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ORIGINAL ARTICLE
Cardiovascular Intervention

Clinical Characteristics and Long-Term Outcomes of Rotational Atherectomy

— J2T Multicenter Registry —

Iwao Okai, MD; Tomotaka Dohi, MD, PhD; Shinya Okazaki, MD; Kentaro Jujo, MD, PhD; Makoto Nakashima, MD; Hisao Otsuki, MD; Kazuki Tanaka, MD; Hiroyuki Arashi, MD, PhD; Ryuta Okabe, MD; Fukuko Nagura, MD; Yugo Nara, MD; Hiroshi Tamura, MD; Takeshi Kurata, MD; Hideyuki Kawashima, MD, PhD; Hiroyuki Kyono, MD, PhD; Junichi Yamaguchi, MD, PhD; Katsumi Miyauchi, MD; Ken Kozuma, MD, PhD; Nobuhisa Hagiwara, MD, PhD; Hiroyuki Daida, MD

Background: Rotational atherectomy (RA) is an adjunct tool for the management of heavily calcified coronary lesions during percutaneous coronary intervention (PCI), but the long-term clinical outcomes of RA use remain unclear in this drug-eluting stent era.

Methods and Results: This multi-center registry assessed the characteristics and outcomes of patients treated by RA for calcified coronary lesions between 2004 and 2015. Among 1,090 registered patients, mean age was 70±10 years and 815 (75%) were male. Sixty percent of patients had diabetes mellitus and 27.7% were receiving hemodialysis. The procedure was successful in 96.2%. In-hospital death occurred in 33 patients (3.0%), and 14 patients (1.3%) developed definite/probable stent thrombosis. During the median follow-up period of 3.8 years, the incidence of major adverse cardiac events (MACE), defined as all-cause death, acute coronary syndrome, stent thrombosis, target vessel revascularization and stroke, was 46.7%. On multivariable Cox hazard analysis, hemodialysis (HR, 2.08; 95% CI: 1.53–2.86; P<0.0001) and age (HR, 1.03; 95% CI: 1.01–1.04; P<0.0001) were strong independent predictors of MACE. Conversely, statin treatment was associated with lower incidence of MACE (P=0.035).

Conclusions: This study has provided the largest Japanese dataset for long-term follow-up of RA. Although RA in calcified lesions appears feasible with a high rate of procedural success, a high incidence of MACE was observed.

Key Words: Calcified coronary lesion; Coronary artery disease; Percutaneous coronary intervention; Rotational atherectomy

Coronary artery calcification is a risk factor for adverse outcomes in both the general population and in patients undergoing coronary revascularization.[1–3] The aging of the population, with the associated rising burden of cardiovascular risk factors, means that complex calcified coronary lesions are increasingly being encountered in everyday clinical practice. Heavily calcified lesions present a special challenge, preventing adequate lumen expansion and leading to failure of stent delivery or expansion.[4]

Rotational atherectomy (RA) is a useful adjunct for treating coronary stenosis and can effectively ablate calcified plaques, facilitating stent delivery and expansion in many cases.[5,6] Although the clinical outcome of RA is improved under the current strategy with stent implantation including drug-eluting stents (DES), adverse event rates remain high.[7–11]

This increase in adverse event rates is thought to be associated with a higher patient risk profile and the complexity of the coronary anatomy, rather than the specific procedure itself.[12] Patient and lesion characteristics are thus important for the long-term outcome of RA for heavily calcified lesions. The in-hospital and midterm clinical outcomes of RA have been described,[13] but data on the long-term outcomes remain limited, particularly for Asian populations. We therefore designed this multicenter registry study to investigate long-term clinical outcome in Japanese patients undergoing percutaneous coronary intervention (PCI) using RA in this DES era.

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Department of Cardiovascular Medicine, Juntendo University School of Medicine, Tokyo (I.O., T.D., S.O., H.T., T.K., K.M., H.D.); Department of Cardiology, Tokyo Women's Medical University, Tokyo (K.J., H.O., K.T., H.A., J.Y., N.H.); and Department of Cardiology, Teikyo University School of Medicine, Tokyo (M.N., R.O., F.N., Y.N., H. Kawashima, H. Kyono, K.K.), Japan

Mailing address: Shinya Okazaki, MD, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: shinya@juntendo.ac.jp

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Table 1. Baseline Clinical Characteristics (n=1,090)

Characteristic	Mean±SD, n (%) or median (IQR)
Age (years)	70±9.7
Male	815 (74.8)
BMI (kg/m^2)	23.2±3.3
Diabetes mellitus	653 (60.0)
Insulin use	227 (20.8)
Hypertension	904 (82.9)
Dyslipidemia	737 (67.6)
Current smoker	214 (19.7)
Family history of CAD	240 (22.3)
ACS presentation	164 (15.0)
Chronic kidney disease	511 (47.1)
Hemodialysis	302 (27.7)
Prior MI	269 (24.7)
Previous PCI	326 (29.9)
Previous CABG	135 (12.4)
Atrial fibrillation	161 (14.8)
LVEF (%)	54.9±13.2
Low LVEF (<50%)	321 (32.8)
Medication at discharge	
β-blocker	559 (51.6)
Ca-antagonist	540 (49.8)
ACEI/ARB	698 (64.4)
Statin	676 (62.3)
Nitrates	345 (31.9)
Nicorandil	277 (25.6)
Aspirin	1,034 (95.4)
Ticlopidine	341 (31.5)
Clopidogrel	639 (58.9)
Cilostazol	66 (6.1)
Warfarin	108 (10.0)
Laboratory data	
Hemoglobin (g/dL)	11.9±1.9
Total cholesterol (mg/dL)	170.0±37.4
Triglycerides (mg/dL)	125.8±77.7
HDL-C (mg/dL)	47.7±15.0
LDL-C (mg/dL)	99.1±33.8
HbA1c (%)	6.4±1.1
CRP (mg/dL)	0.13 (0.05–0.50)

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary arterial bypass grafting; CAD, coronary artery disease; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Methods

Study Design and Patients

To investigate the clinical characteristics and long-term outcomes of RA for calcified coronary lesions, we created a multicenter registry (retrospective cohort study) in Japan. Because the primary purpose of the J2T ROTA registry is quality improvement, participating hospitals are not required to obtain individual informed consent. The present study was conducted in accordance with the ethics guidelines for epidemiological studies, and the relevant review boards of all 3 participating hospitals approved the study protocol. Data were collected at each site using a standardized case report form to record demographic and clinical characteristics, as well as procedural and follow-up data. Follow-up data were collected at the time of registry enrolment, based on medical records and on physician or patient interview. The investigators had full access to the data and control analysis.

Between 2004 and 2015, a consecutive series of patients with heavily calcified de novo lesions and significant stenosis (stenosis ≥70% of vessel diameter) treated with RA was retrospectively identified from each institutional database. Heavily calcified lesions were identified on coronary angiography as radiopacities noted without cardiac motion before contrast injection, generally compromising both sides of the arterial lumen.[14] On intravascular ultrasound (IVUS), calcified lesions were defined as the presence of high-intensity echoes with acoustic shadowing. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2, as calculated using the modification of the diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine.[15]

Procedure

Procedures were performed after obtaining written informed consent. All PCI was performed by experienced, credentialed operators using standard practice in each catheterization laboratory. The choice of artery access site (radial or femoral) and decision to perform RA were made by the operator. All patients received pretreatment with aspirin and thienopyridine (clopidogrel, prasugrel or ticlopidine). During PCI, patients received unfractionated heparin to achieve an activated clotting time of 250–300 s. All clinical decisions during PCI and burr size were at the discretion of the operator. All RA procedures were performed using the Rotablator™ RA system (Boston Scientific, Marlborough, MA, USA). During RA, pauses in ablation runs and i.c. nitroglycerin and/or verapamil were used to avoid coronary spasm and slow flow phenomenon. After RA, patients received a single or multiple stents with or without pre-dilatation with a conventional balloon, cutting balloon or scoring balloon. Angiographic success was defined as achievement of residual stenosis <30% in the presence of grade III Thrombolysis in Myocardial Infarction (TIMI 3) flow. Lifelong low-dose aspirin was recommended for all patients, in addition to dual antiplatelet therapy for a minimum of 12 months after stent implantation.

Endpoints

The primary endpoint of the study was the occurrence of major adverse cardiac events (MACE), defined as all-cause death, acute coronary syndrome (ACS), stent thrombosis, stroke or target vessel revascularization (TVR) after the index PCI. The secondary endpoint was cardiac death following RA. Secondary analyses considered each component of the secondary endpoint. Cardiac death was defined as death due to a cardiac disease such as MI, arrhythmia, or heart failure. Sudden or unexplained death was adjudicated as cardiac. ACS was defined as acute MI (AMI) and unstable angina. We determined AMI based on symptoms of ischemia and elevated concentration of cardiac enzymes such as troponin. Unstable angina was diagnosed in the presence of ischemic symptoms at rest or a crescendo of symptoms or new-onset symptoms associated with

Table 2. Baseline Lesion and Procedure Characteristics (n=1,090)

	n (%)
Target vessel	
LAD	741 (68.0)
RCA	199 (18.3)
LCX	122 (11.2)
LMC	114 (10.5)
Multivessel disease	796 (73.0)
Chronic total occlusion	59 (5.4)
Small vessel (≤2.5 mm)	228 (21.3)
Long stent use (≥23 mm)	791 (74.1)
Guiding catheter (Fr)	
6	392 (36.8)
7	603 (56.6)
8	71 (6.7)
Maximum burr size (mm)	
1.25	83 (7.6)
1.5	458 (42.2)
1.75	344 (31.7)
2.0	165 (15.2)
2.15	26 (2.4)
2.25	10 (0.9)
RA bar step-up	366 (33.6)
Scoring balloon after ROTA	128 (12.2)
IVUS	796 (73.0)
Stent type	
Bare-metal stent	117 (11.2)
1st-generation DES	549 (52.5)
SES	345 (31.7)
PES	229 (21.0)
2nd-generation DES	379 (36.3)
Co-Cr EES	251 (23.0)
Pr-Cr EES	109 (10.0)
Other DES	29 (2.7)
Final TIMI 3 flow	1,049 (96.2)

Co-Cr, cobalt chromium stent; DES, drug-eluting stent; EES, everolimus-eluting stent; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMC, left main coronary artery; PES, paclitaxel-eluting stent; Pr-Cr, platinum chromium stent; RA, rotational atherectomy; RCA, right coronary artery; SES, sirolimus-eluting stent; TIMI, Thrombolysis in Myocardial Infarction.

Table 3. In-Hospital and Long-Term Outcome

	n (%)
In-hospital outcome	
In-hospital death	33 (3.0)
MI	23 (2.1)
Tamponade	10 (0.9)
Major bleeding	17 (1.6)
IABP/PCPS	29 (2.7)
Emergency operation	7 (0.6)
Overall clinical outcomes during follow up	
MACE	495 (45.5)
All cause death	263 (24.2)
Cardiac death	118 (10.9)
ACS	74 (6.8)
TLR	176 (16.2)
TVR	233 (21.4)
Stent thrombosis (definite, probable)	14 (1.3)
Stroke	51 (4.7)

ACS, acute coronary syndrome; IABP, intra-aortic balloon pumping; MACE, major adverse cardiac event; MI, myocardial infarction; PCPS, percutaneous cardiopulmonary support; TLR, target lesion revascularization; TVR, target vessel revascularization.

transient ischemic ST-segment shifts and without release of the enzymes associated with myocardial necrosis. Stent thrombosis was classified according to the Academic Research Consortium criteria (definite+probable).[16] Target lesion revascularization (TLR) was defined as any revascularization inside the stent implanted during the index procedure or within 5 mm proximal or distal to the stent. TVR was defined as the need for a new revascularization, either percutaneous or surgical, of the target vessel previously treated by RA. Stroke (including ischemic and hemorrhagic stroke) was diagnosed according to the clinical presentation and imaging. In this study, all endpoints were analyzed on a per-patient basis.

Statistical Analysis

Quantitative data are presented as mean±SD or median (IQR). Categorical variables are presented as number and percentage. Kaplan-Meier plots for cumulative incidence of MACE, all-cause death, cardiac death, ACS, stent thrombosis, stroke, TLR, and TVR were constructed from the index procedure, and differences between groups were assessed using the log-rank test. Multivariable Cox hazard regression analysis was performed to identify independent risk factors for MACE and cardiac death. Variables entered into the multivariable model were those that reached significance ($P<0.10$) following univariate Cox hazard regression analysis and were judged as clinically significant. Differences were considered significant at $P<0.05$. Statistical analysis was performed using JMP version 12.0 (SAS Institute, Cary, NC, USA).

Results

Baseline Clinical Characteristics

Baseline patient characteristics are summarized in **Table 1**. Mean age was 70±9.7years (range, 24–96 years), and 31% were >75 years old. The prevalence of diabetes mellitus (DM) was 60%, prevalence of ACS was 15%, and prevalence of hemodialysis was 27.7%. A total of 73% of patients had multivessel or left main disease, and left ventricular (LV) function was well preserved with a median ejection fraction of 54.9%.

Procedure Characteristics and In-Hospital Outcome

More than half of the RA (56.6%) were performed through a 7-Fr guiding catheter. Target lesions were primarily located in the left anterior descending artery (68.0%). Chronic total occlusion was seen in 5.4% of lesions and median maximum burr size was 1.75 mm. Almost half of the patients were treated with first-generation DES, including paclitaxel-eluting stents (21.0%) or sirolimus-eluting stents (31.7%). Second-generation DES, including zotarolimus-, biolimus- and everolimus-eluting stents, were used for 390 patients (36.3%) In the majority of cases, lesions were

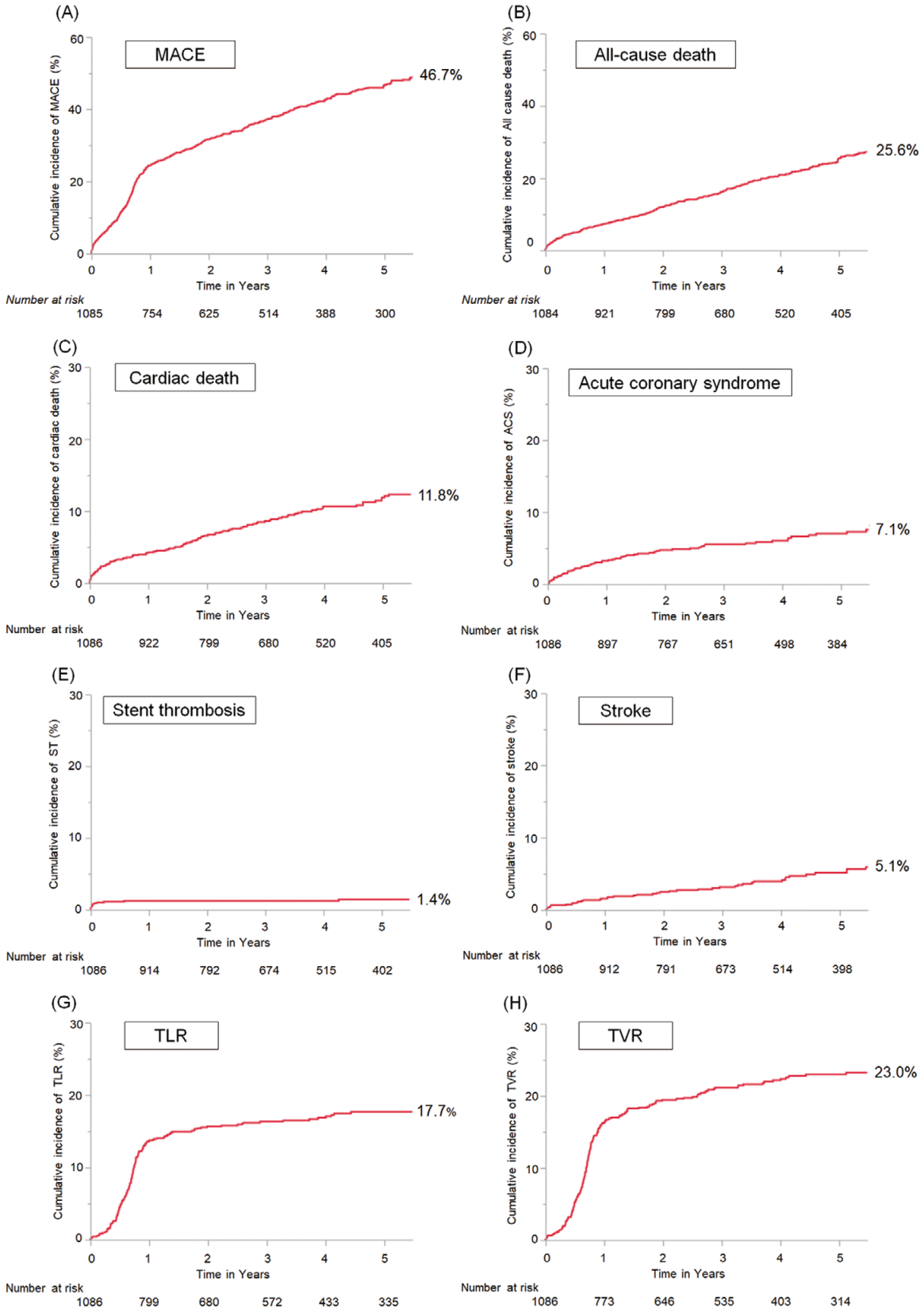

Figure. Cumulative incidence curves for (**A**) major adverse cardiac events (MACE), (**B**) all-cause death, (**C**) cardiac death, (**D**) acute coronary syndrome, (**E**) stent thrombosis, (**F**) stroke, (**G**) target lesion revascularization (TLR) and (**H**) target vessel revascularization (TVR).

Table 4. Univariate Indicators of MACE and Cardiac Death

	MACE			Cardiac death		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (1-year increase)	1.01	1.003–1.02	0.012	1.04	1.02–1.06	0.0005
BMI (1-kg/m^2 increase)	0.96	0.93–0.99	0.007	0.87	0.82–0.93	<0.0001
Diabetes mellitus	1.25	1.04–1.50	0.015	1.85	1.25–2.80	0.002
Chronic kidney disease	2.35	1.96–2.82	<0.0001	3.68	2.48–5.62	<0.0001
Hemodialysis	2.61	2.18–3.13	<0.0001	3.29	2.29–4.73	<0.0001
Atrial fibrillation	1.19	0.93–1.50	0.17	1.85	1.17–2.84	0.01
Statin	0.63	0.52–0.75	<0.0001	0.53	0.36–0.76	0.0006
LDL-C (10-mg/dL increase)	0.99	0.96–1.02	0.53	0.99	0.93–1.04	0.68
CRP (1-mg/dL increase)	1.02	1.003–1.04	0.03	1.04	1.01–1.06	0.008
ACS	2.07	1.65–2.57	<0.0001	2.50	1.62–3.75	<0.0001
LMC	1.24	0.94–1.61	0.13	2.04	1.25–3.18	0.005
Multivessel disease	1.02	0.84–1.25	0.83	1.53	0.99–2.45	0.05
Low LVEF (<50%)	1.85	1.53–2.24	<0.0001	3.54	2.41–5.24	<0.0001
RA bar step-up	1.38	1.15–1.65	0.0006	1.05	0.71–1.53	0.79
IVUS	0.88	0.72–1.07	0.18	0.70	0.48–1.03	0.07
Drug-eluting stent use	0.68	0.53–0.89	0.005	0.84	0.51–1.47	0.53

HR, hazard ratio; IVUS, intravascular ultrasound. Other abbreviations as in Tables 1–3.

Table 5. Multivariate Indicators of MACE and Cardiac Death

	HR	95% CI	P-value
MACE			
Age (1-year increase)	1.03	1.01–1.04	<0.0001
Chronic kidney disease	1.42	1.05–1.89	0.022
Hemodialysis	2.08	1.53–2.86	<0.0001
Statin	0.79	0.64–0.98	0.035
ACS	1.56	1.18–2.02	0.0019
Low EF (<50%)	1.46	1.17–1.80	0.0007
RA bar step-up	1.22	0.99–1.51	0.065
DES	0.72	0.55–0.97	0.029
Cardiac death			
Age (1-year increase)	1.06	1.03–1.08	<0.0001
Chronic kidney disease	2.29	1.26–4.13	0.0078
Hemodialysis	2.40	1.30–4.12	0.0037
Diabetes mellitus	1.74	1.12–2.80	0.014
Statin	0.64	0.42–0.97	0.026
CRP (1-mg/dL increase)	1.05	1.001–1.08	0.062
Multivessel disease	1.79	1.11–3.02	0.012
Low EF (<50%)	2.66	1.76–4.05	<0.0001

EF, ejection fraction. Other abbreviations as in Tables 1–4.

treated with a long stent (≥23 mm, 74.1%; **Table 2**).

Final TIMI 3 flow was achieved in 96.2% of patients. In this study, cardiac tamponade was seen in 0.9% of patients and urgent cardiac surgery was required in 0.6%. A total of 33 deaths (3.0%) occurred during hospitalization (**Table 3**).

Long-Term Clinical Outcomes

Median follow-up was 3.8 years (IQR, 1.9–6.1 years), and the follow-up rate was 99.5%. In total, 263 all-cause deaths (24.2%) were identified during follow-up, including 118 cardiac deaths (10.9%). The cumulative incidence of MACE (Kaplan-Meier estimate) at 5 years was 46.7%. ACS occurred in 7.1%, stent thrombosis in 1.4%, stroke in 5.1%, TLR in 17.7%, and TVR in 23.0%. On Kaplan-Meier curves, plateaus for TLR and TVR rates were observed within 2 years, whereas rates of both cardiac death and all-cause death continuously increased throughout the entire observation period (**Figure**).

Predictors of MACE

Variables with P<0.10 on univariate Cox analysis for MACE were age, body mass index (BMI), DM, CKD, hemodialysis, CRP, ACS, low LV ejection fraction (LVEF), RA bar step-up, DES use and use of statins (**Table 4**). On multivariate Cox hazard analysis, age (P<0.0001), hemo-

dialysis (P<0.0001), ACS (P=0.0019) and low LVEF (P=0.0007) were strong independent predictors of MACE. In contrast, statin use at the time of RA (P=0.035) and DES use (P=0.029) were associated with lower MACE (**Table 5**).

Predictors of Cardiac Death

Variables with P<0.10 on univariate Cox analyses for cardiac death were age, BMI, DM, CKD, hemodialysis, CRP, ACS, atrial fibrillation, multivessel disease, lesion of the left main coronary artery, low LVEF and use of statins (**Table 4**). On multivariate Cox hazard analysis, age (P<0.0001), hemodialysis (P=0.0037), CKD (P=0.0078), DM (P=0.014) and low LVEF (P<0.0001) were strong independent predictors of cardiac death. Only statin use was associated with better long-term prognosis (P=0.026; **Table 5**).

Discussion

This study presents the largest Japanese dataset of long-term follow-up of RA. The major findings were as follows: (1) procedure success was achieved in 96.2% of patients with low overall complication rates; (2) high rates of follow-up MACE and cardiac death were observed, in proportion to the severity of clinical characteristics; (3) even after adjusting for important covariates, age and CKD including hemodialysis were identified as significant predictors for MACE and cardiac death; and (4) statin treatment at the time of RA was associated with better long-term prognosis in terms of both MACE and cardiac death.

Previous studies have reported that use of RA is associated with increased neointimal hyperplasia and restenosis, most likely due to platelet activation and thermal injury.[17,18] When treatment is required for heavily calcified lesions, however, RA remains an important tool for preventing insufficient expansion, asymmetric expansion, or stent malapposition, and improves procedure success rates.[19] In addition, balloon angioplasty alone requires high-pressure dilatation, increasing the risks of coronary dissection and thrombosis when treating a heavily calcified lesion. Higher rates of complications have been noted with the use of atherectomy devices during PCI.[20] Concerning the safety of RA, we demonstrated a high success rate with very few complications. The ROTAXUS trial recently examined whether lesion preparation with RA before implantation of DES provides benefits compared with DES with balloon pre-dilatation alone in patients with calcified lesions.[21] As a result, although strategy success was higher with RA pre-treatment, rates of cardiac events did not differ significantly between groups.[21] In the present study, "RA bar step-up" and "DES use" were significant predictors for only MACE, and not for cardiac death. We consider that these predictors were associated with only lesion-level clinical outcomes such as TVR and TLR. In other words, these factors did not result in a "hard" event outcome such as cardiac death during the follow-up period.

In the present study, overall cumulative 5-year incidences were 11.8% for cardiac death, 25.6% for all-cause death, and 46.7% for MACE, which might be higher than in previous studies.[22–24] Another multicenter registry reported a rate of all-cause death after RA of 5.0% at 1 year and 9.5% at 2 years.[13] This difference might be explained by the fact that the present subjects included more high-risk patients who were elderly (mean age, 70 years) with high prevalences of DM (60.0%) and hemodialysis (27.7%). In addition, the incidence of MACE was principally driven by TVR during approximately the first year, then increased gradually. This may be attributable to in-stent restenosis diagnosed on scheduled follow-up coronary angiography. In a recent study based on data from a large registry, middle-term survival was worse in the RA group compared with PCI without RA, and this survival disadvantage remained after correction for important factors.[12] Based on those and the present results, it is important to note that patients with calcific coronary lesions are at high risk for the development of worse outcomes when intervention includes RA.

Regarding clinical predictors of worsened cardiac mortality following RA, age, DM, hemodialysis, CKD and low LVEF were the only significant strong predictors. Eftychiou et al also showed that DM and ACS presentation were significant predictors of cardiac events, including cardiac death by 22 months of follow-up.[23] Kawamoto et al recently reported hemodialysis as the strongest predictor of MACE at 2-year follow-up.[13] Kyono et al also reported that both angiographic and clinical outcomes were still suboptimal for highly complex, severely calcified lesions requiring RA in patients with hemodialysis, even when using DES.[25] The present study provides one of the largest sets of observational data with the longest follow-up period, and confirms a 21.5% rate of cardiac death, similar to other registry data from smaller samples with shorter follow-up. In contrast, statin use was the only significant predictor associated with more positive outcomes on multivariate analysis. Statins are very well known to reduce cardiovascular events and mortality in patients with coronary artery disease or at high risk of cardiovascular disease. In a serial coronary IVUS study, Puri et al reported that patients with coronary artery disease who are treated with statins have an increased rate of coronary calcification, an effect that is independent of plaque progression or regression.[26] They concluded that calcium within the coronary arteries is not necessarily all the same; rather, the interpretation of calcified lesions likely depends on the context and duration of therapy, as well as on the specific clinical situation. In other words, we thus believe that significant differences exist in calcium morphology within a coronary artery wall between statin use and non-statin use. Further investigation using different modalities is needed to more accurately assess calcium morphology within the arterial wall during PCI as a means of honing risk prediction for future cardiovascular events.

Several limitations to this study must be considered. First, as a single-arm retrospective study, this study did not establish the efficacy of RA compared with other techniques, and was instead limited to whole prognosis in patients undergoing RA. Second, analysis of the angiography did not utilize a core laboratory, and indications for RA, PCI, or clinical follow-up were dependent on daily practice in each hospital. The lack of core laboratory analysis of data may have adversely affected the accuracy of reported outcomes. Third, routine angiographic follow-up (72% of patients) could potentially have induced bias in TVR rate.

Conclusions

This study represents one of the largest investigations of RA for heavily calcified coronary lesions in this DES era. Although RA in calcified lesions appeared feasible and

offered a high rate of procedural success, a high incidence of follow-up MACE was observed. Multivariate analysis identified age and CKD including hemodialysis as strong independent predictors for both MACE and cardiac death. We therefore believe that further studies including innovative pharmacologic and device-based approaches are needed to improve the poor prognosis of heavily calcified coronary lesions.

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