



Different Neointimal Pattern in Early vs. Late In-Stent Restenosis and Clinical Outcomes After Drug-Coated Balloon Angioplasty

— An Optical Coherence Tomography Study —

Jung-Hee Lee, MD; Hae Won Jung, MD; Jung-Sun Kim, MD; Sung-Jin Hong, MD;
Chul-Min Ahn, MD; Byeong-Keuk Kim, MD; Young-Guk Ko, MD;
Donghoon Choi, MD; Myeong-Ki Hong, MD; Yangsoo Jang, MD

Background: There are few data of clinical outcomes after drug-coated balloon (DCB) angioplasty according to neointimal characteristics. This study investigated long-term clinical outcomes according to timing of in-stent restenosis (ISR) and neointimal characteristics in patients with drug-eluting stent (DES) ISR after DCB angioplasty.

Methods and Results: In all, 122 patients (122 ISR lesions), treated with DCB under optical coherence tomography (OCT) examination before and after DCB, were categorized as early ISR (<12 months; E-ISR; n=21) and late ISR (≥12 months; L-ISR; n=101). Associations between OCT-based neointima characteristics and period of ISR, as well as clinical outcomes after DCB were evaluated. Major adverse cardiac events (MACE) were a composite of cardiac death, non-fatal myocardial infarction, or target lesion revascularization (TLR). Quantitative parameters of the neointima were similar, but qualitative characteristics showed significant differences between the E-ISR and L-ISR groups. The incidence of MACE (33.3% vs. 20.8%; P=0.069) and TLR (33.3% vs. 18.5%; P=0.040) was higher in the E-ISR group. In addition, the incidence of MACE was significantly higher for heterogeneous than non-heterogeneous neointima (43.7% vs. 19.6%; P=0.018), but was not significantly associated with neoatherosclerosis (33.4% vs. 18.4%; P=0.168).

Conclusions: DCB angioplasty is less effective for heterogeneous neointima in DES ISR. OCT-based neointimal evaluation may be helpful in guiding treatment of DES ISR.

Key Words: Drug-eluting balloon; In-stent restenosis; Optical coherence tomography

Although the development of drug-eluting stents (DES) has significantly reduced the incidence of in-stent restenosis (ISR) compared with bare metal stents (BMS),¹ DES restenosis still occurs in 3–20% of patients.² For the treatment of ISR, drug-coated balloon (DCB) angioplasty has been shown to have a lower rate of further adverse clinical events compared with uncoated balloons.^{3,4}

Intravascular optical coherence tomography (OCT) evaluation is a useful tool not only for quantitative measurement, but also for qualitative assessment of characteristics.^{5–7} Recent OCT studies suggest that neointimal tissue characteristics differ between early (<1 year) and late (≥1

year) ISR.^{8,9} Differences in tissue morphology and timing of ISR may be associated with different mechanisms of ISR after DES implantation. However, there are few data about the associations between clinical outcomes after DCB and tissue characteristics or timing of ISR. The aim of this study was to investigate clinical outcomes according to tissue characteristics and timing of DES ISR after DCB angioplasty.

Methods

Study Design and Patient Selection

This study was approved by the Institutional Review

Received May 24, 2018; revised manuscript received July 21, 2018; accepted July 31, 2018; released online September 7, 2018
Time for primary review: 32 days

Division of Cardiology, Yeungnam University Medical Center, Yeungnam University College of Medicine, Daegu (J.-H.L.); Department of Cardiology, Daegu Catholic University Medical Center, Daegu (H.W.J.); Severance Cardiovascular Hospital (J.-S.K., S.-J.H., C.-M.A., B.-K.K., Y.-G.K., D.C., M.-K.H., Y.J.), Cardiovascular Institute (J.-S.K., S.-J.H., C.-M.A., B.-K.K., Y.-G.K., D.C., M.-K.H., Y.J.), Severance Biomedical Science Institute (M.-K.H., Y.J.), Yonsei University College of Medicine, Seoul, Korea

The first two authors contributed equally to this work (J.-H.L., H.W.J.).

Mailing address: Jung-Sun Kim, MD, PhD, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, Republic of Korea. E-mail: kjs1218@yuhs.ac

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Table 1. Baseline Clinical and Angiographic Characteristics			
	Early ISR (n=21)	Late ISR (n=101)	P value
Time from index PCI to DCB angioplasty (months)	11.0 [5.5–11.5]	43.0 [23.5–77.0]	<0.001
Clinical variables			
Age (years)	62.2±9.3	64.6±10.2	0.311
Male	15 (71.4)	74 (73.3)	0.863
Diabetes mellitus	9 (42.9)	37 (36.6)	0.592
Hypertension	15 (71.4)	61 (60.4)	0.343
Dyslipidemia	13 (61.9)	47 (46.5)	0.200
Current smoker	8 (38.1)	41 (40.6)	0.832
Chronic renal failure	3 (4.7)	1 (1.4)	0.432
Previous MI	2 (9.5)	4 (4.0)	0.275
ACS at index PCI	11 (52.4)	51 (50.5)	0.875
ACS at DCB angioplasty	5 (23.8)	34 (33.7)	0.378
Serum lipid profile			
Total cholesterol (mg/dL)	137.8±44.0	140.0±37.1	0.235
Triglyceride (mg/dL)	115.8±47.5	111.2±86.3	0.541
HDL-C (mg/dL)	44.8±12.9	43.6±10.4	0.303
LDL-C (mg/dL)	71.3±35.7	73.7±28.9	0.131
Angiographic variables			
Target coronary artery			0.330
LAD	16 (76.2)	67 (66.3)	
LCx	3 (14.3)	10 (9.9)	
RCA	2 (9.5)	24 (23.8)	
Stent types			<0.001
1st-generation DES	1 (4.8)	63 (62.4)	
2nd-generation DES	20 (95.2)	38 (37.6)	
Classification of ISR			
Focal	12 (57.1)	47 (46.5)	0.376
Diffuse	9 (42.9)	54 (53.5)	0.376
Total occlusion	1 (4.8)	10 (9.9)	0.454
Stent diameter (mm)	2.97±0.39	3.05±0.37	0.415
Total stent length (mm)	23.81±7.19	24.87±6.42	0.501
Pre-DCB angioplasty QCA			
Reference vessel diameter (mm)	2.81±0.44	2.82±0.40	0.913
Minimal luminal diameter (mm)	0.92±0.43	0.86±0.52	0.630
Diameter stenosis (%)	67.0±15.7	69.5±18.2	0.558
Lesion length (mm)	14.05±6.43	18.00±10.05	0.087
Post-DCB angioplasty QCA			
Reference vessel diameter (mm)	2.84±0.46	2.87±0.37	0.740
Minimal luminal diameter (mm)	2.21±0.36	2.29±0.42	0.408
Diameter stenosis (%)	21.4±11.7	20.2±10.9	0.640
Acute gain (mm)	1.29±0.58	1.43±0.61	0.339

Data are given as the median [interquartile range], mean±SD, or as n (%). ACS, acute coronary syndrome; DCB, drug-coated balloon; DES, drug-eluting stent; HDL-C, high-density lipoprotein cholesterol; ISR, in-stent restenosis; LAD, left anterior descending artery; LCx, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; QCA, quantitative coronary analysis; RCA, right coronary artery.

Board of Severance Hospital, the Yonsei University, and written informed consent was obtained from all patients enrolled in the study. Clinical data were obtained for analysis from the Yonsei OCT Registry database (ClinicalTrials.gov ID: NCT01308281) between July 2010 and December 2013 for 204 patients with 208 stented ISR lesions who had not been treated previously. Eighty-two patients with 86 lesions were excluded from the present study for the following reasons: ISR lesions treated with a

cutting balloon (n=15 patients), additional stent implantation was required (n=30 patients), poor image quality or hard to acquire pre-interventional OCT images due to tight restenotic lesions (n=34 patients), and loss to follow-up (n=3 patients). Thus, 122 patients with 122 ISR lesions treated with DCB angioplasty were included in this study. The study cohort was divided into early ISR (<12 months; E-ISR; n=21; first-generation DES n=1, second-generation DES n=20) and late ISR (≥12 months; L-ISR; n=101;

Table 2. Optical Coherence Tomography Characteristics			
	Early ISR (n=21)	Late ISR (n=101)	P value
Quantitative variables			
Pre-DCB angioplasty			
Minimal stent CSA (mm ²)	4.84±1.63	4.89±1.54	0.900
Mean neointimal CSA (mm ²)	2.49±1.55	2.71±3.67	0.790
Mean lumen CSA (mm ²)	2.35±1.61	2.18±2.14	0.815
Minimal lumen CSA (mm ²)	1.59±0.92	1.33±0.76	0.234
Maximal neointimal thickness (μm)	920.3±373.6	1011.8±318.4	0.247
% Maximal neointimal stenosis	76.0±13.3	73.2±13.9	0.401
Post-DCB angioplasty			
Minimal stent CSA (mm ²)	5.39±1.94	5.81±1.63	0.303
Mean neointimal CSA (mm ²)	1.51±0.77	1.76±0.73	0.155
Mean lumen CSA (mm ²)	4.68±1.05	4.74±1.21	0.865
Minimal lumen CSA (mm ²)	4.15±1.36	4.22±1.33	0.812
Maximal neointimal thickness (μm)	524.7±163.0	710.5±595.1	0.160
% Maximal neointimal stenosis	40.3±12.9	41.5±11.4	0.677
Qualitative variables			
Neointimal characteristics			0.040
Homogeneous	3 (14.3)	23 (22.8)	0.388
Heterogeneous	6 (28.6)	10 (9.9)	0.021
Layered	9 (42.9)	32 (31.7)	0.324
Neoatherosclerosis	3 (14.3)	36 (35.6)	0.056
Thin-cap fibroatheroma	0 (0.0)	26 (25.7)	0.007
Calcified plaque	1 (4.8)	12 (11.9)	0.463
Neointimal rupture	2 (9.5)	22 (21.8)	0.244
Microvessel within plaque	5 (23.8)	31 (30.7)	0.529
Macrophage infiltration	0 (0.0)	26 (25.7)	0.007
Cholesterol crystals	1 (4.8)	32 (31.7)	0.013

Data are given as the mean ± SD or as n (%). CSA, cross-section area. Other abbreviations as in Table 1.

first-generation DES n=63, second-generation DES n=38) depending on the time of ISR after DES implantation.

Angioplasty Procedure

The decision to perform DCB angioplasty was based on angiographic findings, including a >50% diameter stenosis on a follow-up angiogram with evidence of myocardial ischemia, such as ischemic symptoms or a positive stress test. All patients in the study received at least 100 mg aspirin and a total of 300 mg clopidogrel as a loading dose at least 12 h before DCB angioplasty. After diagnosis of ISR on a conventional angiogram, the OCT procedure was performed using a C7-XR imaging system (LightLab Imaging; St. Jude Medical, St. Paul, MN, USA) before plain balloon angioplasty. The DCB used in the present study was a paclitaxel-coated balloon (Sequent Please; B. Braun, Melsungen, Germany). The DCB angioplasty was performed using current conventional techniques: after predilation with a plain balloon, the DCB was inflated for 60 s. An adequate size of the DCB was determined by the physician according to the length of the target ISR lesion and the diameter of the previously implanted stents. After successful intervention, all patients underwent a final OCT procedure. Dual anti-platelet therapy (100 mg aspirin and 75 mg clopidogrel) was prescribed to all patients for at least 1 month after DCB angioplasty.

Clinical Follow-up

The primary endpoint was major adverse cardiac events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction (MI), and target-lesion revascularization (TLR), based on the Academic Research Consortium.¹⁰ Without an explainable non-cardiac cause, all deaths were considered cardiac death. MI was defined based on the third universal definition of MI.¹¹ TLR was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complications of the target lesion. All revascularizations were considered clinically indicated if angiography at follow-up showed a percentage diameter stenosis (%DS) ≥50% as assessed by quantitative coronary angiography (QCA) analysis with either ischemic symptoms or a positive stress test, or a %DS ≥70% as assessed by QCA analysis without either ischemic symptoms or a positive stress test.

Image Analysis of Coronary Angiography and OCT

QCA were performed using an offline computerized QCA system (CAAS System; Pie Medical Imaging, Maastricht, The Netherlands) in an independent core laboratory (Cardiovascular Research Center, Seoul, Korea). All OCT images were analyzed using certified offline software (QIvus; Medis Medical Imaging System, Leiden, The Netherlands) at a core laboratory (Cardiovascular Research Center) by analysts who were blinded to both clinical and angiographic

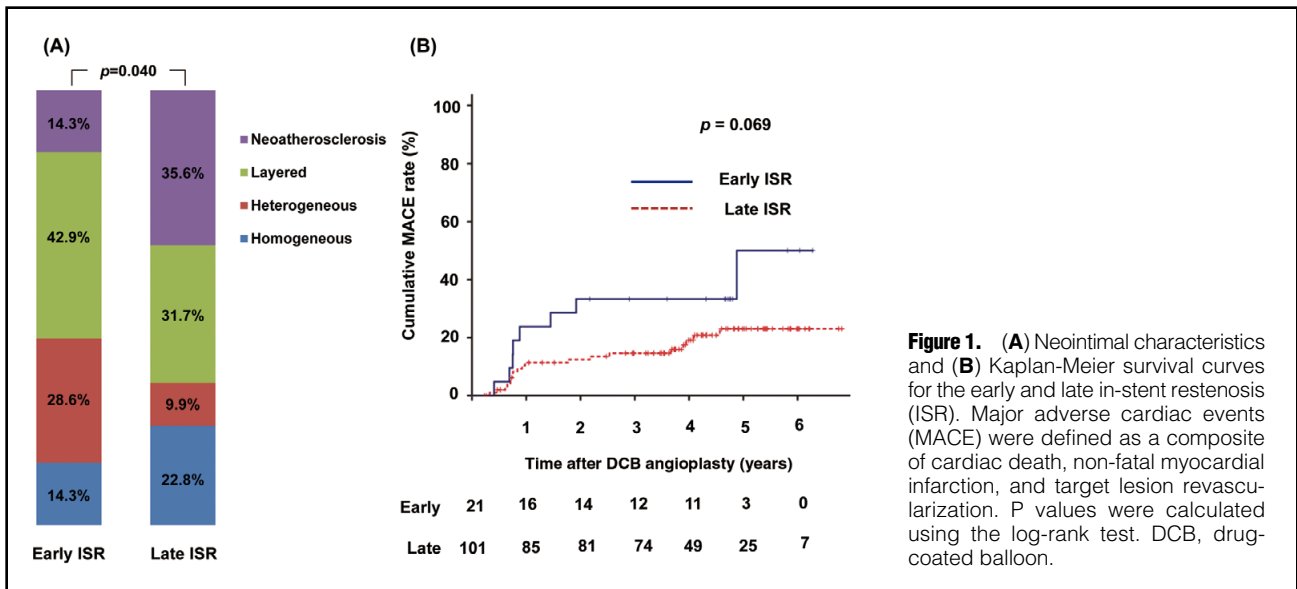


Figure 1. (A) Neointimal characteristics and (B) Kaplan-Meier survival curves for the early and late in-stent restenosis (ISR). Major adverse cardiac events (MACE) were defined as a composite of cardiac death, non-fatal myocardial infarction, and target lesion revascularization. P values were calculated using the log-rank test. DCB, drug-coated balloon.

	Early ISR (n=21)	Late ISR (n=101)	P value
MACE	7 (33.3)	18 (20.8)	0.069
Cardiac death	0 (0.0)	0 (0.0)	1.0
Non-fatal MI	0 (0.0)	4 (4.6)	0.786
TLR	7 (33.3)	16 (18.5)	0.040
All-cause mortality	0 (0.0)	1 (1.1)	0.474

Data are given as n (%). ISR, in-stent restenosis; MACE, major adverse cardiac events, defined as a composite of cardiac death, non-fatal myocardial infarction (MI), or target-lesion revascularization (TLR).

information. Cross-sectional OCT images before angioplasty were measured at 1-mm intervals for quantitative measurements. Stent and luminal cross-sectional area (CSA) was analyzed, and neointimal CSA was calculated as the stent CSA minus luminal CSA. The segment with minimal lumen area and greatest neointimal proliferation could be the representative site of lesions for future clinical follow-up.¹² Therefore, the stented segments at the minimal lumen CSA and greatest neointimal CSA were assessed qualitatively to characterize the neointimal tissue as either homogeneous (a uniform signal-rich band without focal variation or attenuation), heterogeneous (focally changing optical properties and various backscattering patterns), layered neointima (layers with different optical properties, namely an adluminal high-scattering layer and an abluminal low-scattering layer),^{6,8,12} and neoatherosclerosis (lipid-laden plaque, thin-cap fibroatheroma [defined as a plaque with a lipid content in ≥ 2 quadrants and the thinnest part of a fibrous cap $\leq 65 \mu\text{m}$], neointimal rupture, and/or calcification within the neointima).¹³ Neointimal morphologic characteristics were evaluated qualitatively by 2 observers who were blinded to the patient's data and angiographic results. Inter- and intraobserver agreements for the assessment of neointimal tissue characteristics in our core laboratory have been reported previously.¹⁴

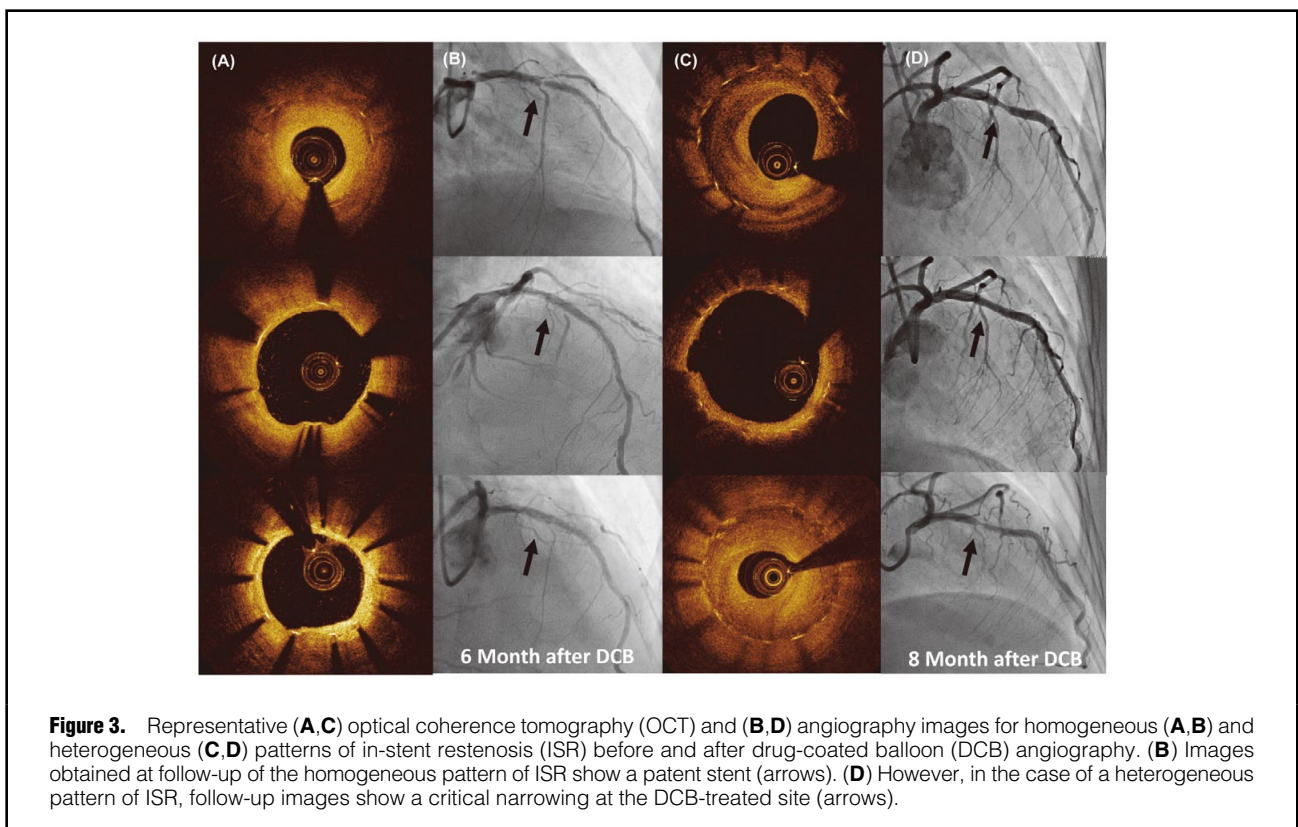
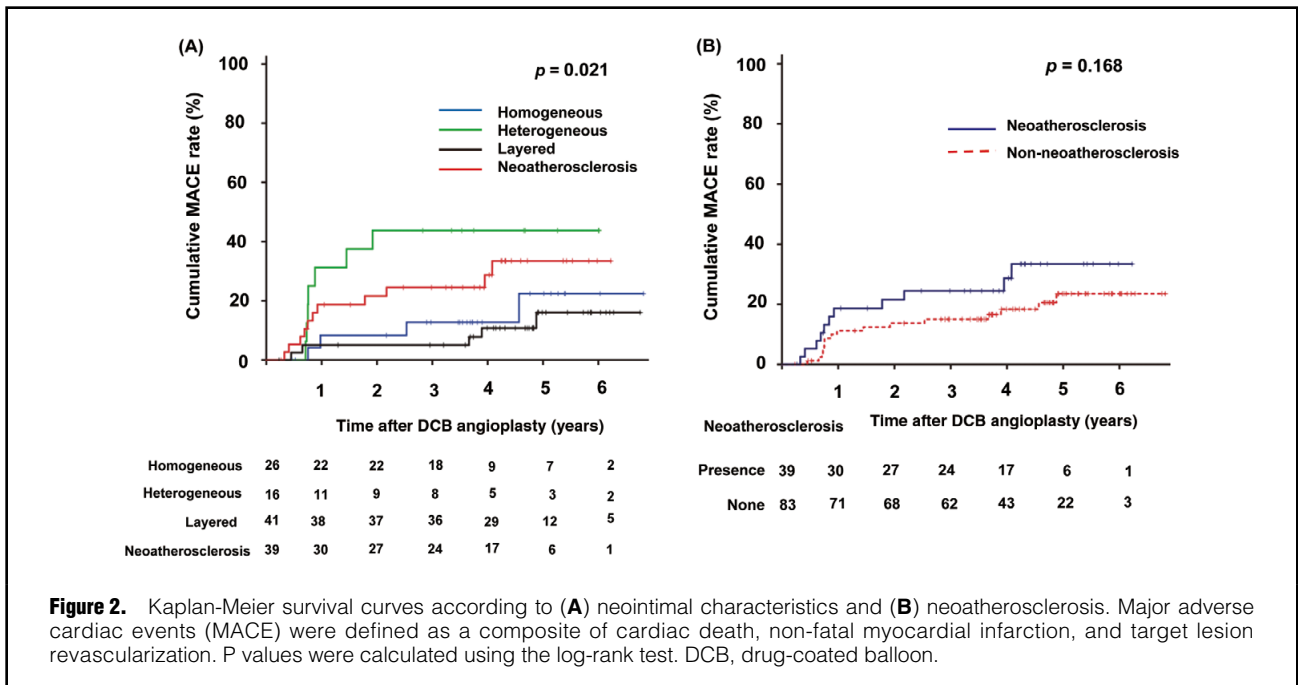
Statistical Analysis

Data are expressed as number (%), mean \pm SD, or median (interquartile range [IQR]). Continuous variables were compared using Student's t-test, and comparisons of categorical data were performed using Chi-squared statistics or Fisher's exact test. Event-free survival was analyzed using Kaplan-Meier survival curves, and differences between event-free survival curves were compared with the log-rank test. Univariate analyses were performed using Cox proportional hazards regression for traditional cardiac risk factors and the qualitative OCT characteristics. Variables achieving $P < 0.10$ in the univariate analysis were entered into the multivariate analysis model to determine the independent predictors for MACE. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 20.0.0 (IBM, Armonk, NY, USA).

Results

Baseline Characteristics

Among the total study population, 21 patients (17.2%) were categorized as E-ISR and 101 patients (82.8%) were categorized as L-ISR. There were significant differences in the median time interval from index percutaneous coronary intervention to DCB angioplasty between the E-ISR and L-ISR groups (11.0 vs. 43.0 months, respectively; $P < 0.001$). The patients' baseline clinical and angiographic



characteristics are summarized in **Table 1**. There were no differences in comorbidities or medications between the 2 groups. Second-generation DESs were more frequently used in E-ISR than L-ISR group (95.2% vs. 37.6%; $P < 0.001$). There were no significant differences in QCA parameters

between the 2 groups. However, lesion length tended to be shorter in the E-ISR than L-ISR group (14.05 ± 6.43 vs. 18.00 ± 10.05 mm; $P = 0.087$). Post-DCB angioplasty QCA and acute gain after procedure did not differ significantly between the 2 groups.

Table 4. Independent Predictors for Major Adverse Cardiac Events

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Diabetes mellitus	0.942 (0.431–2.057)	0.881		
Hypertension	0.872 (0.405–1.881)	0.728		
Dyslipidemia	0.614 (0.285–1.325)	0.214		
CKD	1.597 (0.216–11.789)	0.646		
Previous MI	3.838 (1.145–12.865)	0.029	3.720 (1.105–12.516)	0.034
ACS at index PCI	0.953 (0.448–2.029)	0.901		
ACS at DCB angioplasty	1.381 (0.632–3.020)	0.418		
1st-generation DES	0.708 (0.331–1.513)	0.373		
Heterogeneous ^A	2.730 (1.150–6.478)	0.023	2.686 (1.129–6.390)	0.025
Neoatherosclerosis	1.708 (0.790–3.690)	0.173		
Thin-cap fibroatheroma	1.606 (0.675–3.819)	0.284		
Neointimal rupture	1.265 (0.510–3.138)	0.611		

^ACompared with non-heterogeneous. ACS, acute coronary syndrome; CI, confidence interval; CKD, chronic kidney disease; DCB, drug-coated balloon; DES, drug-eluting stent; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

OCT Findings

OCT findings of the restenotic stented segments are summarized in **Table 2**. The quantitative variables before and after DCB did not differ significantly between the 2 groups. However, in terms of qualitative characteristics, the site of the minimum lumen area exhibited significant differences. A heterogeneous neointima was more frequently observed in the E-ISR than L-ISR group (28.6% vs. 9.9%; $P=0.021$), whereas neoatherosclerosis tended to be more frequent in the L-ISR than E-ISR group (35.6% vs. 14.3%; $P=0.056$). Thin-cap fibroatheroma (0.0% vs. 25.7%; $P=0.007$), macrophage infiltration (0.0% vs. 25.7%; $P=0.007$), and cholesterol crystals (4.8% vs. 31.7%; $P=0.013$) were also more frequent in the L-ISR than E-ISR. **Figure 1A** shows that the incidence of heterogeneous neointima decreased, but the incidence of neoatherosclerosis was higher in L-ISR groups compared to E-ISR group.

Clinical Outcomes

Over the median follow-up duration of 55.3 months (IQR 43.1–66.0 months), 25 MACE occurred. The long-term clinical outcomes of the E-ISR vs. L-ISR groups after DCB angioplasty are summarized in **Table 3**. MACE tended to be more frequent in the E-ISR than L-ISR group (33.3% vs. 20.8%; $P=0.069$; **Figure 1B**). The difference in MACE between the 2 groups was driven by the rate of TLR (33.3% vs. 18.5% in the E-ISR and L-ISR groups, respectively; $P=0.040$). Clinical adverse events according to neointimal characteristics of the minimum lumen area are summarized in **Table S1**. There were also significant differences in the rate of MACE according to neointima characteristics (**Figure 2A**). The heterogeneous neointima group had a significantly higher rate of MACE than the non-heterogeneous group (43.7% vs. 19.6%; $P=0.018$), whereas the incidence of MACE was not significantly associated with the presence of neoatherosclerosis (33.4% vs. 18.4% for patients with and without neoatherosclerosis, respectively; $P=0.168$; **Figure 2B**). **Figure 3** shows representative OCT and angiographic images after DCB angioplasty in groups with different clinical outcomes. However, the rate of MACE was not associated with the generation of the DES used or the type of first-generation DES (**Figure S1**). Multivariate Cox proportional hazards

regression analysis revealed that the following baseline and qualitative OCT variables were associated with an increased risk of MACE: heterogeneous pattern (hazard ratio [HR] 2.686; 95% confidence interval [CI] 1.129–6.390; $P=0.025$) and previous MI (HR 3.720; 95% CI 1.105–12.516; $P=0.034$; **Table 4**).

Discussion

The major findings of this study were as follows: (1) neointimal characteristics, as assessed by OCT, differed between the E-ISR and L-ISR groups, with patients in the E-ISR showing a high rate of long-term adverse clinical outcomes after DCB angioplasty; (2) neointimal characteristics were associated with clinical outcomes after DCB treatment in DES ISR, especially repeated revascularization; and (3) the presence of a heterogeneous neointima was an independent predictor of MACE.

Mechanism of ISR

One of the most important predictors for ISR is stent underexpansion. A recent study by Song et al⁹ showed that early ISR within 1 year was related to minimum stent CSA $<4.0\text{mm}^2$. However, another study by Kang et al¹⁵ suggested that intimal hyperplasia could be a major cause of ISR for stents $\leq 28\text{mm}$ long. Although stent underexpansion within a longer stented segment could be associated with future adverse clinical outcomes, this is a preventable mechanism underlying ISR development with optimal stent implantation. In the present study, quantitative OCT data showed that minimal stent CSA was similar between the E-ISR and L-ISR group (4.84 ± 1.63 vs. $4.89\pm 1.54\text{mm}^2$, respectively; $P=0.900$). These results suggest that stent underexpansion was not main mechanism for the development of ISR in our study population. Another important mechanism of stent failure after DES implantation is neointimal growth. In-stent neoatherosclerosis, defined as an accumulation of lipid-laden foamy macrophages with or without necrotic core formation and/or calcification within the neointima, is also well known as an important mechanism underlying late DES failure.¹⁶ A retrospective OCT analysis demonstrated stent age ≥ 48 months was the most powerful predictor for neoatherosclerosis.¹⁷ Two

recent OCT studies of neointimal characteristics after second-generation DES implantation also showed that there were significant differences in neointimal morphologic characteristics between early and late ISR, and that neoatherosclerosis was commonly associated with late ISR.^{8,9} In the present study, there was a tendency for more frequent observation of neoatherosclerosis in the L-ISR than E-ISR group (35.6% vs. 14.3%, respectively; $P=0.056$), whereas a heterogeneous neointima was more frequently observed in the E-ISR than L-ISR group (28.6% vs. 9.9%, respectively; $P=0.021$). Our findings are consistent with those of previous studies regarding the possibility of different mechanisms in the development of early vs. late ISR.^{8,9} Although the serum lipid profile may affect neointimal plaque characteristics and stent age, cholesterol levels did not differ significantly in the present study. Our data showed that total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations tended to be higher in the neoatherosclerosis group than in the heterogeneous group (TC 149.0 ± 41.0 vs. 128.1 ± 35.8 mg/dL, respectively [$P=0.067$]; LDL-C 76.9 ± 32.2 vs. 64.1 ± 27.1 mg/dL, respectively [$P=0.181$]). However, the relationship between lipid profile and neointimal characteristics could not be fully defined in this study.

Clinical Outcomes After DCB

In the present study, the incidence of TLR was significantly higher in the E-ISR than L-ISR group over the long-term follow-up (33.3% vs. 18.5%; $P=0.040$). Although the incidence of non-fatal MI was numerically lower in the E-ISR than L-ISR group (0.0% vs. 4.6%; $P=0.786$), half of these cases were non-target vessel MI. This finding may be attributed to the native lesion progression, as well as the development of neoatherosclerosis in the late period after stent implantation.

DCB have been reported to be highly effective for the treatment of ISR, superior to conventional balloon angioplasty.^{3,4} In the present study, quantitative OCT data also showed sufficient mechanical effect comparing pre- and post-DCB angioplasty. However, long-term effects after DCB differed between E-ISR and L-ISR.

Although baseline characteristics of the study population were similar except for stent type, there were significant differences in the neointimal characteristics between the 2 groups. Interestingly, a heterogeneous neointima was more frequently observed in the E-ISR than L-ISR group (28.6% vs. 9.9%; $P=0.021$), which is a similar finding to that reported previously in a study evaluating ISR neointimal characteristics of early vs. late ISR.⁹ Furthermore, in the E-ISR group, those with a heterogeneous neointima ($n=6$) showed a higher prevalence of TLR after DCB angioplasty (83.3%).

Evaluating clinical adverse events according to neointimal characteristics also revealed that a heterogeneous neointima was significantly associated with MACE compared with a non-heterogeneous neointima (43.7% vs. 19.6%; $P=0.018$). A previous pathologic study revealed that neointimal abnormalities, such as fibrin deposits or peristrut inflammation, were frequently observed in heterogeneous neointima, as assessed by OCT.⁷ A clinical study about the relationship between neointimal characteristics assessed by OCT and clinical outcomes suggested that a heterogeneous neointima was significantly associated with both old age and initial acute coronary syndrome presentation.¹² These findings suggest that a heterogeneous neointima could be

associated with the formation of an immature neointima due to an abnormal inflammatory reaction with the stent strut or underlying unstable clinical characteristics. Furthermore, a heterogeneous neointima is one of the independent predictors for MACE (HR 2.686; 95% CI 1.129–6.390; $P=0.025$).

A previous OCT study of clinical outcomes for ISR reported similar results to those seen in the present study, namely that when comparing DCB with conventional balloon angioplasty and DES, the incidence of ISR was numerically higher for DCB (38.5% vs. 20.0% and 18.8%, respectively), as was the incidence of TLR (34.6% vs. 20.0% and 18.8%, respectively).¹⁸ It is possible that a heterogeneous neointima is one of the indicators of further adverse events after DCB for the treatment of DES ISR due to its intrinsic instability. Because we did not conduct follow-up OCT examinations, further studies are required to evaluate this hypothesis.

Several studies have reported adverse local effects at the vessel wall after DCB for patients presenting with ISR.^{19,20} Furthermore, the long-term effective treatment modality for DES ISR has not been fully investigated. A previous OCT study about qualitative assessment of ISR reported that vascular response was poor in patients with a homogeneous neointima compared with those with a layered or heterogeneous pattern ($29.5\pm 11.9\%$ vs. $42.2\pm 15.7\%$ and $46.3\pm 12.9\%$, respectively; $P<0.01$).²¹ Another OCT study of neointimal patterns with serial follow-up OCT suggested intensive reduction in LDL-C can prevent neointimal pattern changes from a homogeneous to non-homogeneous pattern.²² These studies suggest that OCT-based neointimal evaluation could be important in making treatment decisions for patients with ISR. A prospective randomized trial demonstrated that for the treatment of patients presenting with DES ISR, everolimus-eluting stents (EES) provided superior angiographic results as well as superior clinical outcome (composite of cardiac death, MI, TLR) (10% vs. 18%; $P=0.04$) compared with DCB.²³ To our knowledge, the present study is the first to compare long-term clinical outcomes of DCB according to the neointima pattern and duration from DES implantation to ISR. Based on the findings of this study, we suggest that OCT-based neointimal evaluation and different treatment strategies, such as intensive medical treatment or implantation of another DES, should be used for the treatment of ISR after DES implantation.

Study Limitations

The present study has several limitations. First, this study was based on single-center OCT registry data with a relatively small population, and the study has intrinsic limitations related to its retrospective design. The imbalance of stent types between groups, driven by temporal differences in stent usage, is a limitation related to the retrospective study design. However, the first-generation DES was not associated with a higher incidence of MACE after DCB angioplasty compared with the second-generation DES (22.5% vs. 24.0%; $P=0.400$). Furthermore, Cox proportional hazards regression analysis showed that first-generation DES was not a significant predictor for future MACE (HR 0.708; 95% CI 0.331–1.513; $P=0.373$). Second, we excluded some patients who had poor image quality or hard to acquire pre-interventional OCT images due to tight restenotic lesions, so this could have led to selection bias. However, these cases accounted for a

relatively small proportion of cases, and we included lesions that had an adequate amount of neointimal tissue for accurate OCT analysis. Third, the neointimal tissue characteristics need to be validated with histology, and the current intravascular OCT system may be limited in its ability to properly evaluate the qualitative characteristics of the neointima. A recent histopathological OCT study showed that neointimal histologic characteristics exhibited considerable variability in tissue components, which were not consistent with characteristic OCT features, except in the case of restenotic tissue.²⁴ So, careful attention must be paid when interpreting OCT images for evaluation of the neointima.

Conclusions

The incidence of heterogeneous neointima was higher in the E-ISR than L-ISR group after DES implantation. DCB angioplasty is less effective for the heterogeneous neointima pattern in DES ISR. The data strongly suggest the need for OCT-based neointimal evaluation and different treatment strategies for the management of patients with ISR.

Acknowledgments

This study was supported by grants from the Korea Healthcare Technology Research & Development Project, Ministry for Health & Welfare, Republic of Korea (A085136 and H115C1277), the National Research Foundation of Korea (NRF), funded by the Korean Government (MSIT; No.2017R1A2B2003191), and the Cardiovascular Research Center, Seoul, Korea.

References

- Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. *JAMA* 2005; **294**: 1215–1223.
- Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol* 2010; **56**: 1897–1907.
- Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006; **355**: 2113–2124.
- Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, 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.
- Kim JS, Hong MK, Shin DH, Kim BK, Ko YG, Choi D, et al. Quantitative and qualitative changes in DES-related neointimal tissue based on serial OCT. *JACC Cardiovasc Imaging* 2012; **5**: 1147–1155.
- Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, et al. Optical coherence tomography patterns of stent restenosis. *Am Heart J* 2009; **158**: 284–293.
- Lee SY, Hong MK, Jang Y. Formation and transformation of neointima after drug-eluting stent implantation: Insight from optical coherence tomographic studies. *Korean Circ J* 2017; **47**: 823–832.
- Jinnouchi H, Kuramitsu S, Shinozaki T, Tomoi Y, Hiromasa T, Kobayashi Y, et al. Difference of tissue characteristics between early and late restenosis after second-generation drug-eluting stents implantation: An optical coherence tomography study. *Circ J* 2017; **81**: 450–457.
- Song L, Mintz GS, Yin D, Yamamoto MH, Chin CY, Matsumura M, et al. Characteristics of early versus late in-stent restenosis in second-generation drug-eluting stents: An optical coherence tomography study. *EuroIntervention* 2017; **13**: 294–302.
- Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115**: 2344–2351.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**: 1581–1598.
- Kim JS, Lee JH, Shin DH, Kim BK, Ko YG, Choi D, et al. Long-term outcomes of neointimal hyperplasia without neoatherosclerosis after drug-eluting stent implantation. *JACC Cardiovasc Imaging* 2014; **7**: 788–795.
- Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation* 2011; **123**: 2954–2963.
- Lee SJ, Kim BK, Kim JS, Ko YG, Choi D, Jang Y, et al. Evaluation of neointimal morphology of lesions with or without in-stent restenosis: An optical coherence tomography study. *Clin Cardiol* 2011; **34**: 633–639.
- Kang SJ, Mintz GS, Park DW, Lee SW, Kim YH, Lee CW, et al. Mechanisms of in-stent restenosis after drug-eluting stent implantation: Intravascular ultrasound analysis. *Circ Cardiovasc Interv* 2011; **4**: 9–14.
- Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol* 2011; **57**: 1314–1322.
- Yonetsu T, Kato K, Kim SJ, Xing L, Jia H, McNulty I, et al. Predictors for neoatherosclerosis: A retrospective observational study from the optical coherence tomography registry. *Circ Cardiovasc Imaging* 2012; **5**: 660–666.
- Tada T, Kadota K, Hosogi S, Miyake K, Ohya M, Amano H, et al. Association between tissue characteristics assessed with optical coherence tomography and mid-term results after percutaneous coronary intervention for in-stent restenosis lesions: A comparison between balloon angioplasty, paclitaxel-coated balloon dilatation, and drug-eluting stent implantation. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 1101–1111.
- Kovarnik T, Mintz GS, Sonka M. The late stent malapposition develops also after paclitaxel balloon predilatation before bare-metal stent implantation: Case description. *Eur Heart J* 2011; **32**: 1432.
- Linares Vicente JA, Lukic A, Gonzalo Lopez N, Ruiz Arroyo JR. Atypical “black hole” phenomenon after treatment of sirolimus stent restenosis with a paclitaxel-coated balloon. *EuroIntervention* 2012; **7**: 1479.
- Nagoshi R, Shinke T, Otake H, Shite J, Matsumoto D, Kawamori H, et al. Qualitative and quantitative assessment of stent restenosis by optical coherence tomography: Comparison between drug-eluting and bare-metal stents. *Circ J* 2013; **77**: 652–660.
- Jang JY, Kim JS, Shin DH, Shin DH, Kim BK, Ko YG, et al. Favorable effect of optimal lipid-lowering therapy on neointimal tissue characteristics after drug-eluting stent implantation: Qualitative optical coherence tomographic analysis. *Atherosclerosis* 2015; **242**: 553–559.
- Alfonso F, Perez-Vizcayno MJ, Cardenas A, Garcia del Blanco B, Garcia-Touchard A, López-Minguez JR, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: The RIBS IV randomized clinical trial. *J Am Coll Cardiol* 2015; **66**: 23–33.
- Lutter C, Mori H, Yahagi K, Ladich E, Joner M, Kutys R, et al. Histopathological differential diagnosis of optical coherence tomographic image interpretation after stenting. *JACC Cardiovasc Interv* 2016; **9**: 2511–2523.

Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier survival curves according to the generation of drug-eluting stents and the type of first generation drug-eluting stent Kaplan-Meier survival curves according to the generation of drug-eluting stents (A) and the type of drug-eluting stents (B).

Table S1. Clinical adverse events at 55 months after drug-coated balloon angioplasty

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-18-0619>