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EDITORIAL COMMENT

Does Neointimal Characterization Following DES Implantation Predict Long-Term Outcomes?*

Kenichi Sakakura, MD, Michael Joner, MD, Renu Virmani, MD

A recent publication by Kim et al. (1) showed that there are 3 optical coherence tomography (OCT) patterns of the neointimal tissue (homogenous, heterogeneous, and layered) following stent implantation in swine coronary arteries. The heterogeneous pattern could histologically have fibrous tissue, fibrin, inflammation, and neovascularization in swine (1). The same pattern has also been described in patients without histologic validation (2). We reported that the presence of foamy macrophages is characterized by high peak intensity and steep attenuation of OCT light, whereas organized thrombus was identified as dark areas with low-intensity images and a weak attenuation rate (3). Therefore, neoatherosclerosis will also have a heterogeneous pattern. On the other hand, a thorough validation of OCT to detect neoatherosclerosis has not been accomplished to date. Recently neoatherosclerosis, which is defined as peristrut or luminal foamy macrophage infiltrates with or without calcification, fibroatheromas, thin-cap fibroatheromas, and ruptures with thrombosis (4), has been recognized as an important mechanism of late stent failure (5). In the past, OCT has frequently been used to detect intrastent rupture and erosion, which only represent the final stage of neoatherosclerosis formation in the aftermath of stent implantation. Accuracy of OCT to determine early stages of neoatherosclerosis may not be sufficiently specific for thin-cap fibroatheroma or fibroatheroma (6,7), or more importantly, foamy macrophage infiltrates. Nevertheless, OCT is the only contemporary imaging technology that enables us to characterize neointima in vivo at high resolution. Serial changes in qualitative characteristics of the neointima have been previously reported by Kim et al. (8), who investigated 72 patients with 76 drug-eluting stented (DES) lesions that had been imaged by OCT at 9 months and 2 years. They found that lipid-laden neointima and thin-cap fibroatheroma were more frequently observed at 2-year follow-up than at 9 months (8).

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In this issue of *iJACC*, Kim et al. (9) report their findings of a prospective observational study that aimed to investigate clinical outcomes relative to different OCT-based neointimal patterns following DES placement. A total of 368 lesions in 336 patients, who received DES placement and had a follow-up OCT examination, were categorized in groups of homogenous (n = 227 [61.7%] lesions in 208 patients), heterogeneous (n = 79 [21.5%] lesions in 73 patients), or layered (n = 62 [16.8%] lesions in 52 patients) neointimal pattern. The median interval between DES placement and OCT follow-up was between 8 and 9 months, and there were no significant differences among groups. Major adverse cardiac events (a composite of cardiac death, nonfatal myocardial infarction, or target lesion revascularization) were compared according to the previously defined neointimal patterns. Following multivariate analysis, independent predictors for the presence of

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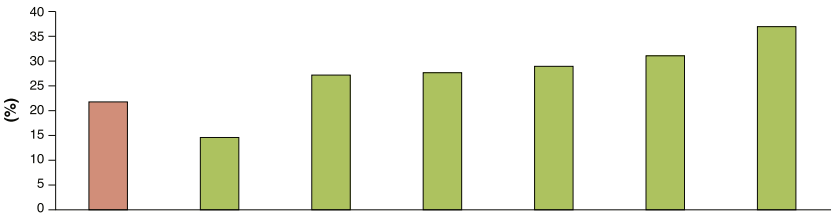
From CVPath Institute, Inc., Gaithersburg, Maryland. Dr. Sakakura has received speaking honorarium from Abbott Vascular, Boston Scientific, and Medtronic CardioVascular. Dr. Joner is a consultant for Biotronik and Cardionovum; and has received speaking honorarium from Abbott Vascular, Biotronik, Medtronic, Cordis, and St. Jude. Dr. Virmani receives research support from 480 Biomedical, Abbott Vascular, Atrium, Biosensors International, Biotronik, Boston Scientific, Cordis Johnson & Johnson, GlaxoSmithKline, Kona, Medtronic, Microport Medical, Orbus-Neich Medical, ReCor, SINO Medical Technology, Terumo Corporation, and W. L. Gore; has speaking engagements with Merck; receives honoraria from 480 Biomedical, Abbott Vascular, Biosensors International, Boston Scientific, CeloNova BioSciences, Claret Medical, Cordis Johnson & Johnson, Lutonix, Medtronic, Terumo Corporation, and W. L. Gore; and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W. L. Gore.

heterogeneous neointima were both age and initial clinical presentation as acute coronary syndrome. Although this study included first-generation DES (86 sirolimus-eluting stents and 39 paclitaxel-eluting stents) as well as second-generation DES (147 zotarolimus-eluting stents, 62 everolimus-eluting stents, and 34 biolimus-eluting stents), DES type was not associated with the presence of heterogeneous neointima. At an average follow-up of 31 months, major adverse cardiac events occurred more frequently in the heterogeneous group (13.7%) than in the nonheterogeneous groups (homogenous [2.9%] or layered [7.3%], p = 0.001) (9). The current study clearly proposes a novel link between heterogeneous neointimal pattern by OCT and the risk of future cardiovascular events, which suggests a new approach to future individualized therapy such as aggressive medical therapy for the high-risk group defined by OCT imaging.

Despite this appealing innovation relevant for the clinical application of OCT imaging, a major limitation of the current study pertains to the lack of histopathologic characterization of heterogeneous neointimal tissue, which could have clinical implications. The lack of accuracy in detecting neoatherosclerosis in the clinical setting can also be seen by the fact that only 3 patients had conventional OCT signs of neoatherosclerosis in the present study population, and these patients were excluded from analysis. Also, at 8 and 9 months following stent implantation, the prevalence of neoatherosclerosis within DES is less in the present study (0.9%) as compared to published data from histopathology studies (4,10), OCT surveillance studies by other groups (11), or the same group (8,12). The reported prevalence of neoatherosclerosis relative to the frequency of heterogeneous neointima in the current study is shown in **Figure 1**. A possible explanation for this discrepancy is that tissue characterization was determined from a representative OCT frame (at the minimal lumen cross-sectional area) in the present study (9), whereas it was determined from several (every 1-mm) OCT frames in the previous study (8). Owing to heterogeneity in vascular healing after stent implantation, it is likely that the optical appearance of neointimal tissue may show substantial variation within the entire pullback, and this finding may be even more pronounced when DES are implanted in the setting of acute coronary syndrome (13).

On the other hand, it needs to be acknowledged that histopathological clarification of tissue composition is inherently absent in patients undergoing



Duration	8-9 Months	9 Months	22 Months (median)	24 Months	7 Months (median)	12 Months (median)	<9 Months
Type of DES	1st & 2nd Generation	1st & 2nd Generation	1st & 2nd Generation	1st & 2nd Generation	2nd Generation	1st Generation	1st & 2nd Generation
Type of Study	OCT	OCT	OCT	OCT	Histology	Histology	OCT
Definition of Neoathero-sclerosis or OCT Heterogeneous Pattern	Heterogeneous neointima, focally changing optical properties and various backscattering patterns	Lipid laden neointima	Lipid laden neointima calcification, or TCFA	Lipid laden neointima	Clusters of foamy macrophages within the neointima with/without necrotic core formation	Clusters of foamy macrophages within the neointima with/without necrotic core formation	Lipid laden neointima
Type of Lesion	Percent NIH CSA 18.8%	Percent NIH CSA 18.7±11.3%	>50 stenosis	Percent NIH CSA 23.4±14.5%	Autopsy	Autopsy	Stable AP (73%) & NSTEMI (27%)
Published Year	2014	2012	2013	2012	2013	2011	2012
Reference	Kim et al. (9)	Kim at al. (8)	Lee et al. (12)	Kim et al. (8)	Otsuka et al. (10)	Nakazawa et al. (4)	Yonetsu et al. (11)

FIGURE 1 Prevalence of Heterogeneous Neointima and Neoatherosclerosis

The prevalence of heterogeneous neointima **(pink bar)** and neoatherosclerosis **(green bars)** reported by different groups is illustrated and each study is highlighted in the table. AP = angina pectoris; CSA = cross-sectional area; DES = drug-eluting stent(s); NIH = neointimal hyperplasia; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; TCFA = thin-cap fibroatheroma.

OCT imaging surveillance after DES implantation. Therefore, valuable insights may be drawn from innovative attempts to characterize neointimal tissue as recently performed by our group. Using OCT grayscale signal intensity analysis was helpful for the detection of immature neointimal tissue including inflammation, fibrin, and macrophage infiltration and incomplete endothelialization (14). Qualitative assessment of neointimal tissue using OCT-based grayscale signal intensity analysis may further facilitate the identification of patients at risk for future events.

Clinical implications of the present study need to be elaborated. Because the homogenous pattern by OCT corresponds to normal neointima (3), both heterogeneous and layered patterns should be considered abnormal neointima. Consequently, abnormal neointima likely includes histopathological substrates such as inflammation, fibrin accumulation, organized thrombus, foamy macrophage, microcalcification, and angiogenesis, which are impossible to differentiate from one another using current OCT devices (3). Although Kim et al. (9) excluded conventional OCT-defined neoatherosclerosis cases, the true prevalence of neoatherosclerosis may have been underestimated in the current study owing to inappropriate clinical validation. In this regard, a substantial number of neoatherosclerosis cases may have been underdiagnosed in the current study population, especially in the group of heterogeneous tissue appearance.

In summary, Kim et al. (9), for the first time, showed an association between the presence of heterogeneous OCT characteristics and future clinical events in patients undergoing routine OCT surveillance after DES implantation. Although the nature of heterogeneous tissue appearance and future cardiovascular events cannot be causally established from the current study, the investigators provided important information justifying the incorporation of OCT in clinical practice.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Renu Virmani, CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, Maryland 20878. E-mail: rvirmani@cvpath.org.

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