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EDITORIAL COMMENT

# In-Stent Neoatherosclerosis and Very Late Stent Thrombosis

## An Endless Fight Against Atherosclerosis*

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Since pathological studies demonstrated the presence of in-stent neoatherosclerosis, intracoronary imaging studies have evaluated its incidence, clinical presentation, and risk factors in patients undergoing stent implantation. To date, optical coherence tomography (OCT) has been the most widely used modality to identify neoatherosclerosis and has revealed the following findings. The frequency of neoatherosclerosis increases with time in patients with restenosis or stent thrombosis. It manifests in various forms, ranging from asymptomatic to acute myocardial infarction. Although several risk factors have been suggested by previous studies, a consistent risk factor is the implantation of drug-eluting stents (DES) compared with bare-metal stents. To be more specific regarding stent thrombosis, recent multicenter prospective registries have demonstrated the OCT-based morphologies of culprit lesions causing stent thrombosis. From the PESTO registry, ruptured neoatherosclerosis was not found in patients with acute or subacute stent thrombosis, whereas it was detected in 28% of those with late stent thrombosis or very late stent thrombosis (VLST) (1). According to a study by Taniwaki et al. (2), neoatherosclerosis was the second most common cause of very late DES thrombosis after malapposition and accounted for 27.6% of 58 analyzed stents. From a report of the PRESTIGE (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort) consortium, neoatherosclerosis was the most common dominant finding causing VLST (3). Therefore, neoatherosclerosis has been established as a leading mechanism of VLST, even considering the heterogeneity of these studies.

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In this issue of *JACC: Cardiovascular Interventions*, Joner et al. (4) report the frequency, timing, and etiologic factors of neoatherosclerosis in patients presenting with VLST, on the basis of data from the PRESTIGE consortium. The study included 134 patients with VLST and is the largest among similar studies. The frequency of neoatherosclerosis was 43.3%. Although it was somewhat higher compared with previous research, the median duration from index stenting was relatively longer (5.6 years vs. 4.7 years in the study by Taniwaki et al. [2]). Implantation of DES increased the risk for neoatherosclerosis compared with bare-metal stent implantation. The novel finding of the present study was that in-stent plaque rupture was found to be the dominant cause in 30% of patients (40 of 134) presenting with VLST. The present study clarifies the role of in-stent plaque rupture among the various forms of neoatherosclerosis. Accordingly, it is speculated that a cascade of thrombogenic processes that begin with the rupture of the cap covering a lipid pool is a main pathophysiology of VLST in patients with neoatherosclerosis. These results are consistent with pathological findings. According to an autopsy stent registry, in-stent plaque rupture was found in 25.6% of cases of VLST (10 of 39) with bare-metal stents and first-generation DES (5). The prevalence of VLST from in-stent plaque rupture increased with time regardless of stent type (5). However, the timing of VLST from in-stent plaque rupture was significantly earlier with

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first-generation DES compared with bare-metal stents (5). Also, the present study demonstrates that macrophage infiltration was abundant in frames showing in-stent plaque rupture. The infiltration of foamy macrophages within the neointima results in the thinning of the fibrous cap to form thin-cap fibroatheroma, which may lead to in-stent plaque rupture (5). Interestingly, previous myocardial infarction in patients with neoatherosclerosis was associated with plaque rupture in the present study. This finding means that susceptibility to plaque rupture may be maintained in lesions treated with stent implantation because of acute myocardial infarction and suggests the presence of predisposing lesions or patients to plaque rupture. Vessel healing at the culprit site in patients treated with DES for acute myocardial infarction was substantially delayed compared with the target site in those treated with DES for stable angina (6). Because necrotic core is an avascular structure, the antiproliferative drug of embedded struts may be persistent for a longer period after stent implantation (5). Consequently, the delayed arterial healing may suppress endothelization and cause dysfunctional endothelium, eventually leading to the development of neoatherosclerosis.

Although the present study demonstrates the clinical features of in-stent plaque rupture, there are several deficiencies. The common limitation of recent prospective OCT registries is that there were no comparable groups consisting of asymptomatic patients with similar implant duration and stent type (1–3). Thus, results from these studies were mainly descriptive, and there was a limit to the interpretation of study results. As shown in the autopsy stent registry, the majority of neoatherosclerosis was an incidental finding (5). Because previous studies have investigated neoatherosclerosis mainly in patients with clinical events, the natural history of neoatherosclerosis remains unknown. The present study included a small number of patients who were treated with second-generation DES. Thus, the association between DES type and neoatherosclerosis was not shown in this study. However, previous pathological and optical coherence tomographic studies reported that there were no differences between first- and second-generation DES regarding the frequency of neoatherosclerosis (7,8). Accordingly, neoatherosclerosis is associated with an intrinsic property of DES such as antiproliferative drugs and polymers. More important, there is a limit to the extent to which OCT detects neoatherosclerosis. Although OCT showed good diagnostic accuracy to identify native coronary plaques, neoatherosclerosis defined by OCT can be other pathological structures, such as fibrin accumulation and excessive inflammation (hypersensitivity) (9). Because these structures look similarly dark on OCT, direct visual discrimination is not possible (9). Therefore, readers should keep the limitations of OCT in mind.

Although neoatherosclerosis causes VLST, there is little research on the proper treatment. Considering that neoatherosclerosis is a kind of atherosclerosis, the long-term maintenance of potent statin therapy for lowering low-density lipoprotein cholesterol during follow-up may have potential benefits to inhibit the development of neoatherosclerosis (8).

Stent therapy is a major step forward in the treatment of patients with ischemic heart diseases. However, atherosclerosis still occurs within neointima, and it worsens long after stent implantation. We have solved many problems in the management of ischemic heart diseases, but we are standing at the starting line again for the prevention and treatment of neoatherosclerosis.

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## REFERENCES

**1.** Souteyrand G, Amabile N, Mangin L, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. Eur Heart J 2016;37:1208–16.

**2.** Taniwaki M, Radu MD, Zaugg S, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. Circulation 2016;133:650–60.

**3.** Adriaenssens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). Circulation 2017;136:1007–21.

**4.** Joner M, Koppara T, Byrne RA, et al. Neoatherosclerosis in patients with coronary stent thrombosis: findings from optical coherence tomography imaging (a report of the PRESTIGE consortium). J Am Coll Cardiol Intv 2018;11:1340–50.

**5.** Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 2015;36:2147–59.

**6.** Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138–45.

**7.** Otsuka F, Vorpahl M, Nakano M, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211–23.

**8.** Lee SY, Hur SH, Lee SG, et al. Optical coherence tomographic observation of in-stent neoatherosclerosis in lesions with more than 50% neointimal area stenosis after second-generation drug-eluting stent implantation. Circ Cardiovasc Interv 2015;8:e001878.

**9.** Nakano M, Vorpahl M, Otsuka F, et al. Ex vivo assessment of vascular response to coronary stents by optical frequency domain imaging. J Am Coll Cardiol Img 2012;5:71–82.

**KEY WORDS** neoatherosclerosis, stent thrombosis