Summary

Drug eluting stents (DES) release drugs that inhibit tissue growth in narrowed coronary arteries in an effort to prevent restenosis, a renarrowing of the artery.1

Several types of DES are under investigation in clinical trials; however, none are currently approved for use in Canada.

Preliminary trial data are encouraging, demonstrating greater lumen diameter and reduced restenosis with DES versus uncoated stents.

If DES prove to be more effective than uncoated stents in the treatment and/or prevention of restenosis, this technology may diffuse rapidly. The total health care costs, including the cost of the stents, post-intervention therapy and possible re-intervention costs, will require assessment to determine the ultimate impact of DES.

The Technology

Coronary stent implantation involves inserting a tubular metal scaffold device into a narrowed coronary artery during the percutaneous transluminal coronary angioplasty (PTCA) procedure. The stent is expanded and left in place to prevent recoiling and remodeling of the artery.1,2 However, debris, platelet clumps or excessive tissue growth stimulated by injury caused by stretching a narrowed artery can cause obstruction known as "in-stent restenosis" (ISR).1,2 DES release drugs locally into a narrowed artery in an effort to prevent restenosis.1

Regulatory Status

None of the DES under current investigation are licensed for use in Canada (Nancy Shadeed, Health Canada, Ottawa: personal communication, 2002 Jul 11), although their release is anticipated in late 2002 or 2003. Recently, the Cypher™ sirolimus-eluting stent [Cordis, a Johnson & Johnson company] was approved for use in Europe for the treatment of de novo coronary artery lesions ≤30 mm in length in native (unaltered from their natural state) coronary arteries with reference diameters ranging from 2.25 to 5.0 mm.3

Patient Group

Coronary artery disease (CAD) is a leading cause of morbidity and mortality around the world.4 It has a major impact on quality of life, including chronic pain or discomfort, activity restriction, disability and unemployment.5 In Canada, CAD was the cause of death in 132 per 100,000 people in 1997.6
Current Practice

PTCA is used to treat coronary stenosis by dilating a narrowed coronary artery using a balloon. Although initially successful, restenosis following PTCA occurs in 30 to 50% of patients, and 20 to 30% of patients require a repeat revascularization within one year. The use of coronary stents has improved both the initial and long-term results of PTCA procedures. However, ISR still occurs in 10 to 35% of stenting procedures and repeat revascularization with repeat angioplasty, restenting or brachytherapy, may still be required. Brachytherapy involves the application of intracoronary radiation locally using either gamma or beta radiation sources. Coronary artery bypass graft (CABG) surgery may be considered for certain patients, such as those with complicated or extensive restenosis, diabetes or significant left ventricular dysfunction.

The reobstruction of coronary stents occurs frequently and has been treated with aggressive pharmacotherapy such as antiplatelet agents (e.g. ASA), ADP receptor antagonists (e.g. ticlopidine, clopidogrel) and glycoprotein IIb/IIIa receptor antagonists (e.g. abciximab), in conjunction with stent implantation. To date, no large-scale clinical trials have demonstrated a significant reduction in the rate of restenosis, and all are associated with an increased risk of bleeding.

Administration and Cost

The Canadian costs of the various DES are not yet known. In the US, DES will be priced between US$2,000 and $3,200 depending on the DES, compared to about US$1,000 for uncoated coronary stents. The Cypher sirolimus-eluting stent is sold in the UK for £1,500 compared to an average selling price of £410 for an uncoated stent.

Rate of Technology Diffusion

If DES prove to be more effective than uncoated stents in the treatment or prevention of restenosis, the technology may diffuse rapidly and replace uncoated stents in some situations. Although more costly, the total cost to the health care system, including post-intervention therapy and possible re-intervention costs, will require assessment to determine the impact of DES. In clinical trials to date, DES are effective in relatively simple lesion types. These new technologies should also be examined for use in patients with various lengths of lesions, sizes of vessels and multi-vessel occlusions. Given cost considerations, DES may be restricted to use in cases considered high-risk due to vessel anatomy or lesions perceived to have a high risk of restenosis.

Concurrent Developments

A wide variety of DES are under investigation; trials are at various stages of development. Potential pharmaceutical candidates to be used for drug elution include: immunosuppressants (tacrolimus, sirolimus), antineoplastics [paclitaxel, taxol derivatives (QP-2)], antithrombins, collagen synthetase, angiopeptinV and vascular endothelial growth factor (VEGF).
The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)

The Evidence

Sirolimus-eluting stents:
Several trials have investigated the use of sirolimus-eluting stents for the management of restenosis. The RAVEL trial involved 238 patients with single primary target lesions in a native coronary artery. Patients were randomized to receive either the Cypher sirolimus-eluting (140 μg/cm²) stent or an uncoated Bx Velocity™ stent (Cordis, a Johnson & Johnson company). Angiographic data on 211 patients (88.7%) were available at six months. The rate of survival free of myocardial infarction (MI) and repeat revascularization was higher in the sirolimus-eluting stent group (94.1%) than in the uncoated stent group (70.9%) (p<0.001) after one year.

The SIRIUS trial was a double blind, multicentre trial in the US involving 1,101 patients with focal de novo native coronary arterial lesions. Patients were randomized to receive either a Cypher sirolimus-eluting (109 μg/cm²) stent or an uncoated Bx Velocity stent. At eight months, interim angiographic data were available for the first 400 patients, 190 patients in the sirolimus group and 210 patients in the uncoated stent group. Target vessel failure (TVF), the primary endpoint, was a composite of cardiac death, MI or target vessel revascularization at nine months post procedure. There was a significant decrease in TVF (10.5% vs. 19.5%, p=0.017) at nine months.

Most trials recorded angiographic data including late loss (defined as the post-operative minimal lumen diameter (MLD) minus the follow-up MLD), diameter stenosis (% of luminal diameter) and restenosis rates.

Paclitaxel-eluting stents:
There have been several trials involving paclitaxel: ASPECT, ELUTES and the TAXUS program. The ASPECT trial involved 177 patients with a single de novo lesion. Patients were randomized to receive a high dose (3.1 μg/mm²) or low dose (1.3 μg/mm²) paclitaxel-eluting SupraG™ stent or an uncoated SupraG stent (Cook Inc.). The ELUTES trial was a multicentre trial involving 192 patients with single de novo lesions. Patients were randomized to receive a 2.7, 1.4, 0.7 or 0.2 μg/mm² paclitaxel-eluting V-Flex™ Plus coronary stent system or an uncoated V-Flex stent (Cook Inc.). Six month angiographic data were available for 88% and 91% of patients in the ASPECT and ELUTES

Table 1: Drug eluting stents currently being investigated

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stent</th>
<th>Manufacturer</th>
<th>Trial</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Tacrolimus-eluting Flex Master stent</td>
<td>Jomed</td>
<td>PRESENT</td>
<td>Ongoing; involves patients with new lesions</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Tacrolimus-eluting coronary stent graft</td>
<td>Jomed</td>
<td>EVIDENT</td>
<td>Ongoing; involves patients with saphenous vein graph stenosis</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Achieve™ drug eluting coronary stent system</td>
<td>Manufactured by Cook Inc., distributed by Guidant Corporation</td>
<td>DELIVER and DELIVER II</td>
<td>Ongoing; DELIVER has completed enrollment of &gt;1,000 patients. DELIVER II will involve over 1,500 patients and up to 3 years follow-up. The primary endpoint is target lesion revascularization.</td>
</tr>
<tr>
<td>Taxol Derivative (QP-2)</td>
<td>QuaDS-QP2 stent</td>
<td>Quanam Medical Corporation</td>
<td>SCORE</td>
<td>Stopped due to excess 30-day MACE*</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>Multi-Link Tetra™-D</td>
<td>Guidant Corporation</td>
<td>ACTION</td>
<td>Stopped due to inability to reduce restenosis as seen in animal studies</td>
</tr>
</tbody>
</table>

* Major adverse cardiac event

Table 2: Comparison of the angiographic data of the trials examining sirolimus-eluting stents vs. uncoated stents

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up (months)</th>
<th>Late Loss (within stented segment)</th>
<th>% Diameter Stenosis</th>
<th>% of Patients with Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL</td>
<td>6</td>
<td>0.01 vs. 0.8 mm*</td>
<td>14.7 vs. 36.7**</td>
<td>0 vs. 26.6*</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>8</td>
<td>0.14 vs. 0.92 mm*</td>
<td>9.5 vs. 37*</td>
<td>2 vs. 31.1*</td>
</tr>
</tbody>
</table>

† a gain in lumen diameter is a negative value and a loss in lumen diameter is a positive value

*p<0.001, **p<0.01
The TAXUS program involves several trials investigating paclitaxel. TAXUS I involved 61 patients randomized to receive either the SR formulation of the paclitaxel-eluting NIR™ stent (1.0 µg/mm³) or an uncoated NIR stent (Boston Scientific Limited). Trial results are pending for TAXUS II, III and IV.²

Table 3: Summary of six month angiographic data for paclitaxel-eluting stent trials¹⁶⁻¹⁸

<table>
<thead>
<tr>
<th>Late Loss</th>
<th>% Diameter Stenosis</th>
<th>% Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPECT*</td>
<td>0.29, 0.57 vs. 1.04 mm (p&lt;0.001)</td>
<td>14, 23 vs. 39% (p&lt;0.001)</td>
</tr>
<tr>
<td>ELUTES†</td>
<td>0.1, 0.47 vs. 0.72 mm (p=0.002)</td>
<td>14.2, 23.2, 26.0 and 32.6 vs. 39.9% (p&lt;0.007)</td>
</tr>
<tr>
<td>TAXUS ‡</td>
<td>0.36 vs. 0.71 mm (p=0.0072)</td>
<td>13.4 vs. 27.2% (p=0.005)</td>
</tr>
</tbody>
</table>

¹ Results for ASPECT are for the 3.1 and 1.3 µg/mm² paclitaxel-eluting SupraG stents vs. uncoated SupraG stent respectively.

† Results for ELUTES are for the 2.7, 1.4, 0.7 and 0.2 µg/mm² paclitaxel-eluting V-Flex Plus coronary stent system vs. the uncoated V-Flex stent, respectively.

‡ Results for TAXUS I are for the 1.0 µg/mm² paclitaxel-eluting NIR stent vs. the uncoated NIR stent, respectively.

Adverse Effects

In the RAVEL trial, there were two deaths in each group at one year.¹⁴ The overall major adverse cardiac event (MACE) rate after one year was lower in the sirolimus stent group due primarily to the increased need for revascularization in the bare stent group (0 vs. 27 patients).¹⁴ Similarly, at nine months, the SIRIUS trial also had fewer MACE in the sirolimus group compared to the control group.¹⁵ However, the definition of MACE may vary among trials.

In the trials involving paclitaxel, an adverse events trend was not obvious.¹⁶⁻¹⁸

The ultimate choice of which DES to use and when will be determined by a combination of factors: further long-term efficacy and safety trial results, availability, cost, operator preference and specific aspects of stent suitability for different subsets of lesions. Overall, DES appear to represent a major advance in the field of interventional cardiology and promise to extend the application and effectiveness of percutaneous coronary interventions to a wider patient population.

Addendum:

Since the external review of this document, the ACHIEVE drug eluting system and the paclitaxel-coated V-Flex Plus PTX coronary stent system have been approved for use in the European Union.¹⁹
References


The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)

