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Editor
Singapore Medical Journal
Singapore Medical Association
2 College Road
Singapore 169850
Fax: (65) 6224 7827
Email: smj@sma.org.sg
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Cover Picture:
Antoine-Laurent Lavoisier (1743 - 1794): founder of modern chemistry.
(Refer to pages 303-304)

Editorial

Drug-eluting stents: the panacea for restenosis?

M C L Lim

Coronary artery disease remains one of the major causes of death in modern societies. Clinicians have been using lifestyle changes and pharmacological measures to prevent the advent of significant coronary artery disease. Invariably, there will be those who eventually develop significant coronary artery stenoses. In Singapore, the introduction of percutaneous balloon angioplasty in the 1980s heralded a new beginning in the treatment of ischaemic heart disease. The initial euphoria was dampened by the problem of vessel closure due to elastic recoil and in the longer term, restenosis due to neointimal proliferation. New devices were developed to address these setbacks in balloon angioplasty. These include cutting devices such as directional atherectomy, and drilling devices such as rotablators and lasers. While there were those who believed that using these devices to create a bigger residual lumen and an optimal angiographical result would result in better long term outcomes, the clinical data did not show this. The extensive damage to the vessel wall during these procedures resulted in significant neointimal proliferation and hence, narrowing of the vessel lumen (restenosis).

The second major milestone in interventional cardiology was the development of stainless steel stents which when deployed in a vessel, would provide a metal scaffolding to mechanically keep the vessel lumen patent[1-3]. While coronary artery stenting reduced the problem of elastic vessel recoil and restenosis following balloon angioplasty, the implantation of a stent also results in injury to the vessel wall and hence a neointimal healing response which if excessive, causes narrowing of the vessel lumen (restenosis). The incidence of instent restenosis six months post-stenting varies from varies from about 10% to 20% for uncomplicated large size vessel short stenoses to about 40% to 50% for complex long stenoses[1-5].

Doctors continued to search for the magic bullet which would give them zero restenosis. One major development along the way was the use of coronary brachytherapy or radiation therapy. The initial euphoria for this new therapy died down when the long term follow-up showed that patients who were treated with brachytherapy in the last five years were worse off than those who did not have brachytherapy. Meanwhile, scientists continued to improve the designs of stents to improve their flexibility and reduce the damage to the vessel during stent implantation. Improvement of stent designs have reduced stenosis but will not overcome the problem of restenosis.

The third major milestone in interventional cardiology was the advent of drug- eluting stents (DES). While stenting provided the mechanical support for keeping the arterial lumen patent initially, what was required was an agent which would prevent excessive neointimal proliferation.

Mt Elizabeth Medical Centre
3 Mount Elizabeth, #06-08
Singapore 228510

M C L Lim, MBBS, MMed, FRCP
Consultant Cardiologist

Correspondence to:
Dr Michael Lim Chun Leng
Tel: (65) 6565 6868
Fax: (65) 6836 7800
Email: mlim_heartcentre@yahoo.com.sg

To deliver the drugs, polymer platforms were developed which would withstand the mechanical stress during stent implantation and yet enable the agent to be delivered in a predictable manner. Among the several agents that have been tested, two are now approved for clinical use. The first agent, sirolimus or rapamycin, is a naturally-occurring macrolite antibiotic with a potent immunosuppressive effect, inhibiting the kinase, target of rapamycin (TOR), resulting in inhibition of cell cycle progression from G0 to G1 cell cycle[6]. Sirolimus has been coated on a Bx Velocity stent (Cypher stent) for clinical use. The other clinically available agent is paclitaxel, an antineoplastic agent, which is delivered through a polymer platform coated on the NIR Conformer or Express stents (Taxus stent).

The initial randomised clinical study with the Cypher stent, the RAVEL (RAndomised study with the sirolimus-eluting Bx VELocity balloon-expandable stent) study, showed 0% restenosis at six months compared to 26% in the bare metal stent (BMS) group[4]. A similar randomised study with the TAXUS stent, the TAXUS 1 (Treatment of *de novo* coronary disease using a single pacliTAXel-elUting Stent) study, showed 0% restenosis at six months compared to 10% in the BMS group[5].

The larger SIRIUS (multicentre randomised double blind study of the SIRolImUS coated Bx Velocity stent in the treatment of patients with *de novo* coronary artery) trial involving 1,058 patients with more complex lesions showed the restenosis rate was 8.9% for the Cypher stent versus 36.3% in the BMS group[7]. A similar study, using the TAXUS stent, TAXUS IV study involving 1,314 patients, showed that the restenosis rate was 7.9% in the TAXUS stent group versus 26.6% in the BMS group[8]. In the recently-released TAXUS VI study where longer lesions and overlapping stents were included in the study cohort, the low restenosis rate was maintained.

The largest barrier to using DES for all patients suitable for coronary stenting is the cost involved[9,10]. The cost of DES is almost twice that of a BMS. In the RAVEL and TAXUS 1 studies, the lesions selected for stenting were de novo lesions, single lesions in native vessels, of short lesion length, and a vessel diameter of 3.0mm to 3.5mm. Such lesions have been shown to have good results with low restenosis rates with BMS. Hence, it was not surprising that for TAXUS 1, the restenosis rate in the BMS group was only 10%. Given the high cost of DES, there is really little justification for routine use of DES for such lesions, especially in the subsidised public health care sector.

However, for patients with diabetes mellitus, long lesions, small vessels, the benefits of DES are significant[7,8,11-15]. For such complex lesions, wherever it is suitable to deploy a stent, DES should be considered in place of BMS. While initial data showed that DES in total occlusions, ostial lesions, acute myocardial infarctions, thrombotic lesions, unprotected left main stenosis, in-stent restenosis and saphenous vein graft stenosis appear to have benefits over BMS, more data and follow-up will be required to better understand the role of DES in complex lesions[16-20].

DES is evolving with the development of new biodegradable polymer platforms and new agents[21,22]. There is no doubt that DES is a major breakthrough in the treatment of coronary artery disease. Lau et al's review in the current issue of the Singapore Medical Journal is therefore timely[23]. With more types of DES available, the prices of DES will

DES will be affordable enough to become the de facto stent for coronary artery disease.

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Singapore Medical Association
Level 2, Alumni Medical Centre
2 College Road
Singapore 169850
Tel: (65) 6223 1264
Fax: (65) 6224 7827
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continue to fall and it will not be unexpected that in the near future, DES will be affordable enough to become the *de facto* stent for coronary artery disease. Until then, we have to use these stents appropriately to achieve the best cost-benefit outcomes. SMJ

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