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Independent predictors of in-stent restenosis after drug-eluting stent implantation for ostial right coronary artery lesions

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ABSTRACT

Objectives: We evaluated the angiographic patterns and predictors of in-stent restenosis (ISR) for ostial lesions of the right coronary artery (RCA) to clarify the mechanism of insoluble restenosis.
Background: Although ISR of the RCA still occurs, limited data is available regarding the associated angiographic findings.
Methods: Between January 2005 and September 2013, we recruited consecutive patients undergoing routine angiography 6–18 months after implantation of a drug-eluting stent (DES). Multiple logistic regression analysis was used to determine the independent predictors of ISR, and the adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were calculated.
Results: Routine angiography revealed that 45 of 131 patients (34.3%) had RCA-ISR, which were classifiable by occlusion type into ostial (24 cases), proximal (17 cases), diffuse (3 cases), and total (1 case). By multivariable analysis, early generation DES was the only independent predictor of overall ISR (aOR, 3.54; 95% CI, 1.59–7.87; $p = 0.002$). In a subgroup analysis of each focal ISR pattern, early generation DES (aOR, 7.76; 95% CI, 2.15–28.0; $p = 0.002$) was associated with increased risk of ostial ISR. On the contrary, larger stent (aOR, 0.21; 95% CI, 0.05–0.84; $p = 0.027$) was associated with decreased risk of ostial ISR. Furthermore, a ratio of the stent to post-balloon size >1.10 (aOR, 3.93; 95% CI, 1.30–11.8; $p = 0.002$) and good left ventricular contractility (ejection fraction >60%) (aOR, 8.27; 95% CI, 1.76–39.0; $p = 0.008$) were associated with increased risk of proximal ISR when stent fracture was observed.
Conclusion: The focal pattern of RCA-ISR was mostly observed after DES implantation, and the mechanisms of proximal and ostial ISR differed.

1. Introduction

Drug-eluting stents (DESs) have significantly reduced the development of in-stent restenosis (ISR) compared with bare metal stents (BMS); [1–3] however, the ISR rate for ostial lesions of the right coronary artery (RCA) remains high [4,5]. Previous studies have reported that excessive intimal growth, chronic stent recoil, and stent fracture (SF) might be important etiologic factors in the development of this ostial RCA-ISR [6,7]. Furthermore, recent studies have reported that the implantation of new generation DES significantly reduced the ISR rate compared with early-generation DES [8,9]. Despite numerous studies regarding ostial RCA lesions, the predictors and angiographic patterns of ostial RCA-ISR after DES implantation are unclear. Therefore, we aimed to describe and evaluate the angiographic patterns and predictors of ISR of ostial RCA lesions.

2. Methods

2.1. Study design

Study flow chart is shown in Fig. 1. We performed a retrospective cohort analysis of consecutive patients with de novo proximal RCA lesions who received DES implants at our institute between January 2005 and September 2013. Patients with a history of acute myocardial infarction, coronary artery bypass graft surgery, ISR, BMS implantation, or plain balloon angioplasty alone were excluded. We also excluded patients who had no angiographic follow-up data within 18 months after DES implantation. Clinical data were collected during hospital visits or by telephone contact at 6-month intervals.

2.2. Protocol

Baseline parameters were defined and recorded as follows. Good left ventricular (LV) contractility was defined as an LV ejection fraction >60% measured by transthoracic echocardiography. Chronic kidney disease was defined as an estimated glomerular filtration

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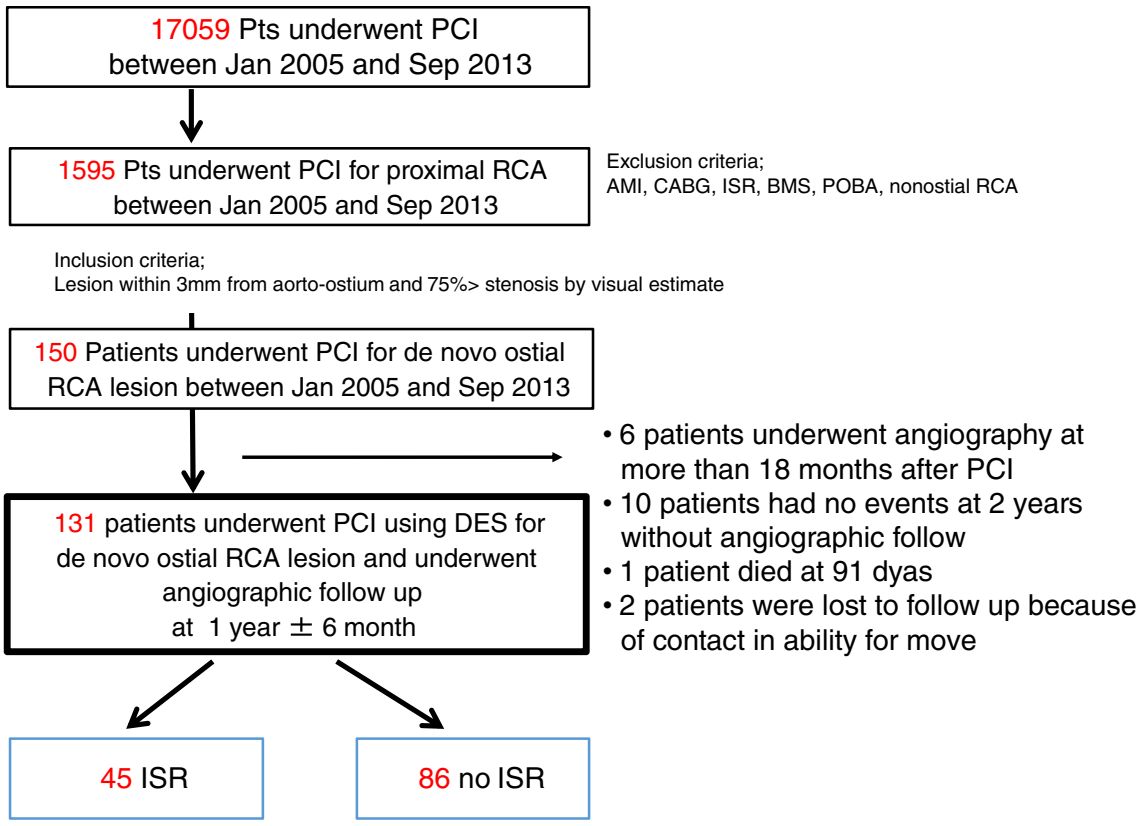

Fig. 1. Study flow chart. Abbreviations: AMI = acute myocardial infarction, BMS = bare metal stent, CABG = coronary artery bypass grafting, DES = drug-eluting stent, ISR = in-stent restenosis, PCI = percutaneous coronary intervention, POBA = plain old balloon angioplasty, Pts = patients, RCA = right coronary artery.

Table 1
Baseline clinical and procedural characteristics.

Patients: *n*	ISR (*n* = 45)	No ISR (*n* = 86)	*p* value
Age	68.9 ± 9.68	71.3 ± 9.67	0.19
Male gender	32 (71.1)	57 (66.3)	0.69
Previous MI	14 (31.1)	29 (33.7)	0.85
Previous stroke	1 (2.2)	9 (10.5)	0.16
Previous PCI	27 (60.0)	48 (55.8)	0.71
DM	17 (37.8)	31 (36.0)	0.85
Insulin DM	5 (11.1)	10 (11.6)	1.00
HT	34 (75.6)	71 (82.6)	0.36
DL	30 (66.7)	65 (75.6)	0.31
CKD (eGFR < 60)	19 (42.2)	35 (40.7)	1.00
HD	8 (17.8)	8 (9.3)	0.17
PAD	9 (20.0)	14 (16.3)	0.63
EF (%)	58.2 ± 9.68	56.4 ± 11.9	0.39
EuroSCORE (logistic)	4.13 ± 3.53	4.52 ± 4.70	0.63
3VD	21 (46.7)	31 (36.0)	0.26
Rotational atherectomy	1 (2.2)	5 (5.8)	0.66
Calcification	24 (53.3)	43 (50.0)	0.85
IABP	1 (2.2)	2 (2.3)	1.00
IVUS	19 (42.2)	43 (50.0)	0.46
Stent size	3.23 ± 0.34	3.37 ± 0.33	0.04
Post-dilation	25 (55.6)	40 (46.5)	0.36
Post-balloon size (mm)	3.80 ± 0.44	3.80 ± 0.49	1.00
Maximum inflation pressure (atm)	21.6 ± 4.00	21.5 ± 3.50	0.90
New generation DES	12 (26.7)	48 (55.8)	0.002

Data are presented as percentages and absolute numbers or means ± standard deviation, unless otherwise specified.
ISR = in stent restenosis. MI = myocardial infarction. PCI = percutaneous coronary intervention. DM = diabetes mellitus. HT = hypertension. DL = dyslipidemia.
CKD = chronic kidney disease. eGFR = estimated glomerular filtration rate. HD = hemodialysis. PAD = peripheral arterial disease. EF = ejection fraction.
EuroSCORE = European System for Cardiac Operative Risk Evaluation score. 3VD = three vessel disease. IABP = intra-aortic balloon pump. IVUS = intravascular ultrasound.
DES = drug eluting stent.

rate <60 mL/min/1.73 m^2. Clinical risk was defined according to the EuroSCORE, as previously described [10].

The following DESs were used. The early stents included sirolimus-eluting stents (Cypher and Cypher Select +, Cordis/Johnson & Johnson, New Brunswick, NJ, USA), paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, MA, USA), and Endeavor zotarolimus-eluting stents (Endeavor and Endeavor Sprint, Medtronic CardioVascular, Santa Rosa, CA, USA). The newer stents included everolimus-eluting stents (Xience, Xience Prime, and Xience Xpedition, Abbott Vascular, Redwood City, CA, USA; and Promus and Promus Element, Boston Scientific, Natick, MA, USA), biolimus-eluting stents (Nobori, TERUMO Corp, Tokyo, Japan), and Resolute zotarolimus-eluting stents (Resolute Integrity, Medtronic CardioVascular, Santa Rosa, CA, USA). Furthermore, antiplatelet therapy was provided with a life-long low-dose aspirin (100 mg daily), plus a thienopyridine (200 mg ticlopidine b.i.d. or 75 mg clopidogrel o.d.) for a minimum of 12 months after stent implantation.

Angiographic follow-up was scheduled for between 6 and 18 months, or earlier if clinically indicated by evidence or suspicion of ischemia on clinical presentation or noninvasive evaluation. For comparison, quantitative coronary angiography (QCA) was performed before percutaneous coronary intervention (PCI), immediately after PCI, and at follow-up angiography by two interventional cardiologists, using the CAAS 5 software (Pie Medical Imaging, Maastricht, Netherlands). They assessed the minimal lumen diameter, percent diameter stenosis, reference diameter, and lesion length, in addition to the acute gain. Ostial RCA lesions were defined as those within 3 mm of the aortic ostium, with >75% stenosis, as assessed by QCA methods described in previous reports [11,12]. ISR was defined as a stenosis within 5 mm distance, proximal or distal to the previously placed stent, with ≥50% diameter stenosis. As previously described, angiographic patterns of ISR were classified as focal (lesion length ≤ 10 mm), diffuse (lesion length ≥ 10 mm), or total occlusion [13]. Furthermore, we divided the focal ISR into ostial and proximal depending on the location of the RCA-ISR. We defined ISR within 10 mm from ostium as ostial ISR and ISR of 10 mm beyond as proximal ISR. Furthermore, we defined aggressive post-dilation the ratio should be >1.10 for balloon to stent ratio. In this study, SF included both complete and partial SF identified on plain fluoroscopy without contrast injection at the first scheduled follow-up angiography, as previously described [14,15]. The diagnosis of SF required an independent review and agreement by the two interventional cardiologists.

2.3. Statistical analysis

Continuous variables are expressed as means ± standard deviations. Comparisons of clinical, echocardiographic, angiographic, or procedure-related characteristics were made

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