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Original Article

Statin Therapy for the Prevention of Cardiac Event in Instent Restenosis Patients Treated with Drug-Eluting Balloon

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SUMMARY

Background: The clinical efficacy of paclitaxel-coated balloon (PCB) and statin therapy have been proven in the treatment of instent restenosis (ISR). However, there are no data with clinical follow-ups to support statin therapy in ISR patients treated after PCB. The aim of this study was to investigate the impact of statin therapy in ISR patients treated after PCB.
Methods: A retrospective study was performed of patients who underwent PCB for ISR from 2012 to 2014. A total of 102 patients (mean age: 70.9; 70% men; 69.5% with statin therapy) with 131 lesions [(bare-metal stent restenosis (BMS-ISR); 90 lesions, drug-eluting stent restenosis (DES-ISR); 41 lesions)] were analyzed in this study. The mean of follow-up days is 786.03 ± 350.80 days.
Result: DES-ISR has higher target lesion revascularization (TLR) [14 vs. 9, $p < 0.001$] and major adverse coronary events (MACE) [16 vs. 16, $p < 0.01$] than BMS-ISR. Statin therapy was associated with a significant reduction in the occurrence of TLR [11 vs. 12, $p = 0.01$] and MACE [15 vs. 17, $p < 0.001$]. DES-ISR (AOR: 3.43, CI: 1.30 to 9.04, $p = 0.01$) and statin therapy (AOR: 0.33, CI: 0.10 to 0.96, $p = 0.04$) were independent predictors of TLR. DES-ISR (AOR: 2.46, CI: 1.08 to 5.58, $p = 0.03$) and statin therapy (AOR: 0.31, CI: 0.13 to 0.77, $p = 0.01$) also were independent predictors of MACE.
Conclusion: It was the first time that statin therapy had proven to improve clinical cardiac outcome in ISR patients treated after PCB.

1. Introduction

In-stent restenosis (ISR) has been an important issue after percutaneous coronary intervention. The clinical efficacy of paclitaxel-coated balloon (PCB) has been well proven in the current treatment of ISR.[1–8] Hyperlipidemia is the leading cause of atherosclerosis and cardiovascular disease. Many clinical trials have demonstrated that statins reduce the incidence of coronary events in both primary and secondary prevention.[9–11] Additionally, statins also reduced the incidence of restenosis after coronary stent implantation[12] and balloon angioplasty.[13] However, there were no data to investigate the relationship between statin therapy and ISR patients post PCB. The aim of this study was to evaluate the impact of statin therapy in ISR patients after PCB angioplasty.

2. Materials and Methods

2.1. Subjects

The retrospective study aimed to assess the clinical efficacy of statin therapy in ISR patients treated with PCB. We observed 117 patients who underwent PCB fortotal 131 ISR lesions in Mackay Memorial Hospital during 2012~2014. After PCB treatment, these patients had received statin therapy for at least six months. All lesions were treated with SeQuent Please paclitaxel-coated balloon catheter (B. Braun Melsungen AG, Vascular Systems, Berlin, Germany). Patients with below situation were excluded from the study: bail-out stenting for an unsatisfied result after PCB therapy, lesions located in bypass vessel, neoplasm, hematological disorders or incomplete lipid therapy follow-up data. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Mackay Memorial Hospital. Patient-related records and information were hided and de-identified prior to analysis.

2.2. Data collection and definitions

Demographic data, disease history (such as hypertension [HTN] or diabetes mellitus [DM]), current tobacco use, coronary angiographic results, and prescribed medications were obtained from the hospital medical registry. The blood lipid profile (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides [TG]), and creatinine (Cr) levels were evaluated on the same day that the patients underwent PCB and 6 months thereafter. All blood samples were collected

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from venous blood after at least 8 hours of fasting. All patient were treated with dual-antiplatelet therapy (DAPT) of aspirin (100 mg daily) and clopidogrel (75 mg daily) before the intervention. DAPT was used for at least 1 month after PCB according to the guideline. All procedures were based on standard practice guidelines. All ISR lesions were dealt with non-compliant balloon predilatation at 1:1 balloon-to-vessel ratio before PCB.

The length of the PCB was chosen to overlap ISR lesion by at least 2 mm at the proximal and distal margins. The inflation time for the PCB was 30 to 60 seconds. Lesion length and vessel reference diameter were measured with quantitative coronary angiography or visual estimation. We used four patterns of classification system to evaluate ISR lesion as previous study.[14]

2.3. Clinical outcomes

The outcome was measured from the date of receiving PCB to the first occurrence of endpoint. The primary endpoint was target lesion revascularization (TLR), defined as lesion being necessary to be treated if > 50% stenosis occurred within 5 mm upstream or downstream of the stent. The secondary endpoint was the occurrence rate of major adverse cardiac events (MACE), defined as the composite of cardiovascular (CV) death (caused by ischemic event, refractory heart failure, ventricular arrhythmia or as any death in which a CV cause could not be excluded), myocardial infarction, and TLR. Patients had been followed up via telephone or hospital visits until December 31, 2015.

2.4. Statistical analysis

Results were expressed as mean ± SD or percentages. Student's *t* test was used to compare differences of groups with continuous variables, and the chi-square test was employed for categorical data. A Cox proportional hazards model was used to calculate hazard ratios (HRs) and to determine the factors contributing to TLR and MACE. The HRs (95% confidence intervals [CIs]) were adjusted for age, gender, drug-eluting stent in-stent restenosis (DES-ISR), bare-metal stent in-stent restenosis (BMS-ISR), current smoker, DM, HTN, hemodialysis (HD), baseline LDL-C level, LDL-C level reduction ratio post statin therapy for 6 months. Kaplan-Meier survival curves were constructed and compared using the log-rank test. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS software, version 19 (IBM SPSS Statistics, State of New York) and STATA (version 11.0, College Station, Texas).

3. Results

3.1. Patient characteristics (Table 1)

117 patients (mean age: 70.5; 69.7% men; 70.1% with statin therapy) were observed and 131 lesions [BMS-ISR; 90 lesions, DES-ISR; 41 lesions)] were analyzed in this study. 64 patients had DM (54.7%), 89 patients had HTN (76.1%) and 26 patients required HD (22.2%). Each lesion was treated with PCB anioplasty at 1:1 balloon-to-vessel ratio. The mean length of PCBs was 27.1 ± 9.3 mm and the mean diameter was 2.9 ± 0.3 mm.

3.2. Statin therapy

In order to investigate the association between the statin therapy and clinical outcomes, we divided the lesions into two groups: with statin therapy and without statin therapy. Table 1 showed the baseline characteristics of two groups. Statin therapy group had more percentage of male (73.6% vs. 55.0%, p = 0.04) and contained less comorbidity of HD (13.2% vs. 45.0%, p < 0.001). No significant differences were found in baseline lipid profile between these two groups, but the LDL-C level in statin therapy group after six months (77.49 ± 28.75 mg/dL vs. 97.78 ± 23.41 mg/dL, p < 0.001) is lower than the group without statin therapy. Table 2 indicated no differ-

Table 1
Patient characteristics.

	With statin N = 40	Without statin N = 91	p value
Male (%)	22 (55.0%)	67 (73.6%)	0.04
Age (years)	73.43 ± 10.87	69.84 ± 10.53	0.08
Current cigarette smoker (%)	5 (12.5%)	11 (12.1%)	0.947
Hypertension (%)	28 (70.0%)	72 (79.1%)	0.26
Diabetes mellitus (%)	25 (62.5%)	49 (53.8%)	0.36
Dialysis (%)	18 (45.0%)	12 (13.2%)	< 0.001
Cholesterol (mg/dL)	156.65 ± 39.42	156.96 ± 45.61	0.97
Triglycerides (mg/dL)	147.43 ± 127.84	172.60 ± 162.98	0.39
Low-density lipoprotein cholesterol (mg/dL)	92.25 ± 24.95	87.68 ± 33.72	0.39
Low-density lipoprotein cholesterol post 6 months (mg/dL)	97.78 ± 23.41	77.49 ± 28.75	< 0.001
Acute coronary syndrome (%)	13 (32.5%)	22 (24.2%)	0.32

Table 2
Angiographic and procedural characteristics.

	With statin N = 40	Without statin N = 91	p value
Drug eluting stent (%)	14 (35%)	27 (29.7%)	0.55
Previous stent diameter (mm)	2.96 ± 0.33	3.00 ± 0.35	0.5
Previous stent length (mm)	29.70 ± 14.48	31.56 ± 13.31	0.48
In-stent restenosis lesion length (mm)	16.80 ± 7.99	16.69 ± 9.71	0.95
Coronary artery			0.37
Left main (%)	1 (2.5%)	8 (8.8%)	
Left anterior descending artery (%)	18 (45.0%)	33 (36.3%)	
Left circumflex artery (%)	5 (12.5%)	18 (19.8%)	
Right coronary artery (%)	16 (40.0%)	32 (35.2%)	
Classification of in-stent restenosis			0.15
1B (%)	3 (7.5%)	5 (5.5%)	
1C (%)	9 (22.5%)	30 (33.0%)	
2 (%)	10 (25.0%)	34 (37.4%)	
3 (%)	13 (32.5%)	14 (15.4%)	
4 (%)	5 (12.5%)	8 (8.8%)	

ences in previous stent type, stent size, stent diameter, lesion length, lesion location or ISR type between two groups.

3.3. Clinical outcomes

23 events of TLR (17.6%) and 32 events of MACE (24.4%) occurred during the follow-up period. All patients received clinical follow-up with a median duration of 786 days. From Table 3, patients with statin therapy had a lower TLR rate compared to those without statin therapy (12.1% versus 30%, $p < 0.01$) and the absolute risk reduction (ARR) in TLR was 17.9% (the needed to treat (NNT) was 5.6). In statin group, a lower rate of MACE (16.5%) was also seen (versus 42.5% for those who had no statin therapy; $p < 0.001$) and a 26% ARR of MACE was observed (the NNT was 3.8). The Cox proportional hazards regression model was used for multivariate analysis of TLR and MACE. The predictors of TLR and MACE were shown in Table 4. After adjustment for the parameters mentioned above, DES-ISR (adjusted HR [AHR]: 3.43, 95% CI: 1.3–9.04, $p < 0.01$) and statin therapy (AHR: 0.33, 95% CI: 0.11–0.96, $p = 0.04$) were independent predictors for TLR. DES-ISR (AHR: 2.46, 95% CI: 1.08–5.58, $p = 0.03$) and statin therapy (AHR: 0.31, 95% CI: 0.13–0.77, $p < 0.01$) were also independent predictors for MACE.

Statin therapy was found as a shared and strong predictor of TLR and MACE, Kaplan-Meier analysis was performed to examine the univariate association between these two groups (with versus without statin therapy) and the outcomes of the cohort (Figure 1 and Figure 2). Compared to patients without statin therapy, the patients with stain therapy exhibited a significantly lower cumulative incidence rate of TLR (84% vs. 52%, respectively; log rank: $p = 0.016$) and MACE (54% vs. 40%, respectively; log rank: $p = 0.003$).

4. Discussion

Various factors have been suggested to be predictors and involved in post-PCI restenosis, including patient factors, lesion, and inflammatory mediators (cytokines, CRP, adhesion molecules, and oxygen radicals). Statins was also noted for the significant reduction in clinical endpoints of atherosclerosis in several large-scale clinical trials. Previous study showed these outcome improvements were mainly from the pleiotropic effect of statins instead of cholesterol-

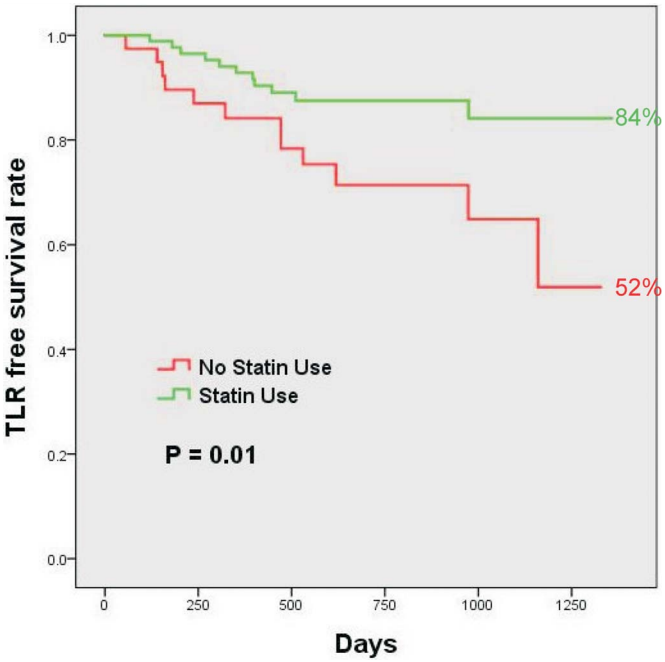

Figure 1. Kaplan-Meier analysis of TLR and statin use.

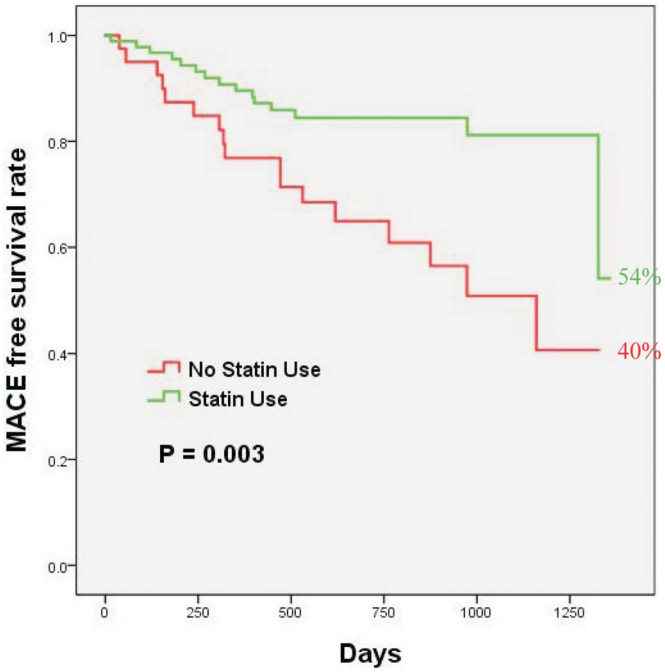

Figure 2. Kaplan-Meier analysis of MACE and statin use.

Table 3
Clnical outcomes of statin use.

	With statin N = 40	Without statin N = 91	p value
Target lesion revascularization	12 (30.0%)	11 (12.1%)	< 0.01
Major adverse cardiac events	17 (42.5%)	15 (16.5%)	< 0.001

Table 4
Multivariate analysis of TLR and MACE.

	TLR		MACE	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
ISR (DES vs. BMS)	3.43 (1.30–9.04)	< 0.01	2.46 (1.08–5.58)	0.03
Statin (with vs. without)	0.33 (0.11–0.96)	0.04	0.31 (0.13–0.77)	< 0.01
Age (years)	0.97 (0.92–1.02)	0.25	0.98 (0.94–1.03)	0.41
Gender (men vs. women)	0.91 (0.31–2.62)	0.86	0.79 (0.33–1.88)	0.59
Smoker (yes vs. no)	1.17 (0.71–1.94)	0.54	1.01 (0.65–1.56)	0.97
ACS (yes vs. no)	0.30 (0.07–1.19)	0.09	0.79 (0.32–1.97)	0.62
DM (yes vs. no)	1.23 (0.46–3.28)	0.68	1.47 (0.64–3.33)	0.36
HTN (yes vs. no)	0.70 (0.24–2.01)	0.50	1.04 (0.41–2.61)	0.94
Dialysis (yes vs. no)	1.29 (0.41–4.01)	0.67	1.52 (0.61–3.79)	0.37
LDL	1.00 (0.98–1.02)	0.94	1.01 (0.99–1.02)	0.44
LDL reduction ratio	0.99 (0.97–1.02)	0.57	0.99 (0.97–1.00)	0.13
Previous stent length	0.99 (0.95–1.02)	0.41	0.99 (0.96–1.02)	0.69

lowering.[15] The pleiotropic effect of statins included effects on endothelial function (NO generation and NO-mediated vascular relaxation), the recruitment of monocytes and T cells into the arterial intima, the subsequent activation and expression of proinflammatory factors, the proliferation of vascular smooth muscle cells (VSMCs), and other events that result in arterial remodeling.[16] It has also been established that statins may inhibit atherogenesis by reducing the formation of superoxide and other oxygen radicals which modulate many intracellular signaling pathways.[17] Finally, statins may affect the consequences of plaque rupture by modulating thrombosis and fibrinolysis.

Many studies suggested that statin preteatment might reduce the occurrence of coronary stent restenosis. However, less studies were designed to investigate the prevention effect of statin therapy in ISR patients post PCB. In Table 5, the different outcomes of statin therapy between ISR and post PCB ISR were observed. From views of ISR, patients with statin therapy showed lower MACE, TLR, restenosis rate and larger minimal lumen diameter.[18] In our study, statin therapy was independent predictor for TLR and MACE. DES-ISR was the same, too. However, the reduction ratio of LDL after 6 months statin treatment (see Table 2) was not the independent predictor for cardiac event. The findings in our study are inconsistent with those of previous studies. There are two possible explanations to elaborate the results. First, the LDL (77.5 mg/dl) level did not meet the guidelines goals in our statin group. Second, higher HD prevalence (22.2%) was seen in our study group compared to those in other clinical studies (7.8% in SeQuent Please World Wide Registry[7] and 10% in Kurashiki Central Hospital data[19]). HD was found to be an independent predictor of late restenosis[19] and late restenosis might eliminate the benefit of LDL reduction ratio in the following cardiac events.

From previous studies, the occurrence rate of MACE was significantly higher in DES-ISR patients compared to those with de novo coronary artery stenosis.[20] The main reason was because DES-ISR was characterized by arterial damage and subsequent neointima proliferation, while the underlying atherosclerotic plaque formation of de novo CAD was composed of fibro fatty, calcified, or necrotic core. The neointima proliferation that leads to near-total obstruction of the lumen and compromised flow will end as athrombotic event and ACS. Other possible mechanisms of DES-ISR involving several drug and stent specific factors were also discussed, such as localized hypersensitivity of drug, nonuniform drug deposition, the existence of polymers, drug resistance, focal stent under-expansion, stent fracture, loss of stent longitudinal integrity, and incomplete stent apposition. Based on these possible reasons, DES-ISR was associated with higher occurrence rate of TLR and MACE. About DES-ISR post PCB, one of previous studies found that the half one year restenosis rate of PCB treated lesions was 9.1% in patients with DES-ISR.[21] In another retrospective study, the occurrence rate of restenosis was 21.1% in the DES-ISR group after using PCB for half a year.[19] According to these studies, the occurrence rate of late restenosis and delayed late lumen loss were significantly higher in the DES-ISR group after PCB angioplasty.[19,21] As a result, PCB angioplasty for DES-ISR could not show the optimal treatment outcomes. In our study, we observed the same result as previous investigations. Even after using PCB, DES-ISR was still an independent predictor for TLR and MACE.

4.1. Limitations

This was a retrospective single-hospital study with observational analysis. Imaging analysis using ivus and optical coherence tomography was not performed in our study, so we lacked the image analysis to investigate which kind of neointimal formation occurred post PCB. Otherwise, the higher proportion of HD patients was noted in our study, a subgroup analysis to investigate the effect of statin in ISR patient with HD after PCB treatment should be considered.

Table 5
Compare difference in statin therapy for ISR and post PCB ISR.

Patients (with statin vs without statin)	
ISR	ISR post PCB
Low TLR	Low TLR
Low MACE	Low MACE
Low restenosis rate	DES-ISR had worse outcome
Large minimal lumen diameter	Lack quantitative coronary angiography analysis

5. Conclusion

From previous studies, many clinical factors were independent predictors for late restenosis after PCB but there was no treatment being proved for the improvement of outcome after PCB. Our data revealed that DES-ISR and statin therapy were independent predictors for TLR and MACE. Statin is feasible to treat ISR patient post PCB.

References

1. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary instent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med.* 2006;355:2113–2124.
2. Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol.* 2008;97:773–781.
3. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation.* 2009;119:2986–2994.
4. Habara S, Mitsudo K, Kadota K, et al. Effectiveness of paclitaxeleluting balloon catheter in patients with sirolimus-eluting stentrestenosis. *JACC Cardiovasc Interv.* 2011;4:149–154.
5. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: The PEPCAD-DES study. *J Am Coll Cardiol.* 2012;59:1377–1382.
6. Scheller B, Clever YP, Kelsch B, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *JACC Cardiovasc Interv.* 2012;5:323–330.
7. Wöhrle J, Zadura M, Möbius-Winkler S, et al. SeQuent Please World Wide Registry: Clinical results of SeQuent Please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol.* 2012;60:1733–1738.
8. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): A randomised, open-label trial. *Lancet.* 2012;381:461–467.
9. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333:1301–1307.
10. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349–1357.
11. Hatzitolios AI, Athyros VG, Karagiannis A, et al. Implementation of strategy for management for overt dyslipidemia: The IMPROVE-dyslipidemia study. *Int J Cardiol.* 2009;134:322–329.
12. Walter DH, Schächinger V, Elsner M, et al. Effect of statin therapy on restenosis after coronary stent implantation. *Am J Cardiol.* 2000;15;85:962–968.
13. Sahni R, Maniet AR, Voci G, et al. Prevention of restenosis by lovastatin

after successful coronary angioplasty. *Am Heart J.* 1991;121:1600–1608.
14. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: Classification and implications for long-term outcome. *Circulation.* 1999;100:1872–1878.
15. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation.* 2000;101:207–213.
16. Palinski W, Napoli C. Unraveling pleiotropic effects of statins on plaque rupture. *Arterioscler Thromb Vasc Biol.* 2002;22:1745–1750.
17. Napoli C, de Nigris F, Palinski W. Multiple role of reactive oxygen species in the arterial wall. *J Cell Biochem.* 2001;82:674–682.
18. Kamishirado H, Inoue T, Sakuma M, et al. Effects of statins on restenosis after coronary stent implantation. *Angiology.* 2007;58:55–60.
19. Habara S, Kadota K, Shimada T, et al. Late restenosis after paclitaxel-coated balloon angioplasty occurs in patients with drug-eluting stent restenosis. *J Am Coll Cardiol.* 2015;66:14–22.
20. Buchanan KD, Torguson R, Rogers T, et al. In-stent restenosis of drug-eluting stents compared with a matched group of patients with de novo coronary artery stenosis. *Am J Cardiol.* 2018;121:1512–1518.
21. Habara S, Iwabuchi M, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. *Am Heart J.* 2013;166:527–533.