Coronary stents: in these days of climate change should all stents wear coats?
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The most significant advancement in percutaneous coronary intervention (PCI) since the introduction of angioplasty in 1978 has been the routine coronary stenting of de novo lesions. The resultant improvement in short term procedural outcome and reduced restenosis has made PCI the treatment of choice for single vessel coronary artery disease and launched it into more complex anatomy.

Restenosis has, however, not been eliminated and angiographically occurs in 20–30% of cases where bare metal stents are used, with the clinical recurrence rate approximately half of that. Restenosis following balloon angioplasty was largely as a result of immediate elastic recoil and/or the subsequent phenomenon of maladaptive vessel shrinkage in response to injury or negative remodelling. In the era of routine coronary stenting these have been usurped by neointimal hyperplasia as the cause of restenosis within stented segments or in-stent restenosis (ISR).

Histologically, this is in part a giant cell mediated foreign body reaction and partly a vascular response to injury. A higher frequency of further restenosis limits the long term clinical outcome following treatment of ISR, and preventing or limiting the initial restenotic process seems a more plausible way of reducing the problem and hence the need for target lesion revascularisation (TLR). The most promising options for this are, however, not without potential problems.

Adjunctive intravascular brachytherapy leads to grossly delayed endothelialisation and the need for long term antplatelet treatment to prevent stent thrombosis. In addition the long term phenomena of “restenotic catch-up” and changes in vascular wall architecture are still being evaluated.

Drug eluting stents offer the possibility of delivering therapeutic levels of active metabolite locally (assuming stents are well opposed) while systemic levels are negligible. There are potential concerns regarding long term arterial thinning and, as with brachytherapy, delayed endothelialisation with thrombosis and late restenosis have been reported although there may be differences between the various active agents.

Incomplete coverage of the stent struts by endothelial cells or a delay in the speed of endothelialisation necessarily leads to an increased risk of subacute stent thrombosis (SAT); the clinical consequences of which are typically abrupt, unpredictable, and severe (myocardial infarction) unlike the situation with ISR, which is usually a gradual resumption of pre-existing symptoms. The frequency of SAT is low (< 2% for elective and 5% for bailout stenting) and as with any low frequency event, statistical evaluation requires a large population to evaluate potential treatment effects.

Reducing restenosis and thrombogenicity by improved biocompatibility has previously been the focus of attention, but latterly interest has shifted more toward producing inert biocompatibility has previously been the focus of attention, and changes in vascular wall architecture are still being evaluated.

METALLIC COATINGS: GOLD AND TITANIUM

Gold is regarded as a relatively inert medium and is also radio-opaque, which is an advantage in terms of radiographic visualisation. The experimental data for gold coated stents are generally disappointing despite encouraging early work.

Abbreviations: ANTARES, Aspirin alone antiplatelet regimen after intracoronary placement of the carbocont; COAST, heparin-coated stent placement for the treatment of stenoses in small coronary arteries of symptomatic patients; DISTINCT, BiodivYsio stent in controlled trial; EASI, European antiplatelet stent investigation; ISR, in-stent restenosis; PC, phosphorylcholine; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; SAT, subacute stent thrombosis; SiC, silicon carbide; SOPHOS, study of phosphorylcholine coating on stents; STRIDE, study of anti-restenosis with the BiodivYsio dexamethasone-eluting stent; TLR, target lesion revascularisation; TRUST, Tenax for the prevention of restenosis and acute thrombotic complications.
Two randomised, and a number of non-randomised, series show gold coatings to be associated with higher rates of restenosis.24 The issues surrounding gold coating may be more complex than immediately apparent as work in a pig model by Edelman suggests that the “finish” on the stent may be vital with the thermal processing following the gold coating negating the relative disadvantage with respect to ISR.36

Some preliminary experimental data exist suggesting titanium may be associated with reduced intimal growth, although this will need substantiating in clinical trials.19 Copper coatings have also been evaluated following either a galvanising or ion bombardment process. When compared to stainless steel they have been found to induce/increase both neointimal proliferation and stent thrombosis in animal models.18 19

**SURFACE TREATMENTS AND FINISHING**

As alluded to, when addressing “gold” stents, the issue regarding metallic coatings is complicated further by differences in the way coatings are applied or finished. When compared to ion bombardment, galvanised surfaces show cracking under scanning electron microscopes and are associated with more neointimal proliferation and experimental SAT.27 Small studies suggest that polishing can reduce clot and fibrinogen deposition and may affect neointimal hyperplasia.18

**CARBON COATING**

Carbon, as a coating, has theoretical appeal because it is thought to be inert.

Experimental data have confirmed that it may indeed reduce platelet activation (CD62p, CD63) and metal ion elution20 but has no impact on peripheral plasma markers of inflammation.20 Single layer “diamond like carbon coating” was found to reduce neointimal hyperplasia in a pig model whereas two layers were not beneficial.21

Non-randomised data from the ANTARES (aspirin alone antiplatelet regimen after intracoronary placement of the carbostent) registry 22 and a second Italian registry,23 using “Carbostents” (a turbostratic carbon film coated stent), found no stent thromboses in 222 patients. This included the 110 patients in the ANTARES registry who received stand alone aspirin in the absence of thienopyridines or glycoprotein IIb/IIIa inhibitors. There was a significant reduction in major adverse stents and discouraged the use of glycoprotein IIb/IIIa inhibitors. There was a significant reduction in major adverse

**PHOSPHORYLCHOLINE COATING**

Phosphorylcholine (PC) is a synthetic mimic of the outer wall of the red blood cell.30 In a variety of animal models PC has been shown to be biologically inert with no difference in neointimal thickness.31 32 The integrity of the coating has been confirmed following high pressure deployment and at 12 weeks post-implant.33 Experimentally, endothelialisation is similar in both PC coated and uncoated stents.34 35 36 Platelet and endothelial activation are reduced compared to bare metal stents in a small human study.37

In non-randomised clinical series the SAT rates have been consistently low (< 0.7%) and ISR rates in moderate sized cohorts including the SOPHOS (study of phosphorylcholine coating on stents)38 and DISTINCT (BiodivYsio stent in controlled trial) studies have been comparable to contemporary bare stents.

The results of studies such as the small vessel study, which had a 30 day major adverse cardiac event rate of 3.5% in vessel with an average diameter of 2.2 mm, may open additional clinical niches for PC coated stents.39

The clinical value of PC coating, however, lies not solely in its “stand alone” qualities but in its capacity to act as a delivery platform for biologically active entities.39 In a porcine model, animals receiving oestrogen eluting PC coated stents had reductions of neointimal area by 40% with normal endothelialisation documented.40 It has also been used as the delivery platform for dexamethasone elution in the STRIDE (study of anti-restenosis with the BiodivYsio dexamethasone-eluting stent) trial where the binary ISR rate was reduced but not eliminated (13.3%).

While one can debate the advantages of PC coating per se, as a delivery system, unlike some of its polymer counterparts, it is biologically inert and stable in the medium term.

**HEPARIN COATING**

Several antithrombogenic stent coatings41 44 have been investigated, with heparin being the most well known and extensively tested. Heparin has been studied while covalently bound to the stent, as a “passive” coating, and also as an eluted drug.

Heparin coated stents were associated with reduced platelet and endothelial activation when compared to bare metal controls by plasma S-plex-selectin and E-selectin assessment in small human study.38

White cell and platelet activation in vitro have been shown to be reduced when heparin coated stents are compared to gold.43 SiC,46 47 or bare metal stents. Prolongation of thrombosis time has also been shown.48 49

As with some non-randomised series evaluating heparin coated stents, the clinical incidence of SAT was low in BENESTENT II (randomised comparison of implantation of heparin coated stents with balloon angioplasty in selected patients with coronary artery disease) although there was no control bare stent group compared to the heparin coated Palmaz-Schatz group.50 Other randomised (COAST, heparin-coated stent placement for the treatment of stenoses in small coronary arteries of symptomatic patients51 and non-randomised comparisons to bare metal stents suggest similar SAT and ISR rates.52 53

Other stent coatings allowing manipulation of the surrounding micro-environment, such as nitric oxide donors, have shown variable results in animal models. While some authors have shown a reduction in thrombus adhesion44 and neointimal proliferation,54 others have found no difference to control animals.55 These treatments may be better considered
under the heading of drug elution and will not be discussed further.

CONCLUSION
The field of intracoronary stent coatings remains complex and applying generalised summaries is difficult. Some stent coatings may well reduce the risk of SAT and the best data for potential to deliver drugs or genetically active viruses. However, all delivery platforms are not created equal and the primary importance of stent coatings will be their coating that reduces the risk of stent thrombosis would be this specifically applies to PC and heparin coated stents. Coatings may well reduce the risk of SAT and the best data for coatings with uncoated steel stents in patients with coronary artery disease. Benestent study group. Circulation 2000;102:2478–83.

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