Original Article

Predictors of clinical outcome after rotational atherectomy-facilitated percutaneous coronary intervention in hemodialysis patients

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Background: Percutaneous coronary intervention (PCI) in hemodialysis patients with severely calcified and diffused lesions is associated with extremely high rates of major adverse cardiovascular events (MACE), even when facilitated by rotational atherectomy (ROTA). Potential risk factors for MACE with ROTA-facilitated PCI in hemodialysis patients should be identified.

Methods: We retrospectively analyzed a consecutive cohort of patients from the Sapporo Cardiovascular Clinic database, who were on maintenance hemodialysis with severe calcified lesions and treated with ROTA-facilitated PCI. Clinical and interventional procedure characteristics were collected and compared between patients with and without MACE, defined as all-cause death, hospitalization due to heart failure, definite stent thrombosis, or target lesion revascularization (TLR) at 1-year follow-up. The individual outcomes of MACE and TLR in the cohort were presented as Kaplan-Meier percentages. Cox regression analyses were performed to identify independent predictors of MACE.

Results: A total of 138 patients undergoing hemodialysis and followed up for 362.50 (243.75, 382.25) days. Sixty-one patients in the cohort had MACE, most of which were TLR (47.5%, 29/61). Cumulative all-cause death at 30-day and 1-year follow-up were 6.52% and 18.8%, respectively. Patients with right coronary artery (RCA) lesions, in-stent restenosis (ISR) lesions, and were more likely to have MACE, even with larger reference vessel diameter and greater acute gain after PCI. Cox regression analysis demonstrated that ISR lesion was positively associated with both MACE (HR 3.21, 95% CI: 1.59–6.48) and TLR (HR 5.08, 95% CI: 1.78–14.47), latter of which was also proved to be significantly related to greater acute gain (HR 1.95, 95% CI: 1.12–3.39). In subgroup analysis, RCA was found to be positively associated with MACE in *de novo* lesion (HR 2.83, 95% CI: 1.28–6.28).

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Conclusions: We found that the overall prognosis of ROTA-facilitated PCI in hemodialysis patients was poor. ISR was a significant risk factor for MACE, especially TLR.

Keywords: Hemodialysis; rotational atherectomy; calcification; target lesion revascularization

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Introduction

Patients with maintenance hemodialysis (HD) have a 10 to 20 times higher rate of cardiovascular mortality than the general population (1-3). Uremia-related risk factors in addition to traditional risk factors accelerate arteriosclerosis in HD patients (3); disturbance of calcium-phosphorus homeostasis and uremic toxins may lead to accelerated calcification of arterial media (4).

HD and severe calcification of coronary lesions are high-risk factors for restenosis after percutaneous coronary intervention (PCI), even with use of a drug-eluting stent (DES) facilitated by rotational atherectomy (ROTA) (5-7). In our previous overview report on ROTA-facilitated PCI, HD was found to be significantly associated with major adverse cardiovascular events (MACE) and target lesion revascularization (TLR), with the highest hazard ratio (HR) value (8). However, there are limited and conflicting data regarding independent risk factors of ROTA-PCI outcomes in HD patients (8-10). Since the selection bias for ROTA bailout use and the interventionist's discretion on an individualize lesion, RCT and even registry or retrospective data about ROTA utility in HD patients is of paucity. ROTA is well known as an effective plaque debulking and modification tool in PCI, but the predictors for MACE in HD patients with ROTA-PCI is still unknown. For better and earlier management of the contributing risk factors, we enrolled HD patients with ROTA-facilitated PCI, and retrospectively evaluated data and compared outcome to identify potential risk factors for MACE. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1658).

Methods

Patient enrollment and exclusion criteria

During the period from January 2013 to December 2015, a consecutive cohort of patients undergoing maintenance HD owing to end-stage renal failure who were treated with ROTA-facilitated PCI were retrospectively included. The data source was the Sapporo Cardiovascular Clinic (SCVC) database. Exclusion criteria were: (I) incomplete follow-up data; (II) non-HD patients; (III) PCI without ROTA pretreatment; and (IV) temporal bailout HD (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Sapporo Heart Center Institutional Review Board (No. SCVC20210011) and individual consent for this retrospective analysis was waived.

All patients underwent a routine clinical follow-up at least once within 2 years in the outpatient clinic that involved an interview with the interventionist. The presence of MACE was recorded based on findings at the visit or on a telephone call. Follow-up with coronary computed tomographic angiography (CCTA) was performed routinely within 6–12 months after PCI, and coronary angiogram (CAG) was done for new-onset patient symptoms, evidence of cardiac ischemia, or high index of clinical suspicion for significant coronary disease. Blood samples were drawn before and 12 months after PCI to assess the hemoglobin level and lipid profile.

Definitions

Angiographic success for ROTA + stenting was defined as successful stent delivery and expansion with attainment of ≤20% in-stent residual stenosis of the target lesion in the presence of TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. Angiographic success for ROTA + plain old balloon angioplasty (POBA) and ROTA + drug-coated balloon (DCB) was defined as ≤30% residual diameter stenosis by quantitative coronary angiography with TIMI flow grade 3 and no perforation. Follow-up MACE included all-cause death, hospitalization due to heart failure, definite stent thrombosis (ST), and ischemia-driven TLR.

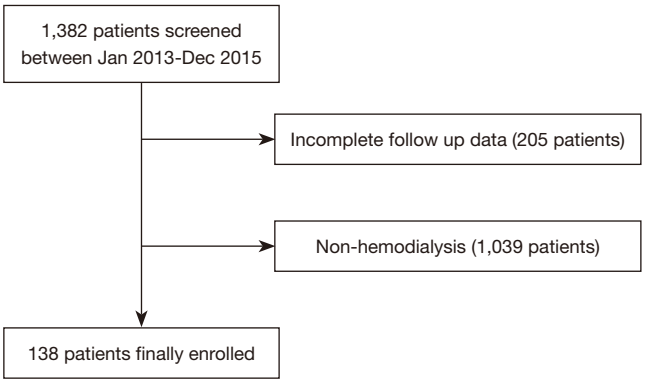

Figure 1 Study population screening procedure in the database.

TLR was defined as a repeat intervention within 5 mm proximal or distal to the target lesion previously treated in the index procedure or coronary artery bypass graft surgery (CABG) of a lesion in the same epicardial vessel treated in the index procedure. Calcifications were classified as previously reported as mild with a single image or multiple images of non-linear well-defined calcium density located on the target lesion, moderate with an image of linear calcium density located on one side of the target lesion that was not visible under detailed fluoroscopic imaging with 15 frame per second X-ray fluoroscopy with or without contrast filling, and severe with a linear calcium density image located on both sides of the target lesion that was visible under detailed fluoroscopic imaging (11,12).

PCI procedure and medication

The PCI strategy and decision to perform ROTA was at the interventionist's discretion. The general indications for ROTA in HD included: (I) lesions with moderate to severe superficial calcification or fibrous calcification compound, identified using imaging methods such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT); (II) calcified lesions with difficulty in passing devices, such as a balloon catheter, imaging catheter, or stent; (III) residual indentation was identified, even when utilizing high-pressure balloon dilatation; (IV) chronic total occlusion lesions, in which the guidewire has been correctly positioned but low-profile balloons cannot be advanced; (V) selected cases of diffuse in-stent restenosis. The ROTA procedure in the SCVC has been described previously (8). Quantitative coronary angiography (QCA) analysis was performed according to the previously reported method using CAAS software ver. 5.9.1. (Pie Medical Imaging, Maastricht, the Netherlands) (13).

With regard to antiplatelet strategy, dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitor (ticlopidine, 100 mg twice daily or clopidogrel, 75 mg once daily) was administrated in all cases at least 48 hours before PCI and continued for at least 1 year regardless of DES implantation or POBA alone. Statins as well as other secondary prevention drugs and antihypertensive and hypoglycemic agents were prescribed according to current guidelines.

Statistical analysis

Missing data were not imputed because <1% of data for any predictor variable were missing from the cohort data set. Baseline patient characteristics, angiographic data, and parameters during each procedure were compared between patients in the MACE (+) *vs.* MACE (–) groups in the cohort. The individual outcomes of MACE and TLR were prespecified end points, presented as Kaplan-Meier percentages. Continuous data are presented as mean ± standard deviation or median (interquartile range) (25th and 75th percentiles), as appropriate, and categorical variables are presented as frequency (%). For continuous variables, the Shapiro-Wilk test was used to test the normal distribution of continuous variables. The Student *t*-test or U test was used to analyze continuous variables depending on the normality of the data distribution, and the Pearson χ^2 test or Fisher's exact test was used for categorical variables, as appropriate. Univariate and multivariate Cox regression analysis was performed to evaluate the independent predictors of MACE. The results are presented as HR with 95% confidence intervals (CIs). All P values were not adjusted for multiple testing. All analyses were performed using IBM SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). All reported P values are two-sided and P values <0.05 were regarded as statistically significant.

Results

Population demographics

A total of 305 HD patients underwent PCI during the study period, and 138 patients with 179 lesions were eligible to enroll the study; of these, 131 patients initially had ROTA-facilitated PCI and bailout was used in 7 patients owing to devices not crossing the lesion or

Table 1 Baseline characteristics by patients with and without MACE in the study cohort (n=138)

Variable	MACE (+) (n=61)	MACE (–) (n=77)	P value
Age (y)	68 (54–78)	71 (65–76)	0.176
BMI (kg/m^3)	23.7 (22.0–26.8)	22.4 (20.5–24.4)	0.003
Male sex, n (%)	24 (39.3)	14 (18.2)	0.006
Current smoker, n (%)	5 (8.2)	12 (15.6)	0.391
HD duration (m)	74.0 (48.0–112.0)	76.0 (30.5–163.5)	0.822
Diabetes mellitus, n (%)	33 (54.1)	40 (51.9)	0.802
Insulin use, n (%)	11 (18.0)	5 (6.5)	0.036
Hypertension, n (%)	59 (96.7)	67 (87.0)	0.044
Hyperlipidemia, n (%)	43 (70.5)	47 (61.0)	0.247
OMI, n (%)	27 (44.3)	18 (23.4)	0.009
Previous PCI, n (%)	46 (75.4)	46 (59.7)	0.052
Previous CABG, n (%)	11 (18.0)	12 (15.6)	0.702
Atrial fibrillation, n (%)	5 (8.2)	2 (2.6)	0.137
LVEF (%)	60.0 (48.5–64.7)	61.5 (54.3–67.7)	0.096
Admission laboratory data			
Hemoglobin (g/dL)	11.3 (10.3–12.1)	11.5 (10.3–12.1)	0.339
HDL-C (mg/dL)	37.0 (30.0–48.5)	40.0 (33.0–52.0)	0.087
LDL-C (mg/dL)	81.5 (54.5–112.0)	77.0 (62.5–96.0)	0.539
HbA1c (%)	5.8 (5.3–6.9)	5.5 (5.1–6.2)	0.059

MACE, major adverse cardiovascular events; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.

inadequate balloon dilatation. Clinical follow-up was available in 97.5% of patients. Of the 138 enrolled patients, 61 (44.2%) experienced MACE (*Table 1*). Patients who developed MACE tended to have higher body mass index [BMI; 23.7 (22.0–26.8) *vs.* 22.4 (20.5–24.4), P=0.003] and included more men (39.3% *vs.* 18.2%, P=0.006) when compared with MACE (–) patients; in addition, more MACE (+) patients used insulin (18.0% *vs.* 6.5%, P=0.036) and had hypertension (96.7% *vs.* 87.0%, P=0.044) and old myocardial infarction (44.3% *vs.* 23.4%, P=0.009). Age, HD duration, proportion of current smokers, diabetes mellitus, hyperlipidemia, previous PCI or CABG, and atrial fibrillation were comparable between the two groups. Left ventricular ejection fraction (LVEF), hemoglobin, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and glycated hemoglobin (HbA1c) were not significantly different between the groups.

Lesion and procedural characteristics

Lesion characteristics were compared between MACE (+) and MACE (–) groups (*Table 2*). Most lesions were type B2 and C lesions, according to the modified American College of Cardiology/American Heart Association classification system. There were more in-stent restenosis (ISR) lesions (50.8% *vs.* 20.8%, P<0.001) in the MACE (+) group than the MACE (–) group. Moreover, the percentage of target vessel right coronary artery (RCA) was much higher (52.5% *vs.* 33.8%, P=0.027), but that for LAD was lower (21.3% *vs.* 48.1%, P=0.001) in the MACE (+) group. Other lesion features, such as lesion angulation, bifurcation, ostial lesion, chronic total occlusion (CTO), and lesion length, were comparable between the groups.

Table 2 Baseline lesion characteristics by patients with and without MACE in the study cohort (n=138)

Variable	MACE (+) (n=61)	MACE (–) (n=77)	P value
Target vessel, n (%)			
LMT	3 (4.9)	6 (7.8)	0.497
LAD	13 (21.3)	37 (48.1)	0.001
LCX	14 (23.0)	11 (14.3)	0.189
RCA	32 (52.5)	26 (33.8)	0.027
De novo lesion, n (%)	30 (49.2)	61 (79.2)	<0.001
ISR, n (%)	31 (50.8)	16 (20.8)	<0.001
Lesion angulation >45°, n (%)	34 (55.7)	42 (54.5)	0.058
Bifurcation lesion, n (%)	26 (42.6)	35 (45.5)	0.739
Ostial lesion, n (%)	29 (47.5)	30 (39.0)	0.312
Aorto-ostial lesion, n (%)	12 (19.7)	10 (13.0)	0.287
CTO, n (%)	7 (11.5)	5 (6.5)	0.302
Lesion length (mm)	29.0 (18.0–40.0)	29.8 (20.3–40.6)	0.327
Reference vessel diameter (mm)	3.3 (2.6–3.6)	2.7 (2.4–3.3)	0.004
Lesion type, n (%)			0.195
A	0 (0.0)	0 (0.0)	
B1	0 (0.0)	0 (0.0)	
B2	13 (21.3)	18 (23.4)	
C	48 (78.7)	59 (76.6)	

MACE, major adverse cardiovascular events; LMT, left main trunk; LAD, left anterior descending coronary; LCX, left circumflex artery; RCA, right coronary artery; ISR, in-stent restenosis; CTO, chronic total occlusion.

All intervention procedural characteristics are also listed in *Table 3*. IVUS or OCT was applied during all PCI procedures. Of note, the maximum stent diameter, minimum lumen diameter (MLD) after PCI, and acute lumen gain were larger in the MACE (+) group; however, the stent-to-artery ratio [0.8 (0.0–1.0) *vs.*1.0 (0.0–1.1), P=0.071] and maximum burr-to-artery ratio [0.5 (0.4–0.7) *vs.* 0.7 (0.6–0.7), P=0.011] were lower in MACE (+) group than MACE (–) group. The total stent length, number of burrs use (≥2), and number of stents use were similar between the two groups. There was also no difference in the PCI strategy (ROTA + POBA, ROTA + DES, ROTA + DCB) or PCI complications [slow/no flow perforation, burr stuck, residual dissection type (A/B)] between groups.

Clinical follow-up data

Patients were followed up for 362.50 (243.75, 382.25) days. The cumulative rates of MACE and TLR were 44.2% (61/138) (*Figure 2A*) and 21.01% (29/138) (*Figure 2B*), respectively. BMI, male sex, target vessel RCA, ISR, and diameter stenosis before PCI were risk factors, and left anterior descending coronary (LAD) was a protective factor for MACE in the univariate analysis. Furthermore, ISR (HR 3.21, 95% CI: 1.59–6.48, P=0.02) was an independent predictors for MACE, in multivariate regression analysis (*Table 4*). In addition, we further found that ISR (HR 5.08, 95% CI: 1.78–14.47, P=0.02) and acute lumen gain (HR 1.95, 95% CI: 1.12–3.39, P=0.017) were independent predictors for TLR (*Table 5*).

Because the risk factors related to outcome may be different for *de novo* and ISR lesions, we stratified the sub-analysis. For *de novo* lesions, male sex (HR 3.71, 95% CI: 1.66–8.29, P=0.001), target vessel RCA (HR 2.83, 95% CI: 1.28–6.28, P=0.010) and LVEF (HR 0.95, 95% CI: 0.92–0.98, P=0.008) were risk factors for MACE. However,

Table 3 PCI procedure and QCA data in the study cohort (n=138)

Variable	MACE (+) (n=61)	MACE (–) (n=77)	P value
ROTA bailout usage	2 (3.2)	1 (1.3)	0.584
Image device, n (%)	61 (100.0)	77 (100.0)	>0.999
Fluoroscopy time (min)	27.0 (18.9–38.0)	26.5 (18.8–37.1)	0.973
Maximum stent diameter (mm)	3.5 (3.0–3.5)	3.0 (2.5–3.5)	0.027
Maximum burr size (mm)	1.8 (1.5–2.0)	1.8 (1.5–2.0)	0.896
Maximum burr-to-artery ratio	0.5 (0.4–0.7)	0.7 (0.6–0.7)	0.011
Maximum balloon-to-artery ratio	1.0 (0.9–1.3)	1.1 (1.0–1.3)	0.180
Maximum stent-to-artery ratio	0.8 (0.0–1.0)	1.0 (0.0–1.1)	0.071
Total stent length (mm)	38 [23–42]	38 [22–48]	0.898
No. of burrs used (≥2)	33 (54.1)	38 (49.4)	0.579
No. of stents used	1 (0–1)	1 (0–1)	0.411
PCI strategy			0.395
ROTA+POBA	21 (32.8)	19 (24.7)	
ROTA+DES	34 (55.7)	52 (67.5)	
ROTA+DCB	6 (9.8)	6 (7.8)	
Immediate QCA			
MLD before PCI (mm)	0.8 (0.5–1.2)	1.0 (0.7–1.3)	0.189
%DS before PCI	69 [61–79]	61 [54–72]	0.071
MLD after PCI (mm)	3.1 (2.4–3.6)	2.8 (2.3–3.2)	0.005
%DS after PCI	7 (–2.8 to 17.8)	8 (–4.0 to 17.0)	0.904
Acute gain (mm)	2.0 (1.6–2.5)	1.7 (1.4–2.1)	0.030
PCI complications, n (%)			0.521
Slow/no flow	0 (0.0)	0 (0.0)	
Perforation	1 (1.6)	1 (1.3)	
Burr stuck	1 (1.6)	0 (0.0)	
Residual dissection type (A/B)	0 (0.0)	0 (0.0)	

PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; MACE, major adverse cardiovascular events; ROTA, rotational atherectomy; POBA, plain old balloon angioplasty; DES, drug-eluting stent; DCB, drug-coated balloon; MLD, minimum lumen diameter; DS, diameter stenosis.

for ISR lesions, only %DS before PCI was an independent risk factor for MACE in the multivariate regression analysis (*Table 6*).

Although the proportion of POBA in the MACE (+) group was slightly higher than the MACE (–) group (*Table 3*), the PCI strategy was not associated with the studied outcomes with univariate analysis (*Tables 4-6*). Sensitivity analysis was conducted to furtherly adjust the PCI strategy in the multivariate models, and showed similar finding with the original results (Tables S1-S3), in spite of fluctuation in the confidence intervals due to small sample size.

Because the target vessel location is an important factor for adverse events, we compared the clinical and lesion characteristics between different target vessels. The proportion of RCA location (42.0%, 58/138) was the

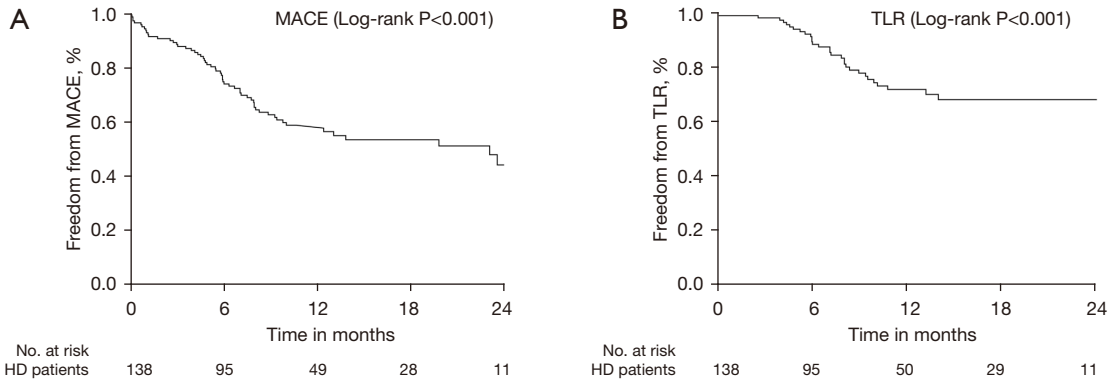

Figure 2 Kaplan-Meier curves for patients' outcome were illustrated in (A) and (B) respectively. (A) Survival curve for the MACE in HD patients. (B) Survival curve for the TLR in HD patients. MACE, major adverse cardiac events; TLR, target lesion revascularization; HD, hemodialysis.

highest in all target vessels. There were more lesions with angulation >45° but less with bifurcation among RCA than LAD and LCX. The reference vessel diameter was larger in RCA (3.2±0.5 mm) than LAD (2.7±0.6 mm) and LCX (2.7±0.8 mm) (P<0.001) (*Table* 7).

Discussion

We had previously found that ROTA was beneficial for an excessive amount of calcified and fibrotic plaque, and HD was the most significantly related risk factor for cardiac events and TLR in patients undergoing PCI, even facilitated with ROTA (8,14). Furthermore, the present paper demonstrated that the risk of MACE remained high after PCI for calcified lesions in HD patients, even when facilitated with ROTA. TLR contributed half of the MACE in these patients. ISR lesion while RCA in *de novo* lesion were the main risk factors for MACE in multivariate analysis.

In SCVC, we have ROTA, directional coronary atherectomy (DCA), excimer laser coronary angioplasty (ECLA), cutting/soring balloon and high pressure non-compliant balloon for calcium-modification on hand. And we did not have orbital atherectomy or intravascular lithotripsy yet. As the indication mentioned above, rotational atherectomy is the first choice for the calcium-modification technique in severe calcification cases in our routinely clinical practice. For the moderate and severe calcified lesion, ROTA has the three advantages of device passing, creating crack and plaque debulking. DCA was easy to cause hematoma for deep cutting and, ECLA or cutting balloon were not effective in passing and cracking in severe calcification. Patients with HD and ROTA-needed CAD should be followed up carefully because of their poor prognosis. And the MACE and TLR rates were so high in the first year that early screening and treatment of ISR or ischemia was indispensable before ACS attacked. CCTA presents as an accurate and ideal diagnostic method for vessel noninvasive assessment (15), and limited contrast (less than 20 mL) was needed for CCTA in SCVC clinical practice even though contrast dosing was not that influential for HD patients. Therefore, CCTA was positive and necessary for such group of patients.

Patients with end-stage renal failure have more diffuse coronary disease and more vascular calcification (16,17). Therefore, revascularization for HD patients with coronary artery disease is one of the main challenges for interventional cardiologists owing to the complexity of lesions and high occurrence of target vessel failure. Because inadequate dilatation or spiral dissection owing to severe coronary calcification and barotrauma from non-compliant ballooning may account for a higher restenosis rate, severely calcified lesions may interfere with the diffusion of more hydrophilic antiproliferative drugs in patients undergoing HD. We assumed that superficial calcification debulking would allow for more effective revascularization in HD patients, and the threshold of ROTA use in these patients is relatively low in our center. For sufficient dilatation, the purpose of ROTA here was plaque "modification" and "debulking" as well. An aggressive ablation strategy (higher burr/vessel ratio and low speed polishing) with IVUS guidance can safely and effectively guarantee a smooth and dilatable lumen. In the present cohort, we found that ROTA-facilitated PCI

Table 4 Predictors of MACE in univariate and multivariate analysis

Variable	Univariate analysis, HR (95% CI)	P value	Multivariable analysis, HR (95% CI)	P value
PCI strategy		0.872		
ROTA+DCB	1.22 (0.51–2.94)			
ROTA+POBA	1.10 (0.63–1.91)			
ROTA+DES	1.00			
BMI	1.10 (1.02–1.20)	0.019		
Male sex	2.02 (1.20–3.38)	0.008		
Current smoker	0.73 (0.48–1.10)	0.128		
HD duration (m)	0.99 (0.99–1.00)	0.060		
Diabetes	1.02 (0.61–1.68)	0.952		
Statins used	0.96 (0.56–1.66)	0.964		
Insulin used	1.65 (0.85–3.21)	0.140		
Hypertension	2.74 (0.67–11.26)	0.161		
OMI	1.73 (1.03–2.89)	0.037		
Target vessel				
LAD	0.38 (0.21–0.71)	0.002	0.31 (0.12–0.76)	0.011
RCA	1.99 (1.20–3.30)	0.008		
Previous PCI	1.38 (0.77–2.48)	0.284		
LDL-C	0.99 (0.99–1.01)	0.853		
Hemoglobin	0.88 (0.75–1.03)	0.109		
HbA1c	1.24 (1.01–1.53)	0.044		
LVEF	0.98 (0.86–0.99)	0.040		
ISR	1.90 (1.15–3.15)	0.013	3.21 (1.59–6.48)	0.001
Contrast volume	0.99 (0.99–1.00)	0.093		
Reference vessel diameter	1.46 (1.02–2.09)	0.038		
Lesion length	0.99 (0.98–1.01)	0.44		
Immediate QCA				
%DS before PCI	1.03 (1.01–1.06)	0.006		
MLD after PCI	1.33 (0.83–2.14)	0.242		
Acute gain	1.71 (1.07–2.75)	0.026		
Maximum burr-to-artery ratio	0.29 (0.05–1.54)	0.146		
Maximum stent-to-artery ratio	0.91 (0.57–1.43)	0.674		

MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; LAD, left anterior descending coronary; RCA, right coronary artery; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; ISR, in-stent restenosis; QCA, quantitative coronary angiography; DS, diameter stenosis; MLD, minimum lumen diameter; HR, hazard ratio; CI, confidence interval.

Table 5 Predictors of TLR in univariate and multivariate analysis

Variables	Univariate analysis, HR (95% CI)	P value	Multivariable analysis, HR (95% CI)	P value
PCI strategy		0.313		
ROTA+DCB	2.21 (0.79–6.13)			
ROTA+POBA	1.24 (0.56–2.73)			
ROTA+DES	1.00			
BMI	1.12 (0.99–1.25)	0.053		
Male sex	1.43 (0.68–3.05)	0.348		
Current smoker	0.91 (0.55–1.51)	0.712		
HD duration (m)	0.99 (0.99–1.00)	0.268		
Diabetes	1.41 (0.68–2.91)	0.352		
Statins used	1.64 (0.80–3.38)	0.180		
Insulin used	2.86 (1.26–6.49)	0.012		
Hypertension	23.38 (0.09–5,989.25)	0.265		
OMI	2.20 (1.08–4.49)	0.030		
Target vessel				
LAD	0.25 (0.09–0.65)	0.004	0.29 (0.08–0.99)	0.049
RCA	4.27 (2.00–9.12)	<0.001		
Previous PCI	4.33 (1.31–14.27)	0.016		
LDL-C	1.00 (0.99–1.01)	0.437		
Hemoglobin	0.91 (0.72–1.14)	0.394		
HbA1c	1.40 (10.6–1.83)	0.016		
LVEF	0.99 (0.96–1.03)	0.898		
ISR	5.49 (2.45–12.33)	<0.001	5.08 (1.78–14.47)	0.002
Contrast volume	0.99 (0.98–0.99)	0.023		
Reference vessel diameter	1.80 (1.10–2.94)	0.019		
Lesion length	0.99 (0.97–1.02)	0.493		
Immediate QCA				
%DS before PCI	1.05 (1.01–1.08)	0.005		
MLD after PCI	3.08 (1.47–6.44)	0.003		
Acute gain	3.54 (1.98–6.35)	<0.001	1.95 (1.12–3.39)	0.017
Maximum burr-to-artery ratio	0.13 (0.01–1.80)	0.128		
Maximum stent-to-artery ratio	0.69 (0.36–1.32)	0.262		

TLR, target lesion revascularization; PCI, percutaneous coronary intervention; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; LAD, left anterior descending coronary; RCA, right coronary artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; ISR, in-stent restenosis; QCA, quantitative coronary angiography; DS, diameter stenosis; MLD, minimum lumen diameter; HR, hazard ratio; CI, confidence interval.

Table 6 Predictors of MACE stratified by category of ISR in univariate and multivariate analysis

Variables	*De novo*				ISR			
	Univariate analysis, HR (95% CI)	P value	Multivariable analysis, HR (95% CI)	P value	Univariate analysis, HR (95% CI)	P value	Multivariable analysis, HR (95% CI)	P value
PCI strategy		0.521				0.802		
ROTA+DCB	–				0.72 (0.26–1.98)			
ROTA+POBA	1.34 (0.54–3.30)				0.95 (0.43–2.10)			
ROTA+DES	1.00				1.00			
BMI	1.05 (0.93–1.19)	0.387			1.18 (1.03–1.35)	0.014		
Male	2.56 (1.23–5.33)	0.012	3.71 (1.66–8.29)	0.001	1.78 (0.84–3.78)	0.133		
Current smoker	0.71 (0.41–1.22)	0.218			1.37 (0.70–2.68)	0.353		
HD duration (m)	0.99 (0.99–1.00)	0.212			0.99 (0.99–1.00)	0.086		
Diabetes	0.51 (0.24–1.10)	0.082			2.09 (0.96–4.57)	0.058		
Statins used	0.94 (0.42–2.13)	0.890			0.84 (0.41–1.77)	0.661		
Insulin used	0.46 (0.06–3.36)	0.441			2.56 (1.13–5.76)	0.023		
Hypertension	1.72 (0.41–7.25)	0.458			21.73 (0.01–75,101.27)	0.458		
OMI	2.06 (0.98–4.32)	0.056			1.23 (0.60–2.51)	0.573		
Target vessel								
LAD	0.27 (0.11–0.67)	0.005			0.80 (0.34–1.88)	0.612		
RCA	2.42 (1.16–5.04)	0.018	2.83 (1.28–6.28)	0.010	1.25 (0.61–2.58)	0.541		
Previous PCI	1.17 (0.56–2.46)	0.670			0.57 (0.17–1.93)	0.367		
LDL-C	0.99 (0.98–1.01)	0.892			0.99 (0.98–1.01)	0.230		
Hemoglobin	0.81 (0.62–1.06)	0.125			0.96 (0.79–1.16)	0.671		
HbA1c	1.16 (0.78–1.73)	0.462			1.25 (0.96–1.62)	0.098		
LVEF	0.96 (0.93–0.99)	0.019	0.95 (0.92–0.98)	0.008	0.99 (0.96–1.02)	0.680		
Contrast volume	0.99 (0.99–1.00)	0.356			0.99 (0.99–1.00)	0.194		
Reference vessel diameter	1.58 (0.94–2.65)	0.082			(–)	0.320		
Lesion length	0.99 (0.97–1.02)	0.864			0.99 (0.97–1.03)	0.912		
Immediate QCA								
%DS before PCI	1.01 (0.97–1.05)	0.522			1.05 (1.02–1.08)	0.004	1.05 (1.02–1.08)	0.004
MLD after PCI	1.27 (0.61–2.65)	0.522			1.21 (0.69–2.11)	0.498		
Acute gain	1.59 (0.67–3.78)	0.292			1.47 (0.86–2.52)	0.155		
Maximum burr-to-artery ratio	0.08 (0.01–1.20)	0.068			0.45 (0.09–2.25)	0.331		
Maximum stent-to-artery ratio	1.33 (0.62–2.87)	0.463			1.08 (0.54–2.15)	0.819		

MACE, major adverse cardiovascular events; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; LAD, left anterior descending coronary; RCA, right coronary artery; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; QCA, quantitative coronary angiography; DS, diameter stenosis; MLD, minimum lumen diameter; HR, hazard ratio; CI, confidence interval.

Table 7 Characteristics of studied participants by different target vessel in the study cohort

Variables	LAD (n=50)	RCA (n=58)	LCX (n=25)	P value*
Age (y), mean ± SD	71.0±10.4	66.0±11.8	67.1±13.5	0.161
BMI (kg/m^3), mean ± SD	22.5±3.5	23.5±3.3	24.2±3.8	0.234
De novo lesion, n (%) =0	39 (78.0)	32 (55.2)	17 (68.0)	0.043
Lesion angulation >45°, n (%)	4 (8.0)	27 (46.6)	6 (24.0)	<0.001
Bifurcation lesion, n (%)	32 (64.0)	8 (13.8)	18 (72.0)	<0.001
Ostial lesion, n (%)	24 (48.0)	19 (32.8)	14 (56.0)	0.094
Aorta-ostial lesion, n (%)	6 (12.0)	15 (25.9)	0 (0.0)	0.008
CTO, n (%)	1 (2.0)	7 (12.1)	4 (25.0)	0.076
Lesion length (mm), mean ± SD	32.6±16.8	33.2±12.7	25.6±7.5	0.160
Reference vessel diameter (mm), mean ± SD	2.7±0.6	3.2±0.5	2.7±0.8	<0.001
POBA	21 (42.0)	17 (29.3)	12 (48.0)	0.196
DES	28 (56.0)	41 (70.7)	13 (52.0)	0.160
DCB	3 (6.0)	8 (13.8)	1 (4.0)	0.231
Acute gain	1.7±0.5	2.0±0.7	1.8±0.5	0.131

*, no statistical analysis was performed due to small sample size of left main trunk group (n=5). LAD, left anterior descending coronary; RCA, right coronary artery; LCX, left circumflex artery; BMI, body mass index; CTO, chronic total occlusion; POBA, plain old balloon angioplasty; DES, drug-eluting stent; DCB, drug-coated balloon; SD, standard deviation.

was safe, with a relatively high success rate. However, the midterm outcome was still unfavorable, especially for ISR and TLR. In line with our finding, the J2T ROTA registry, which comprises data from a multicenter, retrospective, cohort study that involved 1,090 patients who underwent ROTA for *de novo* calcified coronary lesions between 2004 and 2015 in Japan, also found that ROTA-facilitated PCI was associated with rates of MACE as high as 66.9%. The rates of MACE, any death, TLR, and stroke were significantly higher in the HD group than in the non-HD group in the J2T ROTA registry (18). In concern with the PCI strategy, the current concept recommended stenting (including for ISR) unless the patient already had two layers of stent. In our study, 66.7% (92/138) patients had previous stenting PCI and 34.1% (47/138) patients had ISR lesions. We tended to performed POBA or DCB for previous PCI patients, especially for those with long term dual antiplatelet drugs intolerance. Therefore, the frequency of patients receiving POBA and DCB was relatively high in the studied cohort, with a rate of 30% (40/138) and 8.7% (12/138), respectively.

ISR commonly occurs after coronary stent implantation in patients undergoing HD (19). Patients receiving HD tend to have greater calcification of their coronary arteries, which hampers optimization of PCI results (20) and leads to inappropriate vascular healing (21). In contrast to angioplasty, where restenosis is predominantly caused by elastic recoil and vascular remodeling, ISR is almost exclusively owing to neointimal hyperplasia (21,22). Although the optimal treatment of ISR has not yet been well defined, three treatment approaches are commonly used: (I) POBA; (II) atheroablation (ROTA, excimer laser angioplasty and directional coronary atherectomy); and (III) additional stenting. Adamian *et al.* reported a matched comparison of these three approaches and found that cutting balloon angioplasty was associated with immediate results similar to atheroablation and better clinical and angiographic outcomes at follow-up (23). However, the main application of a cutting balloon is in non-calcified lesions with concentric plaques. In one study, intravascular imaging evaluation (IVUS/OCT) demonstrated that the prevalence of in-stent calcification was also significantly higher in the HD group compared to the non-HD group (75% versus 5%, respectively; P<0.01), despite the time to ISR being shorter in the HD group (median 10.5 versus 23 months; P=0.13). However, the prevalence of in-stent

lipid-rich plaque was significantly lower in the HD group (0% versus 43%, respectively; P=0.03) (24). The calcified character of ISR in HD patients poses a great challenge in treatment. In a previous series, we found that ROTA-facilitated PCI was a safe and efficient technique for the treatment of ISR but was still related to a high MACE rate (25). Further, in our present data of HD patients, ISR lesions had an even worse outcome than *de novo* lesions. The rate of MACE after intervention for ISR was 21.01%, even lower than those in previous reports (26,27).

We found that larger acute gain was related to a higher TLR rate, which indicated that aggressive ROTA may not always be beneficial. Additionally, with the risk of coronary artery perforation, larger acute gain may further injure the intima and media. It has been found that media tears are associated with increased neointima growth (28,29). Farb *et al.* reported that arterial medial fracture was associated with a 29% increase in neointimal thickness compared with arteries that have an intact media in bare metal stents (28). Moreover, neointimal thickness, degree of inflammation, and neovascularization are greater when struts are in contact with a torn media/intima as compared with struts on an intact fibrous cap. The ideal solution to balance the goals of reducing artery fracture with encouraging strut coverage in heavily calcified lesions may depend on developing atherectomy devices that are able to fracture calcium but not cause excessive injury to the arterial wall. Newer approaches such as a lithotripsy may be promising in this regard, but their advantages still need to be proven against more traditional atherectomy methods (21).

RCA lesion was also an independent risk factor for MACE in *de novo* lesion, which could be explained by the frequent existence of calcified nodule, the hinge motion or excessive torsion stress this vessel, as well as the presence of ISR lesion. As reported by Morofuji *et al.* (30), HD patients tended to have calcified nodule in the coronary. Other studies reported calcified nodule is most frequently observed in the RCA (31), and well known to cause poor outcome. However, the lacking of detail information about calcified nodule limited further validation of this hypothesis in the current study. Besides, previous studies showed that hinge motion or excessive torsion stress in RCA is the maximal during the cardiac cycle (31-33). Furthermore, in the current study, RCA had 42.0% of the target lesion located in this vessel, and half of which was ISR lesion. As we known, ISR lesion revascularization was highly associated with poor outcome.

Study limitations

Some limitations should be acknowledged. First, the choice of ROTA was based on the interventionist's discretion, which would inevitably lead to selection bias. Second, interventional coronary angiography driven by clinical symptoms would also numerically decrease the MACE prevalence owing to the misdiagnosis of silent ischemia. Third, our sample size was relatively small.

Conclusions

In this study, we found that the overall prognosis of ROTA-facilitated PCI in patients receiving HD was very poor, with high mortality. TLR was the predominant major adverse event in ROTA-facilitated PCI among HD patients, even with a high rate of successful procedure. ISR lesion was the main risk factor for MACE in multivariate analysis. And patients with RCA target vessel were more likely to have MACE in *de novo* lesion.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Sapporo Heart Center Institutional Review Board (No. SCVC20210011) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Predictors of MACE

Variable	Univariate analysis HR (95% CI)	P value	Multivariable analysis HR (95% CI)	P value
PCI strategy		0.872		0.834
ROTA+DCB	1.22 (0.51–2.94)		0.78 (0.30–2.01)	
ROTA+POBA	1.10 (0.63–1.91)		1.04 (0.58–1.84)	
ROTA+DES	1.00		1.00	
BMI	1.10 (1.02–1.20)	0.019		
Male sex	2.02 (1.20–3.38)	0.008		
Current smoker	0.73 (0.48–1.10)	0.128		
HD duration (m)	0.99 (0.99–1.00)	0.060		
Diabetes	1.02 (0.61–1.68)	0.952		
Statins used	0.96 (0.56–1.66)	0.964		
Insulin used	1.65 (0.85–3.21)	0.140		
Hypertension	2.74 (0.67–11.26)	0.161		
OMI	1.73 (1.03–2.89)	0.037		
Target vessel				
LAD	0.38 (0.21–0.71)	0.002	0.42 (0.22–0.80)	0.009
RCA	1.99 (1.20–3.30)	0.008		
Previous PCI	1.38 (0.77–2.48)	0.284		
LDL-C	0.99 (0.99–1.01)	0.853		
Hemoglobin	0.88 (0.75–1.03)	0.109		
HbA1c	1.24 (1.01–1.53)	0.044		
LVEF	0.98 (0.86–0.99)	0.040		
ISR	1.90 (1.15–3.15)	0.013	1.66 (0.94–2.95)	0.078
Contrast volume	0.99 (0.99–1.00)	0.093		
Reference vessel diameter	1.46 (1.02–2.09)	0.038		
Lesion length	0.99 (0.98–1.01)	0.44		
Immediate QCA				
%DS before PCI	1.03 (1.01–1.06)	0.006		
MLD after PCI	1.33 (0.83–2.14)	0.242		
Acute gain	1.71 (1.07–2.75)	0.026		
Maximum burr-to-artery ratio	0.29 (0.05–1.54)	0.146		
Maximum stent-to-artery ratio	0.91 (0.57–1.43)	0.674		

MACE, major adverse cardiovascular events; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; LAD, left anterior descending coronary; RCA, right coronary artery; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; ISR, in-stent restenosis; QCA, quantitative coronary angiography; DS, diameter stenosis; MLD, minimum lumen diameter; HR, hazard ratio; CI, confidence interval.

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Table S2 Predictors of TLR

Variables	Univariate analysis HR (95% CI)	P value	Multivariable analysis HR (95% CI)	P value
PCI strategy		0.313		0.250
ROTA+DCB	2.21 (0.79–6.13)		0.54 (0.14–2.07)	
ROTA+POBA	1.24 (0.56–2.73)		1.89 (0.69–5.16)	
ROTA+DES	1.00		1.00	
BMI	1.12 (0.99–1.25)	0.053		
Male sex	1.43 (0.68–3.05)	0.348		
Current smoker	0.91 (0.55–1.51)	0.712		
HD duration (m)	0.99 (0.99–1.00)	0.268		
Diabetes	1.41 (0.68–2.91)	0.352		
Statins used	1.64 (0.80–3.38)	0.180		
Insulin used	2.86 (1.26–6.49)	0.012		
Hypertension	23.38 (0.09–5989.25)	0.265		
OMI	2.20 (1.08–4.49)	0.030		
Target vessel				
LAD	0.25 (0.09–0.65)	0.004	0.38 (0.12–1.18)	0.094
RCA	4.27 (2.00–9.12)	<0.001		
Previous PCI	4.33 (1.31–14.27)	0.016		
LDL-C	1.00 (0.99–1.01)	0.437		
Hemoglobin	0.91 (0.72–1.14)	0.394		
HbA1c	1.40 (10.6–1.83)	0.016		
LVEF	0.99 (0.96–1.03)	0.898		
ISR	5.49 (2.45–12.33)	<0.001	4.02 (1.50–10.76)	0.002
Contrast volume	0.99 (0.98–0.99)	0.023		
Reference vessel diameter	1.80 (1.10–2.94)	0.019		
Lesion length	0.99 (0.97–1.02)	0.493		
Immediate QCA				
%DS before PCI	1.05 (1.01–1.08)	0.005		
MLD after PCI	3.08 (1.47–6.44)	0.003		
Acute gain	3.54 (1.98–6.35)	<0.001	2.81 (1.48–5.33)	0.017
Maximum burr-to-artery ratio	0.13 (0.01–1.80)	0.128		
Maximum stent-to-artery ratio	0.69 (0.36–1.32)	0.262		

TLR, target lesion revascularization; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; LAD, left anterior descending coronary; RCA, right coronary artery; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; ISR, in-stent restenosis; QCA, quantitative coronary angiography; DS, diameter stenosis; MLD, minimum lumen diameter; HR, hazard ratio; CI, confidence interval.

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Table S3 Predictors of MACE stratified by category of ISR

Variables	De novo				ISR			
	Univariate analysis HR (95% CI)	P value	Multivariable analysis HR (95% CI)	P value	Univariate analysis HR (95% CI)	P value	Multivariable analysis HR (95% CI)	P value
PCI strategy		0.521		0.462		0.802		0.269
ROTA+DCB	–				0.72 (0.26–1.98)		0.47 (0.14–1.60)	
ROTA+POBA	1.34 (0.54–3.30)		1.49 (0.51–4.40)		0.95 (0.43–2.10)		1.39 (0.55–3.72)	
ROTA+DES	1.00		1.00		1.00		1.00	
BMI	1.05 (0.93–1.19)	0.387			1.18 (1.03–1.35)	0.014		
Male	2.56 (1.23–5.33)	0.012	3.84 (1.71–8.62)	0.001	1.78 (0.84–3.78)	0.133		
Current smoker	0.71 (0.41–1.22)	0.218			1.37 (0.70–2.68)	0.353		
HD duration (m)	0.99 (0.99–1.00)	0.212			0.99 (0.99–1.00)	0.086		
Diabetes	0.51 (0.24–1.10)	0.082			2.09 (0.96–4.57)	0.058		
Statins used	0.94 (0.42–2.13)	0.890			0.84 (0.41–1.77)	0.661		
Insulin used	0.46 (0.06–3.36)	0.441			2.56 (1.13–5.76)	0.023		
Hypertension	1.72 (0.41–7.25)	0.458			21.73 (0.01–75,101.27)	0.458		
OMI	2.06 (0.98–4.32)	0.056			1.23 (0.60–2.51)	0.573		
Target vessel								
LAD	0.27 (0.11–0.67)	0.005			0.80 (0.34–1.88)	0.612		
RCA	2.42 (1.16–5.04)	0.018	2.48 (1.05–5.84)	0.037	1.25 (0.61–2.58)	0.541		
Previous PCI	1.17 (0.56–2.46)	0.670			0.57 (0.17–1.93)	0.367		
LDL-C	0.99 (0.98–1.01)	0.892			0.99 (0.98–1.01)	0.230		
Hemoglobin	0.81 (0.62–1.06)	0.125			0.96 (0.79–1.16)	0.671		
HbA1c	1.16 (0.78–1.73)	0.462			1.25 (0.96–1.62)	0.098		
LVEF	0.96 (0.93–0.99)	0.019	0.95 (0.92–0.98)	0.006	0.99 (0.96–1.02)	0.680		
Contrast volume	0.99 (0.99–1.00)	0.356			0.99 (0.99–1.00)	0.194		
Reference vessel diameter	1.58 (0.94–2.65)	0.082			(-)	0.320		
Lesion length	0.99 (0.97–1.02)	0.864			0.99 (0.97–1.03)	0.912		
Immediate QCA								
%DS before PCI	1.01 (0.97–1.05)	0.522			1.05 (1.02–1.08)	0.004	1.06 (1.02–1.10)	0.002
MLD after PCI	1.27 (0.61–2.65)	0.522			1.21 (0.69–2.11)	0.498		
Acute gain	1.59 (0.67–3.78)	0.292			1.47 (0.86–2.52)	0.155		
Maximum burr-to-artery ratio	0.08 (0.01–1.20)	0.068			0.45 (0.09–2.25)	0.331		
Maximum stent-to-artery ratio	1.33 (0.62–2.87)	0.463			1.08 (0.54–2.15)	0.819		

ISR, in-stent restenosis; BMI, body mass index; HD, hemodialysis; OMI, old myocardial infarction; LAD, left anterior descending coronary; RCA, right coronary artery; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; QCA, quantitative coronary angiography; DS, diameter stenosis; MLD, minimum lumen diameter; HR, hazard ratio; CI, confidence interval.