

# TECHNOLOGY *OVERVIEW*

**Drug Eluting Stents:  
An Economic  
Evaluation**

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**The Canadian Coordinating Office for Health Technology Assessment**

**Drug Eluting Stents:  
An Economic Evaluation**

February 2005

We thank Catherine Allison for her assistance in creating this overview from a longer CCOHTA report authored by Nicole Mittmann *et al.*

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## **Economic Evaluation of Drug Eluting Stents**

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### **Technology Name**

Drug eluting stents

### **Disease or Condition**

Patients with coronary artery disease commonly undergo balloon angioplasty to unblock narrowed arteries carrying blood to the heart. However, a frequent consequence of the treatment is re-narrowing (restenosis) of a blood vessel that has been opened.

### **Technology Description**

Bare metal stents (BMS) were introduced in 1994 to reduce restenosis. Drug eluting stents (DES) are a technological advance on BMS. They are a combination of a wire mesh stent to prop open the artery and a coating that delivers a drug locally to decrease restenosis at the stent site. DES are inserted into coronary arteries during balloon angioplasty when a catheter (a slender tube) is inserted into an artery and guided to the blockage. Two DES are available in Canada: a sirolimus eluting stent (Cypher™) and a paclitaxel eluting stent (Taxus Express<sup>2</sup>™).

### **The Issue**

Even with stent implantation, a significant number of patients will develop restenosis, with the need for repeat angioplasty procedures. A repeat procedure at the same coronary artery site is called a target lesion revascularization (TLR). Compared with BMS, DES reduce the need for a TLR, but they are approximately four times more expensive. As a result, there is a need to analyze their overall cost-effectiveness compared to BMS.

### **Assessment Objectives**

We assess the cost-effectiveness of sirolimus and paclitaxel DES compared to BMS and the potential budget implications if DES were to become widely used in Canada.

### **Methods**

An economic model based on the data and treatment approaches from clinical trials was constructed. The model simulated the clinical outcomes and the use of resources during one year for patients treated with DES or BMS. The cost-effectiveness of DES relative to BMS was assessed by calculating the additional cost needed to prevent a TLR.

### **Conclusions**

- For hospitals using the paclitaxel DES, the additional cost relative to BMS per TLR avoided is estimated to be between \$26,000 and \$29,000. For the sirolimus DES, it is estimated to be between \$12,000 and \$17,000. The two DES, however, were not compared head-to-head in the clinical trials and they were each compared with different BMS.
- There is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective in a Canadian context.
- If BMS were replaced by DES in patients at high risk for restenosis (estimated to be 40% of all coronary heart disease patients), the annual budget impact for Canada is \$37.9 million. But there would be between 1,169 (8.3%) and 2,113 (15%) fewer revascularization events. If DES replaced BMS for all patients who need coronary stents, the budgetary impact is estimated to be \$126.8 million. But there would be between 2,923 (8.3%) and 5,283 (15%) fewer revascularization events.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site ([www.ccohta.ca](http://www.ccohta.ca)): Mittmann N, Brown A, Seung SJ, Coyle D, Cohen E, Brophy J, Title L, Oh P. *Economic evaluation of drug eluting stents*.

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# 1 Introduction

Coronary heart disease, which is a leading cause of mortality and morbidity in Canada,<sup>1</sup> is caused by narrowing or stenosis of the coronary arteries that supply blood to the heart. Clinical effects include angina, myocardial infarction (MI) or death. Treatments include control of risk factors, drug therapy, coronary artery bypass graft surgery (CABG) and percutaneous coronary interventions (PCI), including balloon angioplasty and stenting.<sup>2</sup>

In balloon angioplasty, a slender tube (catheter) is inserted into an artery and guided to the site of blockage, where a small balloon is inflated to widen the vessel and restore the flow of blood and oxygen to the heart. Although balloon angioplasty provides the initial relief of symptoms, complications include acute closure or coronary restenosis, with a need for a repeat angioplasty procedure to open the blocked vessel. A repeat angioplasty is termed target lesion revascularization (TLR).

Coronary stents are used to lower the occurrence of restenosis after angioplasty. A stent is a small wire mesh prosthesis placed in the artery during angioplasty to prop the vessel open. While stents decrease the incidence of restenosis, a persistent problem with in-stent restenosis (ISR) remains. This is usually due to neointimal hyperplasia, which is the excessive growth of smooth muscle tissue in and around the stent. ISR occurs in a high percentage of cases when stents are implanted in complex lesions, long lesions or in small vessels.<sup>3-6</sup>

Drug eluting stents (DES) are a technological advance on bare metal stents (BMS). A coating on the wire mesh gradually releases a potent antimetabolic drug into local tissues, where restenosis is likely to occur, without causing systemic effects.<sup>7</sup> Research has indicated that DES may decrease the rate of ISR. DES are regulated by Health Canada as medical devices.<sup>8</sup>

Two DES are currently available in Canada. The Cypher™ device was approved by Health Canada in November 2002<sup>9</sup> and elutes sirolimus, a macrolide antibiotic with immunosuppressant, antiproliferative and antimigratory properties. The Taxus Express™ device was approved in September 2003<sup>10</sup> and elutes paclitaxel, a microtubule inhibitor that prevents cell migration and proliferation.

While the clinical benefits of DES include a decreased rate of revascularization procedures and avoidance of their associated health care costs, DES are approximately four times more costly than BMS. Decisions to fund DES have varied across Canada, with some provinces allocating specific limited funding for DES, while others include DES costs under general angioplasty budgets. The Ontario Ministry of Health and Long-Term Care allocated approximately \$12 million for DES in 2003 to 2004, instructing hospitals to use the funds for DES in patients considered to be at high risk of restenosis, based on guidelines developed by the Cardiac Care Network.<sup>11</sup> Guideline eligibility criteria include patients with diabetes, long lesions or small coronary vessels or patients in whom restenosis would have severe or life-threatening consequences. These criteria are estimated to apply to 40% of patients undergoing coronary angioplasty.<sup>11</sup>

Given the clinical benefits associated with DES, there is a need to analyze the economic value and budget impact of DES from a Canadian perspective.

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## 2 Objectives

The objective of the report is to examine the cost-effectiveness of DES relative to BMS from the perspectives of a tertiary care hospital and of a provincial ministry of health. The impact on expenditures if DES were to become widely adopted in the treatment of patients with coronary heart disease will also be examined. These questions will be addressed through an economic evaluation and a budget impact analysis.

## 3 Clinical Review

### *Methods*

Clinical inputs to the report's economic model came from a systematic review and meta-analysis by Babapulle *et al.*,<sup>12</sup> which pooled the results of 11 clinical trials<sup>13-23</sup> comparing sirolimus and paclitaxel DES with BMS in 5,090 patients.

The authors conducted an independent literature search of MEDLINE® (1995 to December 2003), a search of Google and a search of the www.tctmd.ca web sites to locate other studies or abstracts. The search results were the same as those found in the Babapulle study.<sup>12</sup>

Economic evaluations were conducted on the clinical results reported in two of the pivotal trials, SIRIUS<sup>13</sup> and TAXUS IV;<sup>19</sup> and on the pooled meta-analysis results. Table 1 presents the clinical outcomes of interest from the meta-analysis. Patients receiving DES had significantly better outcomes, with a TLR rate that was 8.3% to 15% lower than patients in the BMS group.

The main clinical outcomes of interest were rates of death, MI, TLR and major adverse cardiac events (MACE). Results from the meta-analysis show that there were no differences in MI or death rates between BMS and DES. The use of DES, however, was associated with significantly less TLR when compared with BMS.

**Table 1:** Clinical inputs from meta-analysis<sup>12</sup>

Variable	Pooled DES Point Estimate (%)	Pooled BMS Point Estimate (%)
<b>Sirolimus</b>		
Death	1.0	0.7
MI (Q wave and non-Q wave)	3.2	3.2
TLR	3.5	18.5
MACE	6.8	21.0
<b>Paclitaxel (polymeric)</b>		
Death	0.9	1.0
MI (Q wave and non-Q wave)	3.3	4.0
TLR	3.3	12.2
MACE	8.7	16.7
<b>Sirolimus+paclitaxel (polymeric and non-polymeric)</b>		
Death	0.9	0.9
MI (Q wave and non-Q wave)	2.7	2.9
TLR	4.8	14.2
MACE	8.5	17.4

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## 4 Economic Evaluation

### *Methods*

The authors constructed a decision analytic model using DATA software (TreeAge Version 4) to simulate one-year resource consumption and clinical outcomes from provincial and hospital perspectives for patients treated with DES or BMS. The model was based on clinical trial data and commonly accepted treatment approaches for coronary heart disease.

Direct medical costs incurred after the original stent implantation were examined from a hospital and a provincial health system perspective. The analysis from a hospital perspective included acquisition costs for stents and drugs, costs for hospitalization (including the costs of repeat vascularization) and costs for rehabilitation. The analysis from a provincial payer perspective included all these costs, plus physician fees and charges for laboratory and diagnostic testing. Sunnybrook and Women's College Health Sciences Centre (SWCHSC) was used as the base case hospital. Ontario was the base case province. Primary cost sources included stent manufacturers, SWCHSC's drug formulary, Ontario Drug Benefit formulary, Ontario Case Costing Initiative (OCCI) and communication with clinical experts. Costs were presented in 2002 to 2003 Canadian dollars. No discounting was applied.

Hospital acquisition costs for DES and BMS were often unclear, as they often involved complex and confidential purchasing negotiations with stent manufacturers. As a result, personal communications with cardiologists were used as the primary source for device costs. A cost of \$2,400 for the sirolimus and paclitaxel DES and \$608 for the BMS was used.

A cost-effectiveness analysis was performed to determine the cost per TLR avoided. The incremental cost-effectiveness ratio (ICER) for DES was compared to the ICER for BMS using the following formula:

$$\text{ICER} = \frac{\text{cost of DES} - \text{cost of BMS}}{\text{outcome of DES} - \text{outcome of BMS}}$$

A simulation exercise determined what DES to BMS cost differences were needed to attain a particular ICER. The robustness of the results was tested with one-way sensitivity analyses and with a probabilistic sensitivity analysis using a Monte Carlo simulation.

### *Results*

The expected costs during one year ranged from \$4,350 to \$4,430 per patient for DES and \$1,939 to \$2,505 for BMS. Table 2 presents the incremental cost-effective ratios calculated from both hospital and provincial health ministry perspectives for the DES, BMS, SIRIUS and TAXUS IV studies.

**Table 2:** Incremental cost-effective ratio (ICER) from hospital and provincial perspectives

Results	Hospital perspective	
	Sirolimus DES	Paclitaxel DES
Incremental cost-effective ratio (ICER) per TLR avoided	\$12,527 to \$16,600	\$26,562 to \$29,048
	Provincial perspective	
	Sirolimus DES	Paclitaxel DES
	\$11,133 to \$15,192	\$25,202 to \$27,687

a) **Simulation Analysis for ICERs and Cost Differentials**

For the sirolimus DES, there would need to be a \$750 difference in cost between BMS and DES to obtain an ICER of \$5,000 per TLR avoided. If the ICER was \$20,000 per TLR avoided, the difference in cost would need to be \$3,000. In contrast, for the paclitaxel DES, the difference in cost between BMS and DES to obtain an ICER of \$5,000 per TLR avoided would need to be \$445. The difference in cost for an ICER of \$20,000 would be \$1,780. The lower cost difference is due to better outcome results using paclitaxel.

b) **Sensitivity Analysis Results**

Results of the one-way sensitivity analysis are presented in Table 3. The threshold value is the point at which the DES cost would approximate the BMS cost if the two types of stent had an equivalent incremental cost-effective ratio.

**Table 3:** One-way sensitivity analysis

Analysis	Threshold Value for DES	
	Hospital Perspective	Ministry of Health Perspective
SIRIUS (sirolimus eluting stent)	\$1,180	\$1,283
Sirolimus pooled	\$1,295	\$1,418
TAXUS IV (paclitaxel eluting stent)	\$981	\$1,048
Paclitaxel pooled	\$1,009	\$1,081

c) **Probabilistic sensitivity analysis results**

For the probabilistic sensitivity analysis, the expected additional cost of DES relative to BMS was \$1,848 [95% confidence interval (CI) \$510, \$5,278] for an absolute reduction in TLR of 9.4% (95% CI 7.8, 11.0). The incremental cost per TLR avoided with DES was calculated to be \$19,640, but a large credible interval (ranging from \$5,177 to \$57,420) reflects a great degree of uncertainty with this figure.

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## 5 Budget Impact Analysis

### *Methods*

The authors performed a budget impact analysis to assess how the use of DES would affect hospital and provincial budgets. The SWCHSC was used as the base case hospital and actual procedure data from its cardiac catheterization laboratory were evaluated. Ontario was the base case province. The budget impact was calculated in 2003 Canadian dollars with a cost of \$2,400 assumed for sirolimus and paclitaxel DES and a cost of \$608 assumed for BMS. The results were extrapolated to give a result for Canada.

Several sub-analyses were conducted, including the estimated cost to hospitals for treating patients at high risk of restenosis (considered to be 40% of the population) and the total cost to hospitals if all BMS were converted to DES. Three-year projections for DES utilization and costs were calculated based on Ontario angioplasty procedure statistics.

A formal cost-benefit analysis to determine the potential savings associated with a reduction in revascularization was not conducted. However, using the reductions in TLR rates found in the SIRIUS and TAXUS IV trials (12.5% and 8.3% respectively), beneficial effects for the hospital and the province could be hypothesized including fewer repeat procedures and fewer hospitalizations. For example, for the annual average of 1,520 PTCA procedures performed at SWCHSC, there would be a reduction of 190 and 126 post-procedural TLR events respectively. Using the incremental costs from the SIRIUS (\$2,075) and TAXUS IV (\$2,411) studies, this would result in a net savings of \$394,250 and \$303,786 per base case site. A reduction in the need for CABG and additional PTCAs may be a further benefit.

### *Results*

#### a) Sunnybrook and Women's College Health Sciences Centre (SWCHSC)

Of the 1,674 patients undergoing a percutaneous coronary intervention (PCI) at the SWCHSC in 2003, 90% had a stent implanted. A total of 2,582 stents were implanted during this period.

If all stents implanted were BMS, the projected cost to the hospital would be almost \$1.6 million. If DES stents were used in 40% of patients estimated to be at high risk of restenosis, the total cost to the SWCHSC would increase to \$3.4 million. If all stents implanted were DES, the total cost to the hospital would rise to \$6.2 million.

#### b) Projections for all Ontario Catheterization Laboratories

The Cardiac Care Network Ontario (CCNO) reported a monthly average of 1,258 angioplasty procedures from July to September 2003,<sup>24</sup> which was used to calculate an annual number of 15,096 angioplasties for 2002 to 2003. In Table 4, the number of stents was calculated based on 90% of angioplasty patients receiving an average of 1.5 stents per procedure. The cost of implanting DES in 40% of patients at high risk for in-stent restenosis was calculated to be \$19.6 million. The exclusive use of DES in all patients would cost the province \$48.9 million, which is \$36.5 million more than the BMS cost of \$12.4 million.

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### c) Canada-wide Projection

Table 4 also includes an extrapolation of the analysis to the entire Canadian system by weighting the provincial sample size and assuming that 0.1% of the Canadian population will require an angioplasty procedure. There is a projected cost of \$50.7 million for DES implantation in 40% of patients considered to be at high risk of restenosis. If all BMS patients were converted to DES across Canada, the projected cost is \$126.8 million, compared with \$32.1 million for BMS.

### d) Three-year Projection to 2006

The authors applied both linear and exponential analyses of numbers the CCNO provided to project angioplasty rates to 2006. The province would need to pay between \$22 million and \$27 million (linear and exponential increases respectively) for DES in high risk patients, compared to \$5 million to \$7 million for BMS. This amounts to an additional \$17 million to \$20 million for the high risk of restenosis group. If all BMS were replaced with DES, the cost to the province would be between \$54 million to \$67 million. This would be an additional \$40 million to \$50 million more than BMS for all patients undergoing stent implantation by 2006.

**Table 4:** Budget impact analysis: total cost projections for DES versus BMS in Ontario and Canada\*

	<b>Ontario</b>	<b>Canada</b>
Population	12,096,627	31,361,611
Number of annual angioplasty procedures	15,096	39,136
Patients receiving stent implantation (90% of angioplasties)	13,586	35,222
Number of stents (1.5 per angioplasty procedure)	20,379	52,833
Total cost with 100% BMS implants (\$608 per BMS)	\$12.4 million	\$32.1 million
Total cost using 40% DES implants in high risk patients (\$2,400 per DES)	\$19.6 million DES + \$ 7.4 million BMS = \$27.0 million total	\$50.7 million DES + \$19.3 million BMS = \$70.0 million total
Total cost with 100% DES implants	\$48.9 million	\$126.8 million

\* Based on Cardiac Care Network of Ontario statistics for 2002 to 2003.

## 6 Policy Implications

### *Impact on the Health Sector*

The number of angioplasty procedures has steadily increased in Ontario since 1994 to 1995.<sup>25</sup> Based on these increases, the use of DES will have a sizable impact on provincial and hospital budgets. Uptake of the new technology has been rapid in the US, with one report describing an 85% adoption rate of DES from BMS.<sup>26</sup>

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## *Implications for Policy Makers*

There is a need for uniform utilization and funding strategies for DES across Canada. Specific patient eligibility criteria based on clinical evidence may help to identify which patients should receive DES and help to contain costs. Current funding commitments range from dedicated funds for DES in Quebec and Ontario, to no funding in other provinces.

The hospital acquisition costs for DES and BMS vary according to complex, confidential purchasing negotiations with stent manufacturers. Since acquisition price is essential for an accurate analysis of the economic benefit of stents, there is a need for Canadian health ministries to encourage manufacturers and hospitals to disclose price information. A national cardiovascular database to record procedural data and costs would be helpful.

Stents that elute a variety of different medications are being developed by manufacturers and will soon be available.<sup>27-29</sup> The choice of device-drug combination will likely depend on the size of the coronary vessel. The introduction of new DES products to the marketplace may have an impact on prices.

There is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective. Some might think spending an extra \$5,000 to avoid a TLR is reasonable, while others may be willing to spend as much as \$20,000 per TLR avoided. By contrast, outcome measures such as cost per life-year or cost per quality adjusted life-year (QALY) gained have well established ranges for cost-effectiveness.

Incremental cost-effective ratios for other cardiovascular procedures in a few US studies have ranged from US\$1,333 per TLR avoided for an intravascular ultrasound<sup>30</sup> to US\$18,619 per TLR avoided for brachytherapy.<sup>31</sup> A limited number of studies have reported an ICER of US\$10,000<sup>32</sup> to US\$15,000<sup>33</sup> per TLR avoided for balloon angioplasty with stenting. The report's analysis would place the sirolimus DES in the upper portion of this range, with an ICER of \$11,133 to \$15,192 per TLR avoided. The paclitaxel eluting stent is above this range, with an ICER of \$25,202 to \$27,687. The Canadian context for cardiovascular procedures, however, is unknown.

An analysis was conducted to vary the allowable price difference between BMS and DES to achieve an acceptable ICER. If one is willing to accept a cost of \$5,000 per TLR avoided, then the maximum price premium that one would be willing to pay for a DES rather than a BMS would be \$750. If \$20,000 per TLR avoided is an acceptable amount, then one might be willing to pay a \$3,000 premium for DES.

## **7 Conclusions**

While DES are more costly than BMS, their use is associated with a significantly lower one-year rate of restenosis, which avoids associated treatment costs. Long-term survival data are unavailable.

For the paclitaxel eluting stent, from a hospital perspective, there was an additional cost relative to BMS of \$2,365 to \$2,411, but a 8.3% to 8.9% reduction in TLR yielded an ICER between \$26,562

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and \$29,048 per TLR avoided. From a provincial health ministry perspective, the ICER was \$25,202 to \$27,687 per TLR avoided.

For the sirolimus eluting stent, the ICER for hospitals was \$12,527 to \$16,600 per TLR avoided, based on an additional cost of \$1,670 to \$1,899 more than BMS and a 12.5% to 15% reduction in TLR. From a provincial health ministry perspective, the ICER was \$11,133 to \$15,192 per TLR avoided. The lower cost per TLR for the sirolimus DES should be interpreted with caution, as the two DES were not compared head-to-head and the BMS comparators in the clinical trials were different for paclitaxel and sirolimus.

The ICER for DES declines as the price difference between BMS and DES is lowered. The ICER for DES also declines by targeting populations at high risk for restenosis post-procedure, such as patients with diabetes. Negotiating a lower DES acquisition cost or implementing criteria for the treatment of high risk patients may make it more acceptable for hospitals and provinces to adopt DES on a wider scale.

There is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective. The limited literature available suggests a cost-effectiveness threshold of \$10,000 to \$15,000 per TLR avoided may be acceptable for balloon angioplasty with stent implantation. However, most of the literature cannot be used in a Canadian context and is based on BMS data.

The budget impact analysis found that in Ontario, for the estimated 40% of coronary stent patients at high risk of restenosis, the use of DES (\$19.6 million) rather than BMS (\$4.96 million) would increase costs by \$14.6 million. For Canada, the use of DES rather than BMS in high risk of restenosis patients would increase costs by \$37.9 million annually. If all coronary stent patients were given DES instead of BMS, the budget impact is estimated at \$48.9 million for Ontario and \$126.8 million for Canada.

DES offer a promising alternative for the management of coronary artery disease, particularly in patients at high risk for restenosis. Given that costs were the key source of uncertainty in the analysis, there is a need for better data collection at the provincial and national levels. A national cardiovascular database to record procedural data and costs would meet that need.

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