Coronary Arteries And Sirolimus-Eluting Stents - Applications, Benefits And Future Potential

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Percutaneous coronary intervention (PCI) is, for the responsible interventional cardiologist, not only an appealing method of coronary revascularisation but also a permanent challenge, as the technical progress must be balanced against the perceived and foreseeable risks to the patient. Stents were conceived to make balloon angioplasty safer and more effective. They controlled elastic recoil and negative remodelling, but also stimulated the cellular mechanisms yielding to in-stent restenosis. Restenosis after bare-metal stenting (BMS) is mostly due to neointimal proliferation. It was a pure mechanical solution to an important biological problem. The development of an antiproliferative drug-coated stent followed extensive research on the understanding of vascular biology, pharmacology and experimental and clinical research. Sirolimus (rapamycin) and paclitaxel target the cell cycle, inhibiting the effects of injury-mediated growth factors and cytokines that produce vascular smooth muscle proliferation and intimal hyperplasia.

The Cypher® stent utilises a non-erodable methacrylate co-polymer matrix for controlled endovascular delivery of the drug to the arterial tissue. Sirolimus is blended with the polymer and a thin coating is applied to the surface of the Bx Velocity™ Cordis stent. A second coat of drug-free polymers serves as a diffusion barrier. The quantity of sirolimus loaded onto each stent is approximately 140mg/cm^2, and the system provides controlled release of sirolimus over a period of four weeks.

The sirolimus-eluting stent (SES) was the first stent-based pharmacological therapy approved for the prevention of restenosis and the first to be approved by the European Community. It was introduced into clinical practice in 2002, bringing in the current drug-eluting stent (DES) era of interventional cardiology. Together with the paclitaxel-eluting stent (PES), approved later, they form the so-called first-generation DES. A pivotal randomised controlled trial (RCT) was the Randomized Study with the Sirolimus-coated Bx Velocity Balloon- Expandable Stent in the Treatment of Patients with *De Novo* Native Coronary Artery Lesions (RAVEL),[1] in which 238 patients were randomised to a single SES and a BMS. The result was an unexpected outcome of 0% restenosis in the SES group compared with 26% restenosis in the BMS group at six months. This was followed by the larger (1,058 patients) Sirolimus-eluting Stent in *De Novo* Native Coronary Lesions (SIRIUS) trial[2] in the US, and the E-SIRIUS[3] (n=352) in Europe and C-SIRIUS[4] (n=100) in Canada. The combined data from the last three studies (NEW-SIRIUS) reported a 5.1% in-lesion restenosis rate.

The true measure of the efficacy of DES, representing the best angiographic surrogate of neointimal proliferation with the unique ability to separate it from other procedural and intrinsic vessel variables, is in-stent late luminal loss (LL). It can reliably predict the restenosis propensity and the clinical consequence of target lesion revascularisation (TLR).[5] The SES has always showed the smallest in-stent LL compared with other DES.

The on-label indications for the Cypher SES were single *de novo* lesions in patients with stable coronary artery disease (CAD) in vessels with reference diameters between 2.5 and 3.5mm and in lesions ≤30mm. Stimulated by the remarkable results of the initial studies, cardiologists have progressively expanded the use of SES to almost all clinical situations and more complex lesions. The off-label use of DES is current clinical practice, and may account for as many as 75% of procedures.

An impressive number of publications have dealt with SES implantation in diabetic patients, patients with acute myocardial infarction (MI), very small vessels (<3.0mm), very long lesions (>30mm), multivessel disease, bifurcation lesions, unprotected left main disease, chronic total occlusions, saphenous vein grafts and BMS in-stent restenosis. Many of the data collected are derived from single or multicentre studies and from registries, but in some cases RCTs have been performed.

Data from these RCTs have confirmed the efficacy of SES versus BMS and PES in significantly reducing restenosis rates and the need for further reintervention (TLR). Three RCTs were in acute MI,[6–8] two in small vessels[9,10] (the Sirolimus-Eluting and an Uncoated Stent in the Prevention of Restenosis in Small Coronary Arteries [SES-SMART][9] trial also showed a decreased incidence of MI comparing SES with BMS, and in the Intracoronary Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries-III [ISAR-SMART III][10] SES was seen to be superior to PES), one in long lesions (Sirolimus-eluting Stent Versus Paclitaxel-eluting Stent for Patients with Long Coronary Artery Disease [Long-DES-I])[11] and in the first and only RCT in saphenous vein grafts (Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent [RRISC]).[12] Finally, a meta-analysis of four RCTs[13] (three with SES and one with PES) have confirmed the superiority of DES versus balloon angioplasty or vascular brachytherapy in 1,230 patients with BMS in-stent restenosis.

Despite the undisputable efficacy of SES based on the extensive clinical research performed, our concern lately has been focused on DES safety. The real possibility of late stent thrombosis has created the current period of reflection regarding indications, limitations and future developments. Safety data are currently derived from the initial RCTs that allowed the introduction of SES into clinical practice, as they offer the longest follow-up available. A recent pooled analysis[14] of the initial four RCTs (1,748 patients) with SES[1–4] with a follow-up at four years was reassuring in terms of safety for on-label indications. The survival rate at four years was 93.3% in the SES group and 94.6% in the BMS group (p=0.28), and there were no differences in the rates of myocardial infarction and stent thrombosis. The only significant survival difference was found in diabetic patients in favour of the BMS group (87.8 versus 95.6%; p=0.008), and this was due to an increase in both cardiovascular and non-cardiovascular deaths. Using the protocol definition of stent thrombosis, the rate of thrombosis was 1.2% with the SES versus 0.6% with BMS (p=0.20); using the Academic Research Consortium (ARC) definitions of 'definitive' or 'probable' stent thrombosis, the rate was 1.5% with SES versus 1.7% with BMS (p=0.70). The incidence of definite or probable events occurring one to four years after implantation was 0.9% in the SES group and 0.4% in the BMS group.[15]

An analysis of data on 4,958 patients enrolled in 14 RCTs comparing SES with BMS[16] (mean follow-up interval 12.1–58.9 months) showed that the risk of death (hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.80–1.30) or the combined risk of death and myocardial infarction (HR 0.97; 95% CI 0.81–1.16) was similar in patients receiving SES or BMS. A significant advantage of SES over BMS was found in the combined risk of death, myocardial infarction and reintervention (HR 0.43, 95% CI 0.34–0.54). Regarding safety, there was no significant difference in the overall risk of stent thrombosis with SES versus BMS (HR 1.09, 95% CI 0.64–1.86), but there was evidence of a slight increase in the risk of stent thrombosis associated with SES after the first year.

Further analysis[17,18] has confirmed that mortality is similar with SES, PES and BMS. SES has the lowest risk of MI in that there were no significant differences in the overall risk of definite stent thrombosis and that the risks of late stent thrombosis and MI probably increased with PES. Safety concerns are probably justified regarding the off-label use of DES. Data from the National Heart, Lung and Blood Institute (NHLBI) Dynamic Registry[19] in 6,551 patients using DES for off-label indications showed a decreased risk of death or myocardial infarction (7.5 versus 11.6% with BMS; p<0.001), and a lower rate of repeat revascularisation at one year (12.7 versus 17.5% with BMS; p<0.001).

These data are somewhat rewarding, but we should take into consideration the fact that late stent thrombosis is a real possibility, late follow-up data are not yet available and our current knowledge regarding the potential mechanisms for stent thrombosis is still limited. For clinical purposes common sense recommends maintenance of dual antiplatelet therapy for a more extensive period of time, even if it is recognised that some patients are resistant to one or both antiaggregant drugs. Consideration of the risks of stent thrombosis for some patient and lesion subsets is also recommended. This was actually the recommendation of the American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American Cancer Society/American Diabetes Association (AHA/ACC/SCAI/ACS/ADA) Science Advisory Committee.[20]

Bearing in mind the the issue of stent thrombosis with DES, we should consider the arteries into which stents are implanted and the many unknown factors related to placing an active DES into an artery, a combination that certainly interferes with the healing response. Technical problems at the time of stent implantation, such as stent malapposition and underexpansion, have been well demonstrated by intravascular ultrasound (IVUS), and could be a cause of late stent thrombosis. SES underexpansion can be observed in up to 67% of cases,[21] but late stent malapposition could not be related to stent thrombosis, death or MI after DES implantation.[22] Late incomplete stent apposition may lead to aneurysm formation.[23] A recent randomised study suggests that direct stenting is associated with reduced microvascular dysfunction induced by PCI rather than conventional pre-dilation stenting.[24] Will the long-term effect of stenting eliminate the possibility of positive remodelling if atherosclerosis progresses?

DES induces complex interactions between shear stress and inhibition of neointimal growth. The main components of a DES, the polymer and the drug, may be directly involved in the delayed healing, inflammation (patient-related factors such as genetic control of inflammatory responses or the individual response to sirolimus or paclitaxel), hypersensitivity (to the drug or the polymer) and aneurysm formation that follows its implantation. A serial quantitative IVUS study[25] over four years after implantation of an SES showed that between two and four years peri-stent tissue shrank, with a concomitant increase in echogenicity. This suggests that late chronic artery responses may evolve for up to four years.

The fact that the neointima does not significantly change between two and four years may suggest that the biological phenomenon of a delayed healing response has begun to subside. There is some evidence to suggest that a hypersensitivity reaction can lead to delayed endothelisation and destruction of the medial vessel wall, which may cause late acquired stent malapposition.[26]

An antiarteriogenic effect of DES negatively affecting collateral growth has also been described[27] on average six months after stent implantation, which, considering the protective nature of collateral vessels, could lead to more serious cardiac events in the presence of an abrupt coronary occlusion. In this context, the effect of sirolimus appears to be less pronounced than that of paclitaxel. A major concern is the effect of DES on incomplete endothelisation and endothelial dysfunction. However, there is only limited evidence to support the notion that uncovered stent struts as a consequence of delayed re-endothelialisation are implicated in the process of late stent thrombosis. Angioscopic studies have shown delayed neointimal stent coverage and slower thrombus disappearance in SES than in BMS.[28,29] A histological study of tissue obtained by atherectomy of in-stent restenosis cases from BMS and DES (10 SES and nine PES) showed that a persistent incomplete healing response, which occured as late as two years, was present only in DES. The amount of fibrinoid was greater in PES than in SES (17 versus 5%; p=0.026), and patients with PES in-stent restenosis presented clinically more with unstable angina.[30]

Although limited and short-term, studies of endothelial function after SES raise interesting questions about the future and deserve further investigation. SES has been associated with exercise-induced paradoxic vasoconstriction of the adjacent vessel segments, although vasodilatory response to nitroglycerin was maintained. This endothelial dysfunction was attributed to the antiproliferative drug diffusing from the stent to the peri-stent region.[31] Local endothelial-dependent vasoconstriction after acetylcholine infusion and nitrates after SES implantation have also been described, and are greater than with BMS and in control vessels, particularly arterial segments distal to stents.[32,33]

These are some of many unsolved issues still linked to the permanent implantation of SES and other DES into the coronary arteries. First-generation DES will have to be used as controls for newer stents in RCTs, but post-marketing surveillance of any new device is mandatory to monitor safety, particularly in Europe.

What we have learned with the SES is that it is very effective in reducing lesions, late LL and restenosis rates, and represents a breakthrough in interventional cardiology. In spite of also decreasing TLR in a great variety of clinical situations and in more complex lesions that overpass the on-label approved indications, it has not been shown to be a major contributor to patient survival. This is not unexpected, as stents were first aimed at controlling symptoms. First-generation DES may have revolutionised our perception of treating CAD. We are continuously learning and, so far, the benefits achieved through reduction in restenotic rates markedly outweigh any small risk of stent thrombosis. CAD is progressive and part of a more generalised atherosclerotic process and, above all, requires continued and well-established medical therapies such as statins, ACE inhibitors, antiplatelet drugs and control of risk factors.

There will be continued efforts to overcome current DES failures and the limitations of new technologies, stents, drugs and coatings. It seems clear that abolishing neointimal hyperplasia is no longer the ultimate goal. The perfect carrier for biocompatible absorbable coatings, new drugs targeting thrombotic and inflammatory mechanisms, multilayered polymers for multiple-drug release and antigen–antibody coatings to capture endothelial cells are being searched for. Hopefully, the future control of complex biological mechanisms leading to atherosclerosis will eliminate the need for PCI. For the time being, interventional cardiology is here to stay and current research will make it even safer for the patient.

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