EDITORIAL COMMENT

One Step Forward and Two Steps Back With Drug-Eluting-Stents
From Preventing Restenosis to Causing Late Thrombosis and Nouveau Atherosclerosis*

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Percutaneous coronary intervention with intracoronary stenting is the most widely performed procedure for the treatment of symptomatic coronary disease (1). Although drug-eluting stents (DES) have minimized the major limitation of bare-metal stents (BMS), i.e., restenosis, stent thrombosis has emerged as an important late complication of this technology. The primary pathologic substrate underlying all cases of late stent thrombosis is the lack of complete endothelialization of stent struts. Angioscopy studies have demonstrated that the incidence of uncovered struts in patients receiving DES is substantially high: up to 20% at 2 years (2). However, the reported rate of late stent thrombosis is not as high and it seems that other mechanisms in addition to delayed healing may be important in the pathophysiology of stent thrombosis.

In this issue of the iJACC, Higo et al. (3) propose development of nouveau atherosclerotic plaques within the stented segment as another possible substrate for late thrombosis after DES placement. In their intracoronary angioscopy study in 57 patients, there was a 35% increase in the maximum yellow color grade of the neointima within 10 months after sirolimus-eluting stent (SES) implantation. Even among lesions that did not have yellow plaque at baseline, yellow color was detected in 95% of lesions. Of note, intramural thrombus was exclusively associated with the yellow neointima in the stented segments, and white neointima did not show adherent surface thrombus.

The yellow color on gross pathological examination of the arterial wall indicates the presence of lipid deposition such as fatty streaks and fibroatheroma (4). Fatty streaks consist of minimal intimal thickening with accumulation of lipid-laden foamy macrophages; such a lesion usually corresponds to relatively less intense yellow color on angioscopic examination. On the other hand, fibroatheroma, especially with a large necrotic core and a thin fibrous cap, imparts an intense yellow color on angioscopy (5). The intense yellow appearance has been commonly reported in patients presenting with acute myocardial infarction (AMI) (6,7). It is conceivable that the presence of an intense yellow hue in the stented segments represents an advanced atherosclerotic plaque, which may rupture with time.

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The present study also demonstrated substantially lower neointimal coverage of stent struts of the SES segments as compared with BMS (3). The delayed healing is consistent with results from previous angioscopy reports (8,9), and autopsy studies (10). Histopathologically, the drug-eluting-stented segments are characterized by lack of smooth muscle cell proliferation, persistent fibrin deposition, and incomplete endothelialization (10). The presence of “uncovered struts” is significantly greater in DES with thrombosis as compared with those without, and the number of uncovered struts is closely associated with an increased incidence of late stent thrombosis (11). Therefore, lack of strut coverage should lend itself to in vivo imaging techniques for assessment of risk of future thrombotic complications. In addition to angioscopic studies, optical coherence tomography (OCT) has been used to identify uncovered struts or stent malapposition (12–14). Unfortunately, it is difficult to conduct large clinical trials using these invasive imaging modalities. Therefore, such studies have been limited by small sample size and are more challenging for the detection of low incidence end points such as late stent thrombosis. Currently, there are no prospective data available for in vivo imaging and its impact on clinical outcomes.

**Does Angioscopic Yellow in Stented Segment Represent Nouveau Atherosclerosis?**

To find a pathological explanation of the observations of yellow neointima in SES segments presented by Higo et al. (3), we reviewed autopsy cases from the CVPath (Gaithersburg, Maryland) stent registry. Sixty-six SES segments from 52 cases were compared with 77 BMS lesions. In the stented segments, restenosis was defined as >75% cross-sectional area narrowing by neointimal formation, and an atherosclerotic change was defined as the presence of lipid-laden foamy macrophage infiltrates within the neointima above the stent (with or without necrotic core formation) that did not communicate with the underlying atherosclerotic plaque. Restenosis was significantly more frequent in BMS (33 of 77; 43%) than DES (5 of 66; 8%, p < 0.0001). However, the incidence of atherosclerotic change was seen in 10% of BMS lesions (8 of 77) compared with a significantly higher incidence in DES lesions (35%; 23 of 66; p = 0.0004). There was a significant difference in the timing of atherosclerotic change; earliest atherosclerotic change in DES, which consisted of foamy macrophage infiltration, was observed at 4 months after stent implantation. On the other hand, the atherosclerotic change occurred only beyond 2 years in BMS and remained a rare finding until 4 years (Figs. 1 and 2). The earliest necrotic core formation in DES was observed at 9 months compared with 5 years in BMS. Of the 9 DES restenosis cases, 2 lesions showed severe atherosclerotic change consisting of necrotic core formation with cholesterol clefts and plaque hemorrhage.

Although the patient population in the study by Higo et al. (3) and our autopsy study are different, we believe that yellow neointima by angioscopy most likely corresponds to either foamy macrophage infiltration and/or necrotic core formation; the intensity of yellow likely signifies necrotic core with a thin fibrous cap as previously reported in patients presenting with AMI.

**Why is There Greater Incidence of Angioscopic Yellow in DES?**

Angioscopy studies have reported that the neointimal coverage in BMS, which mostly consists of a white neointima (3,15), typically occurs by 3 months. This finding is consistent with the pathologic studies wherein neointimal coverage of BMS is almost completed by 3 to 6 months (16). The neointima in BMS is made up of smooth muscle cells and extracellular matrix (17), which typically imparts a white hue on angioscopic examination. Conversely, a yellow neointima was more commonly encountered in the SES lesions, suggestive of...
an atherosclerotic change. The question arises as to why SES induces (or accelerates) the process of atherosclerosis. Normally, coronary artery vessel walls are protected from lipid transport across the vessel wall by maintaining an efficient endothelial barrier. Plaque progression is initiated by endothelial dysfunction or damage that allows increased permeability of lipoproteins and upregulation of adhesion molecules (18). As reported previously both at autopsy and in animal models of DES, the endothelial lining is incompetent and therefore it is not surprising that it will allow accelerated infiltration of lipid as well as monocyte adherence and subendothelial migration. Sirolimus suppresses not only smooth muscle cell but also endothelial cell regrowth and therefore may further enhance the formation of atherosclerotic change. It is possible that underlying atherosclerotic lesions progress even more rapidly after DES implantation than do native coronary plaques with eventual luminal thrombosis (19).

The findings from the study by Higo et al. (3) and our pathological data presented here support the concept that DES therapy may enhance atherosclerosis while reducing restenosis. Indisputably, coronary stents help to improve quality of life by relieving anginal symptoms, but stent therapy remains only palliative. The treatment of coronary artery disease would need a multidimensional approach, and the fight against atherosclerosis is yet to be won. The technology of DES has certainly moved the field forward but at a price—late stent thrombosis and now accelerated atherosclerosis and potentially greater late thrombosis.

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References


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