Vascular pathology as a result of drug-eluting stents

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Drug-eluting stents (DES) comprise more than 60% of stent implants in the UK (BCIS audit figures, 2005). This implantation rate has been driven by landmark clinical trials demonstrating that restenosis and target lesion revascularisation rates are lower with DES than with bare-metal stents (BMS), both acutely and after long-term follow-up.^{1,2} In randomised controlled trials, death rates^{3,4} and late stent thrombosis (LST) rates⁵ were no different between BMS and DES. However, LST has been consistently reported in "real-world" stenting,⁶⁻⁸ including recent reports from the TAXUS-II-IV trials and Basel Stent Cost-effectiveness-Late Thrombotic Events Trial (BASKET-LATE). In the latter trial, cardiac death or non-fatal myocardial infarction (MI) rates in the year after stopping dual antiplatelet treatment were higher in patients with DES than in those with BMS (4.9% vs 1.3%), probably owing to LST.

CAUSE OF LST

LST can be explained by the effects of stenting on the artery and the processes leading to arterial repair. Overdistension of the diseased vessel by either angioplasty or stent insertion causes endothelial disruption, fracture of the internal elastic lamina and dissection of the media, often extending into the adventitia (reviewed by Bennett and O'Sullivan⁹). Vessel injury also causes adventitial damage, seen both macroscopically and microscopically. Lumen enlargement is due to a combination of plaque reduction (compression/embolisation), axial plaque redistribution within the lesion (towards the proximal and distal vessel segments outside the stent or angioplasty balloon), plaque extrusion and vessel expansion.

Repair of the vessel after stenting comprises a series of temporally related processes, including endothelial regeneration and return of its anticoagulant properties, reorganisation of thrombus through cellular invasion from the adjacent wall and/or circulating cells, vascular smooth muscle cell (VSMC) proliferation and/or migration to cover the stent struts, deposition of extracellular matrix and resolution of inflammation, including the foreign body reaction around the stent struts (reviewed by Bennett and O'Sullivan⁹). Although the success of DES in reducing restenosis is due to their ability to inhibit the repair reaction, particularly neointima formation, it is clear that DES substantially impair arterial healing compared with BMS up to 6–12 months after stenting,^{10,11}

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and LST after DES use is a consequence of inhibition of repair.

The major DES in use in the UK comprise polymer-based delivery of the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, and the anti-mitotic agent, paclitaxel. Both drugs are potent anti-proliferative agents, inhibiting VSMC proliferation in vitro and in vivo. Both drugs may also have additional effects on cell matrix synthesis, although these effects may be secondary to inhibition of proliferation, and there is some evidence that sirolimus may exert anti-inflammatory effects. Unfortunately, anti-proliferative effects are not specific to VSMCs, and both agents inhibit re-endothelialisation, resulting in a procoagulant surface, and loss of vascular reactivity. Both drugs also prevent VSMC coverage of stent struts, resulting in delayed healing and prolonged inflammation, particularly at areas of high local drug concentrations such as overlap sites.¹² Finally, the polymer itself has been linked to chronic inflammation in the vessel wall. Although some animal studies suggest that paclitaxel and sirolimus have different effects on vessel repair, for example in a paper in this issue of *Heart* (see article on page 922),¹³ delayed healing and inflammation are potential problems with both drugs.

The substrate for LST has recently been clarified in a pathological study of 23 cases of death >30 days after DES use compared with 25 cases of BMS use.¹⁴ In 14/23 DES cases, patients had late thrombosis, with stent-related acute MI or sudden cardiac death (SCD) being the cause of death. Occlusions were either total thrombotic occlusion of the stent or subacute thrombosis with distal embolisation. In 2/23 cases, acute MI or SCD was ascribed to in-stent restenosis (ISR). In comparison, 2/25 of cases of BMS died of LST, and 5/25 died of ISR leading to acute MI or SCD. DES cases displayed delayed healing, as shown by persistent fibrin deposition, and delayed re-endothelialisation compared with BMS, and this correlated with LST. LST was also associated with local inflammation (consisting of lymphocytes, eosinophils, macrophages and giant cells around stent struts), ostial and/or bifurcation stenting, malapposition/incomplete apposition, ISR with superimposed thrombosis, and strut penetration into the necrotic core of a plaque. In comparison, inflammation and fibrin formation, particularly eosinophils, were significantly less in BMS. BMS were associated with increased neointima formation, but complete

Abbreviations: BMS, bare-metal stents; DES, drug-eluting stents; ISR, in-stent restenosis; LST, late stent thrombosis; MI, myocardial infarction; mTOR, mammalian target of rapamycin; SCD, sudden cardiac death; VSMC, vascular smooth muscle cell

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coverage of stent struts at 120 days. In other studies, DES have been shown to have a higher incidence of incomplete stent strut coverage and subclinical thrombus formation than BMS on angiography 3–6 months after stenting.¹⁵ In addition, unusual but worrying appearances of both massive positive vessel remodelling, resulting in aneurysm formation¹⁶ and “black holes”, have been found after DES; the pathological processes leading to these appearances are not known.

These studies strongly implicate the anti-proliferative effect of DES delaying healing, with persistent fibrin formation, inflammation and incomplete strut coverage, and delayed, if not incomplete, re-endothelialisation. The studies also cannot exclude the possibility of functional defects in endothelium. Clearly, some of mechanisms that lead to the beneficial effect of DES on neointimal formation are also the cause of their failure.

HOW DO WE PREVENT LST?

So how do we prevent LST, and is there room for development of DES that can exert short-lived beneficial effects on neointima formation, while still allowing strut coverage and not preventing re-endothelialisation? In the first instance, LST strongly argues for the long-term maintenance of antiplatelet agents, as we cannot predict whether an individual patient has re-endothelialised, and whether that endothelium is functionally anticoagulant. Clearly, the risk of LST has to be balanced against the bleeding risk associated with these regimens. There is also considerable room for the development of more specific anti-restenosis drugs to be mounted on stents. Neither sirolimus nor paclitaxel are specific for VSMCs, and although mTOR has a higher relative expression in intimal VSMCs than in medial VSMCs, this protein has multiple functions within the cell, including endothelial cells. Thus, the sirolimus “mimetics” are likely to have the same problems of non-specificity, and lead to LST.

In contrast, DES require an agent that is relatively specific to intimal VSMCs, and preferably overexpressed in ISR cells compared with VSMCs from primary plaque or the normal vessel wall. Agents that target these differences have been shown to have relative specificity *in vitro*.¹⁷ Alternative strategies include combinations of agents to enhance re-endothelialisation delivered at the same time as antiproliferative agents targeted at VSMCs, or degradable stents where the healing processes are delayed, but not totally inhibited over time. It seems that the prevention of one iatrogenic disease

(ISR) produces another iatrogenic disease (LST), which requires a further level of treatment/prevention for its solution.

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