REVIEW

Drug-eluting stents: new era and new concerns

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At present there is much excitement about drug-eluting stents, which hold promise for the treatment of coronary artery disease. This ingenious therapy involves coating the outside of a standard coronary stent with a thin polymer containing medication that can prevent scarring at the site of coronary intervention. Early trials with sirolimus coated stents showed that they might prevent coronary artery restenosis, but later studies, involving more complex coronary lesions, did not show a complete absence of restenosis. Recent studies have demonstrated the long term cost effectiveness of drug-eluting stents as they have reduced the need for revascularisation procedures. At present there are few data on the safety and effectiveness of stents over follow up periods exceeding two years, and data obtained from animal models of stenting might not be completely applicable to humans. There are concerns that drug-eluting stents might delay, rather than inhibit, restenosis. Also there is concern regarding the inflammation caused by the polymer substrate. This article reviews the present data on drug-eluting stents and their benefits, shortcomings, and concerns.

GP Ib (alpha) and through cross linking with fibrinogen to the GP IIb/IIIa receptor. The migration of leucocytes across the platelet-fibrin layer and into the tissue is driven by chemical gradients of cytokines released from smooth muscle cells (SMCs) and resident leucocytes. Growth factors are released from platelets, leucocytes and SMCs, which influence the proliferation and migration of SMCs from the media into the neointima.

The resultant neointima consists of SMCs, extracellular matrix, and macrophages recruited over several weeks. Over even longer periods of time, there is a shift to fewer cellular elements with, and greater production of, extracellular matrix. In addition, there is eventual re-endothelialisation of at least part of the injured vessel surface.

PREVENTING RESTENOSIS

Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium channel blockers, angiotensin converting enzyme inhibitors, cholesterol lowering agents and antioxidants, has been almost universally negative.

These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to an insufficient concentration of the drug at the injury site or to a lack of chronic dosing. In general, although animal models provide new insights into the mechanism of restenosis, biological and mechanical differences between animal models and humans mean that antirestenotic therapies may not be successful in humans. Intracoronary radiation has recently emerged as a promising modality to attenuate the intimal hyperplastic reaction.^{16–18} Despite its failure to prevent restenosis in de novo lesions, brachytherapy was effective in reducing recurrent restenosis. However, larger studies and long term follow up showed alarming long term sequelae, such as edge restenosis and late thrombosis, providing some concerns about the potential lifelong effects of such a cytotoxic approach.^{16–19–21} Similarly the results of oral administration of the antiproliferative agent sirolimus have failed to show any benefit, and, in fact, there was a higher incidence of adverse side effects in the recipients of such therapy.²²

A lot of research has been done on mechanical devices and drugs to prevent restenosis after coronary angioplasty, providing the rationale for an enormous number of clinical trials, but none have been proven to be effective.^{1–4} Despite the use of multiple percutaneous revascularisation techniques, including balloon angioplasty, repeated stenting, laser therapy, platelet inhibitors, heparin coated stents and atheroablation, approximately half of the 30% of patients in whom restenosis (defined as a more than 50% diameter stenosis) occurs after coronary stenting have recurrent restenosis.^{5–15}

PATHOLOGY OF STENT RESTENOSIS

The initial events immediately after stent placement result in de-endothelialisation and deposition of a layer of platelets and fibrin at the injured site in the coronary artery (see fig 1).

Activated platelets express adhesion molecules such as P-selectin and glycoprotein (GP) Ib (alpha), which attach to circulating leucocytes via platelet receptors such as P-selectin glycoprotein ligand and begin a process of migration along the injured surface. Under the influence of cytokines, leucocytes bind tightly to the leucocyte integrin (Mac-1) class of adhesion molecules via direct attachment to platelet receptors such as

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Abbreviations: GP, glycoprotein; IVUS, intravessel ultrasound; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; QCA, quantitative coronary angiogram; QP2, 7-hexanoyltaxol; SES, sirolimus-eluting stents; SMC, smooth muscle cell

Figure 1 (A) Mature atherosclerotic plaque before intervention. (B) Immediate result of stent placement with endothelial denudation and platelet and fibrinogen deposition. (C and D) Leucocyte recruitment, infiltration, and SMC proliferation and migration in the days after injury. (E) Neointimal thickening in the weeks after injury, with continued SMC proliferation and monocyte recruitment. (F) Long term (weeks to months) change from a predominantly cellular to a less cellular and more extracellular matrix rich plaque.

Drug-eluting stents

The potential usefulness of immunosuppressive agents in the treatment of restenosis arises from similarities between tumour cell growth and the benign tissue proliferation that characterises intimal hyperplasia. Avoiding systemic toxicity, stent based local drug release at the site of vascular injury via a polymer coated stent is an attractive therapeutic method to achieve an effective local concentration of the drug for a designed period. The safety and efficacy of such an approach critically depends on the delicate combination of drug, polymer, and kinetics of release.²³ A drug-eluting stent is a device that releases into the bloodstream single or multiple bioactive agents that can deposit in or affect tissues adjacent to the stent. The drug can be simply linked to the stent surface, embedded and released from within polymer materials, or surrounded by and released through a carrier. The carrier can coat (strut adherent) or span (strut spanning) the stent struts. Sirolimus is a natural macrocyclic lactone with potent immunosuppressive and antimitotic action, which was approved in 1999 as an antirejection drug in renal transplant recipients. The cellular action of sirolimus (rapamycin), a natural fermentation product produced by *Streptomyces hygroscopicus*, is mediated by binding to the FK506 binding protein. By inhibiting a kinase known as the target of rapamycin, it restricts the proliferation of SMCs by blocking the progression of the cell cycle at the G1-S transition. The finding that rapamycin possesses both antiproliferative and antimigratory activity suggests that it could contribute to the control of arterial renarrowing after percutaneous intervention. Marie Claude Morice and colleagues reported the first randomised double blind trial (RAVEL study) comparing a coronary stent coated with sirolimus with a standard

uncoated stent.²⁴ The trial included 238 patients with single coronary lesions who were treated at 19 different medical centres. Patients with complex coronary lesions were excluded. Sirolimus-eluting stents (SES) were prepared by coating the stent with a mixture of synthetic polymers blended with sirolimus and a second coat of drug free polymers, which served as a diffusion barrier. The polymers act as a drug reservoir and permit the gradual elution of sirolimus. The stent was designed to release 80% of the drug within 30 days of implantation. The angiographic rate of restenosis at six months was 26.6% in the control group and 0% in the SES group. There were no reported cases of subacute thrombosis. The mean late luminal loss was zero in the SES group and 0.80 mm in the control group. During a follow up period of up to one year, the overall rate of major cardiac events was 5.8% in the SES group and 28.8% in the control group. The results of this trial created a lot of enthusiasm and many surgeons started to believe that it heralded the end of restenosis after percutaneous coronary interventions (PCIs). At two years' follow up in a subgroup of patients the beneficial impact of inhibiting neointimal growth persisted.²⁵ These results have been further tested in a large US multicentre randomised trial, called SIRIUS, in which 1101 patients with de novo coronary lesions, 2.5–3.5 mm in diameter and 15–30 mm in length, were randomised to receive either the SES (n = 545) or the bare stent (n = 556) (see summaries of all the trials in fig 2 and table 1).²⁶ Patients were assessed at nine months for target vessel failure, a primary composite endpoint of cardiac death, myocardial infarction, and target vessel revascularisation. In-stent restenosis was defined as more than 50% diameter stenosis as determined by a quantitative coronary angiogram (QCA).

Figure 2 Comparison of restenosis rates in major trials with drug-eluting stents.

The preliminary analysis of 700 patients showed that, compared with the control group, patients treated with SES had significantly lower rates of in-stent (3.2% v 35.4%, $p<0.001$) and in-segment (8.9% v 36.3%, $p<0.001$) restenosis, as measured by a QCA at eight months, equivalent to dramatic reductions of 91% and 75%, respectively. In the persistent segment analyses, restenosis was noted to be significantly reduced in the distal margin of the stent (2.0% v 7.2%, $p<0.002$); however, there was no significant difference between the SES and control groups in the rate of restenosis in the proximal margin, suggesting, perhaps, that uneven drug distribution and/or balloon injury outside the treated segment may be problematic. At nine months' follow up, the composite end point of target vessel failure was significantly reduced, by 59%, in patients treated with the SES (8.5% v 21.0%, $p<0.001$). Thus a 0% restenosis rate with SES as seen in the RAVEL trial is unlikely when these devices are used in more complex and challenging coronary lesions. Sousa *et al* recently conducted a trial using slow release and fast release SES in 30 patients, who were followed up clinically, angiographically, and using intravessel ultrasound (IVUS) for two years.²⁷ In all, 28 patients underwent two year angiographic and IVUS follow up. No patient had in-stent

restenosis. At two years' follow up, only one patient had a 52% diameter stenosis within the lesion segment, which required repeat revascularisation. The rate of target vessel revascularisation for the entire cohort was 10% (3/30) at two years. All other patients had a 35% diameter stenosis or less. This study demonstrates, for the first time, the safety and efficacy of SES two years after implantation in humans. The same group of investigators demonstrated the safety and the potential utility of SES for the treatment of in-stent restenosis.²⁸ Guagliumi *et al* described the pathological findings at autopsy in a SES recipient in the RAVEL trial who died after 16 months.²⁹ This stent was widely patent at 16 months with more than 80% endothelial coverage. Neointimal healing was nearly complete, with only rare fibrin deposits. The results of the C-SIRIUS trial were declared recently; this was a Canadian multicentre randomised double blind trial enrolling 100 patients.³⁰ It showed the safety and effectiveness of SES in patients with long lesions in small vessels (lesion length of 15–32 mm and vessel diameter of 2.5–3.0 mm) by measuring the in-stent minimal lumen diameter at eight months angiographically. The results of this trial showed that the minimal lumen diameter at eight months was 64% greater in the SES group than in the control group (2.46 mm v 1.50 mm) and in-stent late loss was 91% less in the SES group (0.09 mm v 1.01 mm) compared with the controls. There was no in-stent stenosis in the SES group. Hence the positive results of the RAVEL and SIRIUS trials can possibly be extended to patients with long lesions in smaller vessels.³⁰ All the major trials of SES showed benefit in diabetic patients also. The total lack of restenosis in the RAVEL trials in diabetic patients is striking. Data from SIRIUS show 83% reduction in in-stent restenosis and a 65% reduction in in-segment restenosis in diabetic patients, and bypass surgery is often performed in this group in preference to primary angioplasty or stenting. Diabetes is a formidable limitation to the success of conventional PCI. If the data from the RAVEL study are borne out, it will have a great impact on how patients with diabetes are managed with coronary revascularisation.

Cost effectiveness of the SIRIUS trial

In a preliminary early cost effectiveness substudy of the SIRIUS trial, use of a drug-eluting stent, compared with a standard bare metal stent, added more than \$2500 (£1470) to the procedure's initial cost. The drug-eluting stent reduced

Table 1 A summary of major clinical trials investigating drug-eluting stents										
Study	Coating	No of patients	Restenosis risk	Follow up (months)	Major cardiac events (%)			Binary restenosis (%)		
					Coated	Uncoated	p Value	Coated	Uncoated	p Value
Morice <i>et al</i> ²⁴	Sirolimus	238	Low	12*	5.8	28.8	0.001	0.0	26.6	0.001
RAVEL trial										
Moses <i>et al</i> ²⁶	Sirolimus	700†	Low	9	8.5	21.0	<0.001	3.2	35.4	<0.001
SIRIUS trial										
Schampaert <i>et al</i> ³⁰	Sirolimus	100	Low	8	18‡	4‡	0.05	0.0	41.9	<0.001
C-SIRIUS										
Park <i>et al</i> ²⁴	Paclitaxel (high dose)	177	Low	6	NA	NA	NA	4	27	<0.001
	Paclitaxel (low dose)	177	Low	6	NA	NA	NA	12	27	NA
Gershlick <i>et al</i> ^{23§}	Paclitaxel	192	Low	6	11	11	NS	0	21	0.055
Grube <i>et al</i> ²²	Paclitaxel	61	Low	6	NA	NA	NA	3	11	0.106
Grube <i>et al</i> ²⁸	QP-2	266	Low	6	NA	NA	NA	10.1¶	36.9	<0.001

NS, not significant; NA, data not available.
*Angiographic follow up at six months.
†Total n = 1101; this was the preliminary data presented.
‡Major cardiac events at nine months.
§The values given here are for the highest dose paclitaxel group (2.7 µg/mm).
¶9.4% due to subacute and delayed stent thrombosis.

the need for later medical care, but the resulting cost savings only partly erased its extra initial cost. The final results of the cost effectiveness study of these stents in the SIRIUS trial showed that, during initial hospitalisation, costs were higher in the group treated with drug-eluting stents, which was caused by the cost of the device itself.³¹ During the 12 month follow up period, there were substantial reductions in the need for repeat revascularisation. Despite higher in-hospital costs, the group receiving the SES showed cost savings of about \$2800 (£1640) at 12 months' follow up. Given the initial cost differential of about \$2500 (£1470) associated with the drug-eluting stent, the difference at one year was only about \$300 (£170) per patient.

Paclitaxel-eluting stents

The taxanes (for example, paclitaxel) are potent antiproliferative agents used in cancer.

Paclitaxel promotes polymerisation of the α and β subunits of tubulin by reversibly and specifically binding the β subunit of tubulin, thus stabilising microtubules. A stent coated with paclitaxel is also safe and effective for decreasing neointimal proliferation within the stented segment and reduces the incidence of clinically significant in-stent or edge restenosis. Three randomised trials (TAXUS I, ELUTES, and ASPECT) found that the paclitaxel-eluting stent (PES) significantly reduced late lumen loss, neointimal volume index, and angiographic restenosis at six months (0%–4% v 10%–27% for a bare stent).^{32–34} PES dramatically inhibited neointimal hyperplasia, as evidenced by angiography and IVUS evaluations at six months, according to the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT) results.³⁴ The binary restenosis rate was reduced significantly from 27% in patients receiving control bare metal stents to 12% in those receiving low dose PES and to just 4% in patients receiving higher dose PES, demonstrating an important dose dependent relationship. Mean diameter stenosis was reduced from 38% in the control group to 24% in the low dose group and to only 12% in patients treated with higher dose PES. IVUS analysis also demonstrated a dose dependent reduction in the volume of intimal hyperplasia (31, 18, and 13 mm³, in the high dose, low dose, and control groups, respectively). Favourable preliminary results have also been reported in the TAXUS II,³⁵ TAXUS III, and the pivotal randomised TAXUS IV trials, which are due to be presented shortly. A prospective randomised single blind multicentre trial called Deliver-1 showed no significant effect of paclitaxel coated versus metallic stents for the treatment of coronary lesions at nine months. The Deliver trial used the ACHIEVE stent, which does not employ a polymer coating to elute paclitaxel, leading many to speculate that it was the lack of polymer in Deliver that foiled the trial. Others feel that paclitaxel is very fat soluble and can be retained in the tissue, especially in atherosclerotic plaque, for a long time after it is delivered. There may have been early loss during insertion, or there may have been variability from stent to stent, and that could have caused the failure of the Deliver trial. The outcomes have also not been so good with a paclitaxel derivative (7-hexanoyltaxol, QP2)-eluting stent, in which late lumen loss has been described.^{36–38} The study to compare restenosis rates in *Quest* (stent without sleeves or any approved bare metal stent) and *QuaDDS-QP2* (drug-eluting stent with five polymer sleeves that contain 4000 mg of QP2) (SCORE) was a randomised multicentre trial that was terminated prematurely after interim analysis showed a dramatically increased predisposition for subacute and delayed stent thrombosis (9.4%) in the QP2 stent group compared with the uncoated stent group (0%).

Drug-eluting stents, edge stenosis, and restenosis pattern

The RAVEL trial included only lesions covered by an 18 mm long stent (mean lesion length of 9.56 ± 3.33 mm), and no patient had restenosis. The SIRIUS trial, dealing with longer lesions (mean lesion length of 14.4 ± 5.7 mm), had 9.2% stent restenosis. The restenosis segment occurred at the stent margin or at the site of a gap in 64.5% of the cases, and 87% of the restenosis was focal. The TAXUS II trial dealing with PES also reported 83.3% of restenotic lesions to be located near the stent margin or at the site of a gap between two stents. This "edge stenosis" was originally described in radioactive stents. In the trials with drug-eluting stents, edge stenosis can possibly be explained by stenosis at a site that is injured during angioplasty (either at the stent margin or at the site of a gap between two stents) but is not covered by the drug-eluting stent. A recent study of patterns of in-stent restenosis in 368 patients with 735 lesions treated with 841 rapamycin-eluting stents showed a predominantly focal pattern of stent restenosis.³⁹ In contrast to the SIRIUS and TAXUS II trials, none of the patients had persistent restenosis. Mean baseline lesion length was 17.48 ± 12.19 mm, and mean stent length was 27.59 ± 14.02 mm; SES were used with the objective of fully covering the baseline lesions. This approach contributed to lower persistent restenosis with the occurrence of only one pattern of restenosis: in-stent. Whether this approach of fully covering the lesion with wide stent margins was the cause of the lower incidence of persistent restenosis is unclear but it is certainly possible. Subsequent studies will be required to confirm the validity of this technique.

Adverse effects seen in trials

There have been few adverse effects associated with trials of drug-eluting stents. In the RAVEL trial, out of 238 patients, three in each group had an myocardial infarction at the time of stenting.²⁴ During a follow up period of up to one year, two patients in the control group (1.7%) died: one had a myocardial infarction and died suddenly several weeks later, and the other had a gastric haemorrhage. Two patients in the SES group (1.7%) also died: one had a subarachnoid haemorrhage, and the other had gastrointestinal cancer. In the 138 patients receiving ticlopidine or clopidogrel in the ASPECT trial investigating PES, the only event reported at one month was a non-Q-wave myocardial infarction due to closure of a side branch evident during stent placement, which was dilated.³⁴

CONCERNS AND CONTROVERSIES

It is still premature to comment on the safety profile of stents coated with potent antimitotic agents such as sirolimus and paclitaxel. These agents inhibit SMC proliferation and therefore have a mechanism of action similar to that of radioactive stents. Synthetic polymers are often used as carriers for these agents, and polymer biocompatibility remains a concern, as polymers often induce an exaggerated inflammatory reaction. Chronic low grade inflammation, poor wound healing responses with incomplete endothelialisation, and in-traitmental haemorrhage have been noted in porcine coronary arteries treated with paclitaxel coated stents.⁴⁰ Accelerated atherosclerosis immediately proximal and distal to QP2 coated stents has also been reported in humans, although preliminary trial data suggest that this may not be a major issue.^{41–42} Delayed stent thrombosis has also been described with QP2 coated stents.⁴³ Concern regarding this phenomenon has prompted many clinical trials investigating stents that elute antimitotic agents to treat enrolled patients with oral antiplatelet agents on a long term basis. The CREDO trial demonstrated that, following a PCI procedure, maintaining

dual antiplatelet therapy with aspirin and clopidogrel for up to one year significantly reduces the risk of adverse thrombotic events by 26.9%.⁴⁴ However, patients randomised to clopidogrel had a significant increase in the number of major bleeding complications. The time at which treatment is administered can also affect outcome, as a loading dose of at least 300 mg clopidogrel is likely to be beneficial only if started more than six hours before a planned PCI procedure.

Lack of a long term effect on restenosis, as described with radioactive stents, may also become apparent in the future.⁴⁵ It has been postulated that the prevention of restenosis in recent clinical trials of drug-eluting stents reflects a near absent or incomplete phase of intimal healing.⁴⁶ To this point, the negative findings of 90 day and 180 day animal studies of drug-eluting stents, at a time when healing is complete, may correspond to a reasonable approximation of 2–3 years in humans. However, there is still a paucity of long term trial data (covering more than two years). Continued long term follow up of patients with drug-eluting stents for major cardiac events and angiographic restenosis is therefore imperative. At best, drug-eluting stents may have solved the in-stent restenosis problems; at worst, they may lead to adverse long term late thrombosis and restenosis. The added cost of these stents may, at least initially, limit their use to patients at high risk of in-stent stenosis. Another issue that may lead to different outcomes is operator experience, and this needs to be addressed. Although many other potential problems with these stents may be foreseen, the small numbers of patients enrolled and the short follow up periods of the clinical trials evaluating drug-eluting stents remain the most important limitations.

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IMAGES IN MEDICINE.....

Suture granuloma

Figure 1 Histology showing evidence of suture granuloma.

Figure 2 Polarised microscopy showing the suture material.

A 68 year old woman presented with haemoptysis and left upper lobe shadow in 2002. Computed tomography of the thorax revealed a 2 cm soft tissue mass. Bronchoscopy was normal. She had a quadruple coronary artery bypass in 1999. She underwent a thorcotomy and the abnormal area in left upper lobe was removed. Histology showed evidence of suture granuloma but no evidence of malignancy (fig 1). Under polarised microscopy you can see the suture material very clearly (fig 2).

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