI: 0.27–0.83, P<0.01; Figure 4B). In the landmark analysis at 1 year, there was a significant difference between the 2 groups within the first year (TLR within the first year: HR, 0.52; 95% CI: 0.26–0.99, P=0.047), whereas late TLR beyond 1 year did not show significant difference (HR, 0.43; 95% CI: 0.11–1.34, P=0.18; Figure 4C). In the present crude cohort, there was significant difference in ST between first- and second-generation DES (HR, 0.15; 95% CI: 0.008–0.97, P=0.04; Figure 4D).

**Figure 3.** Cumulative incidence of (A) target lesion revascularization (TLR), (B) TLR within (≤) 1 year, and at 1–5 years by the 1-year landmark analysis, (C) stent thrombosis (ST), (D) ST within 1 year, and 1–5 years by the 1-year landmark analysis.
might be due to a higher angiographic follow-up rate within the first year, and more complex patient and lesion characteristics in the present study than in previous studies.24,25 Late adverse events such as VLST and late TLR beyond 1 year after DES implantation have emerged as unsolved issues.24 In the j-Cypher Registry, VLST and late TLR beyond 1 year occurred at a constant rate up to 5 years after first-generation SES implantation (0.26%/year and 2.2%/year, respectively).25 Recently, Miura et al and Kuramitsu et al reported a similar tendency in terms of late adverse events up to 10 years after first-generation SES implantation.26,27 As shown in the present study, the patient and lesion characteristics associated with RA were more complex, which might lead to worse long-term clinical outcome. The long-term clinical outcome of DES following RA, however, remains unclear. In the present study, late TLR beyond 1 year after DES implantation continued to occur at a constant rate up to 5 years (1.9%/year). Interestingly, the annual rate of late TLR beyond 1 year was similar to that of an unselected population, regardless of the fact that the present cohort had high-risk baseline characteristics.

Considering these findings, late TLR beyond 1 year after DES implantation requiring RA remains a concerning problem for at least 5 years, but it was reassuring that we found no evidence for increase or decrease of late TLR rate beyond 1 year in those patients. ST is a rare, but potentially life-threatening, complication that has raised an intriguing issue in the DES era.20 Although the cause of ST is multifactorial, a lesion with severe calcification requiring RA is a risk factor for ST because of inadequate stent expansion and incomplete stent apposition.20 Definite ST in patients treated with first-generation DES following RA was reported to occur in 0.9–2.1% at 9–13 months, which is similar to the present rate but higher than that in unselected patients.4,17 To date,

### Table 4. Indicators of TLR

<table>
<thead>
<tr>
<th></th>
<th>TLR within (≤) 1 year</th>
<th>TLR beyond (&gt;) 1 year</th>
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<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age ≥80 years</td>
<td>0.75 (0.30–1.60)</td>
<td>0.48</td>
</tr>
<tr>
<td>Male</td>
<td>1.34 (0.68–2.89)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.91 (1.01–3.78)</td>
<td>0.047</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.62 (0.30–1.38)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.03 (0.55–1.94)</td>
<td>0.93</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.94 (0.28–3.34)</td>
<td>0.90</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.76 (0.29–1.69)</td>
<td>0.52</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.29 (0.64–2.46)</td>
<td>0.46</td>
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<tr>
<td>Previous CABG</td>
<td>1.54 (0.53–3.60)</td>
<td>0.39</td>
</tr>
<tr>
<td>CVD</td>
<td>1.63 (0.70–3.38)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1.45 (0.73–2.75)</td>
<td>0.28</td>
</tr>
<tr>
<td>PAD</td>
<td>1.34 (0.67–2.55)</td>
<td>0.40</td>
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<tr>
<td>ACS</td>
<td>1.74 (0.10–7.99)</td>
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<tr>
<td>MVD</td>
<td>1.33 (0.70–2.55)</td>
<td>0.38</td>
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<tr>
<td>Statin</td>
<td>0.90 (0.48–1.71)</td>
<td>0.74</td>
</tr>
<tr>
<td>EF ≤40%</td>
<td>1.14 (0.54–2.10)</td>
<td>0.44</td>
</tr>
<tr>
<td>First-generation DES</td>
<td>1.81 (0.96–3.45)</td>
<td>0.07</td>
</tr>
<tr>
<td>RD before procedure ≤2.25 mm</td>
<td>1.12 (0.59–2.11)</td>
<td>0.72</td>
</tr>
<tr>
<td>Post-intervention MLD ≤2.25 mm</td>
<td>1.75 (0.91–3.59)</td>
<td>0.09</td>
</tr>
<tr>
<td>Lesion length ≥30 mm</td>
<td>1.07 (0.56–2.00)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

DES, drug-eluting stent; HR, hazard ratio; MLD, minimum luminal diameter; RD, reference diameter. Other abbreviations as in Tables 1,3.
however, data on the incidence of VLST during long-term follow-up in patients treated with DES following RA are scarce. In the present study, it was intriguing that VLST occurred only in 1 patient treated with SES, which was remarkably lower than in previous studies.47 Furthermore, most ST patients were treated with first-generation DES. Recently, network meta-analyses have shown that second-generation DES, especially cobalt-chromium everolimus-eluting stents, are safer than first-generation DES.28,29 The current study suggests better long-term safety of second-generation DES even in lesions requiring RA. Previous studies have reported on the risk factors for TLR within and beyond 1 year in patients treated with DES. The risk factors for TLR after DES implantation following RA, however, have not been fully evaluated. Abdel-Wahab et al reported that the risk factors for TLR after DES implantation following RA at a median follow-up period of 15 months were DM and age.18 In addition, Rathore et al also showed that male gender, previous CABG, CTO and non-aorta ostial lesion predicted re-}

nossis at 6–9 months after BMS or DES implantation following RA.11 In the present study, first-generation DES (vs. second-generation DES) was a risk factor for TLR within 1 year. In addition, we suggested the possibility of DM and post-intervention MLD ≤2.25 mm (which are well-known predictors of TLR) as predictors of TLR within 1 year. Furthermore, the predictors of TLR in the long-term after DES implantation following RA are still unknown. The present study has identified hemodialysis as a risk factor for late TLR beyond 1 year. Therefore, careful long-term follow-up is needed in patients who have already received DES following RA, especially in those patients who require hemodialysis. Second-generation DES have improved safety and similar efficacy compared with first-generation DES, whereas there has been to date no study comparing the difference in clinical outcomes of RA between first- and second-generation DES.25,26 In the current study, the cumulative 5-year incidence of TLR was significantly lower for second-generation DES than for first-generation DES.

Figure 4. Comparison between first- and second-generation drug-eluting stent (DES): (A) target lesion revascularization (TLR) in the crude population, (B) TLR after multivariable adjustment, (C) TLR within (≤) 1 year, and at 1–5 years by the 1-year landmark analysis after multivariable adjustment, and (D) stent thrombosis in the crude population.
Stent under-expansion, stent recoil, damage to the polymer and secondary insufficient drug effect are potential causes of a high TLR rate in calcified lesions. Compared with first-generation DES, second-generation DES have improved stent delivery systems and stent platforms. These features may reduce the damage to the polymer in severely calcified lesions requiring RA, which might account for the significant difference in TLR rate between first- and second-generation DES. Considering these findings, second-generation DES may improve long-term clinical outcomes compared with first-generation DES in patients with complex lesions such as calcified lesions requiring RA.

Clinical Implications

At 5 years, the cumulative incidence of TLR was very high in patients with DES following RA. In addition, late TLR beyond 1 year continued to occur up to 5 years. Therefore, careful long-term clinical follow-up is mandatory, especially in patients who have already been treated with first-generation DES following RA and who have been on hemodialysis. Furthermore, it may be important for interventionists to obtain larger post-intervention MLD in heavily calcified lesions using RA and balloon at index procedure.

Study Limitations

There were several limitations in the present study. First, this study was a retrospective and observational study at a single center. Therefore, selection bias might have affected the conclusions. To our knowledge, however, this is the first study to report on 5-year clinical outcomes of DES implantation following RA. Second, routine follow-up CAG might have biased the incidence of TLR. Third, we did not have information on bleeding complications and antplatelet therapy during follow-up. Fourth, we could not assess the predictors of ST and compare first-generation DES with second-generation DES after multivariable adjustment, because the incidence of ST was low. Finally, very long-term clinical outcomes in patients undergoing PCI with DES following RA remain unclear. Therefore, careful follow-up should be continued, in order to assess very long-term clinical outcomes in these patients.

Conclusions

Late TLR beyond 1 year continued to occur up to 5 years at a constant rate, but VLST was rare in patients treated only with DES following RA. The risk factor for TLR beyond 1 year was hemodialysis, and second-generation DES might improve the TLR rate for complex lesions such as calcified lesions compared with first-generation DES.

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Disclosures

The authors declare no conflicts of interest.

References


