

Clinical outcomes of rotational atherectomy in severely calcified in-stent restenosis: a single-center, retrospective study

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ABSTRACT

Neointimal calcification after stent implantation has been reported as one of the forms of neoatherosclerosis. There are a few patients with in-stent restenosis (ISR) and an undilatable calcified neointima who require rotational atherectomy to achieve sufficient acute gain in lumen diameter. However, the clinical outcomes of rotational atherectomy for undilatable calcified ISR have not been fully elucidated. Therefore, we investigated the safety and efficacy of rotational atherectomy for treating calcified ISR. This retrospective study included 17 patients (20 lesions) who had undergone percutaneous coronary intervention including rotational atherectomy to treat ISR with severely calcified neointima. Kaplan-Meier analysis was used to analyze the data. The mean age of the enrolled patients was 67±18 years, and 71% were men. The patients had highly atherogenic characteristics: 65% had diabetes mellitus and 53% were receiving hemodialysis. Procedural success was obtained in 19 (95%) patients, and the acute gain in lumen diameter was acceptable (1.7±0.6 mm). However, during a median follow-up of 571 days, the incidences of major adverse cardiac and cerebrovascular events per patient and clinical-driven target lesion revascularizations per lesion were relatively high. There were no differences in clinical outcomes according to the baseline characteristics, type of restenotic stents, and therapeutic strategy. In conclusion, clinical outcomes of rotational atherectomy for severely calcified ISR were unfavorable despite a high success rate and acceptable acute gain in lumen diameter.

Keywords: in-stent restenosis, calcified neointima, rotational atherectomy, and major adverse cardiac and cerebrovascular events

Abbreviations:

ISR: in-stent restenosis

PCI: percutaneous coronary intervention

BP: blood pressure

DESs: drug-eluting stents

MACCEs: major adverse cardiac and cerebrovascular events

TLR: target lesion revascularization

TVR: target vascular revascularization

CABG: coronary artery bypass grafting

QCA: quantitative coronary angiography

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BMSs: bare metal stents

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INTRODUCTION

In-stent restenosis (ISR) remains a challenging issue of percutaneous coronary intervention (PCI) even in the drug-eluting stent era.¹ Several techniques, including balloon angioplasty, plaque debulking, vascular brachytherapy, additional stent implantation, and use of a drug-coated balloon have been performed for the treatment of ISR, and the implantation of a new-generation drug-eluting stent or angioplasty with a drug-coated balloon is currently recommended.^{2,3}

In PCI for lesions with ISR, intracoronary imaging has been shown to provide therapeutic insights, such as anatomical information, possible underlying mechanisms, and optimization of the treatment.⁴⁻⁶ In terms of achievement of sufficient acute gain in lumen diameter, procedural success is obtained in most cases. However, there are rare cases with undilatable ISR owing to a severely calcified neointima. In prior case reports, rotational atherectomy has been reported as a solution for sufficient dilatation.^{7,8} Yet, the clinical features of severely calcified ISR and the effectiveness of rotational atherectomy remain unknown. Herein, we investigated the safety and efficacy of using rotational atherectomy for treating calcified ISR.

METHODS

Study Population

We retrospectively reviewed cases of PCIs including rotational atherectomy for lesions with ISR between October 2010 and September 2017 (Fig. 1). Patients were followed until March 2018. Clinical and procedural data were obtained from patients' medical records. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from each patient, and the study was approved by the hospital's ethics committee (Approval No. R18-011, May 21, 2018).

The decision to perform rotational atherectomy depended on the attending physician, when near-circumferential calcification was found by intravascular ultrasonography (Fig. 2), or when sufficient lesion expansion could not be achieved by balloon angioplasty owing to intra-stent calcification. All procedures of rotational atherectomy were performed using the Rotablator™ system (Boston Scientific, Marlborough, MA, USA). Selection of the wire, burr size used in rotational atherectomy, and subsequent therapeutic strategy were also left to the physicians' judgement. The antiplatelet regimen included low-dose aspirin (typically 100 mg/day) and thienopyridine (75 mg/day of clopidogrel or 3.75 mg/day of prasugrel). Dual antiplatelet therapy was continued according to the guidelines of the Japanese Circulation Society or the attached documents of the devices used in the treatment as follows; at least one month after balloon angioplasty, three months after the use of drug-coated balloon, or six months after the implantation of new generation drug-eluting stents (DES).⁹

Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on repeated measurements, and/or receipt of antihypertensive treatment. Diabetes mellitus was defined according to the diagnostic criteria of the Japan Diabetes Society.¹⁰ Dyslipidemia

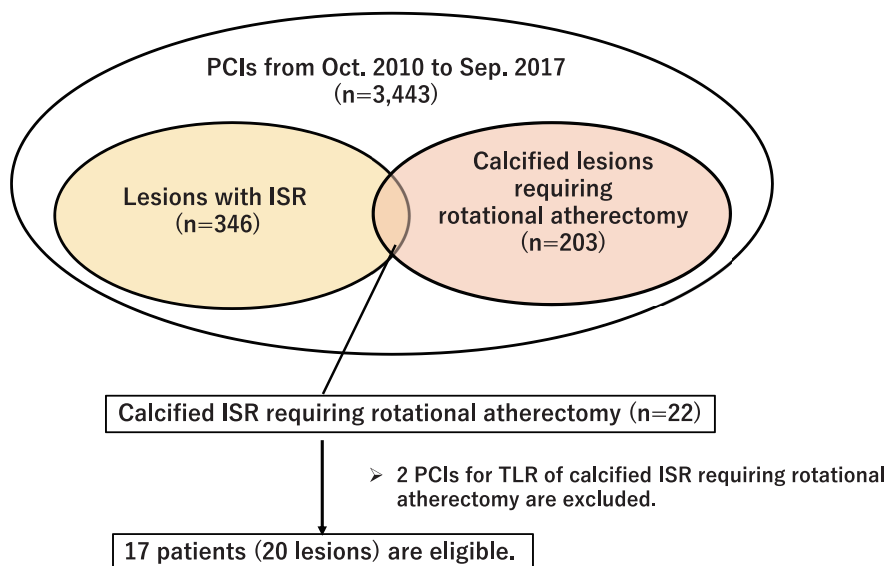


Fig. 1 Flow chart of the study population.

PCI, percutaneous coronary intervention; ISR, in-stent restenosis; TLR, target lesion revascularization.

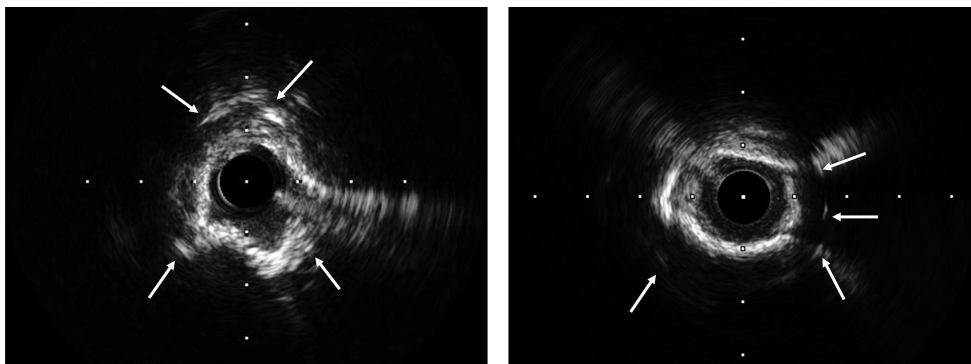


Fig. 2 Representative images of in-stent restenosis with near-circumferential calcified neointima detected by intravascular ultrasonography.

White arrows demonstrate stent struts behind the calcifications.

was defined as levels of total cholesterol ≥ 220 mg/dL, triglyceride ≥ 150 mg/dL, low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL and/or receipt of lipid-lowering therapy. Focal patterns of ISR were defined as Mehran classes IA to ID, and diffuse pattern classes II to IV.¹¹

In our study, the first-generation DES comprised durable polymer sirolimus-eluting stents (Cypher™, Cordis, Miami Lakes, FL, USA) and durable polymer paclitaxel-eluting stents (Taxus™, Boston Scientific). The new-generation DES included durable polymer everolimus-eluting stents (Promus™, Boston Scientific and Xience™, Abbott Vascular, Santa Clara, CA, USA), biodegradable polymer biolimus A9-eluting stents (Nobori™, Terumo Corp., Tokyo, Japan), and biodegradable polymer everolimus-eluting stents (Synergy™, Boston Scientific).

Echocardiographic examination was performed by an experienced sonographer using the Vivid E9™ with XDclear ultrasound system (GE Healthcare, Tokyo, Japan). The images were recorded on a console and analyzed offline. Left ventricular ejection fraction was calculated using the modified Simpson's rule.

Follow-up and Assessment of Clinical Outcomes

All patients underwent regular follow-up examinations by means of outpatient clinical visits. Incidences of major adverse cardiac and cerebrovascular events (MACCEs) per patient and clinical-driven target lesion revascularization (TLR) per lesion were evaluated. A MACCE was defined as a composite of cardiac death, nonprocedural myocardial infarction, stroke, and ischemic-driven target vascular revascularization (TVR). Cardiac death was determined as the composite of myocardial infarction, heart failure, or sudden death due to clinically suspected coronary heart disease based on the patient's clinical examination. TVR and TLR were defined as either PCI or coronary artery bypass grafting (CABG) for the recurrence of ISR or stent thrombosis of the target vessel and lesion, respectively. Stent thrombosis was diagnosed according to the Academic Research Consortium criteria.¹²

Quantitative coronary angiography (QCA) analyses were performed using an automated edge-detection system (Goodnet, Goodman Corp., Nagoya, Japan). The reference vessel diameter, minimum lumen diameter, percentage diameter stenosis, lesion length, and acute gain in lumen diameter were measured. Procedural success was defined as reduction of the percentage diameter stenosis <50% by QCA.

Statistical Analysis

Continuous variables are presented as means±standard deviations or medians with interquartile ranges, as appropriate. Categorical variables are presented as numbers and/or percentages. The event-free rate for MACCEs was determined by Kaplan-Meier analysis. In all analyses, $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS Statistics 21 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Seventeen patients (20 lesions) who underwent PCI for ISR with rotational atherectomy were included in this study. Table 1 shows the patients' baseline characteristics. Patients mean age was 66.9 ± 17.7 years, and 70.6% were men. Overall, 64.7% had diabetes mellitus, and insulin users accounted for 54.5% of diabetic patients. Fifty-three percent of the patients were receiving hemodialysis with an average duration of 5.9 years.

Baseline lesion and procedural characteristics are shown in Table 2. Most restenotic stents were implanted primarily in calcified lesions. Regarding the type of stents, the average number of years after the last stent implantation during PCI for restenosis was longer with bare metal stents (BMSs) (7.6 ± 3.7 years) than with DESs (4.0 ± 3.6 years), but the difference was not statistically significant ($p=0.092$). Angiographic and procedural characteristics were not different between the BMS and DES groups.

There were no peri-procedural deaths. However, two major complications occurred. In one case, the wire for rotational atherectomy was disrupted in one PCI, in which the target lesion of rotational atherectomy was the ostial right coronary artery. After retrieval of the disrupted wire, rotational atherectomy with a new wire led to successful results. In another case, peri-procedural bleeding was identified after manual hemostasis due to retroperitoneal hemorrhage requiring

transfusion. Table 3 shows the acute results of QCA. Average reduction of the percentage diameter stenosis was $73.9 \pm 15.3\%$. Procedural success, defined by findings of QCA, was achieved in 19 (95%) patients. Acute gain in lumen diameter was 1.67 ± 0.55 mm.

The median follow-up duration was 571 days (interquartile range, 473–1178 days). Kaplan-Meier estimates for the incidence of MACCEs per patient during the follow-up period are shown in Fig. 3a. Myocardial infarction due to definite acute thrombosis occurred in one patient 23 days after PCI. Actual numbers of the other MACCEs during the follow-up period were as follows; 4 cardiac deaths, 1 stroke, and 10 clinical-driven target vessel revascularizations. Fig. 3b shows Kaplan-Meier estimates for the incidence of TLRs per lesion. Neither patient characteristics nor therapeutic strategies after rotational atherectomy, such as the usage of a drug-coated balloon or drug-eluting stent, were associated with the incidence of MACCEs and TLRs (Table 4). Among 10 cases of TVR, CABG was performed in four. Among the other six patients who underwent re-PCI, two patients required rotational atherectomy again, and five were treated without additional stenting.

Table 1 Patients' baseline characteristics (n = 17)

Baseline Variables	
Age (years), mean \pm SD	66.9 \pm 17.7
Male sex (%)	12 (70.6%)
BMI (kg/m ²), mean \pm SD	23.0 \pm 3.1
Hypertension (%)	12 (70.6%)
Dyslipidemia (%)	17 (100%)
LDL cholesterol level (mg/dL), mean \pm SD	88.4 \pm 19.9
HDL cholesterol level (mg/dL), mean \pm SD	48.8 \pm 18.1
Presence of diabetic mellitus (%)	11 (64.7%)
Insulin user (%)	6 (35.3%)
HbA1c level (%), mean \pm SD	6.7 \pm 1.4
Current smoker (%)	1 (5.9%)
Prior CABG (%)	4 (23.5%)
Prior stroke (%)	1 (5.9%)
Presence of peripheral artery disease (%)	1 (5.9%)
Kidney dysfunction (eGFR <60) (%)	11 (64.7%)
Dialysis (%)	9 (52.9%)
LV ejection fraction (%), mean \pm SD	55.2 \pm 7.6

SD, standard deviation; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LV, left ventricular.

Table 2 Lesion and procedural characteristics (n=20)

Baseline variables		
Underlying lesion characteristics	Type of restenotic stent	
	Bare metal stent	4 (20%)
	First-generation drug-eluting stent	7 (35%)
	New-generation drug-eluting stent	9 (45%)
	Restenotic stent size (mm), mean \pm SD	3.1 \pm 0.4
	Calcified lesion	17 (85%)
	Calcified lesion requiring rotational atherectomy	5 (25%)
Angiographic characteristics	Lesion location	
	Left anterior descending	8 (40%)
	Left circumflex	1 (5%)
	Right coronary artery	10 (50%)
	Ostial right coronary artery	2
	Graft	1 (5%)
	ISR pattern according to Mehran's classification	
	Focal (IA/IB/IC/ID)	9 (45%)
	Diffuse (II/III/IV)	11 (55%)
	Acute coronary syndrome	9 (45%)
Chronic total occlusion	0 (0%)	
Procedural characteristics	Use of IVUS	20 (100%)
	Number of burrs, mean \pm SD	1.6 \pm 0.5
	Maximum burr size (mm), mean \pm SD	1.8 \pm 0.2
	Total run time (seconds), mean \pm SD	67.1 \pm 42.8
	Mean rotational speed (\times 1000 rpm), mean \pm SD	201.6 \pm 6.1
	Cutting or scoring after rotational atherectomy	8 (40%)
	New stent implantation	6 (30%)
	New-generation drug-eluting stent	6
	Stent size (mm), mean \pm SD	3.3 \pm 0.3
	Stent length (mm), mean \pm SD	22.8 \pm 8.4
Use of a drug-coated balloon	4 (20%)	

SD, standard deviation; IVUS, intravascular ultrasonography; ISR, in-stent restenosis.

Table 3 Findings of quantitative coronary angiography findings (n=20)

Pre-procedure	
Reference diameter (mm), mean \pm SD	2.70 \pm 0.46
Lesion length (mm), mean \pm SD	18.5 \pm 9.4
Minimal lesion diameter (mm), mean \pm SD	0.55 \pm 0.34
Percent diameter stenosis (%), mean \pm SD	79.1 \pm 12.8
Post-procedure	
Reference diameter (mm), mean \pm SD	2.87 \pm 0.55
Minimal lesion diameter (mm), mean \pm SD	2.24 \pm 0.44
Percent diameter stenosis (%), mean \pm SD	20.3 \pm 11.8

QCA, quantitative coronary angiography; SD, standard deviation.

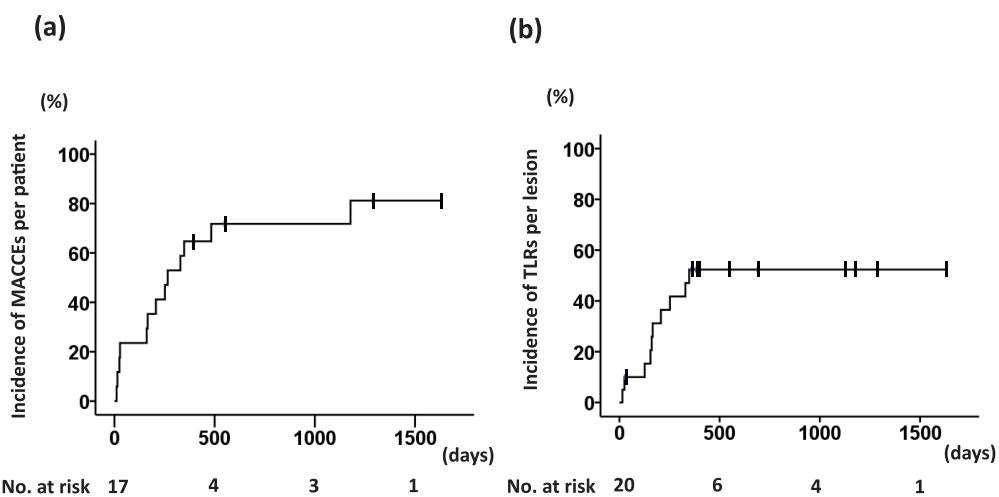


Fig. 3 Kaplan-Meier estimates of the incidence of (a) major adverse cardiac and cerebrovascular events (MACCE) per patient and (b) target lesion revascularization (TLR) per lesion.

No., number.

Table 4 Univariate cox proportional hazards regression analyses for MACCEs and TLRs

	MACCEs			TLRs		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.001	0.964–1.038	0.978	0.984	0.953–1.017	0.345
Male	0.500	0.162–1.538	0.227	0.799	0.206–3.097	0.745
Body mass index	0.971	0.815–1.156	0.740	0.866	0.692–1.084	0.210
Hypertension	1.540	0.414–5.734	0.519	0.964	0.248–3.752	0.958
HDL-cholesterol	1.008	0.975–1.042	0.636	1.017	0.985–1.050	0.313
LDL-cholesterol	0.978	0.951–1.006	0.120	0.972	0.944–1.001	0.062
Diabetes mellitus	0.759	0.239–2.416	0.641	0.481	0.133–1.742	0.265
Creatinine	1.174	0.962–1.433	0.114	0.975	0.821–1.157	0.769
Hemodialysis	1.686	0.544–5.226	0.365	1.547	0.433–5.528	0.501
Current smoker	1.203	0.151–9.555	0.862	1.713	0.213–13.753	0.613
Rotational atherectomy for underlying lesion	1.342	0.353–5.107	0.666	0.682	0.145–3.216	0.628
In-stent restenosis of DES	1.318	0.408–4.254	0.644	0.819	0.173–3.868	0.801
Post minimal lumen diameter	0.677	0.165–2.775	0.588	0.474	0.085–2.641	0.394
Acute gain in lumen diameter	0.623	0.183–2.120	0.449	1.067	0.322–3.540	0.915
Usage of DCB or DES after rotational atherectomy	1.177	0.382–3.628	0.777	0.879	0.251–3.018	0.826

MACCE, major adverse cardiac and cerebrovascular event; TLR, target lesion revascularization; HR, hazard ratio; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; DCB, drug-coated balloon; DES, drug-eluting stent.

DISCUSSION

This study highlighted the clinical outcomes of patients who underwent PCI with rotational atherectomy for calcified ISR. Procedural success rate and acute gain in lumen diameter were acceptable. However, the incidences of MACCEs and TLRs were relatively high, despite the subsequent use of a new-generation drug-eluting stent or a drug-coated balloon. These results suggest that heavily calcified ISR is one of the achilles heel of PCI.

Neointimal calcification was identified in 5–10% of the neointima of the stent in one pathological study.¹³ Investigations of in-stent neointima using intracoronary imaging modalities have demonstrated that calcified neointima is found in 10–20% of the stents.^{14–16} The incidence of calcified neointima was associated with time after stenting, renal function, and calcific lesion characteristics before stent implantation. These findings implicated the neointimal calcification as a part of in-stent neoatherosclerosis. Generally, in-stent neoatherosclerosis is characterized by an accumulation of lipid-laden foamy macrophages within the neointima with or without necrotic core formation and/or calcification.^{13,17} However, as shown in our data and prior case reports, there are rare cases with undilatable ISR due to severely calcified neointima.¹⁸ Herein, most of the enrolled patients had diabetes and/or received dialysis. Furthermore, the duration since the last stenting was an average of 4.75 years. Therefore, severely calcified neointima can be regarded as a form of extremely advanced in-stent neoatherosclerosis involving various factors that cause and predispose the patient to calcification.

A calcified neointima has been reported to be associated with the treatment results. In optical coherence tomographic examination of the stent-in-stent strategy, the presence of neointimal calcification has been shown to cause stent underexpansion, which might lead to thrombosis and

the recurrence of restenosis.¹⁹ In drug-coated balloon treatment for ISR, inadequate angiographical predilatation is a predictor of TLR.²⁰ In prior case reports on undilatable calcified ISR, debulking with rotational atherectomy seemed to be promising for achieving favorable lesion expansion.^{7,8} Conversely, we investigated the clinical follow-up data after the debulking of calcified neointima with rotational atherectomy and demonstrated that the incidences of MACCEs and TLRs were relatively high in spite of acceptable lesion expansion after the index procedure.

Considering previous studies that failed to show the long-term clinical benefit of rotational atherectomy in de novo lesions, our results might be not surprising.^{21,22} Of course, optimization of the burr-to-lesion ratio or more aggressive debulking with a larger burr size might provide sufficient plaque modification and lead to better outcomes. However, the use of larger burrs could induce more platelet activation and thermal injury. In addition, lesion modification using a large burr with guidewire bias may compromise the occurrence of complications, such as coronary slow flow phenomenon and vessel perforation, especially in a tortuous artery. From this viewpoint, future new devices are expected. Orbital atherectomy has the potential to achieve a larger gain in lumen diameter with less heat generation.²³ Laser coronary atherectomy has been reported to affect the underlying deep calcification behind the stent strut.^{24,25} Furthermore, recent reports have demonstrated that coronary lithoplasty could achieve more significant acute gain in lumen diameter and the modification of deep-seated calcium.^{26,27}

The current study has several limitations. First, it was a single-center, retrospective study with a small sample size and single-arm. Future prospective studies of a larger population are required to assess the long-term clinical results of rotational atherectomy in undilatable calcified ISR. Second, the method of performing rotational atherectomy, such as the choice of imaging device, burr size, and pre-dilation methods, were left to the treating physicians' discretion. Finally, planned follow-up CAG data were obtained in only less than half of the enrolled patients because of the early incidence of MACCEs and patients' preference.

In conclusion, our findings suggest that the clinical outcomes of rotational atherectomy for severely calcified ISR were unfavorable despite a high success rate and acceptable acute gain in lumen diameter. Interventionalists should recognize the limitation of PCI with the current debulking technique, although some advances are anticipated.

CONFLICT OF INTEREST

Y.U. received lecture fees from Otsuka Pharma Ltd. H.I. received lecture fees from Astellas Pharma Inc., Daiichi-Sankyo Pharma Inc., and Otsuka Pharma Inc. T.M. received lecture fees from Bayel Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Sanofi-aventis K.K., and Takeda Pharmaceutical Co., Ltd. T.M. received unrestricted research grants for the Department of Cardiology, Nagoya University Graduate School of Medicine from Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kowa Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Otsuka Pharma Ltd., Pfizer Japan Inc., Sanofi-aventis K.K., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd.

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