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Impact of Native Coronary Artery Calcification on Lesion Outcome Following Drug-Coated Balloon Angioplasty for Treatment of In-Stent Restenosis

Kosuke NOMURA*[1)], Yasushi AKUTSU[1,2)], Hiroaki TSUJITA[1)], Seita KONDO[1)], Teruo SEKIMOTO[1)], Shunya SATO[1)], Hideaki TANAKA[1)], Ken ARAI[1)], Yosuke OISHI[1)], Kunihiro OGURA[1)], Shigeto TSUKAMOTO[1)], Toshihiko GOKAN[1)], Hiroki TANISAWA[1)], Kyoichi KANEKO[1)], Yusuke KODAMA[1)], Hidenari MATSUMOTO[1)] and Toshiro SHINKE[1)]

Abstract: This study aimed to clarify whether native coronary artery (CA) calcification before index percutaneous coronary intervention (PCI) has an impact on the effectiveness of drug-coated balloon (DCB) angioplasty for the treatment of in-stent restenosis (ISR). 100 consecutive patients with 166 ISR lesions underwent quantitative coronary angiography (QCA) before and after index PCI and before and after DCB angioplasty for ISR. CA calcification before index PCI was assessed by angiography and results were analyzed to reveal the predictive values for target lesion revascularization (TLR) and major adverse cardiac events (MACE). During 1.03±1.03 years of follow-up, TLR occurred in 44 lesions (26.5%) and MACE in 33 patients (33%). On multivariate analysis, CA calcification before index PCI ($p=0.016$), and % diameter of stenosis (%DS) ≥73% ($p=0.023$) and minimal lumen diameter (MLD) <0.65 mm ($p=0.001$) before DCB angioplasty were independent predictors for TLR after DCB angioplasty. MACE was also associated with CA calcification before index PCI ($p=0.01$), and %DS ≥ 73% ($p=0.001$) and MLD < 0.65 mm ($p=0.01$) before DCB angioplasty, but only %DS ≥ 73% before DCB angioplasty was an independent predictor for MACE after DCB angioplasty ($p=0.039$). The combination of CA calcification before index PCI and these QCA factors before DCB angioplasty was an independent and more powerful predictor for MACE than the QCA factors alone ($p<0.001$). Thereafter, the combination of CA calcification and %DS ≥ 73% before DCB angioplasty stratified the risk of MACE after DCB angioplasty ($p<0.05$). CA calcification before index PCI, as well as anatomical information at ISR, have an impact on outcome after DCB angioplasty for ISR.

Key words: coronary artery calcification, drug-coated balloon angioplasty, in-stent restenosis, percutaneous coronary intervention

[1)] *Department of Medicine, Division of Cardiology, Showa University School of Medicine,* 1-5-8 Hatanodai, Shinagawaku, Tokyo 142-8666, Japan.
[2)] *Showa University Clinical Research Institute for Clinical Pharmacology and Therapeutics.*
* To whom corresponding should be addressed.

Introduction

In-stent restenosis (ISR) is still a major issue following percutaneous coronary intervention (PCI), and PCI for complex coronary lesions is prone to develop ISR with an incidence of more than 20%[1,2]. Coronary artery (CA) calcification often leads to stent underexpansion and subsequent adverse events including ISR[3,4].

Drug-coated balloon (DCB) angioplasty has recently been introduced in interventional cardiology and has become an attractive option for the treatment of ISR[5]. Previous studies have reported that DCB angioplasty for bare metal stent (BMS)-ISR or drug-eluting stent (DES)-ISR provides better results compared with plain old balloon angioplasty, such as significantly lower recurrent restenosis and target lesion revascularization (TLR). Although DCB angioplasty was expected to be an alternative to other treatments for ISR, recurrent ISR still occurs in clinical practice.

The SYNTAX score[6] and the standard American College of Cardiology/American Heart risk score[7] include CA calcification data and have been used by interventional cardiologists as a guide for the selection of treatment strategies for patients undergoing PCI with stent implantation. When ISR has occurred, angiographic patterns of ISR are associated with the incidence of recurrent TLR[8], however, the impact of original CA calcification before the index PCI has not been systematically assessed. This is partly because the stent metal may hamper the discrimination of CA calcification behind the implanted stent, since they have a similar density on fluoroscopy. Therefore, we decided to evaluate CA calcification in the original angiogram taken at the time of the index PCI, and hypothesized that the presence of CA calcification before the index PCI is associated with the prognosis after DCB angioplasty.

Materials and methods

Study patients

This prospective observational study enrolled consecutive ISR patients who underwent PCI using DCBs at Showa University Hospital, Tokyo, Japan, from April 2014 to March 2017. Inclusion criteria were stable or unstable angina with documented ischemia and significant ISR with a percent diameter of stenosis (%DS) $\geq$ 50%. The study was approved by the School of Medicine, Showa University Ethics Committee (Permit Number: 2868), and written informed consent was obtained from all patients. A total of 150 patients with 199 lesions were treated with DCB (SeQuent Please; B. Braun, Melsungen, Germany) angioplasty for BMS-ISR or DES-ISR during the study period, and finally, 100 patients (age, 70 $\pm$ 10 years; 83% male) with 166 lesions who underwent successful DCB angioplasty were followed up.

PCI using DCBs for ISR

Cardiac catheterization was performed according to standard practice. At the beginning of the procedure, 7,000 to 8,000 units of heparin was administered. The PCI strategy was dependent on the individual operator; however, general principles included predilation (balloon-to-vessel

ratio of 0.8 to 1.0 and/or balloon-to-previous stent ratio of 1 : 1) performed with noncompliant balloons inflated to high pressures (>18 atm). Three different catheters were used to perform predilation: Scoreflex balloon catheter (OrbusNeich, Tokyo, Japan), Lacrosse® NSE balloon catheter (Goodman, Nagoya, Japan), or Cutting balloon catheter (Boston Scientific, Marlborough, MA, USA). Balloon catheters were available in lengths ranging from 10 to 30 mm and diameters ranging from 2.0 to 4.0 mm. DCBs with paclitaxel were inflated at a nominal pressure for a minimum of 30 to 60 sec to allow drug delivery to the vessel wall. All patients were prescribed dual antiplatelet therapy with aspirin (100 mg daily) and either clopidogrel (75 mg daily) or prasugrel (3.75 mg daily) for at least 3 months.

Angiographic assessment of CA calcification

Coronary angiography performed at the index PCI was retrospectively reviewed to assess the original characteristics of the lesion which induced ISR following stent placement. Angiographic CA calcification of the target lesion before stent implantation was graded according to the definition of standard criteria for preprocedural lesion morphology[9]; CA calcification was shown as readily apparent densities noted within the apparent vascular wall at the site of the stenosis and was defined as radiopacities noted without cardiac motion prior to contrast injection (Fig. 1).

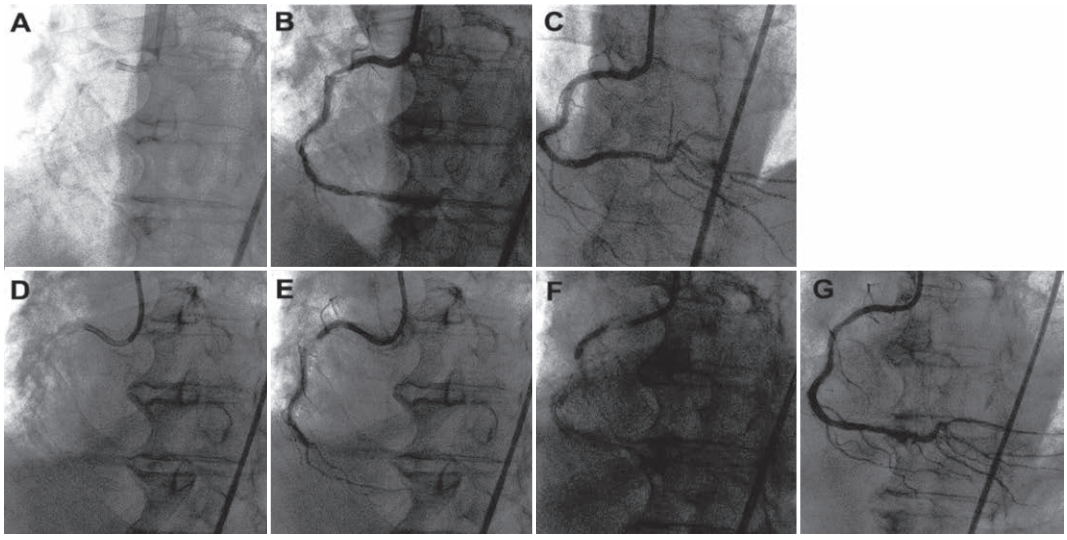

Fig. 1. Coronary angiogram showing coronary artery (CA) calcification before the index percutaneous coronary intervention (PCI)

CA calcification appears as readily apparent densities noted within the apparent vascular wall at the site of the stenosis and was defined as radiopacities noted without cardiac motion prior to contrast injection. In a 70-year-old male patient with angina pectoris, coronary angiography showed a diffuse CA calcification (A) of the right CA including severe coronary stenosis of segment 1 on the American Heart Association classification (B), and the index PCI with stent improved the CA stenosis of the target lesion (C). He had symptoms with angina pectoris again. CA calcification after the index PCI on the coronary angiogram is masked by the stent in the target lesion of segment 1 (D). Coronary angiography showed the severe CA stenosis into the stent (E), and drug-coated balloon angioplasty (F) improved the in-stent restenosis of the target lesion (G).

Quantitative coronary angiography (*QCA*)

Coronary angiography was performed after intracoronary nitrate injection and all images before and after interventions were digitally stored. Quantitative analysis of the coronary angiographic images was performed by evaluating the matched orthogonal views in the catheterization laboratory using the CAAS V system (Pie Medical Imaging BV, Maastricht, The Netherlands). Reference vessel diameter, minimal lumen diameter (MLD), %DS, and lesion length were analyzed by experienced cardiologists, blinded to the clinical procedure and outcomes (Fig. 2). The SYNTAX score for each patient was calculated prospectively by scoring all coronary lesions with a %DS ≥ 50% in vessels ≥ 1.5 mm using the SYNTAX score algorithm[6]. An in-stent analysis (from shoulder to shoulder of the dilated DCB) was performed. Restenosis was defined as recurrent %DS ≥ 50% and categorized according to the Mehran classification[8]: type I, focal ISR lesion < 10 mm in length; type II, diffuse intra-stent lesion > 10 mm without extending outside the margin of the stent; type III, diffuse proliferative ISR lesion > 10 mm and extending beyond the margin of the stent; and type IV, ISR lesion with total occlusion.

Angiographic success was defined as achievement of a final residual stenosis < 30% by visual estimate and Thrombolysis In Myocardial Infarction flow grade 3.

Endpoint

After DCB angioplasty, all patients underwent regular clinical follow-up at the out-patient clinic once every 4 to 8 weeks. The endpoint was major adverse cardiac events (MACE) according to the Academic Research Consortium recommendations[10], which included cardiac death, non-fatal myocardial infarction (MI), TLR, and non-TLR. Binary restenosis after DCB

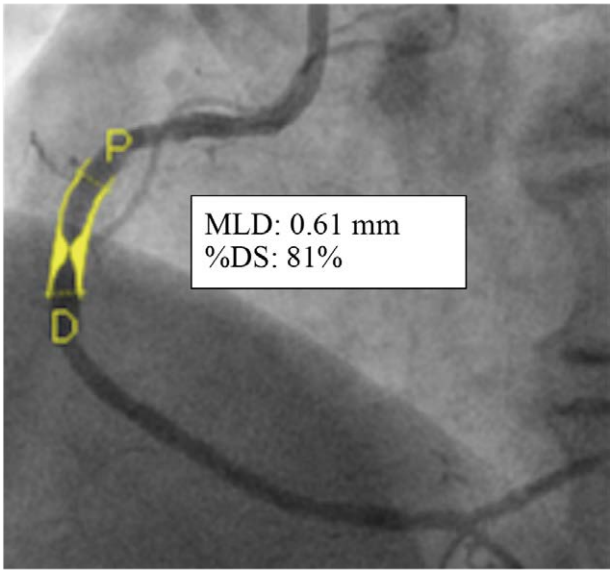

Fig. 2. Quantitative coronary angiography analysis.
MLD, minimal lumen diameter; %DS, percent diameter of stenosis.

angioplasty was defined as angiography during follow-up showing a %DS>50% related to the target lesion, with a history of recurrent angina pectoris and objective signs of documented ischemia related to the target lesion. TLR was defined as repeat PCI or CA bypass grafting for restenosis of the target lesion following DCB angioplasty to the previously stented segment. Non-TLR was defined as PCI or CA bypass grafting for a de-novo lesion during follow-up.

Statistical analysis

All continuous variables are shown as mean ± tandard deviation. Comparisons between groups were performed with unpaired *t* tests or Fisher's exact tests for continuous variables and the chi-square test for categorical variables. Associations among the predictors, such as CA calcification and QCA data, for TLR and MACE were formally tested by construction of a Cox proportional hazards model with regression analysis. Pearson's correlation analysis was performed to assess dependence. A receiver-operating characteristic analysis was performed to define cutoff values, and the cutoff values were defined by minimizing the expression of $(1-\text{sensitivity})^2+(1-\text{specificity})^2$. The patients were divided into 2 groups for the log-rank test with construction of Kaplan-Meier curves. All multivariable analyses employed the forward stepwise method, with entry and removal probability values set at 0.1. Statistical analysis was performed with SPSS for Windows, version 20 (SPSS Inc., IBM, Chicago, IL, USA). A probability value of <0.05 was considered significant.

A total sample size of 100 patients with ISR was required because 30 patients with CA calcification and 70 patients without CA calcification were estimated by the traditional technique of Cochran's formula with an allowable error of 5 % at a 95% confidence level to prove our hypothesis, using the fact that ISR occurs in 5 % of patients with CA calcification and 2 % of those without CA calcification according to previous studies of ISR after index PCI with stentings[11, 12].

Results

Patient Characteristics

During the study period, 100 ISR patients were enrolled in this study. When the target lesions were divided into 2 groups based on the presence or absence of CA calcification before the index PCI, CA calcification was noted in 27 patients (27%) with 52 lesions (31.3%).

No significant differences were found between the patients with and without CA calcification for age, sex, and cardiovascular risk factors, but the patients with CA calcification had a significantly greater history of chronic kidney disease ($p<0.001$; Table 1). Patients with CA calcification had higher levels of N-terminal brain natriuretic peptide than those without CA calcification ($p=0.02$), and were more likely to have left main trunk CA disease or 3 vessel disease ($p=0.008$).

Lesion characteristics

The lesions with CA calcification before the index PCI were associated with a higher

Table 1. Patient characteristics

	Coronary artery calcification before index PCI		
	Yes (n=27)	No (n=73)	*p* value
Age (years)†	72±8	70±11	0.42
Female	7 (25.9%)	10 (13.7%)	0.23
History of diabetes	18 (66.7%)	42 (57.5%)	0.49
History of hypertension	24 (88.9%)	58 (79.5%)	0.38
History of hyperlipidemia	18 (66.7%)	55 (75.3%)	0.45
History of current smoking	13 (48.1%)	46 (63.0%)	0.25
History of myocardial infarction	23 (74.2%)	42 (63.6%)	0.36
History of coronary artery bypass graft	0	5 (6.8%)	0.32
History of chronic kidney disease	21 (77.8%)	28 (38.4%)	< 0.001
History of cerebrovascular disease	1 (3.7%)	10 (13.7%)	0.28
Low-density lipoprotein cholesterol (mg/dl)†	70.0±22.9	80.8±25.7	0.06
High-sensitivity C-reactive protein (mg/dl)†	0.717±1.594	0.420±1.273	0.34
N-terminal brain natriuretic peptide (pg/ml)†	780±1106	260±918	0.02
Echocardiographic LVEF (%)†	47.9±13.2	52.2±9.2	0.07
Coronary angiographic findings before DCB angioplasty			
SYNTAX score†	14.1±10.0	10.7±10.7	0.15
Vessels involved: LMT or 3 VD	9 (33.3%)	8 (11.0%)	
2VD	11 (40.7%)	24 (32.9%)	0.008
1VD	7 (25.9%)	41 (56.2%)	
Medications			
Use of ACE or ARB	11 (40.7%)	43 (58.9%)	0.12
Use of beta-blocker	13 (48.1%)	42 (57.5%)	0.50
Use of calcium antagonist	9 (33.3%)	31 (42.5%)	0.50
Use of nitrite drugs	10 (37.0%)	20 (27.4%)	0.46
Use of statin	18 (66.7%)	66 (90.4%)	0.007
Use of aspirin	27 (100%)	70 (95.9%)	0.56
Use of clopidogrel	18 (66.7%)	43 (58.9%)	0.50
Use of prasugrel	7 (25.9%)	21 (28.8%)	0.81

Values are number of patients (%), unless indicated otherwise. †Mean±standard deviation. PCI: percutaneous coronary intervention, LVEF: left ventricular ejection fraction, DCB: drug-coated balloon, LMT: left main trunk coronary artery, VD: vessel disease, ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin-II receptor blocker.

incidence of type I ISR, whereas those without CA calcification were associated with type IV ISR ($p=0.006$; Table 2).

There were no significant differences in stent type, stent size, balloon types, and DCB size between the lesions with and without CA calcification before the index PCI. When the QCA data were analyzed, the lesions with CA calcification before the index PCI had a lower %DS before index PCI and a higher MLD after index PCI than those without CA calcification before

Table 2. Lesion characteristics of coronary angiography

	Coronary artery calcification before index PCI		*p* value
	Yes (n=52)	No (n=114)	
Coronary angiographic findings before DCB angioplasty			
Diameter of stenosis on AHA classification ≥ 90%	35 (67.3%)	76 (66.7%)	>0.99
DCB vessel: LMT	4 (7.7%)	2 (1.8%)	
LAD	13 (25.0%)	58 (50.9%)	0.006
LCX	10 (19.2%)	20 (17.5%)	
RCA	25 (48.1%)	34 (29.8%)	
Ostium lesion	25 (48.1%)	19 (16.7%)	<0.001
Bifurcation of target lesion	16 (30.8%)	38 (33.3%)	0.86
CTO lesion	0	15 (13.2%)	0.006
In-stent classification: Type I	40 (76.9%)	60 (52.6%)	
Type II	11 (21.2%)	36 (31.6%)	0.004
Type IV	1 (1.9%)	18 (15.8%)	
Index PCI findings			
Stent type: BMS	9 (17.3%)	12 (10.5%)	0.31
DES	43 (82.7%)	102 (89.5%)	
Minimum stent diameter < 2.5 mm	4 (7.7%)	15 (13.2%)	0.43
Maximum stent length ≥ 30 mm	16 (30.8%)	49 (43.0%)	0.17
DCB angioplasty findings			
DCB diameter < 3 mm	11 (21.2%)	40 (35.1%)	0.07
DCB length ≥ 20 mm	48 (92.3%)	102 (89.5%)	0.59
Rotational atherectomy	2 (3.8%)	5 (4.4%)	>0.99
Directional coronary atherectomy	1 (1.9%)	2 (1.8%)	>0.99
Balloon type before DCB angioplasty			
Non-complaint balloon	21 (40.4%)	29 (25.4%)	0.07
Semi-compliant balloon	6 (11.5%)	5 (4.4%)	0.10
Scoring balloon	12 (23.1%)	39 (34.2%)	0.21
Cutting balloon	13 (25.0%)	41 (36.0%)	0.21
QCA findings†			
Before index PCI			
Lesion diameter of stenosis (%)	65.4±20.0	73.1±21.9	0.03
Minimum lesion diameter (mm)	0.82±0.55	0.64±0.59	0.07
Lesion length (mm) (without CTO)	16.6±8.8	18.9±7.4	0.12
After index PCI			
Lesion diameter of stenosis (%)	17.3±12.0	18.6±10.8	0.49
Minimum lesion diameter (mm)	2.51±0.50	2.28±0.49	0.007
Before DCB angioplasty			
Lesion diameter of stenosis (%)	66.8±16.4	71.9±17.9	0.08
Minimum lesion diameter (mm)	0.82±0.47	0.69±0.47	0.10
Lesion length (mm) (without CTO)	14.9±6.6	18.8±7.3	0.002
After DCB angioplasty			
Lesion diameter of stenosis (%)	22.9±12.1	23.2±11.1	0.96
Minimum lesion diameter (mm)	2.17±0.59	2.05±0.44	0.15

Values are number of patients (%), unless indicated otherwise. †Mean±standard deviation. PCI : percutaneous coronary intervention, DCB : drug-coated balloon, AHA : American Heart Association, LMT : left main trunk coronary artery, LAD : left anterior descending coronary artery, LCX : left circumflex coronary artery, RCA : right coronary artery, CTO : chronic total occlusion, BMS : bare metal stent, DES : drug-eluting stent, QCA : quantitative coronary angiography.

the index PCI. On the other hand, those with CA calcification had a shorter lesion length before DCB angioplasty than those without CA calcification ($p=0.002$).

Angiographic predictors of targeted ISR

The %DS before index PCI was correlated with the %DS before DCB angioplasty ($r=0.174$, $p=0.03$), and MLD before index PCI was correlated with MLD before DCB angioplasty ($r=0.214$, $p=0.006$). Lesion length before index PCI was also correlated with lesion length before DCB angioplasty ($r=0.621$, $p<0.001$).

Predictors of TLR after DCB angioplasty

During 1.03±1.03 years of follow-up (up to 2.5 years) after DCB angioplasty, TLRs occurred in 44 lesions (26.5%). There was no significant difference in the follow-up duration for the presence of TLRs between lesions with and without CA calcification (272±117 vs. 342±156 days, respectively; $p=0.10$). The area under the curve for predicting TLR was greater for %DS before and after DCB angioplasty than for %DS before and after index PCI (0.62 and 0.65 vs. 0.51 and 0.52, respectively), and the area under the curve was also greater for MLD before and after DCB angioplasty than for MLD before and after index PCI (0.64 and 0.61 vs. 0.51 and 0.6, respectively; Fig. 3). TLR after DCB angioplasty was 4.8% (1 of 21 lesions) with BMS and 29.7% (43 of 145 lesions) with DES ($p=0.016$). TLR after DCB angioplasty was associated with CA calcification before index PCI ($p=0.007$) and QCA data, such as %DS ≥ 73% ($p=0.03$), MLD < 0.65 mm ($p=0.002$), and balloon type ($p<0.05$) before DCB angioplasty, and %DS ≥ 26% after DCB angioplasty ($p=0.01$; Table 3).

On multivariate analysis, after adjustment for potential confounding variables, CA calcification

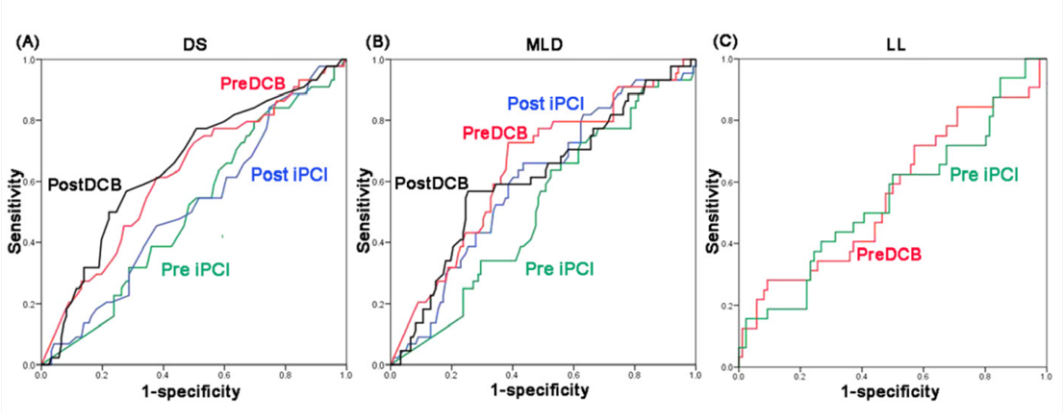

Fig. 3. Receiver-operating characteristic analysis of quantitative coronary angiography (QCA) data for predicting the lesions of target lesion restenosis (TLR) after drug-coated balloon (DCB) angioplasty with paclitaxel

QCA data collected included percent diameter of stenosis (%DS), minimum lesion diameter (MLD), and lesion length (LL) before the index percutaneous coronary intervention (Pre iPCI, green line) and after the index PCI (Post iPCI, blue line) and before DCB angioplasty (Pre DCB, red line) and after DCB angioplasty (Post DCB, black line).

Table 3. Descriptive variable lesion factors predicting target lesion revascularization

	Regression analysis	Wald	Univariate analysis	
	Coefficient (beta)	χ^2	Hazard ratio (95% CI)	p value
Coronary calcification before index PCI	0.835	7.291	2.3 (1.26-4.22)	0.007
Coronary angiographic findings before DCB angioplasty				
Diameter of stenosis on AHA classification ≥ 99%	0.264	0.691	1.30 (0.70-2.43)	0.41
Left anterior descending artery lesion	0.130	0.180	1.14 (0.63-2.07)	0.70
Chronic total occlusion lesion	0.172	0.151	1.19 (0.50-2.83)	0.70
Type Ⅳ ISR classification	0.506	1.816	1.66 (0.80-3.47)	0.18
Diffuse lesion (type Ⅱ, Ⅲ, and Ⅳ) ISR classification	−0.030	0.009	0.97 (0.53-1.77)	0.92
Index PCI findings				
Drug-eluting stent	1.890	3.486	6.62 (0.91-48.11)	0.06
Stent length ≥ 30 mm	0.362	1.420	1.44 (0.79-2.60)	0.23
Stent diameter<2.5 mm	−0.713	3.210	2.04 (0.93-4.46)	0.07
DCB angioplasty findings				
Length ≥ 20 mm	0.596	0.986	1.82 (0.56-5.88)	0.32
Diameter < 3 mm	−0.346	1.220	1.41 (0.76-2.62)	0.27
Directional coronary atherectomy	0.993	1.960	2.70 (0.65-11.30)	0.17
Non-complaint balloon	0.761	5.910	2.10 (1.16-3.95)	0.02
Semi-compliant balloon	0.181	0.092	1.20 (0.37-3.88)	0.76
Scoring balloon	−0.055	0.029	0.95 (0.50-1.79)	0.87
Cutting balloon	−0.749	4.310	0.47 (0.23-0.96)	0.04
QCA findings				
Before index PCI				
Lesion diameter of stenosis ≥ 73%	−0.059	0.038	0.94 (0.52-1.71)	0.85
Minimum lesion diameter < 0.68 mm	−0.297	0.889	1.35 (0.73-2.49)	0.35
Lesion length ≥ 20.7 mm (without chronic total occlusion)	−0.297	0.889	0.74 (0.40-1.38)	0.35
After index PCI				
Lesion diameter of stenosis ≥ 21%	0.116	0.146	1.12 (0.62-2.04)	0.70
Minimum lesion diameter < 2.4 mm	−0.536	2.920	1.71 (0.92-3.16)	0.09
Before DCB angioplasty				
Lesion diameter of stenosis ≥ 73%	0.700	5.020	2.02 (1.09-3.72)	0.03
Lesion diameter of stenosis ≥ 73% and severe calcification before PCI	1.298	14.533	3.66 (1.88-7.13)	<0.001
Minimum lesion diameter < 0.65 mm	−1.066	9.880	2.91 (1.49-5.65)	0.002
Minimum lesion diameter < 0.65 mm and severe calcification before PCI	1.706	25.117	5.51 (2.83-10.73)	<0.001
Lesion length ≥ 16.2 mm (without chronic total occlusion)	−0.139	0.162	0.87 (0.44-1.71)	0.69
After DCB angioplasty				
Lesion diameter of stenosis > 26%	0.780	6.470	2.18 (1.2-4.00)	0.01
Minimum lesion diameter < 1.9 mm	−5.930	3.710	1.91 (1.00-3.31)	0.054

CI : confidence interval, PCI : percutaneous coronary intervention, DCB : drug-coated balloon, AHA : American Heart Association, ISR : in-stent restenosis, QCA : quantitative coronary angiography.

before index PCI (hazard ratio [HR], 2.23; 95% confidence interval [CI], 1.16-4.29; p=0.016), and %DS ≥ 73% (HR, 2.03; 95% CI, 1.1-3.75; p=0.02) and MLD < 0.65 mm (HR, 3.37; 95% CI, 1.69-6.67: p=0.001) before DCB angioplasty were independent predictive factors for TLR

after DCB angioplasty.

Further, the combination of CA calcification before index PCI and %DS ≥ 73% or MLD < 0.65 mm before DCB angioplasty was an independent and more powerful prognostic factor for TLR after DCB angioplasty than QCA data alone ($p < 0.001$).

Patient factors for predicting MACE

During the follow-up, MACE were observed in 33 patients (33%): cardiac death, 2 patients; non-fatal MI, 6 patients; TLR, 18 patients; target vessel revascularization, 2 patients; and non-TLR, 5 patients. The presence of MACE after DCB angioplasty was associated with a history of chronic kidney disease ($p = 0.03$), a serum high-sensitivity C-reactive protein (hsCRP) level ≥ 0.14 mg/dl ($p = 0.02$), a SYNTAX score ≥ 14 ($p = 0.01$), CA calcification before index PCI ($p = 0.01$), and QCA data before DCB angioplasty, such as %DS ≥ 73% ($p = 0.001$) and MLD < 0.65 mm ($p = 0.01$; Table 4).

On multivariate analysis, after adjustment for potential confounding variables, %DS ≥ 73% before DCB angioplasty was an independent predictive factor for MACE after DCB angioplasty (HR, 2.46; 95% CI, 1.05-5.79, $p = 0.039$). The combination of SYSTAX score ≥ 14 before DCB angioplasty and CA calcification before the index PCI was an independent powerful prognostic factor for MACE ($p = 0.001$).

Further, the combination of CA calcification before the index PCI and %DS ≥ 73% or MLD < 0.65 mm before DCB angioplasty was an independent and more powerful prognostic factor for MACE than QCA data alone ($p < 0.001$), and the combination of CA calcification before index PCI and %DS ≥ 73% before DCB angioplasty stratified the risk of MACE after DCB angioplasty ($p < 0.05$; Fig. 4).

Discussion

CA calcification before the index PCI, and %DS ≥ 73% and MLD < 0.65 mm ($p = 0.01$) before DCB angioplasty were associated with TLR and MACE after DCB angioplasty. Further, the combination of these factors was an independent and more powerful prognostic factor for TLR and MACE than the QCA data alone, and the combination of CA calcification before the index PCI and %DS ≥ 73% before DCB angioplasty stratified the risk of MACE after DCB angioplasty.

CA calcification for predicting prognosis after DCB angioplasty for ISR

With the introduction of contemporary new-generation DESs, the rate of repeat revascularization due to ISR has decreased, but the ISR rate after PCI is higher if PCI is performed in patients with complex coronary lesions, including CA calcification[13]. A greater amount of CA calcification impairs stent delivery, and expansion results in a smaller and more elliptical stent area[14], which may lead to an increased risk of subsequent cardiovascular events after PCI[15]. In patients with peripheral disease, the severity of CA calcification in de novo stenotic lesions has been reported to be associated with TLR after DCB angioplasty, and various procedures, such as atherectomy and intravascular lithotripsy, from the new generation options

Table 4. Descriptive variable patient factors for predicting major adverse cardiac events

	Regression analysis	Wald	Univariate analysis	
	Coefficient (beta)	χ^2	Hazard ratio (95% CI)	*p* value
Age ≥ 73years	0.314	0.786	1.38 (0.68-2.74)	0.38
Left ventricular ejection fraction < 52%	−0.159	0.201	1.17 (0.58-2.35)	0.65
History of chronic kidney disease	0.793	4.777	2.21 (1.09-4.50)	0.03
High-sensitivity C-reactive protein ≥ 0.14 mg/dl	0.861	5.796	2.37 (1.17-4.77)	0.02
Coronary artery calcification before index PCI	0.926	6.634	2.52 (1.25-5.11)	0.01
Coronary angiographic finding before DCB angioplasty				
SYNTAX score ≥ 14	0.898	6.448	2.45 (1.23-4.91)	0.01
SYNTAX score ≥ 14 before DCB angioplasty and coronary artery calcification before index PCI	1.532	11.470	4.63 (1.91-11.23)	0.001
Left anterior descending coronary artery lesion	0.301	0.729	1.35 (0.68-2.70)	0.39
Ostium lesion	0.333	0.803	1.40 (0.67-2.90)	0.37
Maximum diameter of stenosis on AHA classification ≥ 99%	1.152	10.73	3.17 (1.59-6.31)	0.001
LMT or three vessel disease	0.605	2.191	1.83 (0.82-4.08)	0.14
Type Ⅳ in-stent classification	0.679	2.252	1.97 (0.81-4.79)	0.13
Index PCI findings				
Bare metal stent	−0.225	0.177	1.25 (0.44-3.58)	0.67
Drug-eluting stent	−0.405	0.641	0.67 (0.25-1.80)	0.67
Stent length ≥ 30 mm	0.320	0.835	1.38 (0.69-2.74)	0.36
Stent diameter < 2.5 mm	−0.234	0.264	1.26 (0.52-3.09)	0.61
DCB angioplasty findings				
Maximum length ≥ 30 mm	0.458	1.711	1.58 (0.80-3.14)	0.19
Minimum diameter < 2.5 mm	−0.017	0.001	1.02 (0.24-4.35)	0.98
Directional coronary atherectomy lesion	0.590	0.335	1.81 (0.24-13.3)	0.56
QCA findings				
Before index PCI				
Maximum lesion diameter of stenosis ≥ 78%	0.065	0.035	1.07 (0.54-2.12)	0.85
Minimum lesion diameter < 0.65 mm	−0.017	0.002	1.02 (0.49-2.11)	0.96
Maximum lesion length ≥ 22 mm (without CTO)	0.765	3.605	2.15 (0.98-4.73)	0.06
After index PCI				
Maximum lesion diameter of stenosis ≥ 21%	0.278	0.620	1.32 (0.66-2.63)	0.43
Minimum lesion diameter < 2.2 mm	−0.536	2.168	1.71 (0.84-3.50)	0.14
Before DCB angioplasty				
Maximum lesion diameter of stenosis ≥ 73%	1.271	10.510	3.56 (1.65-7.69)	0.001
Maximum lesion diameter of stenosis ≥ 73% and coronary calcification before index PCI	1.385	13.470	4.00 (1.91-8.38)	<0.001
Minimum lesion diameter < 0.65 mm	−0.989	6.335	2.69 (1.24-5.81)	0.01
Minimum lesion diameter < 0.65 mm and coronary calcification before index PCI	1.584	15.180	4.87 (2.20-10.80)	<0.001
Maximum lesion length ≥ 17.1 mm (without CTO)	−0.094	0.052	1.10 (0.49-2.46)	0.82
After DCB angioplasty				
Maximum lesion diameter of stenosis > 25%	0.469	1.665	1.60 (0.78-3.26)	0.20
Minimum lesion diameter < 1.86 mm	−0.555	2.431	1.74 (0.87-3.5)	0.12

CI : confidence interval, PCI : percutaneous coronary intervention, DCB : drug-coated balloon, AHA : American Heart Association, LMT : left main trunk coronary artery, QCA : quantitative coronary angiography, CTO : chronic total occlusion.

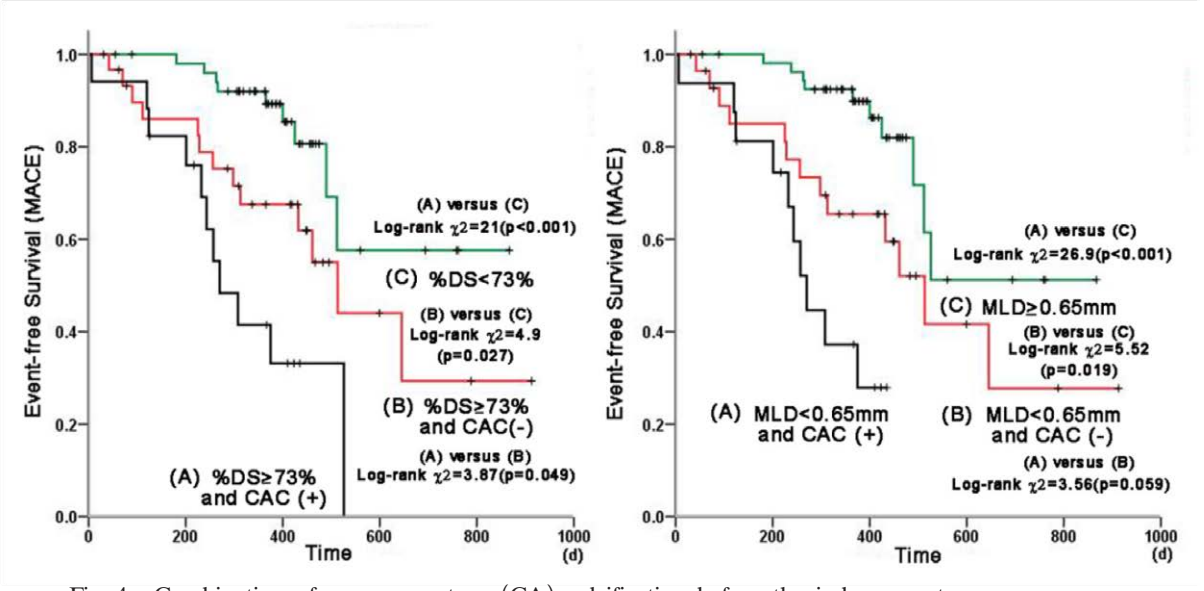

Fig. 4. Combination of coronary artery (CA) calcification before the index percutaneous coronary intervention (PCI) and quantitative coronary angiography (QCA) data before drug-coated balloon (DCB) angioplasty with paclitaxel for predicting major adverse clinical events (MACE) in patients after DCB angioplasty

QCA data collected before DCB angioplasty included percent diameter of stenosis (%DS, left panel) and minimum lesion diameter (MLD, right panel). (A) %DS≥73% or MLD<0.65 mm, and CA calcification (CAC [+], black line); (B) %DS≥73% or MLD<0.65 mm, and no CA calcification (CAC [−], red line); (C) %DS<73% or MLD≥0.65 mm (green line). Left panel (%DS and CAC): group A vs. B, $p=0.049$; group B vs. C, $p=0.027$; group A vs. C, $p<0.001$. Right panel (MLD and CAC): group A vs. B, $p=0.059$; group B vs. C, $p=0.019$; group A vs. C, $p<0.001$.

have been conducted to overcome the great difficulty associated with the presence of calcium[16]. However, there are currently inadequate data about the use of DCB angioplasty for lesions with CA calcification because the calcification behind the implanted stent cannot be accurately detected and measured on an angiogram or computed tomography angiography. Intravascular ultrasound or optimal coherence tomography enables accurate detection of CA calcification in stents[17, 18], and previous studies demonstrated that the magnitude of CA calcification was inversely correlated to stent expansion, even after high-pressure balloon inflations[19, 20]. Further, recent studies reported that the accurate detection of abnormal vessel reactions associated with stent implantation measured by optimal coherence tomography predicts the prognosis of patients undergoing DCB angioplasty after ISR[21, 22]. However, in clinical practice, it may be difficult to routinely obtain an invasive intravascular assessment of coronary plaque in all patients undergoing DCB angioplasty for treatment of ISR because of cost or time-effectiveness. In the present study, we found that angiographical information of CA calcification before DCB angioplasty is useful for predicting TLR and MACE after DCB angioplasty.

Severe CA calcification often requires high-pressure dilation, and the pressure applied from the balloon to the vessel wall might not be uniform across the length of the lesion because of varying amounts of calcification, which increases the risk of dissection and acute vessel

closure, MI, restenosis, and MACE[23]. DCB angioplasty can inhibit neointimal formation by homogeneous drug transfer to the vessel wall[5], but the calcified plaque might prevent the transfer of an antiproliferative drug to the vessel wall, and incomplete suppression of neointimal hyperplasia might occur.

Combination of CA calcification and QCA data for predicting prognosis after DCB angioplasty

It is known that the severity of ischemia is associated with the magnitude of ISR based on QCA data[24]. Using QCA data, Rathore *et al*[25] demonstrated that the focal pattern of ISR and baseline %DS were independent predictors of ISR recurrent restenosis after DCB treatment. Rhee *et al*[26] also demonstrated using QCA data that a composite of cardiac death, target vessel-related MI, or clinically-indicated TLR during a 2-year follow-up after DCB angioplasty were associated with DCB size, %DS, MLD, and lesion length before DCB angioplasty and residual %DS after DCB angioplasty[26]. Similarly, our study showed that %DS and MLD before DCB angioplasty from QCA data were predictors of MACE after DCB angioplasty. More importantly, we found that the combination of CA calcification and QCA data before DCB angioplasty was an independent and more powerful prognostic factor for TLR and MACE than only QCA data ($p<0.001$).

DES-ISR is associated with poorer outcomes than BMS-ISR after treatment with a DCB, whereas index PCI is more effective with DES stenting than BMS stenting in calcified lesions[27]. On the other hand, Miglionico *et al*[28] showed a similar event rate after DCB angioplasty in ISR lesions between BMS and DES in high-risk patients. In the present study, MACE after DCB angioplasty occurred in 4 of 14 patients (28.6%) who had BMS-ISR and in 29 of 86 patients (33.7%) who had DES-ISR, with no significant difference between the two groups. Furthermore, the balloon type before DCB angioplasty treatment has been also reported to be associated with TLR[29], and the use of a cutting balloon improved the prognosis in the present study. However, after adjustment for stent and balloon types, CA calcification and QCA data before DCB angioplasty, and the combination of these two factors predicted the prognosis after DCB angioplasty independently.

Other factors for predicting prognosis after DCB angioplasty

The SYNTAX score before the index PCI can be used to stratify risk in patients treated with index PCI, and Garg *et al*[30] demonstrated a poor prognosis after the index PCI in patients with a SYNTAX score >17. On the other hand, the residual SYNTAX score after the index PCI with stenting is also reported to predict prognosis[31], but the impact of the SYNTAX score in the case of ISR has not been clarified in previous studies. In the present study, we found that higher SYNTAX scores ≥ 14 before DCB angioplasty predicts MACE after DCB angioplasty in patients with ISR. Further, we found the combination of CA calcification (the SYNTAX score number of CA calcification is estimated as 2) and SYNTAX scores ≥ 14 before DCB angioplasty is an independent powerful prognostic factor for MACE after DCB angioplasty ($p=0.001$).

CRP is a sensitive and nonspecific inflammatory marker, and increased CRP levels have

been reported to be associated with MACE, including ISR after the index PCI[32]. We showed that hsCRP is also predictive of MACE after DCB angioplasty in patients with ISR, similar to patients undergoing PCI for native coronary lesions. Our result indicates that the promotion of neointimal proliferation through the stent struts in ISR lesions results from higher hsCRP levels[33].

Study limitations

The major limitations of the present study are the small sample size in a single center. Given the rarity of the disease, a large cohort study is warranted to verify these findings. CA calcification before the index PCI was detected retrospectively using cineangiography in patients undergoing DCB angioplasty following ISR. However, the increase in CA calcification after ISR compared with before the index PCI may have influenced the prognostic accuracy of predicting TLR or MACE after DCB angioplasty. Further, CA calcification was simply measured using cineangiography, sacrificing diagnostic accuracy[34]. Coronary angiography has low-to-moderate sensitivity for detecting CA calcification compared with intravascular ultrasound or computed tomography, but it is very specific (high positive predictive value)[34].

Conclusions

CA calcification before the index PCI and QCA data before DCB angioplasty are associated with TLR and MACE after DCB angioplasty, and the combination of these factors is an independent and more powerful prognostic factor for TLR and MACE than using QCA data alone. The addition of CA calcification to anatomical information of ISR is important for predicting the prognosis of patients, post-DCB angioplasty. The angiographic anatomical data with CA calcification provides important clinical information for selecting the treatment strategy for ISR, because the combination of CA calcification and QCA data before DCB angioplasty predicts the risk after DCB angioplasty.

Compliance with Ethical Standards

Funding: none.

Conflict of Interest: none.

Ethical approval: 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: Informed consent was obtained from all individual participants included in the study..

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