Prevention of in-stent stenosis: Drug-eluting stents create new hope in the PCI
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Abstract
The long term outcome of stent implantation is affected by a process called in-stent stenosis. Smooth muscle cell migration and proliferation in the intima produce neointimal hyperplasia, which is pathognomic of in-stent stenosis. Increased extracellular matrix form the bulk of the neointimal hyperplasia tissue. Emerging evidence of the role of inflammatory cytokines and suppressors of cytokine signalling make this an exciting and novel field of antirestenosis research. Several drugs have been used systemically and locally (Drug-eluting stents), to prevent proliferation and migration of smooth muscle cells. Drug-eluting stents have now become the medium for local drug delivery to the site of the lesion. Stents coated with any of several pharmacotherapeutic agents such as sirolimus and paclitaxel can be used. Initial result with Drug-eluting stent was promising.

Keywords
Drug-eluting stent, in-stent stenosis, percutaneous coronary intervention (PCI).

Introduction
Over 1.5 million percutaneous coronary revascularisation procedures are performed annually world wide, most being intracoronary stenting. Despite enormous advances in devices, the major limitation of PCI is in-stent stenosis. Although in-stent stenosis rates are 10-20% in selected patients, but rates are much higher, up to 59% in some high risk lesions. On average, stents appear to have a 10% lower rate of restenosis compared with angioplasty and the favourable results due to stent usage have been reported in several studies. The risk factors of restenosis include the method (stented or not), lesion location (the left anterior descending artery is found to be less susceptible to restenosis), diabetes, residual stenosis, number of stents, the stent length, total occlusion and late total occlusion, and bifurcating or ostial lesions. Experimental studies suggest that the process of cellular proliferation starts between the first few days and up to 2-3 weeks after stent implantation. In an attempt to further reduce the degree of restenosis, numerous adjunctive strategies, such as use of high pressure stent, use of specific materials and designs, prior debunking and no pre-dilatation have been tried.

Brachytherapy represents a potentially powerful way to prevent restenosis. The delivery of local radiation to the target site after angioplasty has now been shown to help reduce restenosis. Brachytherapy is not universally accepted, due predominantly to late thrombosis and the logistics of administering radioactivity.

Several drugs have been used systemically and locally (Drug-eluting stents), to prevent proliferation and migration of smooth muscle cells. Drug-eluting stents have now become the medium for local drug delivery to the site of the lesion. Drug-eluting stents containing the immunosuppressive agent rapamycin and...
the antimitotic agent paclitaxel have shown encouraging reductions in in-stent stenosis.\textsuperscript{20,21}

Definition and classification of in-stent restenosis
In-stent stenosis can be defined clinically or angiographically. Clinically it is defined as the presentation of recurrent angina or objective evidence of myocardial ischaemia, whereas angiographic in-stent stenosis is the presence of >50% diameter stenosis in the stented segment.\textsuperscript{22} Traditionally, in-stent stenosis has been classified based on the length of the lesion, as focal (<10 mm) or diffuse (>10 mm).

In-stent stenosis: an epidemic
Currently, over 1.5 million percutaneous coronary intervention procedures are performed each year worldwide, and the rate doubles every 5 to 8 years.\textsuperscript{23} Despite the steady and continuous advancement in the field of interventional cardiology, restenosis remains an important limitation of percutaneous coronary revascularization.\textsuperscript{24} In the United States, about one quarter of the procedures are performed in lesions that were previously treated with PCI. Considering that more than 700,000 cases are performed in the United States annually, this translates to a cost of $3.5 billion/year for the treatment of restenosis. Because the number of procedures performed is increasing each year, the absolute number of patients affected by restenosis may continue to rise until definitive measures for the prevention and treatment of restenosis are discovered and implemented.

Mechanisms of restenosis
Following angioplasty there is dissection of both the intima of the plaque and the vessel media, associated with an enlargement of the treated segment. Restenotic lesions develop over weeks to months. The vessel's response to coronary intervention is a complex process. Luminal narrowing can be considered as an expected but excessive healing response. In brief, restenosis following vascular injury is due to three interrelated processes, early elastic recoil and late remodeling, activation of hemocoagulative pathway and thrombus formation, and neointimal growth. The vessel may also remodel chronically in response to the mechanical arterial wall injury, resulting in an increase (positive remodeling) or decrease (negative remodeling) of the overall cross-sectional area, the so-called Glagov phenomenon.

Reorganisation of thrombus
Fibrin and platelets are deposited on stent struts early after implantation. The association of fibrin and platelets with neointimal accumulation and extensive neovascularisation at in-stent stenosis sites suggests that organisation of mural thrombus promotes in-stent stenosis.

Neointimal formation
Arterial injury induces vascular smooth muscle cell undergo either cell proliferation, migration or both, with subsequent synthesis of extracellular matrix and collagen, resulting in neointima formation. Neointimal formation is the major cause of in-stent stenosis. Neointima increases up to three months after the procedure, with little change to six months, and a gradual reduction between six months and three years.

Cellular and molecular pathophysiology of restenosis
The complex mechanisms leading to in-stent stenosis can be divided into an "early" (days to weeks) and a "late" (weeks to months) phase. Endothelial injury produces some element of thrombus formation,\textsuperscript{25} and fibrin and platelet deposition at the site of injury provides the foundation for the inflammatory aggregate. There is increased leukocyte trafficking to the stent site and subsequent migration into the vessel wall,\textsuperscript{26} the predominant cells being monocyte derived.
macrophages. Sustained production of adhesion molecules, cytokines, chemoattractants and growth factors lead to further leukocyte recruitment and infiltration. The weeks following injury lead into the late phase. The main event of the late phase is the phenotypic modification of medial smooth muscle cells followed by their migration and subsequent proliferation in the intima. Coordinated extracellular matrix synthesis by these smooth muscle cells is responsible for the increasing volume of intimal tissue, and the bulk of the new intimal hyperplasia is composed of extracellular matrix proteoglycans and collagens, with cellular elements making up only about 11%. Thus, over the months subsequent to stent implantation, there is a shift towards greater extracellular matrix synthesis rather than smooth muscle cell proliferative activity.

Treatement and prevention of in-stent stenosis

Brachytherapy and Drug-eluting stents are the modality of treatment for prevention of restenosis.

Drug-eluting stents: Drug-eluting stent has been developing to minimize in-stent restenosis.

Rapamycin: Rapamycin (sirolimus) possesses weak antibiotic activity, but is a potent modulator of immune function. Sirolimus is a natural macrocyclic lactone produced by Streptomyces hygroscopicus with potent antiproliferative, anti-inflammatory, and immunosuppressive effects. The mammalian target of rapamycin (mTOR) is the phosphatidylinositol kinase (PIK) related kinase family that regulates protein translation, cell cycle progression, and cell proliferation. Rapamycin enters cells easily where it is bound to a specific intracellular receptor FKBP12-the rapamycin/FKBP12 complex is a highly specific inhibitor of mTOR.

Firstly, sirolimus is a potent inhibitor of vascular smooth muscle cells migration. Secondly, rapamycin reduces vascular smooth muscle cells migration. Thirdly, rapamycin is a potent inhibitor of cell size. Fourthly, rapamycin may have significant effects on cell matrix synthesis. Finally, rapamycin is an inhibitor of inflammation in vessels after injury. Both sirolimus (rapamycin) and tacrolimus inhibit T lymphocyte proliferation and activation, acting as both anti-inflammatory and immunosuppressant agents.

These biological properties mean that rapamycin eluting stents are potent inhibitors of in-stent stenosis and low levels of restenosis are seen in upto 2-3 years. The result of 15 slow-release rapamycin-coated Bx VELOCITY stents has been reported by Reusing and colleagues. At 6-month follow-up; no adverse cardiac events were reported, and no patients had angiographic restenosis. No in-stent or edge restenosis was observed. Randomized Study with the Sirolimus-Eluting VELOCITY Balloon Expandable Stent (RAVEL) trial showed restenosis rates (>50% diameter stenosis) among who received the drug-eluting device was reported as 0% compared with 26.2% in the group that received the uncoated stent. The Sirolimus-Coated Bx VELOCITY Balloon Expandable Stent (SIRIUS) trial with 1101 subjects with single de novo coronary artery lesions, showed the safety and efficacy of sirolimus-coated devices.

Paclitaxel: Another agent considered for local delivery for the prevention of restenosis is paclitaxel. Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules. The stabilized microtubules are dysfunctional, and inhibits cell replication. Micro-tubular stabilization also affects cell motility, shape and intracellular transport. Paclitaxel is highly lipophilic, which enables it to easily pass through cell membranes, resulting in a longlasting antiproliferative action. The European Evaluation of Paclitaxel Eluting Stent (ELUTES) trial examined the safety, efficacy and dosing of a paclitaxel-coated...
stent in patients implanted with paclitaxel coated V Flex Plus stents. Paclitaxel-eluting V Flex Plus stents have also been shown to be effective for the prevention of recurrent in-stent restenosis. Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) shows at 6-month follow-up, a significant, dose-dependent reduction in binary restenosis rates. The TAXUS I study showed the feasibility and safety of low-dose paclitaxel-eluting stents (NIRx) used for the treatment of de novo and restenotic lesions. TAXUS IV study represents the safety and efficacy of a moderate-release paclitaxel formulation, using an Express stent platform, on both de novo lesions and in-stent restenosis.

7-hexanoyltaxol (QP2): A more hydrophobic derivative of paclitaxel, 7-hexanoyltaxol (QP2), a taxane, has been tested on a unique stent delivery platform for the prevention of restenosis. The mechanism of activity is similar to that of paclitaxel, in that it inhibits microtubule formation by inhibiting microtubule depolymerization, thus interfering with the cell cycle. Study to compare restenosis rate between QueST and QuaDDS-QP2 (SCORE) shows unfavorable result.

Actinomycin D: Guidant has developed an actinomycin D-eluting stent, the MULTI-LINK TETRA D stent, for the prevention of restenosis. Actinomycin D is an antibiotic that has been approved as an anticancer chemotherapeutic agent. It binds DNA, preventing cell division and protein production. Actinomycin D affected cells in all phases of the proliferation cycle. The Actinomycin Eluting Stent Improves outcomes by reducing neointimal hyperplasia (ACTION) trial shows actinomycin Drug-eluting stents were not effective in preventing restenosis.

Dexamethasone: The Study of Anti-restenosis with BiodivYsio Matrix LO Dexamethasone Eluting Stent (STRIDE), objectives were to evaluate the safety and efficacy of the MATRIX LO stent with dexamethasone. Dexamethasone is a steroid (corticosteroid) anti-inflammatory drug that is used to inhibit the inflammatory response and reduce tissue injury resulting from trauma. Dexamethasone’s mode of action targets many of the inflammation processes, including (1) the inhibition of cyclo-oxygenase-2, which reduces prostaglandin synthesis (2) the inhibition of the transcription gene for phospholipase A2, which gives rise to the prostanoids, platelet-activating factor, and leukotrienes; and (3) the induction of the anti-inflammatory protein mediator lipocortin-1. It is thought that the delivery of dexamethasone to the site of injury from a stent could prove beneficial in the inhibition of cytokines, leading to a reduction in the proliferation of inflammatory cells around the stent struts, with a resultant reduction in restenosis.

Batimastat: Batimastat, a broad-spectrum MMPI developed by British Biotech (Oxford, UK), is a low-molecular-weight peptide mimic containing a hydroxamate group that chelates the zinc atom in the active site of the matrix metalloproteinase (MMP) and thereby inhibits the enzyme. Batimastat is a potent, but reversible, inhibitor of MMPs: collagenases, stromelysins, and gelatinases. Collectively, these enzymes can degrade all of the components of the extracellular matrix and induce cell migration and proliferation. The injury caused by the stent to the vessel wall and the resulting smooth muscle cell proliferation causes expression of several members of the MMP family, and batimastat can inhibit the cell migration and proliferation process. The BiodivYsio Batimastat SV Stent versus Balloon Angioplasty for the Reduction of Restenosis in Small Coronary Arteries (BATMAN) (Americas) and Batimastat (BB-94) Antirestenosis Trial Utilizing the BiodivYsio Local Drug Therapy PC Stent (BRILLIANT) (European Union) programs were a series of clinical studies designed to evaluate the safety and efficacy of the batimastat-eluting BiodivYsio MATRIX stent. BATMAN I was a pilot safety trial recently completed in Latin America. BRILLIANT I
show the batimastat BiodivYsio stent had no extra benefit. These results led to the suspension of recruitment into the 400-patient BRILLIANT II randomized trial.

**Biodegradable stent with pharmacologically active agents:** The development of a suitable biodegradable stent with pharmacologically active agents incorporated into the polymeric matrix has waned considerably in interest. To be effective, a drug-releasing biodegradable stent must be bio-compatible and not cause an inflammatory reaction, and the breakdown products must be nontoxic. Stent delivery must be reliable, the devices must have high radial strength, and stent degradation should occur in a reasonable time period (12 to 24 months). The ideal stent would deliver drugs locally that inhibit restenosis, in concentrations that are effective without inducing tissue injury. The Duke Biodegradable Stent and the Igaki-Tamai bio-degradable stent are capable of incorporating pharmacologically active agents.

**Sirolimus versus paclitaxel:** In the Kastrati et al meta-analysis, all six trials were pooled to describe angiographic and clinical outcome for 3669 patients. At follow up there was no difference in mortality, death or MI and stent thrombosis in the sirolimus or paclitaxel treated patients. Although major safety measures were similar, angiographic results favoured sirolimus including target lesion revascularization and angiographic restenosis were less.

**Des versus brachytherapy:** The Sirolimus-Eluting Stent Versus Brachytherapy in Patients with Bare Metal In-Stent Restenosis (SISR) trial shows overall results indicate that use of SES is superior to brachytherapy for prevention of recurrent in stent restenosis.

**New non drug coated stents for restenosis:** Titanium nitride oxide stent coating has a superior biocompatibility to stainless steel, has been shown to reduce vascular inflammation and neointimal hyperplasia. Windecker et al found this stent had a significantly lower late loss, binary restenosis, and neointimal volume compared with patients who received a non coated stent.

**Update in adjunctive pharmacologic therapy to limit restenosis**

Oral medications to reduce restenosis may be benefit. In the multicenter Cilostazol for Restenosis Trial (CREST), shows cilostazol had significant reduction in angiographic restenosis at six months. Benefit was also seen in subjects with diabetes and small vessels. Piogliatrazone has antirestenotic properties. Marx et al study shows without diabetes undergoing stent implantation, pioglitazone treatment had a significantly reduced neointimal volume within stented segment and lower binary restenosis rate compared with control patients. Troglitazone inhibited neo-intimal hyperplasia in a small human study. Tranilast reduced in stent restenosis in a porcine model, but could not elicit similar results in a human study. Valsartan and some statins have also been studied without any conclusive benefits.

**Potential toxicity**

Drug-eluting stents are local drug delivery vehicles, ability to deliver high local concentrations of drugs whose systemic concentrations would lead to unacceptable side effects. Drug toxicity also depends upon the dose of drug on the stent, the elution profile, the amount of drug bound and retained in the vessel, and blood concentrations. Major concern with Drug-eluting stents relates to failure of complete vessel healing, with subsequent lack of re-endothelialisation and late thrombosis, and medial thinning with stent malapposition. Clinical studies with high dose paclitaxel cases failure of re-endothelialisation and thinning of the media. Long term treatment with antiplatelet therapy may thus be required to prevent late occlusion. Taxanes may be beneficial as anti-angiogenesis in atherosclerosis, but may also underlie some incomplete healing.
Conclusion
Although stents reduce the risk of restenosis compared with plain PTCA, the prevailing rates of in-stent stenosis are still unacceptably high. Theoretical "ideal" properties of an antirestenosis drug are lipophilic with good tissue retention, strong binding/slow elution from polymer, antiproliferative without inducing cell death, potent inhibitor of vascular smooth muscle cells but not endothelial cells, specific to intimal smooth muscle cells, antimigration action on vascular smooth muscle cells, anti-inflammatory action and antiplatelet action. Rapamycin and paclitaxel affect a number of biological processes responsible for in-stent stenosis. Drug-eluting stent reduce in-stent stenosis almost zero. In-stent stenosis is a major challenge in interventional cardiology, Drug-eluting stent creates a new hope to prevent this challenge.

References
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