OHTAC Recommendation

Based on the Final Report of the Programs for Assessment of Technology in Health (PATH) Research Institute Field Evaluation of Drug Eluting Stents (DES)

March 30, 2007

Drug Eluting Stents

OHTAC Ontario Health Technology Advisory Committee

The Ontario Health Technology Advisory Committee (OHTAC) met on March 30, 2007 to review the final results of a field evaluation of outcomes of use of drug eluting stents (DES) in Ontario.

Coronary artery disease (CAD) results from a build up of atherosclerotic material that eventually causes stenosis and occlusion of coronary arteries. Occlusions can result in myocardial infarction (MI).

There are a variety of medical interventions available to control CAD including diet, drugs, coronary arterial bypass graft (CABG) and percutaneous coronary interventions (PCIs). PCI procedures include the permanent insertion of a stent to keep the vessel open. Stent insertion has two major limitations: vessel closure due to thrombosis and restenosis during followup. Restenosis can result in the need for repeat hospitalization, diagnostic procedures, and repeat interventions.

Stents may be especially important in patients with long stenotic lesions (greater than 15 mm), narrow lesions (less than 3mm) and in patients with diabetes. These three factors are associated with higher risk of re-stenosis following dilatation of the coronary artery. Bare metal stents (BMS) can induce thickening of the inner surface of the coronary artery in which it is placed and this in turn may result in restenosis. There is a reported in-stent restenosis rate of 10% to 35% among patients who receive BMS.

DES contain drugs which diffuse from the stent to inhibit the cell growth and thickening in the vessel wall, designed to reduce the risk of restenosis.

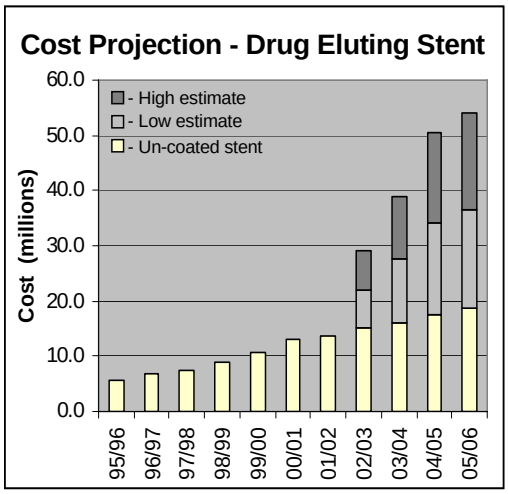
Background

In 2002 (updated in January 2003), the Medical Advisory Secretariat (MAS) conducted a systematic review of the literature on the effectiveness of DES and concluded that:

- There was considerable heterogeneity between studies with respect to the types of DES used, the types of concurrent systemic drugs used to reduce in-stent restenosis, and the selection of patients in terms of the extent of stenosis or number of vessels involved.
- There were no long-term followup studies of DES.

Drug Eluting Stents

- The published trials focused on relatively low risk patients with shorter wider lesions. The impact of DES on restenosis and in-stent thrombosis on other/higher risk patients with restenosis, small vessel occlusions or diabetes should await the results of further clinical trials.
- A switch to DES in Ontario in all cases as was suggested at the time would not realize long-term cost savings. It would have required additional funding from the MOHLTC in the range of $800 to $3,040 per case or between $7.5M to $28.6M for the approximately 9,400 annual stent cases in Ontario. The price of DES stents would need to decrease substantially in order to realize cost savings under a general switch to DES.
- Based on Cardiac Care Network (CCN) projections in 2002, it was expected that PCIs (almost all of which would require stenting) would increase another 37% over the next five years. This would have potentially increased the costs for stents by an additional $17.6 to $35.2M annually by 2005/06 depending on the price of the stents. The differences found between the low and high estimates are illustrated in the chart below and varied depending upon the stent cost.



Baseline data from CCN projections of PCI volumes.

This chart does not account for cost-avoidance

A recommendation was made by MAS in 2002 that, because restenosis rates for high risk patients in particular were unknown and there could be gradual diffusion with stents being used in lower risk patients, a field evaluation of drug eluting stents should be undertaken.

In 2003/04, MOHLTC approved $12M for drug eluting stents to be used within a field evaluation to independently evaluate the effectiveness and cost-effectiveness of DES through a field evaluation conducted by the Program for Assessment of Technology in Health (PATH). Information obtained from the 2 year evaluation would assist MOHLTC in determining its final funding policy with regard to DES. This field evaluation was conducted by PATH in collaboration with CCN and funding for DES was predicated on participation in the evaluation.

Drug Eluting Stents

PATH presented their preliminary results for the DES field evaluation to OHTAC on August 11, 2005. As a result of the initial cohort analysis, OHTAC requested more specific analyses of data in patient groups at higher risk of restenosis, in particular patients having diabetes, narrow lesions (less than 2.75mm) or long lesions (greater than 20mm).
On October 21, 2005, PATH presented interim results and OHTAC made the following interim recommendations with regard to DES for PCI interventions in Ontario:

1. *That DES be offered to those patients considered for stent placement and who have any 2 or more of the following:*
   - *long lesions (greater than 20 mm)*
   - *narrow lesions (less than 2.75 mm)*
   - *diabetes*

2. *That the current support of DES not be increased at this time.*

3. *That these recommendations be provided to hospitals and cardiologists as soon as possible.*

The total annual supply of DES stents required based on OHTAC's recommendation is 9,085 stents. By targeting DES use to high risk patients, the expected number of patients managed with DES will decrease. As a result, the total number of DES stents used in the province will remain approximately the same as in 2003/04 and 2004/05.

OHTAC also wishes to bring to your attention that, while it supports these recommendations, PATH's economic analysis of the interim data for the DES field evaluation shows this technology has a high incremental cost per quality adjusted life year gained, even for the target patient groups referred to above. The one factor that would make this technology more cost-effective is to decrease the unit cost for DES.

In January 2007, PATH presented the final results of the DES field evaluation to OHTAC and the ensuing discussion was tabled to continue at the February 23, 2007 meeting. At that meeting, OHTAC requested a mortality based cost analysis to assist OHTAC in finalizing its recommendations.

On March 30 2007, PATH presented the final results, including a mortality based cost analysis, to OHTAC.

Final PATH Report of the DES Field Evaluation (March 30, 2007)

Overall, the literature and the field evaluation do not support a mortality benefit in favour of DES over BMS. Inclusion of mortality data into the economic analysis had a large impact on the results (e.g., $580K per quality adjusted life year to $37K per quality adjusted life year from a 0.7% difference in mortality at 2 years). However, it was acknowledged that inclusion of non-significant

mortality benefits in the cost analysis can give rise to considerable variation and uncertainty in the cost effectiveness results.

Updated information regarding the licensed indications for DES by Health Canada, along with the vessel diameter and lesion lengths used in the field evaluation, is summarized in Table 1. In accordance with the Health Canada regulatory conditions for DES, OHTAC did not make recommendations for "very long lesions" since these particular lesion lengths do not generally fall within the Health Canada licensed indications for DES and would be considered "off label" use.

Table 1: Vessel Diameter and Lesion Length - Ontario Field Evaluation and Health Canada License Indications

	Ontario Field Evaluation	Health Canada License Indications		
		Cypher® * (Sirolimus)	Cypher Select® † / Select Plus ® † (Sirolimus)	Taxus Express 2® ‡ / Express 2 SR® ‡ (Paclitaxel)
Vessel Diameter (mm)	≤2.75 (narrow)	2.5 to 3.5	2.25 to 3.5 (2.25 for bail out use only)	2.25 to 5.0
Lesion Length (mm)	>20 (long) >30 (very long)	≤30	≤30	<32

***** Discrete de novo lesions in native coronary arteries
† Discrete de novo lesions and in-stent restenotic lesions in native coronary arteries
‡ De novo lesions in native coronary arteries & abrupt or threatened closure in patients with failed interventional therapy

An analysis of the two-year target vessel revascularization rates with at least a 6% difference between DES and BMS showed that diabetes patients with long and/or narrow lesions benefited the most from DES placement. A 6% difference was used as the cutoff for target vessel revascularization rates since published clinical trials incorporated a similar figure in their sample size calculations and experts in the field felt that this cutoff was reasonable as a minimum percent decrease in revascularization that would have an impact on patient outcomes.

Based on the above, OHTAC recommends the following with regard to DES for PCI interventions in Ontario:

1. That DES be offered to those patients considered for stent placement and who have:
   - Diabetes, and
   - Long lesions (greater than 20 mm) and/or narrow lesions (less than or equal to 2.75 mm)

2. That PATH continue to collect data on patients who received DES.

3. That the current support of DES not be increased at this time.

4. That these recommendations be provided to hospitals and cardiologists as soon as possible.