Guest Editorial

Drug Eluting Stent: A Major Advance in Fighting Coronary Artery Restenosis

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Since the first use of coronary angioplasty in 1977, there have been major growth and development in percutaneous coronary intervention (PCI). Due to the advances in techniques, experiences, devices, and newer potent antiplatelet and antithrombotic medications, PCI is increasingly performed in highly complex and high-risk patients with a reasonably low complication rate. Coupled with reduced discomfort, shorter hospital stay and recovery time, it has far outnumbered the volume of coronary artery bypass surgery. Currently, 1.7 million PCI procedures are performed annually worldwide with increases by 15-20% per year the last decade.

Problems in the early years of balloon angioplasty included dissection, abrupt closure and restenosis, the first two of which are largely controlled by coronary stenting since early 1990's. Moreover, stents significantly reduce coronary artery restenosis from an average of 30-50% post balloon angioplasty to 20-30% after stenting. Thus, stents improve the short-term success rate and the safety of PCI. In longer term, they decrease the restenosis and the need for repeat revascularization. As a major breakthrough in PCI, stents are currently widely used in about 80% of such procedures.

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However, stenting does not eliminate restenosis. The three major pathogenic factors in restenosis are elastic recoil, negative arterial remodeling and neointimal hyperplasia. Stents virtually eliminate elastic recoil and counteract the arterial remodeling. But neointimal hyperplasia after stenting can still cause significant and refractory restenosis. Depending on the pattern of in-stent restenosis, treatment with balloon angioplasty alone is still followed by a further restenosis in 45-55% of cases. Intravascular brachytherapy has been used in recent years and found to be effective in managing in-stent restenosis, but the recurrence after brachytherapy is still in the order of 26-32%.[1-3] Moreover, the procedure itself adds extra cost, and technical difficulty and consumes extra procedure time. The long-term safety with the extra radiation is still uncertain and meritorious of concern. Thus, to prevent the development of restenosis right after PCI is a critical issue. Enormous amount of research is being conducted to achieve this ideal goal.

The process of neointimal hyperplasia is initiated from the arterial injury sustained during PCI. The arterial injury and intimal denudation trigger off inflammatory responses. Growth factors and cytokines produced would activate smooth muscle cell (SMC) proliferation and migration and elicit production of extracellular matrix. Together these processes significantly limit intra-arterial lumen leading to restenosis. Stent-based drug delivery to intervene this process has been developed in an attempt to counteract this phenomenon. A number of drugs have been studied and additional ones are being pursued at present: anticoagulants (heparin, hirudin), antiplatelet agents (abciximab), anti-inflammatory drugs (dexamethasone), and antiproliferative agents

(sirolimus, paclitaxel, actinomycin D and batimastat). To date, the sirolimus-eluting stents appear to demonstrate a remarkable efficacy and safety in preventing restenosis.

Sirolimus is the generic name of Rapamycin, a drug used in preventing renal transplant rejection. Food and Drug Administration (FDA) in the USA had approved this clinical use in 1999 and CE Mark in Europe was obtained in 2000. Sirolimus is a cytostatic agent, by virtue of cell cycle inhibition which suppresses SMC proliferation and inflammatory cell activity. A small fractional amount of systemtic dose of sirolimus is incorporated into a polymer matrix surrounding a balloon-expandable metallic stent (Bx Velocity, Cordis, Johnson & Johnson). In vivo, the drug is released slowly and gradually over 30 to 45 days after deployment in the coronary artery.

The First-In-Man (FIM) study[4] was a small pilot trial involving 45 patients with de novo coronary lesions of length <18 mm and vessel diameter 3.0-3.5 mm. All patients were treated with an 18 mm long sirolimus-eluting stent. Follow-up to 24 months revealed 0% in-stent restenosis and minimal neointimal hyperplasia. There was no subacute or late stent thrombosis. Only one patient required another PTCA at 14th month due to new progression at a site outside the previously stented segment.

A RAndomized double-blind study with the sirolimus-eluting Bx VElocity balloon expandable stent in the treatment of patients with de novo native coronary artery Leision (RAVEL)[5] involved 238 patients from 19 centers. One hundred and twenty patients received the sirolimus-eluting stents while 118 patients received the bare stents as control. At 6 months, there was 0% restenosis rate in the sirolimus arm as opposed to 26% in the control arm ($p<0.0001$). At 12 months, target lesion revascularization (TLR) rate was 0% in the sirolimus group. There was no difference in death rate and myocardial infarction (MI) but the major adverse cardiac event (MACE) rate was 5.8% in the sirolimus group versus 28.8% in the control arm ($p<0.0001$), mainly due to the 27% TLR rate in the latter.

Subsequently, the results of a multicenter, randomized double blind study of the SIRolImUS-coated Bx Velocity balloon expandable stent in the treatment of patients with de novo coronary artery leisions (SIRIUS-400),[6] were presented in May 2002. SIRIUS involved over 1,100 patients from 53 sites in the U.S. with half of whom received sirolimus stents. All received 3 months of dual antiplatelet therapy (aspirin and clopidrogrel). The patient cohort was more complex than in RAVEL: 28% diabetes, 72% hyperlipidemia, 42% multivessel disease, 24% Type C lesions and 100% with a longer lesion length of 15 mm-30 mm. The primary endpoint was Target Vessel Failure (TVF: cardiac death, MI or TVR) at 9 months. Preliminary findings of the first 400 patients showed that the 8-months in-stent restenosis rate as assessed by protocol-based reangiogram was reduced from 31% in the control arm to 2% in the treated arm ($p<0.001$). Independently, intravascular ultrasound confirmed a 94% reduction in neointimal hyperplasia in the sirolimus group, as compared with control. The in-lesion (defined as in-stent plus 5 mm proximal and distal to the stent margin) restenosis decreased from 32.3% in the control group to 9.2% in the sirolimus group ($p<0.001$). Target lesion revascularization was reduced from 16.7% in the control to 4.7% in the sirolimus group (a 72% reduction). At 9-months follow-up, the event-free (from death, MI, CABG and Re-PTCA) survival was 90.8% in the sirolimus group versus 80.6% in the control ($p=0.001$). There was no acute, subacute or late stent thrombosis in the treatment group.

Though long-term safety beyond 2 years is still pending, the data obtained in the last few years are encouraging enough by the demonstrated superiority of the sirolimus-eluting stents in significantly reducing coronary artery restenosis and TLR. Such stent has been approved by CE Mark in April and is available for use in Hong Kong since May 2002.

There are other ongoing trials using sirolimus-eluting stents. The E-SIRIUS trial involves 350 patients in Europe. The C-SIRIUS trial involves 100 patients in Canada. Another coronary bifurcation trial on 75 patients will be completed later this year.

However, the cost of the sirolimus-eluting stent is substantially higher than its bare stent counterpart by more than ten thousand Hong Kong dollars (~US$1,300). Despite the higher initial cost, such stents can markedly reduce the need of repeated revascularization procedure (and potential complications). Cost-effectiveness analysis based on more clinical data and local patient demographics is needed before any definite recommendation can be made. It is likely that two groups of patients will benefit most from using the drug eluting stents: patients with high risk of coronary artery restenosis like diabetes, small coronary vessel and long diffuse lesion; and patients with high clinical risk due to restenosis such as those with poor ventricular function and artery supplying a large proportion of remaining viable myocardium. Meanwhile, cardiologists should exercise clinical judgement in individual situation and should refrain from routine widespread use of sirolimus-eluting stents until further health economic data of such stent are available.

In summary, sirolimus-eluting stents represent a major advance in our battle against coronary artery restenosis. They will likely alter the use and approach of PCI in managing a major cause of death in developed countries including Hong Kong. Nevertheless, primary and secondary prevention with healthy life style, exercise and low cholesterol diet and control of smoking, hyperlipidemia, diabetes, as well as hypertension should be the fundamental strategy in fighting against coronary artery disease.

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