Revealing the Silver and Red Lining in Drug-Eluting Stents With Angioscopy

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Drug-eluting stents (DES) are widely used in percutaneous coronary intervention and have resulted in significant reductions in target-vessel revascularization as compared with bare-metal stents (BMS) in randomized, controlled trials and in unrestricted patient and lesion subsets. Comprehensive analyses have proven the safety of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) compared with BMS, with similar rates of death and myocardial infarction after as much as 4 years of follow-up; however, a valid safety concern remains, given that DES increase the risk of late (>30 days) and very late (>1 year) stent thrombosis compared with BMS. Our understanding of the risk factors for stent thrombosis has been derived from experimental models, pathological findings, and clinical trials. The mechanisms underlying the increased thrombogenicity of DES are multifactorial and include patient, lesion, and procedural factors, as well as compliance with and response to antiplatelet therapy. However, all currently available DES may be susceptible to late and very late stent thrombosis because of the delayed arterial healing and impaired endothelialization that accompany the drugs used to inhibit neointimal hyperplasia. We can postulate that the rate of healing varies from patient to patient, and even from lesion to lesion within the same patient, but we do not have a method to assess or measure healing after stenting. Therefore, we have empirically recommended that dual-antiplatelet therapy be extended for at least 12 months after DES implantation in an effort to reduce events during the period when the stent is prone to thrombus formation.

Articles see pp 20 and 28

In terms of assessing the mechanisms of stent failure, including restenosis and stent thrombosis, intravascular ultrasound (IVUS) has been helpful. Subacute stent thrombosis (<30 days) in BMS and DES alike often has a cause that is identifiable by IVUS, such as severe stent underexpansion, edge dissections, or inflow–outflow disease. Restenosis due to intimal hyperplasia remains a cause of DES failure, albeit at a low incidence. In many cases, suboptimal stent deployment is found, and neointimal volume is a small contributing factor. Late or acquired malapposition by IVUS is associated with less neointimal growth, is more common in DES than BMS (with an incidence of 5% to 10%), and has been implicated in late and very late stent DES thrombosis. Although IVUS is widely available for use in clinical practice, limitations for evaluating mechanisms of DES failure include the resolution and poor ability to visualize thrombus. In this regard, optical coherence tomography and angioscopy have emerged as potential tools. Optical coherence tomography imaging uses infrared light and has 10 times the axial resolution of IVUS. This technology, therefore, is better able to assess neointimal coverage of stent struts than IVUS. Angioscopy uses xenon light to visualize the vessel lumen and can qualitatively assess the coronary luminal surface, including plaque characteristics, presence of neointima, and thrombus. Blood must be replaced with transparent fluid to acquire images, which makes it impractical for routine use, but angioscopy has been used to evaluate the macroscopic pathology of stents.

In this issue of Circulation: Cardiovascular Interventions, 2 complementary articles provide insight into vascular healing in the presence of DES using angioscopy. The studies, which are the first to present angioscopic data for PES, confirm pathological observations that nonuniform neointimal growth occurs with DES and is associated with thrombus formation. Confirm prior reports of coronary endothelial dysfunction related to DES, and highlight our lack of understanding of the disconnect between the common occurrence of abnormal vascular healing with DES and the rare occurrence of stent thrombosis.

In the article by Takano et al, the relationship between angiographic late loss and angioscopic thrombus was examined 6 months after SES or PES implantation in de novo native lesions in patients undergoing dual-antiplatelet therapy. High-risk patients, such as those with acute myocardial infarction, low ejection fraction, and graft lesions, were excluded. Compared with SES, maximum neointimal stent coverage and late loss were greater in PES, consistent with multiple prior studies. Despite greater late loss in PES, uncovered stent struts were observed equally in SES and PES patients, at a rate of approximately 40%, which was explained by a greater heterogeneity of neointimal coverage in PES patients. Conversely, in-stent thrombus was more prevalent in PES (72% versus 40% in SES). The pattern of thrombus deposition varied in the 2 types of stents. In SES, thrombus primarily occurred in uncovered or minimally covered struts, whereas in PES, thrombus occurred equally in uncovered segments and segments with large late loss. The results show that angiographic late loss and angioscopic neointimal cov-
erage cannot be used as surrogates for a functional thrombo-resistant endothelium and protection against stent thrombosis.

In a complementary article, Shinke et al.\textsuperscript{12} in a porcine model, performed in vivo angioscopy followed by histological assessment of overlapping PES and BMS in coronary arteries 30 days after implantation. Similar to prior animal studies, they observed inhibition of neointimal hyperplasia in PES compared with BMS, but unlike prior studies that showed greater endothelialization with BMS, endothelialization was estimated at 75% to 100% in both groups. Mural thrombus, however, was only observed in PES and was most often found in the overlapping stent segment. The prevalence of mural thrombus angiographically correlated with macroscopic histopathology, which demonstrates the utility of in vivo imaging for this purpose. The study demonstrated, however, the inability of angioscopy, a morphological assessment of the vessel wall, to determine characteristics of the neointima or functional recovery of the endothelium. Vasomotor function assessed by endothelium-dependent vasodilation demonstrated that in segments that were angiographically normal, endothelial dysfunction was present. Histologically, neointimal tissue in PES was also abnormal, with the presence of leukocytes and microthrombi. These functional and histological observations may explain the findings by Takano et al.\textsuperscript{13} that mural thrombus occurs in DES in segments where stent struts are covered by neointima.

### Heterogeneity of Stent Strut Coverage in DES

Pathological studies of DES from patients with stent-related and non–stent-related cardiac death have identified nonuniform healing as a risk factor for stent thrombosis.\textsuperscript{4} When lesions with thrombus formation were compared with those of a similar duration after DES implantation without evidence of thrombus, several morphometric and histological differences were observed. DES lesions with thrombus had less neointimal growth and endothelialization and greater fibrin scores than patent DES. There was significant heterogeneity of stent strut coverage within and across sections from the same stent, with some struts bare and others covered with neointima. Analysis of morphological findings revealed that the ratio of uncovered to total stent struts per section correlated with endothelialization and best predicted an increased risk of late stent thrombosis. Within a DES, the most common location of uncovered stent struts was the middle section. Other pathological studies have suggested that stent strut coverage is impaired in areas of stent overlap, penetration into the necrotic core of plaques, malapposition, and bifurcations and with hypersensitivity reactions.\textsuperscript{5,14-17} Thus, the mechanism of delayed and nonuniform healing in DES is multifactorial and dependent on lesion characteristics in addition to stent-related factors such as drug delivery and polymer biocompatibility.

The extent of macroscopic healing, determined by neointimal coverage and prevalence of mural thrombus in stents, has been examined in patients with angiography. There have been several reports of angioscopic findings in SES compared with BMS.\textsuperscript{11} Consistently, at 6 months, the degree of incomplete neointimal coverage of SES was greater than for BMS, with a range of 20% to 46% compared with 0% to 8%, respectively. Similarly, thrombus was present in 33% to 42% of SES compared with 8% to 14% of BMS. Later follow-up, for up to nearly 2 years, demonstrated that 50% of SES had at least some degree of grade zero, or uncovered, stent struts, particularly noted in areas of side-branch ostia and stent overlap. Overall, the extent of neointimal coverage was greater in BMS at all time points, and the degree of coverage correlated with the presence of thrombus, which was only observed in SES. The antiplatelet regimen in these studies included aspirin and a minimum of 3 months of ticlopidine, but many patients were undergoing dual-antiplatelet therapy at the time of 6-month angioscopy. Despite the prevalence of uncovered stent struts and thrombus, clinical stent thrombosis was not observed. Anecdotally, however, angioscopy in a patient with very late SES thrombosis showed massive red thrombi adjacent to exposed struts.\textsuperscript{18} The study by Takano et al.\textsuperscript{14} in the present issue of the journal adds to the literature with angioscopic findings in patients with PES. We now know that despite greater overall neointimal growth in PES, uncovered stent struts were observed equally in SES and PES, with a similar frequency as prior studies at 40%. Accordingly, clinical studies have shown that late and very late stent thrombosis occurs with both types of DES. Although the angiographic studies have been too small to definitively determine patient and lesion characteristics associated with uncovered stent struts, both studies highlight delayed healing with stent overlap. In the study by Takano et al.\textsuperscript{13} 100% of patients with overlapping stents had uncovered stent struts, and in the porcine model, Shinke et al.\textsuperscript{12} showed that mural thrombus was detectable on 100% of PES in the area of overlap at 30 days. A unique finding to PES was the presence of thrombus on stent struts with some degree on neointimal coverage, which highlights the limitation of angioscopy for evaluating recovery of the neointima, which requires a functional endothelium.

### Endothelial Dysfunction After DES

An extensive body of literature exists on the vascular homeostatic functions of the endothelium and the relationship between endothelial dysfunction and cardiac events.\textsuperscript{19} Vascular injury occurs with stenting, and the process of reendothelialization occurs by both migration of endothelial cells from neighboring intact segments and bone marrow–derived endothelial progenitor cells. Reendothelialization is delayed in DES compared with BMS, and even areas covered by endothelial cells may not function normally. In the study by Shinke et al.\textsuperscript{12} endothelium-dependent vasodilation proximal and distal to PES was diminished compared with BMS stented arteries. Previous reports in patients treated with SES showed abnormal endothelial function compared with BMS, with inappropriate vasoconstriction in response to endothelium-dependent vasodilators and exercise.\textsuperscript{15,16} Whether the local endothelial dysfunction observed with DES is solely the result of delayed or impaired vascular repair or a more direct toxic effect of sirolimus or paclitaxel on the vessel is unknown. Furthermore, whether endothelial dysfunction is associated with an increased risk of adverse clinical events such as stent thrombosis is unknown. Further serial examinations of endothelial function and either angioscopy or histopathology would help address the
issue of the duration of endothelial dysfunction and whether it is a surrogate for arterial healing.

**Relationship of Angioscopic Findings to Stent Thrombosis**

There is a tremendous disconnect between the common occurrence of abnormal morphological findings in DES, such as uncovered stent struts and mural thrombus, and the low incidence of late stent thrombosis. This is reminiscent of the question of whether acquired incomplete stent apposition or malapposition causes stent thrombosis. Clinical evidence suggests that dual-antiplatelet therapy is of paramount importance for preventing stent thrombosis, particularly during the first several months.  

6. We know, however, that the majority of patients taking a single antiplatelet agent 6 months after DES implantation do not have stent thrombosis and that dual-antiplatelet therapy does not prevent all stent thrombosis events. As such, we can postulate that in the majority of patients abnormal healing alone will not tip the homeostatic scale toward thrombosis.

Putting together all the available clinical, angiographic, morphological, and histological data on DES, we have been able to identify risk factors for stent thrombosis, but we do not have a way to determine when an individual patient is no longer at risk. Until more data are available on the time course of functional endothelial recovery after DES, we are left with no option but to limit DES to patients capable of complying with dual-antiplatelet therapy for 12 months. Whether all patients, or certain subsets such as those with overlapping stents, benefit from even longer periods of dual-antiplatelet therapy is unknown.

**Disclosures**

None.

**References**


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