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ORIGINAL ARTICLE

Clinical impact of the gap-angle ratio in patients with ostial lesions of the right coronary artery undergoing percutaneous coronary intervention

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Abstract

The aim of this study was to investigate the incidence of binary restenosis and its predictors in patients with ostial lesions of the right coronary artery (RCAos) who underwent percutaneous coronary intervention (PCI). RCAos are associated with a high incidence of restenosis, and the implantations of drug-eluting stents for RCAos have not been fully elucidated. The study participants included 75 patients (72.3 ± 9.5 years, 72% men) who underwent PCI for RCAos at our institution between November 2001 and May 2017. The angle between the greater curvature of the aortic wall and the right coronary artery take-off in the diastolic and systolic phases in the left anterior oblique position view was investigated. Clinical outcome was defined as binary restenosis at follow-up coronary angiography. We also evaluated target lesion failure (TLF) defined as a composite of cardiac mortality, target vessel myocardial infarction, and target lesion revascularization (TLR). The incidence of binary restenosis was 48.0% ($n = 36$) of the entire cohort. The incidence of TLF was 49.3% ($n = 37$) of the entire cohort, which was mainly driven by TLR (36.0%, $n = 27$). The area under the curve of the gap-angle ratio [(difference between the maximum and minimum angles)/(minimum angle); GAR] for binary restenosis was 0.73, and the cutoff value was 0.306 (sensitivity 67%, specificity 82%). The patients were divided into two groups: a low-GAR (< 0.306; $n = 30$) and high-GAR group (> 0.306; $n = 45$). Binary restenosis was more frequent in the high-GAR group than in the low-GAR group (76.7% vs. 28.9%, $p = 0.007$). The cumulative rate of TLF was significantly higher in the high-GAR group when compared with the low-GAR group (53.3% vs. 40.0%, $p = 0.01$), which was mainly driven by TLR (56.7% vs. 22.2%, $p = 0.01$). High-GAR (> 0.306) [OR 2.66 (1.34–5.31), $p = 0.005$] and stent under expansion [OR 2.37 (1.10–5.11), $p = 0.03$] were found to be independent predictors of binary restenosis after adjustment for multiple confounders. Multivariable analysis also revealed that high-GAR (> 0.306) [OR 2.06 (1.02–4.14), $p = 0.03$] and stent under expansion [OR 2.82 (1.28–6.19), $p = 0.01$] were independent predictors of TLF. We suggest that GAR (> 0.306) predicts binary restenosis and TLF in patients undergoing PCI for RCAos.

Keywords Percutaneous coronary intervention · Ostial lesion of RCA · Restenosis

Introduction

Percutaneous coronary intervention (PCI) of aorto-ostial lesions is known to be technically challenging, leading to higher rates of adverse cardiac events compared with that of non-ostial lesions [1–4]. Previous studies with bare-metal stents (BMSs) showed that aorto-ostial lesions have higher restenosis rates than non-aorto-ostial lesions [5–7]. Traditionally, the presence of aorto-ostial stenosis has been a challenge for interventionists since they are most likely to be associated with suboptimal angiographic results due to lesion rigidity and recoil [8]. Although stents provide adequate scaffolding to prevent recoil, in-stent restenosis (ISR) occurs mainly due to neointimal hyperplasia. Sirolimus-eluting stents (SES) (Cypher, Cordis/Johnson & Johnson, Warren, NJ, USA) have been shown to reduce neointimal hyperplasia and the risk of ISR. However, previous studies also showed that 67% of patients who underwent SES implantation for the treatment of ostial lesions of the right

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coronary artery (RCAos) developed ISR that was symptomatic or associated with evidence of ischemia [9].

The challenges associated with PCI of an ostial lesion may depend not only on the lesion's location but also on plaque burden and lesion morphology. Although balloon angioplasty has often led to suboptimal results in ostial lesions, the use of BMSs and first-generation drug-eluting stents (DESs) increased both early procedural success and safety [1, 2, 10]. Various techniques, such as laser, cutting balloon, and debulking devices, have been trialed in an attempt to improve the clinical and angiographic outcomes of RCAos. However, stenting was associated with a higher incidence of ISR in the most proximal coronary segments, and implantation of DES in RCAos has been associated with a tenfold higher risk of repeat revascularization procedures than treatment of left main ostial lesions [11].

Second-generation DESs with more biocompatible durable polymer-based coatings, such as the Resolute zotarolimus-eluting stent (Medtronic, Santa Rosa, CA, USA), Nobori biolimus-eluting stent (Terumo, Tokyo, Japan), and Xience/Promus everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA/Boston Scientific, Marlborough, MA, USA), have shown favorable clinical results [12–14]. In the DES era, data on the outcomes of PCI involving RCAos are limited. The aims of this study were to investigate the incidence of binary restenosis and its predictors in patients who underwent PCI of RCAos and to investigate the mid-term clinical outcomes after treatment of RCAos.

Methods

The institutional review board of Tokyo Metropolitan Bokutoh Hospital approved this study. Written informed consent was obtained from all patients. The records of 2843 consecutive patients who underwent PCI between November 2011 and May 2017 at our institution were reviewed, and 80 patients who underwent PCI of RCAos were identified. We excluded 5 patients: 3 who died during their hospital stays (due to pneumonia and cardiogenic shock) and 2 who never returned for follow-up after their discharge. Overall, 75 patients were included in the final analysis.

The medical charts of all the patients were reviewed for demographic and clinical characteristics. Technical details of the procedures were reviewed from the procedure reports.

A significant ostial lesion was defined as a lesion with > 50% diameter stenosis (% DS) within 3 mm of the aortic orifice. None of the patients had known syphilitic or inflammatory arteritis, and none had undergone radiation therapy for mediastinal neoplasms. Additionally, none of the patients had previous aortic valve replacement, aortic dissection, or Takayasu's arteritis.

All patients underwent PCI using trans-femoral or transradial approaches. All received dual antiplatelet therapy before PCI. A bolus of 8000 U of intravenous heparin was administered at the beginning of the procedure and further supplemented to maintain a target activated clotting time of over 250 s. In all patients, a monorail-type dilation catheter system was utilized. To successfully dilate the stenosis, partially inflating the balloon in the ostium and gently pulling out the guide catheter were often necessary. The use of non-Judkins-type guide catheters, which led to less selective engagement in some cases, precluded the need for this maneuver. Selection of the specific stent type and other devices for use was at the discretion of the operator.

Twelve-lead electrocardiograms were recorded in all patients before, immediately after, and 1 day after the procedure. Serum creatinine kinase and myocardial band isoenzyme levels were also measured in all patients at the same time point.

All 75 procedures were successful, and the % DS by quantitative coronary angiography (CAG) immediately after the procedure was < 25%. No in-hospital major adverse cardiovascular events occurred, which were a composite of death, Q-wave myocardial infarction, emergent coronary artery bypass grafts, or definite early thrombosis, as defined by the Academic Research Consortium described in the United States Food and Drug Administration statement [15]. Regarding anatomical characteristics of the RCAos, take-off angle, coronary anomalies, atypical origin location, and the presence of a "funnel-shaped" ostium were evaluated. Coronary anomalies are classified as (1) anomalous coronary arteries arising from the aorta or from any other coronary trunk; (2) anomalous coronary arteries arising from pulmonary circulation; (3) coronary arteriovenous shunts; or (4) coronary anomalies secondary to other congenital disease. Atypical location of the origin was defined as requiring different projections from the usual left anterior oblique view to adequately visualize the RCAos. The take-off angle was measured by quantitative coronary angiography analysis using quantitative coronary angiography analysis using electronic digital calipers of Cardio Agent Pro (Medis V7.3.96_A). A CTO was defined as a completely occluded vessel with thrombolysis in myocardial infarction, flow grade 0 through the affected segment with estimated duration > 3 months. Calcification of the RCAos was evaluated by fluoroscopy. According to final angiography and IVUS, stent implantation characteristics, including stent under expansion, excessive aortic stent protrusion, and stent edge dissection were evaluated. Stent under expansion was defined as the presence of an obvious stent indentation, and excessive stent protrusion was defined as a presence of the entire circumference of the stent's proximal edge protruding into the aorta, which could be recognized angiographically from different projections and IVUS. All the angiographic

and IVUS reviews were performed by experienced cardiologists who were independent from the procedure.

Follow-up clinical data were obtained from the outpatient clinic visits and the referring physician. The follow-up CAG was performed annually for 3 years. CAG was also performed before the regularly scheduled annual CAG either by physician's request or due to development of cardiac symptoms or suspected ischemia warranting repeat angiography. Quantitative lesion measurements were performed using an electronic digital caliper in LAO view. Electronic digital calipers were used for quantitative CAG analysis, including measurements of reference vessel diameter, lesion minimal luminal diameter, lesion length, and percent DS. Those parameters were measured by quantitative coronary angiography analysis using Cardio Agent Pro (Medis V7.3.96_A).

The angle between the greater curvature of the aortic wall and right coronary artery (RCA) take-off at the diastolic and systolic phases in the left anterior oblique (LAO) position view was measured. In our institution, we use several views to evaluate RCA including the 45° LAO position view. We evaluated all study participants for binary restenosis via angiography at the 45° LAO position view.

The gap-angle ratio (GAR) was defined as follows: (difference between the maximum and minimum angles)/(the minimum angle). This index suggests that high GAR indicates an extremely steep angle of the RCA take-off and large motion of the RCAos; the methodological details are shown in Fig. 1. On a separate occasion, several observers measured the angles on the same angiogram without any input from other observers. Three experienced cardiologists who were independent from the procedure performed angiographic review and measured angles to calculate GAR, all using the same software. We performed kappa statistics one by one to identify the reproducibility of the review data, and there were no significant differences between the intra-observers' measurements of these indices.

Clinical outcome was defined as binary restenosis at the RCAos (> 50% DS at the ostial lesion). We also evaluated the incidence of target lesion failure (TLF) defined as a composite of cardiac mortality, target vessel myocardial infarction (MI), and target lesion revascularization (TLR). MI was defined as a creatinine kinase elevation > 3 times the upper limit of normal, accompanied by an increase in troponin level > 5 times the upper limit of normal at the time of follow-up. TLR was defined as repeat revascularization at the site where stents were implanted or in the adjacent 5 mm.

Continuous variables are reported as averages and standard deviations, while dichotomous variables are expressed as numbers and percentages. Discrete variables were compared using the Chi square test or Fisher's exact test to assess the differences between the patients with restenosis (restenosis group) and without restenosis (non-restenosis group). Receiver operating characteristic (ROC) curves were analyzed to determine the area under the curve (AUC) and the optimal threshold value of risk factors that may predict binary restenosis. Multivariable Cox-proportional analysis was used to identify the independent predictors of binary restenosis and TLF. Variables with a $p < 0.05$ in univariate analysis were entered into a stepwise multivariate model. All probability values were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to incorporate statistical functions frequently used in biostatistics [16].

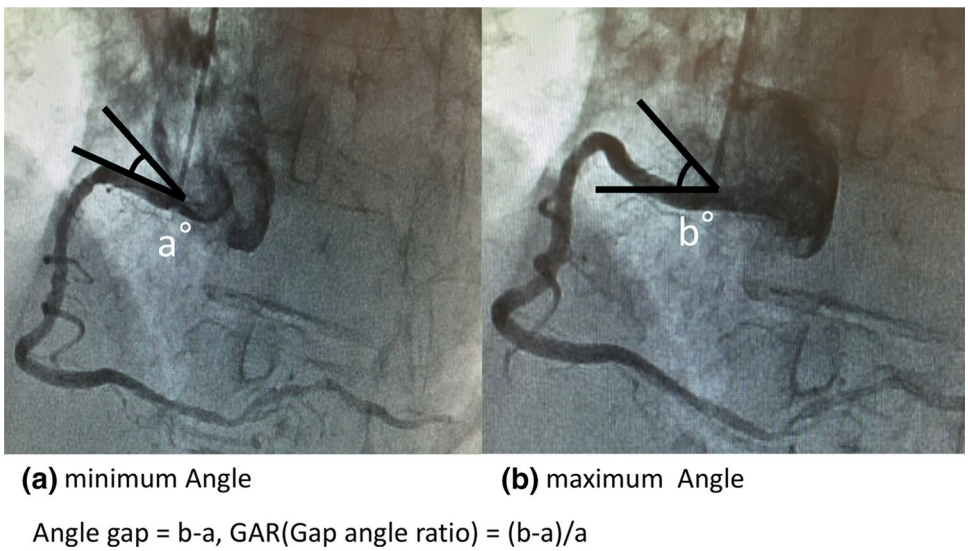

Fig. 1 Angle between the greater curvature of the aortic wall and the right coronary artery take-off. A high gap-angle ratio indicates severe steepness of the right coronary artery take-off angle and extensive motion of the ostial lesion

Results

The incidence of binary restenosis in the entire study cohort was 48.0% ($n=36$) (Fig. 2). The incidence of TLF was 45.3% ($n=34$) of the entire cohort, which was mainly driven by TLR (36.0%, $n=27$). TLR was basically performed when the percentage DS of the target lesion was greater than 75 with ischemic symptoms, and myocardial ischemia was documented in the target vessel area by a noninvasive method. Three patients of the cohort had performed a treadmill exercise test (TMT), and two other patients had performed a fractional flow reserve (FFR) test prior to TLR. Only nine patients in the restenosis group did not require target-lesion revascularization because of the presence of extensive collateral circulation and the absence of ischemic symptoms. The demographic and clinical features of the restenosis group (26 men, 10 women; median age, 70.0 years) and non-restenosis group (28 men, 11 women; median age, 74.4 years) were compared. Of the 75 patients, 63 (84.0%) were current or past smokers. The patients in the restenosis group were significantly younger (70.3 ± 8.1 vs. 74.4 ± 10.2 years; $p=0.04$) than were those in the non-restenosis group. No significant differences were observed between the two groups with respect to body mass index (24.4 ± 4.1 vs. 23.3 ± 3.9 kg/m^2; $p=0.31$) and family history of cardiovascular diseases (36.1% vs. 25.6%; $p=0.33$). In terms of risk factors for coronary artery disease, no significant differences were observed between the two groups with respect to smoking history (91.7% vs. 76.2%; $p=0.12$), hypertension (69.4% vs. 71.8%; $p=0.83$), dyslipidemia (58.3% vs. 48.7%; $p=0.41$), or diabetes (63.9% vs. 46.2%; $p=0.13$). The baseline ejection fractions of the two groups measured using transthoracic ultrasonography were almost equal (61.2 ± 15.7% vs. 60.6 ± 15.4%; $p=0.90$). No significant differences were found between the restenosis group and the non-restenosis group in levels of hemoglobin (11.6 ± 1.8 vs. 12.4 ± 2.3 g/dl; $p=0.09$), platelet counts (22.3 ± 5.7 vs. 21.4 ± 6.6 10^4/μl; $p=0.57$), triglyceride (145.6 ± 79.1 vs. 121.1 ± 61.3 mg/dl; $p=0.14$), total cholesterol (170.4 ± 62.5 vs. 162.3 ± 37.1 mg/dl; $p=0.49$), low-density lipoprotein cholesterol (98.1 ± 48.1 vs. 95.3 ± 33.0 mg/dl; $p=0.49$), high-density lipoprotein cholesterol (47.8 ± 16.4 vs. 42.3 ± 11.6 mg/dl; $p=0.10$), serum creatinine (2.0 ± 2.0 vs. 1.4 ± 1.6 mg/dl; $p=0.16$), and glycated hemoglobin (6.9 ± 1.5 vs. 6.4 ± 1.3%; $p=0.12$). Regarding anatomical characteristics, no coronary anomalies were observed in our cohort. The prevalence of funnel-shaped RCAos and atypical location of the origin were similarly observed in both groups (25.0% vs. 25.6%, $p=1.00$, and 41.7% vs. 43.6%, $p=1.00$, respectively). Moreover, no significant differences were observed between the two groups in the use of non-Judkins-type guide catheters (16.7% vs. 12.6%; $p=0.41$). No significant differences were found in the presence of lesion calcification (55.6% vs. 53.8%; $p=0.88$), collateral circulation (33.3% vs. 15.4%; $p=0.07$), % DS (84.9 ± 11.3% vs. 83.3 ± 12.2%; $p=0.68$), reference vessel diameter (3.43 ± 0.53 vs. 3.40 ± 0.42 mm; $p=0.56$), and minimal luminal diameter (0.81 ± 0.36 vs. 0.84 ± 0.31 mm; $p=0.84$) between both groups. Rates of direct stenting (13.9% vs. 17.9%; $p=0.64$), pretreatment with debulking balloons (69.4% vs. 61.5%; $p=0.48$), stent sizes (3.5 ± 0.3% vs. 3.5 ± 0.3%; $p=0.53$), and stent lengths (19.3 ± 7.4 vs. 17.9 ± 6.4 mm; $p=0.37$) were similar in both groups.

The restenosis group had a higher incidence of known chronic kidney disease (estimated glomerular filtration ratio

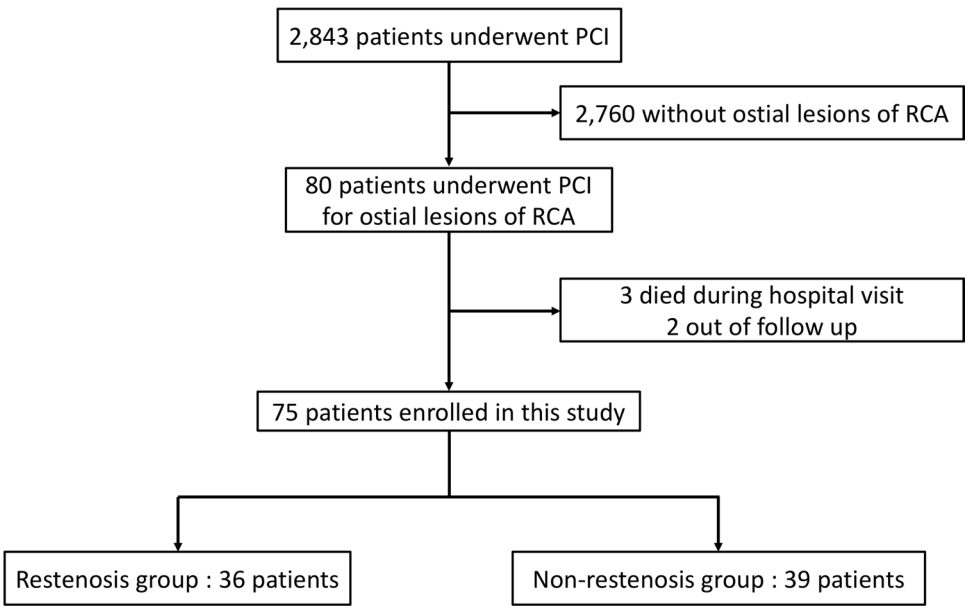

Fig. 2 Flow diagram of patient enrollment

< 60 ml/mg/1.72 m^2) than the non-restenosis group (44.4% vs. 28.2%; $p = 0.02$). In the restenosis group, 13.9% of patients underwent PCI to RCAos due to acute coronary syndrome (ACS), which was less than the non-restenosis group (13.9% vs. 41.0%; $p = 0.02$). The angle gap (19.0 ± 11.4 vs. 11.5 ± 8.1; $p = 0.001$) and GAR (0.40 ± 0.25 vs. 0.24 ± 0.26; $p = 0.008$) were significantly larger in the restenosis group than in the non-restenosis group. Drug-coated balloons (DCB) were significantly more frequently employed in the restenosis group than in the non-restenosis group (27.8% vs. 7.7%; $p = 0.03$). DCB use may be associated with the restenotic lesion in patients with RCAos undergoing PCI. There were 47 patients (61.8%) in our cohort treated with 2nd or 3rd generation DES. The rate of using 2nd or 3rd generation DES was significantly lower in the restenosis group than in the no-restenosis group (50% vs. 74.6%; $p = 0.03$).

Figure 3 shows the ROC curve demonstrating GAR's ability to predict binary restenosis. The AUC was 0.73 and the optimal cutoff value was 0.306. The sensitivity and specificity at the cutoff value were 67% and 82%, respectively. All patients were divided into two groups: the low-GAR group (GAR < 0.306) and high-GAR group (GAR > 0.306), and the clinical features were compared (Table 1). The patients were older in the low-GAR group than in the high-GAR group (73.8 ± 9.6 vs. 70.1 ± 9.5 years; $p = 0.10$). There were significantly more patients on hemodialysis in the high-GAR group than in the low-GAR group (23.3% vs. 4.4%; $p = 0.01$). The incidence of binary restenosis was significantly higher in the high-GAR group than in the low-GAR group (76.7% vs. 28.9%, $p = 0.007$). The levels of serum triglyceride (162.5 ± 76.5 vs. 113.2 ± 62.1 mg/dl; $p = 0.003$) and creatinine (2.4 ± 2.4 vs. 1.2 ± 1.1 mg/dl; $p = 0.004$) were higher in the high-GAR group than in the low-GAR group. No significant differences were observed in procedural data between the two groups.

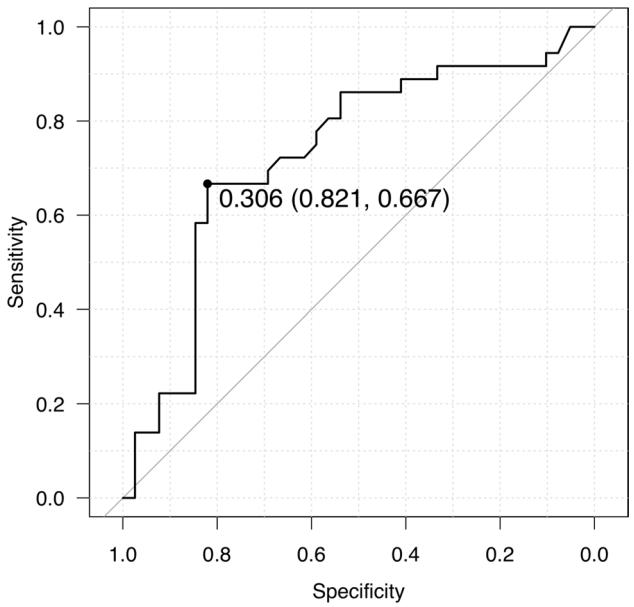

Fig. 3 Receiver operating characteristic curve of sensitivity and specificity of the gap-angle ratio for binary restenosis. The receiver operating characteristic curve shows the sensitivity and specificity of the gap-angle ratio with respect to the outcome according to restenosis of > 50%. The area under the curve is 0.73 (95% confidence interval 0.61–0.85). The cutoff value of 0.306 has the highest combined sensitivity and specificity to binary restenosis (sensitivity 67%, specificity 82%)

During median follow-up period (25.3 months), Kaplan–Meier analysis revealed that a more favorable outcome (freedom from restenosis and TLF) was associated with low GAR (Fig. 4). In the total population, multivariable analysis using Cox-proportional analysis demonstrated that high-GAR (> 0.306) [OR 2.66 (1.34–5.31), $p = 0.005$] and stent under expansion [OR 2.37 (1.10–5.11), $p = 0.03$] were found to be independent predictors of binary restenosis (Table 2). We also found that high-GAR (> 0.306) [OR 2.06 (1.02–4.14), $p = 0.03$], and stent under expansion [OR 2.82 (1.28–6.19), $p = 0.01$] were independent predictors of TLF (Table 3).

Discussion

Our analysis of patients who underwent PCI of RCAos at a single center found that binary restenosis and TLF were significantly more frequent in the high-GAR group than in the low-GAR group. According to multivariate analysis, GAR > 0.306 was an independent predictor of binary restenosis and TLF, as well as stent under expansion. Severe steepness of the RCA take-off angle and extensive motion of the RCAos are major risk factors of these adverse clinical events. Several mechanisms are responsible for the increased shear stress and intimal trauma. In this study, the focus was on the steepness of the RCA take-off angle and the motion of the RCAos by defining and validating the GAR (Fig. 1). This index suggests that a high GAR indicated severe steepness of the RCA take-off angle and extensive motion of the RCAos.

A previous study demonstrated the relatively high acute complication rate, high incidence of restenosis, and several distinct technical issues associated with coronary angioplasty of RCAos [17]. In the present study, binary restenosis was quite high (48%), nearly twice as high as that reported in previous large studies [18, 19]. The apparently high restenosis rate has been explained by multiple factors: (1) involvement of the aortic wall, as with the left main, renal, and other ostial/aortic lesions that have been demonstrated to be predisposed for restenosis [19]; (2) increased shear stress associated with an orifice location; (3) increased intimal trauma associated with the procedure, which may

Table 1 Patients' demographics and clinical features of the low-GAR group and high-GAR group

Variables	Total ($n=75$)	Group		p value
		GAR < 0.306 ($n=45$)	GAR > 0.306 ($n=30$)	
Background				
Age (years)	72.3 ± 9.5	73.8 ± 9.6	70.1 ± 9.5	0.10
Male sex	54 (72.0)	33 (73.0)	21 (70.0)	0.76
BMI (kg/m^2)	23.8 ± 4.1	23.6 ± 3.8	24.1 ± 4.5	0.60
Family history	23 (30.7)	14 (31.1)	9 (30.0)	0.76
Smoker	63 (84.0)	35 (77.8)	28 (93.3)	0.07
Hypertension	53 (70.7)	21 (70.0)	32 (70.1)	0.92
Dyslipidemia	40 (53.3)	26 (57.8)	14 (46.7)	0.35
Diabetes	41 (54.7)	23 (51.1)	18 (60.0)	0.46
Chronic kidney disease	27 (36.0)	13 (28.9)	14 (31.1)	0.12
Hemodialysis	9 (12.0)	2 (4.4)	7 (23.3)	0.01
EF (%)	60.8 ± 15.4	61.5 ± 16.8	59.7 ± 13.3	0.62
HR (bpm)	75.0 ± 15.2	70.4 ± 15.7	76.1 ± 14.0	0.13
Atrial fibrillation	13 (17.3)	10 (22.2)	3 (10.0)	0.18
ACS	21 (28.0)	15 (33.3)	6 (20.0)	0.21
Blood tests				
Hb level (g/dl)	12.0 ± 2.1	12.4 ± 2.3	11.5 ± 1.6	0.06
Platelet count (10^4/μl)	21.8 ± 6.1	22.0 ± 6.5	21.7 ± 5.7	0.84
Triglyceride level (mg/dl)	132.9 ± 71.0	113.2 ± 62.1	162.5 ± 76.5	0.003
Total cholesterol level (mg/dl)	166.2 ± 50.7	162.3 ± 64.8	172.1 ± 64.8	0.42
LDL cholesterol level (mg/dl)	96.9 ± 40.7	94.6 ± 32.8	100.4 ± 50.7	0.55
HDL cholesterol level (mg/dl)	44.9 ± 14.3	45.8 ± 15.2	43.7 ± 12.8	0.53
Creatinine level (mg/dl)	1.7 ± 1.8	1.2 ± 1.1	2.4 ± 2.4	0.004
HbA1c level (%)	6.6 ± 1.4	6.4 ± 1.3	6.9 ± 1.4	0.17
Lesion characteristics				
Approach site				
Femoral	33 (44.0)	21 (46.7)	12 (40.0)	0.94
Brachial	1 (1.3)	1 (2.2)	0 (0.0)	0.34
Radial	41 (54.7)	23 (51.1)	18 (60.0)	0.88
Atypical origin location	33 (44.0)	18 (40.0)	15 (50.0)	0.60
Funnel-shaped ostium	19 (25.3)	13 (28.9)	6 (20.0)	0.27
De novo lesion	56 (74.7)	35 (72.2)	21 (70.0)	0.45
Lesion calcification	41 (54.7)	24 (53.3)	17 (56.7)	0.78
Collateral	18 (24.0)	8 (17.8)	10 (33.3)	0.13
Percent diameter stenosis (%)	84.3 ± 11.7	84.0 ± 11.7	84.9 ± 12.0	0.73
Reference vessel (mm)	3.42 ± 0.52	3.39 ± 0.23	3.41 ± 0.76	0.66
Minimal luminal diameter (mm)	0.82 ± 0.30	0.83 ± 0.33	0.81 ± 0.21	0.71
Max angle (°)	73.2 ± 19.7	76.3 ± 20.6	68.7 ± 20.6	0.10
Min angle (°)	57.8 ± 19.6	67.0 ± 18.6	44.1 ± 11.6	< 0.001
Angle gap (°)	15.1 ± 10.5	9.3 ± 5.7	24.0 ± 9.8	< 0.001
GAR	0.31 ± 0.27	0.14 ± 0.08	0.57 ± 0.24	< 0.001
Procedural data				
Non-Judkins-type guide catheters	11 (14.7)	7 (15.5)	4 (13.3)	0.21
Direct stenting	12 (16.0)	6 (13.3)	6 (20.0)	0.44
Debulking balloon	49 (65.3)	28 (62.2)	21 (70.0)	0.48
Rotational atherectomy	3 (4.0)	2 (4.4)	1 (3.3)	0.81
Maximum inflation pressure (atm)	15.5 ± 3.0	15.8 ± 3.0	15.1 ± 3.0	0.31
Stent size (mm)	3.5 ± 0.3	3.5 ± 0.3	3.5 ± 0.3	0.93

Table 1 (continued)

Variables	Total ($n=75$)	Group		p value
		GAR < 0.306 ($n=45$)	GAR > 0.306 ($n=30$)	
Length of stents	18.6 ± 6.9	17.4 ± 5.6	20.4 ± 8.2	0.06
Length of stents > 28 mm	11 (14.7)	4 (8.9)	7 (23.3)	0.09
BMS	5 (6.7)	2 (4.4)	3 (10.0)	0.89
2nd or 3rd generation DES	47 (61.8)	26 (57.8)	21 (70.0)	0.11
DES	50 (66.7)	21 (47.7)	29 (97.7)	0.21
C-SES	5 (6.7)	2 (4.4)	3 (10.0)	0.47
R-ZES	6 (8.0)	3 (6.7)	3 (10.0)	0.84
P-EES	3 (4.0)	1 (2.2)	2 (6.6)	0.54
X-EES	11 (14.7)	4 (8.9)	7 (23.3)	0.34
BES	23 (30.7)	10 (22.2)	13 (43.3)	0.44
S-EES	2 (2.7)	1 (2.2)	1 (3.3)	0.67
Stenting characteristics				
Under expansion	12 (16.0)	8 (17.8)	4 (13.3)	0.27
Excessive aortic stent protrusion	28 (37.3)	12 (26.7)	16 (53.3)	0.09
Stent edge dissection	2 (2.7)	1 (2.2)	1 (3.3)	0.67
DCB	13 (17.3)	6 (13.3)	7 (23.3)	0.34
POBA	7 (9.3)	3 (6.7)	4 (13.2)	0.76
IVUS	73 (97.3)	45 (100)	28 (93.3)	0.28
Clinical outcomes				
Binary restenosis	36 (48.0)	13 (28.9)	23 (76.7)	0.007
TLF	34 (45.3)	14 (31.1)	20 (66.7)	0.001
Cardiac death	10 (13.3)	8 (17.8)	2 (6.7)	0.89
MI	8 (10.7)	4 (8.9)	4 (13.3)	0.91
TLR	27 (36.0)	10 (22.2)	17 (56.7)	0.01

Data are presented as a mean ± standard deviation or number (%)

ACS acute coronary syndrome, *Angle gap* (max angle) − (min angle), *BMI* body mass index, *BES* Nobori biolimus-eluting stent, *BMS* bare metal stent, *C-SES* cypher sirolimus-eluting stent, *DCB* drug-coated balloon, *DES* drug-eluting stent, *EF* ejection fraction, *GAR* (angle gap)/(min angle), *Hb* hemoglobin, *HbA1c* glycated hemoglobin, *HDL* low-density lipoprotein, *IVUS* intravascular ultrasonography, *LDL* low-density lipoprotein, *P-EES* promus everolimus-eluting stent, *POBA* plain old balloon angioplasty, *R-ZES* resolute zotarolimus-eluting stent, *S-EES* synergy everolimus-eluting stent, *TLR* target lesion revascularization, *X-EES* Xience everolimus-eluting stent

lead to more rigorous platelet aggregation; and (4) the difficulty in "cracking" and fully dilating some RCAos because of very extensive calcification. These histological features make RCAos particularly rigid, which increases the chance of lesion recoil under expansion and are associated with high rates of restenosis [20]. In order to modify the lesion, the efficacy of debulking devices, including cutting balloon, rotation atherectomy, and Excimer laser, have been investigated but have not yet been shown to provide better outcomes [21, 22]. In nearly 15% of the patients, a conventional Judkins guide catheter could not be used, and several alternative designs, including the Amplatz and Ikari, were used. Proper attention to the take-off of the RCA and the anatomy of the aortic root and right sinus of Valsalva is essential in selecting the appropriate guide catheter. Correct catheter placement may be difficult, and deep cannulation of the ostium should be avoided. However, lack of selective cannulation to avoid catheter impaction and trauma may make it more difficult to cross a high-grade lesion with the balloon [17]. In our study, funnel shaped RCAos, atypical location of the origin, and the use of non-Judkins-type guide catheters were not associated with clinical outcomes.

Mitomo et al. proposed that the rate of TLF was lower in new generation DES group compared with the early generation DES group after PCI of RCAos [23]. This could be partially explained by the superior performance of new generation DES, which could be protective for poor outcomes associated with certain suboptimal implantation characteristics when compared with early generation DES. In our study, we also found similar results, in that the rate of using 2nd or 3rd generation DES was significantly lower in the restenosis group than in the no-restenosis group (50% vs. 74.6%; $p=0.03$). However, even using new generation DES, techniques to optimize stent implantation are still required to achieve the best possible results in this challenging lesion subset. Our study population was relatively small compared

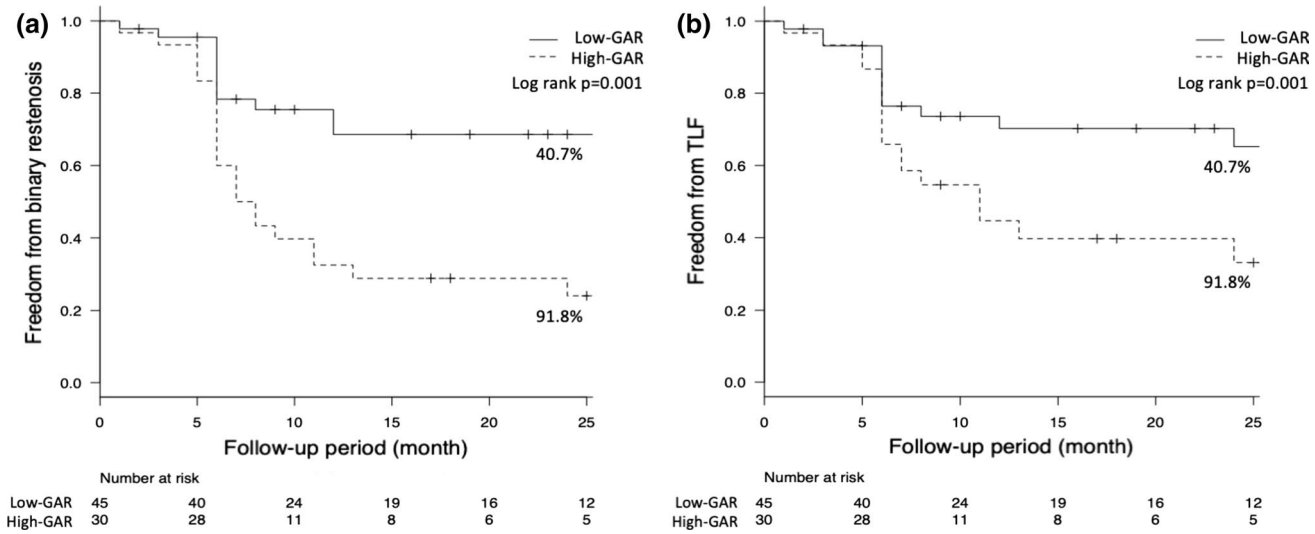

Fig. 4 **a** Kaplan–Meier curve for binary restenosis in RCAos: low-GAR group versus high-GAR group. *RCAos* ostial lesions of the right coronary artery, *GAR* gap-angle ratio. **b** Kaplan–Meier curve for TLF: low-GAR group versus high-GAR group. *RCAos* ostial lesions of the right coronary artery, *GAR* gap-angle ratio, *TLF* target lesion failure

Table 2 Cox-proportional analysis of the association between ISR and clinical findings

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Male sex	1.02	0.33–3.18	0.97			
Obesity	1.42	0.50–4.15	0.22			
Smoker	3.25	0.72–20.40	0.12			
Dyslipidemia	1.46	0.54–4.06	0.41			
Hypertension	0.89	0.29–2.72	0.83			
Diabetes	2.04	0.74–5.79	0.13			
Chronic kidney disease	4.03	1.17–15.1	0.02	1.24	0.62–2.51	0.54
Hemodialysis	2.37	0.46–15.91	0.30			
Atrial fibrillation	0.42	0.09–1.71	0.23			
ACS	0.24	0.06–0.80	0.02	0.50	0.18–1.33	0.16
EF < 40%	1.35	0.31–6.23	0.64			
GAR > 0.306	7.83	2.51–27.38	0.002	2.66	1.34–5.31	0.005
Device > 28 mm	0.89	0.19–3.90	0.86			
Ao protrusion	2.25	0.79–6.65	0.10			
Stent under expansion	3.93	1.87–24.70	0.03	2.37	1.10–5.11	0.03
Stent edge dissection	0.35	0.01–4.56	0.62			
DCB	4.52	1.02–28.07	0.06			
2nd or 3rd DES	0.35	0.16–1.01	0.03	0.68	0.33–1.39	0.29
Debulking balloon use	0.89	0.26–3.09	0.48			

ORs and 95% CIs from univariate and multivariate analyses of various background factors with binary restenosis

Variables with a *p* value < 0.05 in univariate analysis were included in multivariate analysis

ACS acute coronary syndrome, *BES* Nobori biolimus-eluting stent, *CI* confidence interval, *DCB* drug-coated balloon, *EF* ejection fraction, *GAR* gap-angle ratio, *OR* odds ratio

to that of Mitomo et al.; thus, our results are not in line with the aforementioned study. There was no significant statistical difference between the new generation DES and other PCI strategies with respect to the rate of TLF. In multivariable Cox-proportional analysis, the generation of DES was not an independent predictor of both binary restenosis and TLF.

Table 3 Cox-proportional analysis of the association between TLF and clinical findings

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Male sex	1.13	0.30–3.34	0.96			
Obesity	0.83	0.28–2.39	0.81			
Smoker	2.87	0.64–18.00	0.21			
Dyslipidemia	0.97	0.35–2.67	1.00			
Hypertension	1.67	0.55–5.43	0.45			
Diabetes	1.35	0.49–3.77	0.64			
Chronic kidney disease	3.16	1.37–10.6	0.04	1.02	0.49–2.11	0.96
Hemodialysis	2.68	0.52–17.98	0.28			
Atrial fibrillation	0.71	0.16–2.81	0.76			
ACS	0.27	0.07–0.93	0.02	0.50	0.18–1.34	0.17
EF < 40%	1.53	0.35–7.07	0.53			
GAR > 0.306	4.33	1.49–13.4	0.004	2.06	1.02–4.14	0.03
Device > 28 mm	0.65	0.13–2.87	0.74			
Ao protrusion	1.34	0.47–3.83	0.63			
Stent under expansion	4.47	0.99–28.14	0.03	2.82	1.28–6.19	0.01
Stent edge dissection	0.39	0.01–5.10	0.62			
DCB	2.56	0.67–10.96	0.14			
2nd or 3rd DES	0.74	0.26–2.11	0.63			
Debulking balloon use	1.95	0.67–6.01	0.23			

ORs and 95% CIs from univariate and multivariate analyses of various background factors with binary restenosis

Variables with a *p* value < 0.05 in univariate analysis were included in multivariate analysis

ACS acute coronary syndrome, *BES* Nobori biolimus-eluting stent, *CI* confidence interval, *DCB* drug-coated balloon, *EF* ejection fraction, *GAR* gap-angle ratio, *OR* odds ratio

In this study, it had a lower incidence of acute coronary syndrome (ACS) (13.9% vs. 41.0%; $p = 0.02$) in the restenosis group compared with the non-restenosis group. It might be associated with histological differences such as the amount of plaque and/or thrombus between the ACS and the non-ACS group.

Stent under expansion is widely recognized as one of the factors associated with a higher risk of restenosis even after DES implantation. In previous studies, it was reported that (late) stent recoil could play an important role to explain high rates of restenosis after PCI of RCAos [20]. In our study, we evaluated the stent under expansion by use of intravascular imaging. We also found that residual stent indentation at the index procedure was significantly associated with a poor outcome in our study. An under expanded stent results in binary restenosis and TLF, as mentioned in previous studies [24].

This study has some limitations. First, this was a single-center, nonrandomized, retrospective study. Therefore, it is prone to the biases inherent to this research approach. Second, the study population was too small. A larger sample size and multi-center analysis would be necessary for a more powerful analysis of other risk factors. Third, the movement of RCAos occurs in three dimensions. RCAos have unique three-dimensional anatomies including: (1) a "funnel-shaped" morphology, (2) variable ostial locations, and (3) differing take-off angles. Therefore, it is difficult to precisely evaluate the lesion with angiography alone, resulting in a geographic miss (incomplete lesion coverage or aortic stent protrusion), which could be associated with restenosis [25, 26]. However, in this study, only one dimension was analyzed. It may be better to analyze the motion of RCAos using coronary computed tomography (CT) angiography and to measure the indices that we proposed in this report in the optimal angle view. In our cohort, 21 patients (28%) were emergency case of ACS. In such cases, it is difficult to evaluate the motion of RCAos by coronary CT angiography prior to PCI procedure. Preventing and predicting restenosis of RCAos is particularly important because: (1) restenosis could result in a large ischemic territory and (2) repeat PCI would be complex, due to limited therapeutic options. Therefore, we investigated the relationship between the pre-PCI angiographic findings and the clinical outcome and found that the GAR, which is able to be evaluated only by coronary angiography would be a valuable clinical marker to predict ISR and clinical outcomes in patient undergoing PCI to RCAos. Fourth, the GAR mentioned in this study is influenced by the proper LAO view, and it is

difficult to decide which view is the best when evaluating GAR. We recognize that 40°–60° of LAO is commonly used during cannulation of RCAos. In our institution, cannulation of RCAos is performed using a 45° LAO view, and we perform angiography on all cases using this view before and after PCI of RCAos. Therefore, we chose the 45° LAO view to evaluate steepness and motion of RCAos.

The present study's findings show that RCAos are associated with a high incidence of restenosis. Our report suggests that a high GAR (> 0.306) predicts binary restenosis and TLF as well as stent under expansion in patients undergoing PCI of RCAos. The need to cover the RCAos with a DES, especially in cases of severe steepness of the RCA take-off angle and extensive motion, may be considered as an indicator of a generally increased risk of binary restenosis that should be accounted for when planning the initial revascularization therapy with a heart team.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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