Title: Drug Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention: from Clinical Evidence to Policy in Canada.

Date: 29 May 2008

Context and policy issues:

Since it was pioneered in 1977, percutaneous coronary intervention (PCI) has revolutionized the treatment of coronary artery disease with over 1.5 million PCIs performed annually worldwide. The clinical effectiveness of PCI, however, is burdened by a collapse of the vessel wall that causes restenosis of the lumina. The placement of the metal stent into the coronary artery, or coronary stenting, reduces the restenosis rate following PCI, and has been proven to reduce mortality, reinfarction and stroke rates. In Ontario, the number of PCI procedures funded by the Ministry of Health and Long-term Care was expected to increase from approximately 17,780 in 2004/2005 to 22,355 in 2006/2007 (an increase of 26%), with about 95% requiring the placement of one or more stents.

Despite the effectiveness of bare coronary stents, late restenosis continues to occur after 15 – 30% of PCI procedures due to vascular smooth muscle cell proliferation with neointimal formation, which is the major determinant of in-stent restenosis and requires revascularization procedures. Drug eluting stents (DES), or stents coated with smooth muscle cell antiproliferative drugs such as sirolimus or paclitaxel, were created, with the hope to prevent in-stent restenosis and reduce the revascularization rate. Two products are currently available on the Canadian market: Cypher™ Sirolimus-eluting stent (Cordis) and Taxus® Express Paclitaxel-eluting coronary stent (Boston Scientific). A Canadian study reviewed the registry of all patients undergoing PCIs in Ontario between December 1, 2003 and March 31, 2005 and found that 38% of the stents implanted in patients in Ontario during the study period were drug-eluting stents.

The uncertainty about the clinical effectiveness of DES, its high costs, (Can$1,500 to $3,000 per stent) and wide spread use suggest a review of the clinical effectiveness of DES.

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a survey of the use of DES in Canadian jurisdictions, and a comparison of the clinical evidence with the use of DES in Canada is warranted.

Research questions:

1. What is the clinical effectiveness of DES for patients undergoing PCI compared to bare metal stents?

2. What are the criteria used in different Canadian jurisdictions for deciding when to use DES?

3. Is the criterion used by each Canadian jurisdiction for DES use consistent with the clinical evidence?

Methods:

A limited literature search was conducted on key health technology assessment resources, including OVID’s Embase, Pubmed, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and the April 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessment, and systematic reviews studies. In addition, the bibliographies of retrieved publications were scanned for further relevant items.

Summary of findings:

Clinical effectiveness of DES

Our literature search found 12 systematic reviews comparing the clinical effectiveness of DES with bare metal stents. The most recent study is a rigorous review with a systematic literature search covering the literature up to March 2007. This review, which included 38 randomized controlled trials (RCT) covering 18,023 patients undergoing PCI, compared sirolimus-eluting stents with bare metal stents, paclitaxel-eluting stents with bare metal stents, or sirolimus-eluting stents head-to-head with paclitaxel-eluting stents. DES was associated with statistically significant reduction of target revascularization as compared to bare metal stents, with sirolimus-eluting stents having the most pronounced effect (hazard ratio 0.70, 0.56-0.84; P=0.0021). Mortality, however, was similar in the three groups and the risk of late stent thrombosis (>30 days) was increased with paclitaxel-eluting stents (P<0.05). The conclusion of this systematic review on the reduction of target revascularization by DES is in agreement with previous reviews.

A recent Canadian observational study (2007), which was not included in the above systematic review, examined the registry of all 13,353 patients undergoing PCI in Ontario found that 10.7% of the patients receiving a bare-metal stent and 7.4% of those receiving a DES required target-vessel revascularization by year 2 of follow-up (P<0.001). The three year mortality rate was significantly higher in the group with bare metal stents than in the DES group (7.8% versus 5.5%, p<0.001). It is to note that drug-eluting stents are more effective than bare-metal stents in reducing the need for target-vessel revascularization in patients at highest risk (presence of diabetes, small vessel diameter and long lesion length) for restenosis after PCI but offer minimal benefit to patients at lower risk. Even though the strength of this study includes the availability of a large population-based cohort, its observational nature warrants further investigation by large
RCT with long-term follow up, especially on the small absolute difference in mortality in favor of drug-eluting stents.

Of particular focus on the diabetic population, a 2008 systematic review of RCTs of DES versus bare metal stents in patients with diabetes mellitus included 16 studies and 2591 patients. The review found that DES use is associated with a statistically significant decrease in in-stent restenosis [relative risk (RR) 0.31, P<0.001], target vessel revascularization (RR 0.35, P<0.001), and major adverse cardiovascular events (RR 0.42, P<0.001).

The use of DES in Canadian jurisdictions

A survey on the use of DES in various Canadian jurisdictions was conducted and the survey findings are summarized in Table 1. The questions were:

1. Are DES covered or publicly funded in your jurisdiction?
2. Are there criteria used in your jurisdiction for deciding when DES will be used? If yes, what are the criteria?

Table 1: FPT program survey results regarding funding and use of drug eluting stents

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Source</th>
<th>Are drug eluting stents covered or publicly funded in your jurisdiction?</th>
<th>Are there criteria used in your jurisdiction for deciding when to DES will be used? If yes, what are the criteria used to decide when to use a DES?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prince Edward Island</td>
<td>Data provided by the PEI Department of Health</td>
<td>Yes. They are billed inclusive in a daily rate and/or in the high cost procedure billings</td>
<td>Procedure not available in PEI – patients go out of province. The cardiologist determines if the patient qualifies for a DES.</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>Data provided by the NB Heart Centre</td>
<td>No data provided</td>
<td>If a lesion/patient has two of: stent longer than 20 mm, diabetes, stent diameter 2.5 mm or less. There are exceptions, and every lesion is considered on its own merits.</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>Data provided by Eastern Health</td>
<td>Yes</td>
<td>Vessel diameter &lt; 3mm, lesion length &gt; 18mm, high risk anatomy (proximal left anterior descending artery), diabetic, in-stent restenosis (ISR), saphenous vein grafting.</td>
</tr>
<tr>
<td>Jurisdiction</td>
<td>Source</td>
<td>Are drug eluting stents covered or publicly funded in your jurisdiction?</td>
<td>Are there criteria used in your jurisdiction for deciding when to DES will be used? If yes, what are the criteria used to decide when to use a DES?</td>
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<td>Quebec</td>
<td>Data provided by Ministère de la Santé et des Services sociaux</td>
<td>The Health Insurance Board of Quebec will finance ~20%-30%, which is the estimate for the percentage of patients that will meet the criteria for DES implant</td>
<td>Lesion length &gt; 20mm; Vessel diameter &lt; 3mm; Diabetes mellitus.</td>
</tr>
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<td>Manitoba</td>
<td>Winnipeg Regional Health Authority</td>
<td>No, but the program is decreasing costs by covering approximately 20% DES versus bare metal stents</td>
<td>Diabetic patients; Patients with narrow, short lesions; Patients at risk for restenosis.</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>Date provided by Cardiosciences, Critical Care and Respiratory Services, Regina-Qu’Appelle Health Region</td>
<td>Funding allocated to the Cardioscience program, RQHR, to cover costs associated with DES from the Provincial Jurisdiction, Saskatchewan Health</td>
<td>Diabetic Patients; Obese Patients; Patients with “small vessel disease”/small anatomical coronary artery lumens as identified by previous angiography.</td>
</tr>
<tr>
<td>Alberta</td>
<td>Data provided by Division of Cardiology, Capital Health Region</td>
<td>DES are funded through Province wide services</td>
<td>Patients with a long lesion in a small vessel (&lt; 3 mm in diameter), particularly in those with diabetes; In-stent restenosis in small vessels when the ISR is diffuse; Diabetes with diffuse disease; Situations when restenosis is likely to be life-threatening.</td>
</tr>
<tr>
<td></td>
<td>Royal Alexandria Hospital</td>
<td>No information provided</td>
<td>Criteria based on clinical picture, similar to Capital Health Region criteria.</td>
</tr>
</tbody>
</table>
Eight jurisdictions responded to the survey. Overall, the majority of the jurisdictions that responded to the survey fund DES and has criteria to decide when a DES will be used. Most specify the lesion length and lesion diameter as criteria for DES. In addition, patients with diabetes were specified as criteria in six of the jurisdictions that responded.

**Conclusions and implications for decision making:**

In summary, the clinical evidence supports the use of DES, in particular sirolimus-eluting stent, in preventing restenosis in patients with high risk, including those with diabetes, small vessel diameter, and long lesion. DES seems not to affect mortality rate, however, and paclitaxel-eluting stents tend to increase the risk of late in-stent thrombosis.

According to the findings from the survey, DES use in most Canadian jurisdictions is based on criteria that are in agreement with our analysis of the current clinical evidence, which are patients with diabetes, or with small vessel diameter or long lesion. Because the development of DES likely involves new stent and carrier materials, with new costs, and because of the complex
coronary patient populations, it is anticipated that assessment of DES and from there, the policy of DES use, will likely need to be reviewed in the future.

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