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# Long-Term Outcomes of Neointimal Hyperplasia Without Neoatherosclerosis After Drug-Eluting Stent Implantation

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## ABSTRACT

**OBJECTIVES** The aim of this study was to investigate the correlation between in-stent neointimal tissue without features of neoatherosclerosis and long-term clinical outcomes.

**BACKGROUND** Recent studies have reported differential morphological characteristics of in-stent neointimal tissue assessed by optical coherence tomography (OCT).

**METHODS** The study population consisted of 336 patients with 368 drug-eluting stent-treated lesions. Patients received a follow-up OCT examination without any intervention. OCT-based neointima was categorized as homogeneous (n = 227 lesions in 208 patients), heterogeneous (n = 79 lesions in 73 patients), or layered (n = 62 lesions in 55 patients). Major adverse cardiac events (MACE) (a composite of cardiac death, nonfatal myocardial infarction, or target lesion revascularization) were assessed according to neointimal patterns during long-term clinical follow-up after OCT examination.

**RESULTS** The time interval between stent implantation and OCT examination was similar among the 3 groups (p = 0.64). On multivariate logistic regression analysis, the significant determinant for the heterogeneous neointima was age (odds ratio [OR]: 1.037, 95% confidence interval [CI]: 1.007 to 1.068, p = 0.015) and an initial clinical presentation of acute coronary syndrome (OR: 1.967, 95% CI: 1.159 to 3.339, p = 0.012). The overall median follow-up duration for all patients after follow-up OCT examination was 31.0 months, and this was statistically different among the heterogeneous group (22.0 months), the homogeneous group (34.0 months), and the layered group (28.0 months, overall p = 0.002). MACE occurred more frequently in patients with heterogeneous neointima over a median 31-month follow-up period after OCT examination (13.7% vs. 2.9% in homogeneous vs. 7.3% in layered, p = 0.001). A propensity score–adjusted Cox regression analysis showed that independent risk factors for MACE were inclusion in the heterogeneous neointima (hazard ratio: 3.925, 95% CI: 1.445 to 10.662, p = 0.007) and minimal lumen cross-sectional area (hazard ratio: 0.368, 95% CI: 0.242 to 0.560, p < 0.001).

**CONCLUSIONS** Determination of neointimal characteristics is helpful in predicting long-term clinical outcomes. Our data suggest that heterogeneous lesions are linked to poor long-term clinical prognoses. (J Am Coll Cardiol Img 2014;7:788–95) © 2014 by the American College of Cardiology Foundation.

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Pathological studies have demonstrated that neointima within a stent comprises various tissue components including collagen, proteoglycan, smooth muscle, fibrin, and thrombus (1–3). However, previous imaging modalities, such as angiography and intravascular ultrasound, have a limited ability to assess the neointimal characteristics due to low resolution. Intravascular optical coherence tomography (OCT) has higher resolution and is useful for the qualitative as well as quantitative evaluation of neointimal tissue (4,5). Recent OCT studies have reported differential morphological characteristics of neointimal tissue, which correlated well with histological findings (4,6,7). Furthermore, the atherosclerotic change (neoatherosclerosis) of neointimal tissue inside a stent is now thought to be an underlying mechanism of late stent failure (8,9). However, the relationship between different OCT-based neointimal tissue *without features of neoatherosclerosis* and long-term clinical outcomes has not been investigated. Therefore, the aim of this study was to investigate the correlation between in-stent neointimal characteristics without features of neoatherosclerosis as assessed by OCT and long-term clinical outcomes.

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## METHODS

**STUDY PATIENTS AND DESIGN.** This study was approved by the institutional review board of our institution, and written informed consent was obtained from each patient. From the follow-up OCT registry database of our institution, a total of 336 patients with 368 drug-eluting stent (DES)-treated lesions with a neointimal thickness of at least 100 μm in 5 consecutive cross-sectional images at the time of follow-up OCT examination between January 2008 and October 2012 were included in this study. Because lesions with mild to moderate neointimal proliferation <50% of angiographic diameter stenosis by visual estimation were exclusively selected for long-term clinical follow-up after follow-up OCT examination, none of these lesions required further intervention at the follow-up OCT examination. Therefore, lesions treated with target-lesion revascularization due to in-stent restenosis with significant narrowing at the time of follow-up OCT examination were excluded from this study. In addition, lesions with OCT-based evidence of neoatherosclerosis were also excluded. The type of stent type selected was at the discretion of the physician at the time of coronary intervention. Patients were treated with 86 sirolimus-eluting stents (Cypher, Cordis, Miami Lakes, Florida), 39 paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts), 147 zotarolimus-eluting stents (Endeavor Sprint or Resolute, Medtronic, Santa Rosa, California), 62 everolimus-eluting stents (Xience, Abbott Vascular, Abbott Park, Illinois), and 34 biolimus-eluting stents (Nobori, Terumo Corporation, Tokyo, Japan). The first-generation DES was defined as a sirolimus- (Cypher) and paclitaxel- (Taxus) eluting stent and the second-generation DES as zotarolimus- (Endeavor Sprint or Resolute), everolimus- (Xience), and biolimus- (Nobori) eluting stents. DES implantation was performed using conventional techniques. Unfractionated heparin was administered as an initial bolus of 100 IU/kg, with additional boluses administered during the procedure to achieve an activated clotting time of 250 to 300 s. Dual antiplatelet therapy (aspirin and clopidogrel) was recommended to all patients for at least 12 months after DES implantation. General inclusion and exclusion criteria of follow-up OCT procedures were previously reported (10). At the time of OCT follow-up, the clinical presentation of the patients was as follows: 7 patients had acute coronary syndrome, 25 patients had stable angina, and 304 patients were asymptomatic. The reasons for follow-up angiography were: 1) evidence of myocardial ischemia by stress test or clinical presentation of coronary artery disease (n = 32, 9.5%); or 2) planned routine follow-up angiography (n = 304, 90.5%).

A major adverse cardiac event (MACE) was defined as cardiovascular death, nonfatal myocardial infarction, and target-lesion revascularization. Clinical events were defined according to the Academic Research Consortium (11). All deaths were considered cardiovascular deaths unless a definite noncardiovascular cause was established. Myocardial infarction was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of myocardial infarction combined with an increase in creatine kinase-myocardial band fraction >3 times the upper limit of the normal range or an increase in troponin T/troponin I to more than the 99th percentile of the upper limit of normal, all of which were unrelated to an interventional procedure (11,12). Stent thrombosis was defined according to the recommendations of the Academic Research Consortium (11,13). Target-lesion revascularization was defined as a repeat percutaneous intervention or bypass surgery of the target lesions with either of the following findings: ischemic symptoms or a positive stress test and an angiographic minimal lumen diameter stenosis ≥50%

**ABBREVIATIONS AND ACRONYMS**

**CI** = confidence interval
**CSA** = cross-sectional area
**DES** = drug-eluting stent(s)
**IQR** = interquartile range
**MACE** = major adverse cardiac event(s)
**OCT** = optical coherence tomography

assessed by quantitative coronary angiographic analysis or an angiographic diameter stenosis ≥70% assessed by quantitative coronary angiographic analysis without either ischemic symptoms or a positive stress test.

**OCT PROCEDURE AND ANALYSIS.** OCT was performed with either the Model M2 imaging system or the C7-XR imaging systems (LightLab Imaging, Inc./St. Jude Medical, St. Paul, Minnesota). In the former system (Model M2), the occlusion catheter was positioned proximal to the stent and a 0.014-inch wire-type imaging catheter was positioned distal to the stent. During image acquisition, the occlusion balloon (Helios, Avantec Vascular Corp., Sunnyvale, California) was inflated to 0.4 to 0.6 atm and lactated Ringer's solution was infused at 0.5 to 1.0 ml/s. The imaging wire was pulled from distal to proximal with a motorized pull-back system at 1.0 mm/s (10). The frequency-domain OCT system (Model C7-XR) was developed to generate frames at much higher rates, thereby allowing for faster pullback speeds. OCT images were generated at 100 frames/s, whereas the catheter was pulled back at 20 mm/s. A contrast medium was continuously flushed through a guiding catheter at a rate of 4 to 5 ml/s for 3 to 4 s. Continuous images were acquired and stored digitally for subsequent analysis.

All OCT images were analyzed at a core laboratory (Cardiovascular Research Center, Seoul, Republic of Korea) by analysts who were blinded to both patient and procedural information. Cross-sectional OCT images were analyzed at 1-mm intervals for quantitative measurements. Stent area and luminal cross-sectional area (CSA) were measured, and neointimal CSA was calculated as the stent CSA minus the luminal CSA. The segment with minimal lumen area and greatest neointimal proliferation could be the representative site of the lesions for long-term clinical follow-up. Therefore, the stented segments at the minimal lumen CSA and greatest neointimal CSA were assessed qualitatively to characterize the neointimal tissue as: 1) homogeneous neointima, a uniform signal-rich band without focal variation or attenuation; 2) heterogeneous neointima, focally changing optical properties and various backscattering patterns; and 3) layered neointima, layers with different optical properties (i.e., an adluminal high-scattering layer and an abluminal low-scattering layer) (**Fig. 1**) (4,6,14). The interobserver and intraobserver agreements for the assessment of neointimal tissue morphology in our laboratory were previously reported (15).

**STATISTICAL ANALYSIS.** Statistical analysis was performed using PASW (version 18.0.0, SPSS Inc., Chicago, Illinois). Data are expressed as n (%), mean ± SD, or median (interquartile range [IQR]). Comparisons of categorical data were made using chi-square statistics or the Fisher exact test. Continuous variables were compared using 1-way analysis of variance or the Kruskal-Wallis test. Event-free survivals were analyzed by Kaplan-Meier survival curves, and the differences between event-free survival curves were compared with the log-rank test. Then, considering the survival curves, layered and homogeneous neointimas were grouped together to be compared with the heterogeneous neointima. Grouping layered and homogeneous neointimas was done a posteriori. Multivariate logistic analysis with use of generalized estimating equations was performed to determine the independent risk factors for heterogeneous neointima. The variables with a p value <0.2 on univariate analysis and traditional cardiac risk factors

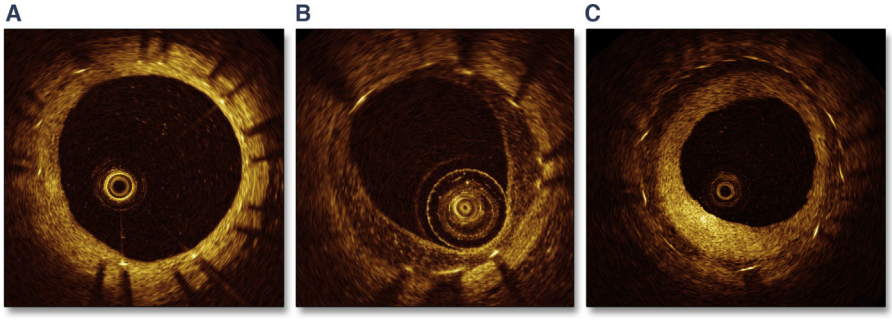


**FIGURE 1 Representative Optical Coherence Tomography Images of Neointimal Tissue**

Homogeneous type **(A)**, heterogeneous type **(B)**, layered type **(C)**.

(age and sex) were entered into the multivariate regression model. A propensity score for heterogeneous versus nonheterogeneous neointima was then calculated (C-statistics = 0.646, 95% confidence interval [CI]: 0.571 to 0.721). The propensity score was used as a covariate in Cox proportional hazard models along with minimal lumen CSA. Cox regression analysis was used to determine the propensity-adjusted risk of MACE during follow-up for patients with heterogeneous versus nonheterogeneous neointima. A p value <0.05 was considered statistically significant.

## RESULTS

Of the total 368 lesions included in this study, 79 were categorized as heterogeneous (21.5% of total lesions) in 73 patients, and 227 in 208 patients and 62 in 55 patients were categorized as homogeneous and layered, respectively. During the course of this study, using the same criteria to define mild to moderate neointimal hyperplasia, there were 3 additional cases meeting the OCT criteria of neoatherosclerosis that were excluded from the 368 study lesions. Baseline characteristics among the 3 groups are listed in Table 1. Mean age was older in the heterogeneous and layered groups. An initial clinical presentation of acute coronary syndrome at the time of stent implantation was more frequently observed in the heterogeneous group compared with the nonheterogeneous group (57.5% vs. 43.3%, p = 0.032). The prevalence of first-generation DES was not different among the 3 groups. The median time interval from stent implantation to OCT examination was similar in the 3 groups: 8.0 months, IQR: 5.0 to 10.0 months in the heterogeneous group versus 9.0 months, IQR: 4.5 to 10.0 months in the homogeneous group, and 9.0 months, IQR: 6.0 to 11.0 months in the layered group, p = 0.64. The mean neointimal CSA was greater and minimal lumen CSA was smaller in the layered group (p < 0.001, respectively).

Using multivariate logistic regression analysis, the significant determinants for the heterogeneous group were age (odds ratio [OR]: 1.037, 95% CI: 1.007 to 1.068, p = 0.015) and an initial clinical presentation of acute coronary syndrome (OR: 1.967, 95% CI: 1.159 to 3.339, p = 0.012) (Table 2). The overall median follow-up duration for all patients after follow-up OCT examination was 31.0 months (IQR: 16.0 to 44.0 months), and this was statistically different among the heterogeneous group (median 22.0 months; range 12.5 to 37.0 months), the homogeneous group (median 34.0 months; range 17.0 to 46.8 months) and layered group (median 28.0 months; range 17.0 to 40.0 months; overall p = 0.002). MACE occurred more frequently in the heterogeneous group (13.7% vs. 2.9% in the homogeneous group vs. 7.3% in the layered group, p = 0.001 (Table 3, Fig. 2). In 3 patients with neoatherosclerosis who were excluded from this study, MACE did not occur during a median of

**TABLE 1 Clinical, Angiographic, and Optical Coherence Tomography Characteristics**

| | Homogeneous Group | Heterogeneous Group | Layered Group | p Value |
|---|---|---|---|---|
| Time interval to OCT, months | 9.0 (4.5-10.0) | 8.0 (5.0-10.0) | 9.0 (6.0-11.0) | 0.64 |
| Clinical variables | 208 Patients | 73 Patients | 55 Patients | |
| Age, yrs | 60.8 ± 9.6 | 64.0 ± 7.9 | 63.5 ± 7.9 | 0.014 |
| Male | 134 (64.4) | 52 (71.2) | 39 (70.9) | 0.45 |
| Diabetes mellitus | 58 (27.9) | 24 (32.9) | 22 (40.0) | 0.21 |
| Hypertension | 125 (60.1) | 40 (54.8) | 36 (65.5) | 0.47 |
| Dyslipidemia | 95 (45.7) | 25 (34.2) | 25 (45.5) | 0.22 |
| Current smoker | 39 (18.8) | 19 (26.0) | 15 (27.3) | 0.24 |
| Chronic renal failure | 3 (1.4) | 1 (1.4) | 0 (0.0) | 0.67 |
| Clinical presentation at index procedure | | | | 0.10 |
| Stable angina | 117 (56.3) | 31 (42.5) | 32 (58.2) | |
| Acute coronary syndrome | 91 (43.8) | 42 (57.5) | 23 (41.8) | |
| Medications | | | | |
| Aspirin | 208 (100.0) | 73 (100.0) | 55 (100.0) | 1.00 |
| Clopidogrel | 208 (100.0) | 73 (100.0) | 55 (100.0) | 1.00 |
| Beta-blocker | 170 (81.7) | 55 (75.3) | 46 (83.6) | 0.41 |
| ACE inhibitor or ARB | 146 (70.2) | 50 (68.5) | 39 (70.9) | 0.95 |
| Calcium channel blocker | 66 (31.7) | 19 (26.0) | 19 (34.5) | 0.54 |
| Statin | 194 (93.3) | 65 (89.0) | 52 (94.5) | 0.41 |
| Angiographic variables | 227 Lesions | 79 Lesions | 62 Lesions | |
| Target coronary artery | | | | 0.033 |
| Left anterior descending | 117 (51.5) | 46 (58.2) | 28 (45.2) | |
| Left circumflex | 58 (25.6) | 14 (17.7) | 9 (14.5) | |
| Right | 52 (22.9) | 19 (24.1) | 25 (40.3) | |
| Stent types | | | | 0.69 |
| First-generation drug-eluting stent | 74 (32.6) | 30 (38.0) | 21 (33.9) | |
| Second-generation drug-eluting stent | 153 (77.4) | 49 (62.0) | 41 (66.1) | |
| Stent diameter, mm | 3.0 ± 0.3 | 3.1 ± 0.4 | 3.0 ± 0.4 | 0.13 |
| Total stent length, mm | 24.1 ± 6.2 | 21.4 ± 6.4 | 23.6 ± 6.6 | 0.006 |
| OCT variables | 227 Lesions | 79 Lesions | 62 Lesions | |
| Total frames | 5,380 | 1,649 | 1,386 | |
| OCT system | | | | 0.10 |
| Old OCT (M2) | 172 (75.8) | 50 (63.3) | 44 (71.0) | |
| New OCT (C7) | 55 (24.2) | 29 (36.7) | 18 (29.0) | |
| Quantitative | | | | |
| Mean stent CSA, $mm^2$ | 7.1 ± 1.9 | 7.1 ± 2.1 | 7.3 ± 1.8 | 0.60 |
| Mean neointimal CSA, $mm^2$ | 1.2 ± 0.7 | 1.4 ± 0.9 | 1.9 ± 1.2 | <0.001 |
| Mean lumen CSA, $mm^2$ | 5.9 ± 1.7 | 5.7 ± 1.9 | 5.5 ± 1.7 | 0.19 |
| Minimal lumen CSA, $mm^2$ | 4.5 ± 1.6 | 4.0 ± 1.9 | 3.7 ± 1.8 | 0.001 |
| Neointimal thickness, μm | 138 ± 68 | 168 ± 119 | 217 ± 133 | <0.001 |
| Neointimal CSA stenosis, % | 16.5 ± 8.1 | 20.1 ± 12.9 | 25.4 ± 13.7 | <0.001 |
| Uncovered stent strut, % | 3.4 ± 5.4 | 4.7 ± 8.0 | 4.1 ± 7.3 | 0.29 |

Values are median (interquartile range), mean ± SD, or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CSA = cross-sectional area; OCT = optical coherence tomography.

**TABLE 2 Independent Predictors of the Heterogeneous Group on Follow-Up Optical Coherence Tomography**

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p Value | OR (95% CI) | p Value |
| Age, per yrs | 1.032 (1.003–1.062) | 0.029 | 1.037 (1.007–1.068) | 0.015 |
| Male | 1.046 (0.616–1.775) | 0.87 | 1.131 (0.647–1.979) | 0.67 |
| First-generation drug-eluting stent | 1.125 (0.662–1.912) | 0.66 | | |
| Initial clinical presentation of ACS | 1.874 (1.130–3.107) | 0.015 | 1.967 (1.159–3.339) | 0.012 |
| Diabetes mellitus | 1.289 (0.758–2.190) | 0.35 | | |
| Hypertension | 0.831 (0.503–1.373) | 0.47 | | |
| Dyslipidemia | 0.662 (0.395–1.109) | 0.12 | 0.746 (0.433–1.282) | 0.29 |
| Chronic renal failure | 0.913 (0.101–8.290) | 0.94 | | |
| Time interval to OCT, months | 1.015 (1.002–1.028) | <0.001 | 1.012 (0.999–1.025) | 0.07 |
| Uncovered stent struts, per % | 1.024 (0.989–1.061) | 0.18 | 1.024 (0.988–1.061) | 0.19 |
| Stent diameter, per mm | 1.258 (0.618–2.580) | 0.53 | | |
| Stent length, per mm | 0.975 (0.938–1.014) | 0.21 | | |
| ACE inhibitor/ARB use | 0.955 (0.555–1.642) | 0.87 | | |
| Statin use | 0.625 (0.263–1.485) | 0.29 | | |

ACS = acute coronary syndrome; CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

12.0 months. In a propensity-adjusted Cox proportional hazards regression model, both heterogeneous tissue type (hazard ratio: 3.925, 95% CI: 1.445 to 10.662, p = 0.007) and minimal lumen CSA (hazard ratio: 0.368, 95% CI: 0.242 to 0.560, p < 0.001) (Table 4) were independent predictors of MACE.

## DISCUSSION

Heterogeneous neointima were detected in 21.5% of DES-treated lesions in the study population. The occurrence of neointimal tissue in this group was significantly associated with both advanced age and initial clinical presentation of acute coronary syndrome. MACE occurred more frequently in patients in the heterogeneous group compared with those in the nonheterogeneous group during the average 31-month follow-up period (13.7% vs. 2.9% in the homogeneous group vs. 7.3% in the layered group, p = 0.001). In addition, we found that inclusion in the heterogeneous group and minimal lumen CSA on follow-up OCT examination were independent risk factors for future MACE. To the best of our knowledge, this is the first study to investigate the clinical significance of neointimal tissue patterns *without features of neoatherosclerosis*. Our data suggest that the heterogeneous neointimal tissue pattern is correlated with poor long-term clinical outcomes.

**TABLE 3 Major Adverse Cardiac Events During Follow-Up After Follow-Up Optical Coherence Tomography Examination**

| Major Adverse Cardiac Events | Homogeneous (n = 208) | Heterogeneous (n = 73) | Layered (n = 55) | p Value |
|---|---|---|---|---|
| A composite of cardiac death, nonfatal myocardial infarction, or target lesion revascularization | 6 (2.9) | 10 (13.7) | 4 (7.3) | 0.001 |
| Cardiac death | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0.78 |
| Nonfatal myocardial infarction | 0 (0.0) | 3 (4.1) | 0 (0.0) | <0.001 |
| Target-lesion revascularization | 5 (2.4) | 7 (9.6) | 4 (7.3) | 0.020 |
| Stent thrombosis | 1 (0.5) | 3 (4.1) | 0 (0.0) | 0.006 |

Values are n (%).

OCT is a valuable intravascular imaging modality for assessing stent strut apposition and coverage. It has 10 times higher resolution than intravascular ultrasound, thereby providing detailed information on the vascular structure and stent (14). Additionally, OCT is able to take advantage of the differential optical properties of the neointima components and is useful for evaluating the tissue characteristics after stent implantation (4). For example, the optical properties of neointima rich in smooth muscle cells and collagen fibers results in high backscattering to optical waves and a high optical density. However, neointima-rich proteoglycan, fibrinoid, or organized thrombi with few smooth muscle cells results in a low optical intensity (16,17). The layered neointimal pattern consists of 2 distinct layers. The inner layer has a high optical density enriched with smooth muscle cells and collagen, and the outer layer has a low optical density consistent with fibrinoid tissue and inflammation surrounding the struts (17,18). Comparing neointima with a marked signal attenuation or a poor signal region assessed by OCT in the late period after bare metal stent implantation (≥5 years), histopathological findings of the neointima in the same regions showed atherosclerotic changes in the neointima consisting of cholesterol crystals, foaming macrophages, and smooth muscle cells with collagen fibers (9).

The heterogeneous neointima in the present study were mostly speckled in pattern. This is similar to previous data examining in-stent restenotic lesions within 1 year after the index procedure (19). Histopathological studies have demonstrated that in-stent restenotic tissue with a speckled pattern exhibited myxomatous neointimal tissue that decreased with time after bare metal stent implantation (2,17). However, the risk factors for the development of heterogeneous neointima have not been sufficiently elucidated. Using multivariate analysis, we show here that both advance age and initial clinical presentation of acute coronary syndrome are independent risk factors for the development of heterogeneous neointimal tissue. These findings suggest that the initial clinical presentation of acute coronary syndrome may

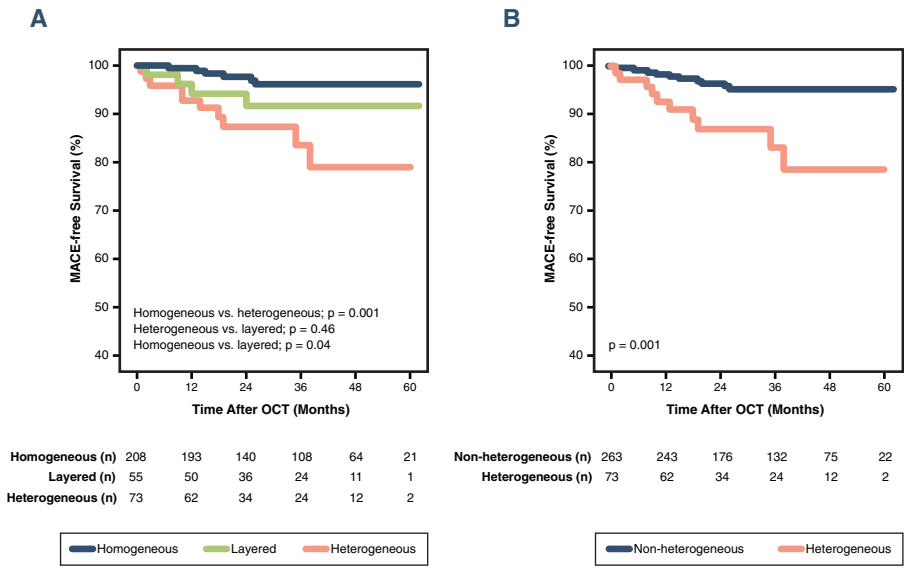


**FIGURE 2 Kaplan-Meier Curves According to Neointimal Pattern**

Kaplan-Meier major adverse cardiac event (MACE)-free survival after optical coherence tomography (OCT) examination among homogeneous, heterogeneous, and layered patterns **(A)** and between heterogeneous versus nonheterogeneous patterns **(B)**. The nonheterogeneous group included homogeneous and layered neointima, with a median of 31.0 (interquartile range: 16 to 44) months of follow-up. **(A)** Homogeneous group versus heterogeneous group ($p = 0.001$); heterogeneous group versus layered group ($p = 0.46$); homogeneous group versus layered group ($p = 0.04$). **(B)** Nonheterogeneous group versus heterogeneous group ($p = 0.001$).

be associated with the formation of immature neointima after stent implantation due to underlying unstable plaque characteristics. A pathological study reported that underlying unstable plaques were identified as one of the independent risk factors for neoatherosclerosis (20). It has also been shown that clinical presentation at the onset of in-stent restenosis is associated with different patterns of neointimal characteristics. Gonzalo et al. (4) demonstrated that the incidence of heterogeneous neointima in patients presenting with stable angina was 6.7% (1 of 15) versus 40% (4 of 10) in patients with unstable angina ($p = 0.08$) (4). Neoatherosclerosis, as traditionally defined by OCT, was rarely observed in patients with mild to moderate neointimal hyperplasia, occurring in 3 patients (<1%) in our study. Because we observed only 3 such patients, additional studies are required to determine the long-term outcomes of such patients.

Although the quantitative growth of neointimal tissue and stent underexpansion were important factors for the occurrence of MACE after stent implantation, the qualitative pattern of neointimal characteristics might be also a possible prognostic parameter. The response of balloon angioplasty in in-stent restenotic lesions could be different according to neointimal characteristics such as the homogeneous, heterogeneous, or layered pattern because of differential histopathological components of these

**TABLE 4 Analysis of a Composite of Cardiac Death, Nonfatal Myocardial Infarction, or Target-Lesion Revascularization**

| | Univariate Analysis | | Propensity Score-Adjusted Cox Regression Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p Value | HR (95% CI) | p Value |
| Age, per yrs | 1.006 (0.959–1.055) | 0.81 | | |
| Male | 0.931 (0.371–2.333) | 0.88 | | |
| Hypertension | 0.688 (0.286–1.652) | 0.40 | | |
| Diabetes mellitus | 1.881 (0.779–4.539) | 0.16 | | |
| Dyslipidemia | 0.953 (0.389–2.332) | 0.92 | | |
| Current smoking | 1.499 (0.576–3.901) | 0.41 | | |
| Initial clinical presentation of ACS | 1.586 (0.648–3.884) | 0.31 | | |
| First-generation drug-eluting stent | 2.440 (0.980–6.075) | 0.06 | | |
| Time interval to OCT, months | 1.018 (1.003–1.033) | 0.017 | | |
| Minimal lumen CSA, per $mm^2$ | 0.325 (0.211–0.501) | <0.001 | 0.368 (0.242–0.560) | <0.001 |
| Stent diameter, per mm | 1.207 (0.322–4.523) | 0.78 | | |
| Stent length, per mm | 1.024 (0.954–1.098) | 0.51 | | |
| Heterogeneous group | 4.236 (1.759–10.200) | 0.001 | 3.925 (1.445–10.662) | 0.007 |

Abbreviations as in Table 2.

tissues (18,21). Atherosclerotic changes or disease progression of the neointima might increase plaque vulnerability and accumulation, ultimately leading to a similar pathophysiology of the native lesion.

However, the clinical implication of neointimal characteristics in DES-treated lesions without significant narrowing and the need for subsequent intervention has not been investigated. In this study, we found the appearance of heterogeneous neointima to be an independent risk factor for MACE. This was true even in lesions without significant narrowing. The DES-treated lesions were divided into 3 groups in the present study: heterogeneous, homogeneous, and layered groups. In contrast to homogeneous or layered neointima, immature neointima and the lack of endothelial cells in the heterogeneous neointima might actually enhance the formation of atherosclerotic changes and be related to MACE. It is possible that the heterogeneous pattern is a precursor to neoatherosclerosis, explaining the increased MACE rate during follow-up. Because we did not perform serial OCT examinations, further study is required to examine this hypothesis.

**STUDY LIMITATIONS.** First, we included only patients with DES-treated lesions ≥100 μm of neointimal thickness and mild to moderate neointimal proliferation <50% of angiographic diameter stenosis. Therefore, the results in this study can be only applicable to lesions with mild to moderate neointimal proliferation at the time of follow-up OCT. Patients in whom only follow-up OCT was performed were included. This may have potential for selection bias. However, these lesions provided an adequate amount of neointimal tissue for accurate quantitative and qualitative OCT analysis. Second, 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. In addition, the heterogeneous or layered pattern may partly overlap with patterns of neoatherosclerosis, which could be a methodological concern in current OCT technology. Third, the interval between stent implantation and OCT examination varied in the study population. Therefore, multivariate analysis was applied to control the different stent age. Fourth, the layered pattern appeared to confer a risk of long-term MACE intermediate between the heterogeneous and homogenous patterns. Finally, because of relatively few MACE events, we were unable to determine other independent predictors of MACE beyond heterogeneous tissue type and minimal lumen CSA. Given the modest number of events, further study is required to examine this issue.

## CONCLUSIONS

Long-term clinical outcomes may vary with the qualitative neointimal tissue characteristics assessed at follow-up by OCT examination. Our data suggest that the neointimal tissue pattern in the heterogeneous group is related to a poor long-term clinical prognosis. These findings strongly suggest the need for further, large, randomized registry studies to validate the effect of neointimal classification by OCT on long-term clinical outcomes.

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**KEY WORDS** coronary artery disease, drug-eluting stent, optical coherence tomography