Drug-eluting stents (DES) have been proven to reduce the rate of restenosis by marked inhibition of neointimal hyperplasia, but unusual vessel responses to DES, such as substantially impaired arterial healing characterized by incomplete endothelialization and persistent inflammatory response, have been recognized. The culprit sites in acute coronary syndrome (ACS), especially acute myocardial infarction, have large necrotic cores with a paucity of smooth muscle cells. In these lesions, penetration of the stent struts into the necrotic core is frequently observed after stent implantation. Pathologic observations have revealed that the lesions stented with DES frequently show greater delay in arterial healing than those treated with bare-metal stents. Thus, ACS culprit sites could be at persistent risk for thrombosis after DES implantation. (Circ J 2010; 74: 2232–2238)

Key Words: Acute coronary syndrome; Drug-eluting stent; Pathology; Stent thrombosis

Drug-eluting stents (DES) have dramatically reduced angiographic restenosis and the clinical need for repeat revascularization procedures. Currently, DES are being used “off-label” in higher-risk patients and in more complex lesions such as the culprit lesions of acute coronary syndrome (ACS), and concerns have arisen about the appropriateness of the routine use of DES in the “real world”. Furthermore, even in patients with acute myocardial infarction (AMI), it has been reported that DES reduces the rate of restenosis compared with that with bare-metal stents (BMS). However, randomized studies comparing DES with BMS in patients with AMI have been relatively small and have had limited periods of follow-up. Furthermore, late (LST) and/or very late stent thrombosis (VLST) has emerged as a distinct entity overshadowing the use of DES, and concerns persist as to whether this phenomenon might jeopardize the long-term outcome after DES implantation. Observational studies comparing DES and BMS in patients with AMI also have conflicting results.

I describe here the safety issues of DES implantation for ACS cases, especially AMI, from a pathological standpoint.

Possibility of Increased Risk of Stent Thrombosis After DES Implantation at Culprit Sites of AMI

The structure of plaques may affect the relationship of the stent struts to underlying tissue and therefore affect arterial responses to stent implantation, especially with regard to vessel healing. Vulnerable plaque (characterized by a necrotic core with an overlying thin-ruptured cap infiltrated by macrophages and with a paucity of smooth muscle cells) is the most common underlying substrate in AMI. In highly necrotic plaques, stent struts penetrate deeply into the lipid core and are not in direct contact with the vessel wall (either arterial media or fibrocellular plaque). Neointimal growth and reendothelialization occur via the migration and proliferation of vascular smooth muscle and endothelial cells from the uninjured arterial edges, adjoining arterial branches, and vasa vasorum. A stent placed in an artery with significant plaque prolapse with a large lipid core could produce delayed development of a compact endothelialized neointima as a result of the relative paucity of migrating and proliferating smooth muscle cells in close proximity to the struts. Thus, even in cases of BMS implantation, the AMI culprit lesion is one of the most important underlying mechanisms of LST identified by pathological study.

It has been reported that DES implantation generally results in delayed arterial healing compared with BMS under similar duration. Therefore, vessel healing at the culprit lesion in AMI cases treated with DES is substantially delayed compared with that in cases receiving DES for stable angina. A clinical study using optical coherence tomography also demonstrated a markedly high frequency of inadequately apposed struts uncovered by neoendothelium in cases of unstable plaque. There is documentation of several likely pathological causes of delayed healing at AMI culprit sites.
Figure 1. (A) Angiograms on the left are from a patient with acute myocardial infarction who underwent successful urgent stent (bare-metal stent) implantation in the segment just proximal segment of the native left circumflex coronary artery (large arrowhead), but who died of cardiogenic shock. The left anterior descending coronary artery shows chronic total occlusion (small arrowhead). The 3 panels on the right show a specimen harvested approximately 5h after stenting, with the well-dilated stent struts on the luminal surface (*blood clot formed at agonal stage). (B) Histological sections (a–d) of the stented segment shown in (A). The culprit site has a large necrotic core and remnants of fibrin-rich thrombi. *Struts deeply penetrating the necrotic core.
lesions. Because sirolimus and paclitaxel are highly lipophilic, it is likely that these agents have greater affinity for lipid-rich plaques and remain within the necrotic core for longer than in fibrotic types of plaque. Greater drug concentrations might also heavily influence healing by retarding smooth muscle proliferation as well as endothelial regrowth. Thrombus burden may also play a role by either increasing or decreasing vessel wall uptake of drug loaded on paclitaxel-eluting stents. These phenomena underscore the concept that stents require some degree of neointimal hyperplasia to become endothelialized and that, although total abolition of neointima will result in a larger lumen, it is at the expense of an increased risk for LST and/or VLST.

Recently, an intravascular ultrasound study revealed that patients with VLST showed evidence of a high incidence of incomplete stent apposition (ISA). As previously described, the frequency of ISA was also high in ACS patients with DES implantation. In addition, it has been reported that large thrombus burden was an independent predictor of major adverse cardiac events, including VLST, in patients treated with DES for AMI. Thrombus compression/displacement by the DES struts in the acute phase, with abluminal thrombus resolution and delayed healing in the infarct-related lesion in the long-term, has been proposed as a potential mechanism. Thus, it is rational that the larger the thrombotic burden, the higher will be the incidence of ISA, which might account for the higher rates of VLST in large thrombus burden cases in the long-term.

Figure 2. (A) Angiograms on the left show thrombotic occlusion in the left main trunk (LMT, arrowhead) immediately after bare-metal stent implantation and balloon angioplasty. On the right is the left coronary artery (LCA) harvested about 2 months after stenting, showing complete coverage with mild neointimal formation (*ostial portion of the left circumflex artery). (B) Histological sections of the stented LMT in (A). Complete neointimal coverage of the stent (*) with endothelialization is evident.
Coronary stenting typically induces extensive injury of the blood vessels,\textsuperscript{25} which in turn engenders a significant and extended tissue reaction (ie, plaque sealing).\textsuperscript{26} The smooth muscle-rich intima observed during the first few months after BMS implantation is substantially transformed into a collagen-rich layer.\textsuperscript{27} The covering of the intimal wound by neointima, involving smooth muscle cell proliferation and extracellular matrix accumulation, induced by stent implantation, may well have the beneficial effect of sealing a large lipid core (Figure 4). However, as mentioned above, only mild neointimal thickening is observed around the circumference of the vessel lumen at the DES stented site. Furthermore, few smooth muscle cells are observed in these sections, and abundant fibrin deposits are present around the struts (Figure 3). Thus, DES implantation may not be able to stabilize lipid-rich plaque for a long time after stenting.
DES Can Accelerate Atherothrombosis at the Stented Site

Recent studies have identified immune cells and mediators at work in atheroma, implicating inflammatory mechanisms in disease development. In DES-implanted segments, inflammation against the durable polymer of the DES, especially heavy infiltration of macrophages around the struts, is typical. Furthermore, the remarkable presence of lipid-laden foamy macrophage infiltration within the neointima is usually evident more than several months after stenting. In addition, extracellular lipid, such as cholesterol crystals, accumulates and early necrotic core formation is frequently observed more than 1 year after DES implantation (Figure 5). It is reported that these lipid-laden macrophages around the stent struts showed collagen-degrading matrix metalloproteinase immunoreactivity, which can degrade the neointimal layer followed by disruption of the stented portion. Recent angioscopy studies have also revealed that DES promoted the formation of atherosclerotic yellow neointima in the stent-implanted
lesion at 10-month follow-up.29 Thus, DES can induce atherosclerotic and thrombogenic lesions with a significantly higher incidence and earlier than with BMS.

**The Most Important Issue of Therapy for Patients With ACS Is Not to Reduce Restenosis, But to Revascularize Completely as Soon as Possible**

Irreversible ischemic injury develops in an increasing number of myocardial cells as the duration of coronary occlusion is prolonged.30 Thus, urgent angiography and triage to revascularization should be a priority in ACS patients.31 Premature interruption of antiplatelet therapy has been reported to be a significant risk factor for stent thrombosis in patients with DES implantation.32 Consequently, the recommendation for post-PCI stented patients receiving a DES include dual-antiplatelet therapy, such as thienopyridine therapy, in addition to aspirin use for at least 12 months.33 The poorly healed ACS culprit site of DES implantation may pose a more significant risk for coronary thrombosis when dual-antiplatelet therapy is prematurely and abruptly discontinued.34 Thus, potent antiplatelet therapy for a longer duration ought to be used in ACS patients with DES implantation. However, in cases of emergency PCI for ACS, especially in severe cases with developments such as cardiogenic shock or heart failure, it is not possible to explain the side-effects of such a potent antithrombotic therapy, such as bleeding,35 to obtain informed consent from the patient.

Therefore, it is reasonable to choose BMS, not DES, for urgent PCI therapy for ACS patients.

**DES Should Be Avoided in ACS Patients Until Longer-Term Data Become Available**

There have been several reports on the safety and efficacy of DES in Asian ACS patients.36–38 However, there is a paucity of reports concerning longer-term prognosis of DES use in ACS.39 Concerns exist regarding the long-term outcomes of DES vs BMS in patients with ACS in the real-world setting. A high frequency of VLST has been steadily observed in DES-implanted ACS patients.40,41 Thus, until DES can present longer-term follow-up data, the “unrestricted” use of DES might not be justified in patients presenting with ACS.

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