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Economic Evaluation of Drug Eluting Stents

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Economic Evaluation of Drug Eluting Stents

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February 2005

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CCOHTA takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CCOHTA and not of its Panel members or reviewers.

Authorship

All authors participated in planning the project, commented on the sections drafted by other authors and responded to reviewers' comments.

Nicole Mittmann is a scientist at Sunnybrook and Women's College Health Sciences Centre; an assistant professor at the department of pharmacology, University of Toronto; and the Executive Director at the Health Outcomes and Pharmacoeconomic (HOPE) Research Centre. She was the principal investigator for the project and involved in all aspects of design, analysis, writing and revision of the report.

Allan Brown is a health economist at CCOHTA. He provided coordination and contributed to the design, analysis, writing, and revision of the report.

Soo Jin Seung is a research assistant at the HOPE Research Centre. She contributed to data acquisition and analysis; and report writing.

Doug Coyle is a senior scientist at the Ottawa Health Research Institute and an associate professor at the University of Ottawa. He undertook the probabilistic sensitivity analysis and provided expert advice on the economic modelling and analysis.

Eric Cohen is an associate professor at the University of Toronto and a staff cardiologist at Sunnybrook and Women's College Health Sciences Centre. He provided clinical expertise and wrote the sections on DES interventions and use of resource; and reviewed and approved manuscript drafts.

James Brophy is an associate professor of medicine in the divisions of cardiology and clinical epidemiology, McGill University; and the director of the McGill University Health Centre's health technology assessment unit. He provided input parameters and efficacy data from a meta-analysis of which he was a co-author; and provided verification of scientific content and validity.

Lawrence Title is an associate professor at Dalhousie University and a cardiologist at the Queen Elizabeth II Health Sciences Centre. He provided expert opinion regarding percutaneous coronary intervention, DES and current standards of practice.

Paul Oh is the medical director of the Cardiac Rehabilitation Program at the Toronto Rehabilitation Institute. He provided expertise and wrote the sections on economic model development and economic analysis. He also reviewed manuscript drafts.

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Conflicts of Interest

Nicole Mittmann and Soo Jin Seung have done research for Janssen Ortho, which is owned by Johnson & Johnson, the manufacturers of the Cordis stent.

Eric Cohen's centre has been involved in research for several stent manufacturers, including Boston Scientific and Medtronic. He has received honoraria, for speaking engagements, from Boston Scientific, Cordis and Guidant. Boston Scientific co-sponsors a conference of which he is co-director.

Lawrence Title owns shares in Johnson & Johnson, Boston Scientific X and Angiotech (<$10,000 per company). He has received a speaker's fee and travel expenses from Johnson & Johnson for an international conference in Japan. He was an investigator for Johnson & Johnson on the C-SIRIUS trial (no compensation received).

Stephane Rinfret has given a conference sponsored by Cordis Canada. He was also responsible for an economic analysis of the C-SIRIUS trial. Chris Skedgel has done contract work for Eli Lilly and Aventis. The other authors and reviewers reported no conflicts.

REPORT *IN BRIEF*

February 2005

Economic Evaluation of Drug Eluting Stents

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^{2}™).

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): 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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EXECUTIVE SUMMARY

The Issue

Coronary heart disease is caused by narrowing (stenosis) of the coronary arteries. Treatment options include balloon angioplasty and placing a stent in the artery to prop it open and increase blood flow to the heart. When compared with balloon angioplasty alone, the use of coronary stents reduces the need for repeat revascularization procedures. Even with stent implantation, however, a significant number of patients will develop in-stent restenosis. Drug eluting stents (DES) have been shown to lower rates of restenosis up to 70% when compared with bare metal stents (BMS).[1,2] Two DES are available in Canada: a sirolimus eluting stent (Cypher™) and a paclitaxel eluting stent (Taxus Express[2]™). However, DES are approximately four times more expensive than BMS.

Objectives

We examine the cost-effectiveness of DES relative to BMS from the perspectives of both a tertiary care hospital and 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 be examined. These questions will be addressed through an economic evaluation and a budget impact analysis.

Methods

A decision analytic model was developed to compare the cost-effectiveness of sirolimus and paclitaxel DES relative to BMS, using a cost per target lesion revascularization (TLR) avoided. The model simulated the one-year resource consumption and clinical outcomes for patients undergoing percutaneous coronary interventions (PCI) and receiving either a DES or BMS in two pivotal studies (SIRIUS and TAXUS IV) and a meta-analysis of sirolimus and paclitaxel DES studies. The model was based on clinical trial data and commonly accepted treatment algorithms for acute coronary syndrome. The perspectives of the economic evaluation were those of a tertiary care teaching hospital (Sunnybrook and Women's College Health Sciences Centre) and of Ontario. The total expected costs and outcomes for DES versus BMS were compared in an incremental cost-effectiveness analysis. The budget impact analysis assessed how hospital and provincial budgets would be affected if DES use became widespread. Several sub-analyses were performed, including estimates to treat only a group at the highest risk of restenosis with DES and the situation wherein all coronary stents were converted to DES.

Results

There was no evidence of differences in mortality and myocardial infarction (MI) rates with DES compared to BMS. DES were associated with higher costs and lower TLR rates, from both a relative and absolute risk reduction perspective when compared with BMS. In the economic evaluation, we found that from a hospital perspective, the paclitaxel eluting stent involved an additional cost (incremental cost-effective ratio or ICER) relative to BMS of between $26,562 and $29,048 per TLR avoided. From a provincial health ministry perspective, the ICER for the paclitaxel stent was estimated at $25,202 to $27,687 per TLR avoided. For the sirolimus eluting stent, from a hospital perspective, the ICER was $12,527 to $16,600 per TLR avoided. From a provincial health ministry perspective, it was $11,133 to $15,192 per TLR avoided.

The impact on the 2003 Ontario budget of converting 40% of patients considered to be at high risk of restenosis from BMS to DES was estimated to be an additional $4.8 to $14.6 million per year depending on the stent cost ($1,200 and $2,400 respectively). If all BMS patients were converted to DES in Ontario, then $12.1 to $48.9 million could be added to the provincial budget.

For Canada, an additional $12.5 to $37.9 million could be needed to convert high risk patients. An additional $126.8 million could be needed if all patients were switched to DES.

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.

The economic evaluation found the incremental cost-effective ratio (ICER) per TLR avoided was higher for paclitaxel DES than for sirolimus DES. This should be interpreted with caution, however, 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 narrowed. The ICER for DES also declines by targeting populations at higher 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 that a cost-effectiveness threshold of $10,000 to $15,000 per TLR avoided may be acceptable. Most of this literature, however, cannot be used in a Canadian context and is based on BMS data.

The budget impact analysis in this report found that in Ontario, for the estimated 40% of coronary stent patients considered to be at high risk of restenosis, the use of DES rather than BMS would increase costs by $14.6 million. For Canada, the use of DES rather than BMS in high risk 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.

ABBREVIATIONS

ARR	absolute risk reduction
BMS	bare metal stent
CABG	coronary artery bypass graft (surgery)
CCN	Cardiac Care Network
DES	drug eluting stent
ICER	incremental cost-effectiveness ratio
DRG	diagnosis related group
ISR	in-stent restenosis
MACE	major adverse cardiac events
MI	myocardial infarction
MOHLTC	Ministry of Health and Long-Term Care
NNT	number needed to treat
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
SWCHSC	Sunnybrook and Women's College Health Sciences Centre
TLR	target lesion revascularization
TVR	target vessel revascularization

GLOSSARY

Angiographic restenosis: Restenosis detected by angiography (associated mostly with clinical trials in which follow-up angiography may be mandated in research protocol).

Balloon angioplasty (sometimes known as angioplasty or as PTCA): In this interventional procedure to unblock a vessel that supplies blood to the heart, a catheter (a slender tube) is inserted into an artery of the heart from the groin or wrist. The catheter is guided through the vessel to the blockage where a small balloon at the tip of the catheter is inflated to widen the vessel and allow an uninterrupted flow of blood and oxygen to the heart.

Brachytherapy: Intravascular brachytherapy or endovascular brachytherapy uses radiation to reduce the incidence of re-narrowing (restenosis) of coronary arteries. Tiny amounts of radiation are delivered to unblock the stent and help it remain open.

Clinical restenosis: Restenosis as defined by clinical events, such as the need for a repeat procedure or recurrence of symptoms.

Coronary stenting (or stenting): Implanting $\geq$1 small wire-mesh "stents" at blockage points during angioplasty to prop open the coronary artery and help prevent re-narrowing of the artery (restenosis).[3]

Cutting balloon: A short angioplasty balloon with tiny longitudinal blades (microtomes) affixed to it. As the balloon is expanded, blades incise restenotic tissue to a depth of several micrometres. This reduces circumferential tension and may reduce elastic recoil of dilated tissue. The cutting balloon costs three to five times as much as a standard angioplasty balloon.

Percutaneous coronary intervention (PCI): All technologies used to unblock, open or dilate coronary arteries, including balloon angioplasty (PTCA), stent implantation and techniques such as atherectomy or thrombectomy. In practice, most PCI procedures are stent procedures. A technique such as thrombectomy may be performed first (to remove thrombus from the lesion). The stent is then placed to dilate the residual narrowing. PCI is a convenient term that is used to refer to the intervention, regardless of the technique.

Percutaneous transluminal coronary angioplasty (PTCA): Also known as balloon angioplasty, PTCA is included in PCI and other technologies to unblock coronary arteries.

Restenosis: This common consequence of percutaneous coronary interventions (PCIs) occurs when there is a re-narrowing of a blood vessel that has been opened by PCI.

Stenosis: A narrowing of a blood vessel. Its severity is often expressed as the percentage by which the diameter is narrowed compared to a normal ("reference") segment of the same vessel. "Lesion" is often used as a synonym of "stenosis."

Target lesion revascularization (TLR): A repeat angioplasty of the original lesion (stenosis) or a coronary bypass operation to bypass the original lesion, generally done for recurrent >50%

narrowing at the site that had been dilated. When a stent is implanted, the target lesion includes an area 5 mm proximal or distal to the original stent, since narrowings near the stent borders are generally related to the implant. The term "revascularization" is confusing, because the original procedure is a revascularization. The repeat procedure should then be called a "target lesion repeat revascularization" or "target lesion re-revascularization." Because these terms are not used in the literature, they are not used in this report.

Target vessel revascularization (TVR): Repeated revascularization (angioplasty or surgery) for treatment of recurrent narrowing or occasionally a new narrowing anywhere in the originally treated vessel. Because TVR encompasses not only the original target lesion, but also new lesions developing elsewhere in the "target vessel," it can occur at a higher incidence than TLR in a given population. Any intervention can injure other areas of the same blood vessel, because of the need to traverse the "upstream" portion of the vessel to deliver a stent to the lesion. In this sense, TVR is an end point that is theoretically more meaningful, because it captures additional events that could be interpreted as complications of the original procedure. In practice, most TVR interventions are done on the target lesion (and hence also counted as a TLR end point), so the numeric difference in number between TLR and TVR tends to be small.

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1 INTRODUCTION

Restenosis, a common consequence of percutaneous coronary interventions (PCI), occurs when there is a re-narrowing of a blood vessel that has been opened by a vascular procedure for the treatment of coronary artery disease. Restenosis has clinical and economic implications, because it requires repeat revascularization procedures.[4] The additional costs of restenosis include hospitalization, medications and diagnostic testing.

Coronary stents are used to lower the occurrence of restenosis compared with conventional balloon angioplasty. Routine stenting with bare metal stents (BMS) to reduce restenosis began in 1994 after the publication of the BENESTENT and STRESS clinical trials. A variety of BMS are available, produced by companies such as Boston Scientific, Medtronic and Cordis.

Coronary stenting, however, is hampered by a high incidence of restenosis (20% to 50% by angiographic definition, 10% to 30% by clinical definition) depending on the characteristics of the patient and the lesion.[5,6] Clinical restenosis is defined by clinical events, such as the need for a repeat procedure or the recurrence of symptoms. Luminal narrowing due to in-stent restenosis (ISR) recurs in a high percentage of cases when stents are implanted in complex lesions, long lesions and small vessels.[7-10] In the US, there were an estimated 150,000 cases of ISR in 2001.[11] This problem led to the development of drug eluting stents (DES) to help reduce or prevent restenosis compared with bare metal stents (BMS). Using a stent as the platform for drug delivery to the site of vascular injury is an innovative approach to suppress neointimal hyperplasia and prevent ISR.

1.1 Drug Eluting Stent Technology in Canada

DES are device-drug combinations regulated as medical devices by the Therapeutic Products Directorate (TPD) in Canada.[12] DES may be a promising alternative to BMS for the prevention of restenosis. These devices, which can deliver high local concentrations of potent antimitotic drug therapy without systemic toxicity, consist of a stent, a drug and a drug-free polymer carrier.[13]

Two DES are available in Canada. The Cypher™ sirolimus eluting stent was approved by Health Canada in November 2002.[14] Sirolimus in its oral form is indicated for preventing renal or cardiac transplant rejection.[15] It is a naturally occurring macrolide antibiotic with potent immunosuppressive, anti-proliferative, anti-migratory and anti-inflammatory properties. It blocks the cell cycle at the late G1 to S phases.[15] The online product monograph for the Cypher stent[16] explains that the thin coating of sirolimus in the polymer is designed to prevent re-narrowing (in-stent restenosis).

The Taxus Express^{2}™ (paclitaxel eluting) stent was approved by Health Canada in September 2003.[17] Paclitaxel is a microtubule inhibitor that prevents cell migration and proliferation at the M cell cycle phase by inducing the microtubules to form abnormally stable and nonfunctional chains. It is indicated in its oral form (Taxol) for the treatment of ovarian, breast or lung carcinoma and AIDS-related Kaposi's sarcoma.[15] The online product monograph[18] states the Taxus stent has a polymer platform that controls the dose and release kinetics of the drug.

Only the polymer-based form of paclitaxel is considered in this analysis, because commercial development of the non-polymer format has not been pursued and it is unavailable for clinical use.

1.2 Evidence on Clinical Efficacy of DES

Several clinical trials have examined the efficacy and safety of DES in reducing restenosis rates after a percutaneous coronary intervention (PCI). The most recent pivotal studies are SIRIUS for sirolimus[2] and TAXUS IV for paclitaxel.[19] The benefits and safety of this new technology have been systematically quantified in a meta-analysis conducted at McGill University,[20] the objective of which was to synthesize data from randomized trials comparing sirolimus and paclitaxel eluting stents with uncoated stents.

1.3 Economics of DES

While the clinical benefits seem promising, the use of DES is associated with significant acquisition costs. Several prices for DES have been reported (Table 1). However, some of these prices are outdated or are discounted by manufacturers. The prices are also reported to have dropped after two types of DES became available. Concurrently, the price of BMS continues to fall. Despite this, DES continue to be approximately four times as costly as BMS. Consequently, there is a need to determine the economic value of these devices; and the trade-off between the additional cost and the improved clinical outcome (i.e., cost-effectiveness).

Table 1: DES prices, from published sources

Source	Stent Type and Price Quote	Canadian Conversion of Stent Costs*
Canada		
Cardiac Care Network of Ontario (CCN)[21]	Incremental cost between DES and BMS=$2,500 to $2,800	
Sridar K, *et al.*[22]	90% Cypher and 10% Taxus	Average=$4,945.65
Other countries		
Fattori R, *et al.*[23]	DES=£2,400; BMS=£500	DES=$4,051; BMS=$844
Lamotte M, *et al.*[24]	Cypher DES=£2,300	Cypher DES=$3,884
Van Hout BA, *et al.*[25]	Cypher DES=£2,000	Cypher DES=$3,377
Cohen DJ, *et al.*[26]	Cypher DES=US$3,000	Cypher DES=$4,000
Morrow T[27]	Cypher DES list price=$3,195; in US, average 1.7 stents per procedure ($5,431.50)	$7,223 per Cypher DES procedure
Peck P[28]	Taxus DES=Cypher DES minus US$1,000	Taxus DES=Cypher DES minus $1,331
Hall J[29]	US Centers for Medicare & Medicaid Services created new DRGs for DES with reimbursement of $1,700 to $1,800	$2,261 to $2,394 reimbursement for DES

*The Bank of Canada's Currency Converter calculator was used.[30]

1.4 Funding for DES in Canada

Different funding decisions related to DES have been made across Canada (Appendix 1). Quebec has the highest level of funding at $13 million.

Ontario was the first province to provide specific funding for DES. In 2003, Ontario's Ministry of Health and Long-Term Care (MOHLTC) allocated approximately $12 million for the province for 2003 to 2004. Hospitals were instructed to use the funds for DES in patients at high risk of restenosis.[21] Broad treatment guidelines for Ontario were developed by a working group of the Cardiac Care Network (CCN) and submitted to the MOHLTC. The guidelines target the use of DES to patients at high risk for ISR (i.e., patients with diabetes, non-diabetic patients with long lesions >18 mm or lesions in small vessels <2.5 mm and patients in whom restenosis would have severe or life-threatening consequences, for example, those with unprotected left main, survival dependent vessel). DES were to be used with glycoprotein IIb/IIIa inhibitor drugs (to prevent acute ischemic events) and in combination ASA-clopidogrel therapy. The CCN report estimated that these criteria encompassed approximately 40% of patients undergoing coronary angioplasty.[21] The funding provided by the MOHLTC was enough to allow the use of DES in approximately 20% of PCI, based on the original market price of the Cypher stent in Canada.

1.5 Use of DES

Canadian health care will be affected by the addition of DES into the cardiovascular device marketplace. Uptake has been rapid in the US, with one report describing an 85% conversion rate to DES from BMS.[31] Given the clinical benefits and high adoption rate in the US, utilization in Canada would be similar if open funding became available. An analysis of the budget impact of DES at the hospital and provincial levels in Canada is included in this report to help guide funding and implementation decisions.

2 RATIONALE FOR STUDY

DES are more expensive than BMS, but are associated with significantly lower TLR. DES are likely to be associated with incremental procedural costs based on the cost of the device, but they may decrease the rate of revascularization procedures and lead to the avoidance of some health care costs. There is a need to conduct an economic evaluation and budget impact analysis for DES utilization in patients undergoing coronary angioplasty from a hospital and a Canadian provincial perspective.

3 OBJECTIVES AND RESEARCH QUESTIONS

What is the cost-effectiveness of DES relative to BMS from a university affiliated, tertiary care hospital perspective and a provincial ministry of health perspective? From a hospital and provincial budget perspective, what would be the expenditure impact if DES became widely adopted? The report will address this question through two analyses:

- phase 1: economic evaluation
- phase 2: budget impact analysis

4 METHODS: ECONOMIC EVALUATION

4.1 Determination of Perspectives for Analysis

The economic analysis was conducted from the perspectives of a hospital providing PCI services and of the provincial health care system. Sunnybrook and Women's College Health Sciences Centre (SWCHSC), a tertiary care centre affiliated with the University of Toronto, was used as the base case hospital. Ontario was used as the base case province.

4.2 Determination of Time Horizon

The time horizon for the decision analytic model was one year, based on short-term (30 days) to medium-term (one year) clinical outcomes presented in the studies. Long-term survival data and other long-term outcomes were unavailable.

4.3 Determination of Type of Analysis

The clinical evidence shows that the implantation of DES is associated with significantly less TLR when compared with BMS. Because of the differences in efficacy, a cost-effectiveness analysis was used to determine the cost per TLR avoided. Base case results and incremental results will be reported in the form of an incremental cost-effectiveness ratio (ICER).

4.4 Retrieval of Literature

The clinical inputs to the economic model came from a systematic review and meta-analysis in a 2004 Babapulle study.[20] This study pooled the results of clinical trials comparing sirolimus and paclitaxel DES with BMS. All included studies (peer-reviewed studies and abstracts) were published between December 1998 and December 2003. Information on the inclusion and exclusion criteria were available from the review and from the original publications. The

population included patients at high or low risk of restenosis. Baseline characteristics of the patient populations included in the Babapulle study are summarized in Table 2.

An independent literature search of MEDLINE® (1995 to December 2003) was conducted by the authors. Search terms included "drug eluting stents," "percutaneous coronary intervention," "stent" and "clinical trial." A search of Google and the www.tctmd.ca web sites was used to locate any studies or abstracts not referenced in MEDLINE.® The search results were the same as those found in the Babapulle study (Table 2).

The authors also conducted economic evaluations on the clinical results reported in two key trials (Table 2) that looked at stents approved and used in Canada (SIRIUS[2] and TAXUS IV[19]).

4.5 Comparators

BMS was compared to the DES results from SIRIUS (sirolimus eluting), TAXUS IV (paclitaxel eluting), sirolimus pooled (Babapulle[20] meta-analysis) and paclitaxel pooled (Babapulle[20] meta-analysis).

4.6 Design of Decision Analytic Model

A decision analytic model was constructed using DATA software (TreeAge Version 4) based on the clinical data and treatment algorithms. The model simulated the clinical outcomes and resource consumption of the patient population who were being evaluated in the clinical trials and treated with DES (sirolimus, paclitaxel or combined) or BMS implantation during a year. The design of the decision trees was based on interventional cardiology clinical pathways and on other decision analytic models for angioplasty and brachytherapy.[32,33] Patients undergoing a PCI could have the following clinical outcomes: no event, myocardial infarction (MI), TLR or death. If ISR occurs and is focal, it is generally treated using a repeat PCI procedure, with or without the use of a cutting balloon or an additional stent. If the pattern of ISR is more diffuse, then brachytherapy, implantation of a DES inside the original stent or coronary artery bypass graft surgery (CABG) are treatment options. The clinical pathway was confirmed through interviews with three cardiologists (two interventional and one non-interventional) who perform PCI procedures in medical centres across Canada.

Four hospital and four provincial analyses were done for this report. The medium-term (one year) decision analytic model is shown in Figure 1. The root of the decision tree is the patient undergoing an urgent or elective PCI with stent implantation. The population is stratified into DES and BMS treatment groups at the therapeutic decision node. For each stent, there is a probability that a patient will experience a TLR or no TLR at nine to 12 months post-PCI. Treatment options for a TLR include coronary angioplasty (PTCA), PTCA plus cutting balloon, CABG, brachytherapy, BMS implantation, DES implantation or drug therapy. The proportion of patients treated with any of the treatments options for TLR was unavailable from the published medical literature. This is partly because of centre to centre variation in the use of the different modalities, perhaps because evidence and practice are evolving rapidly.

Table 2: Characteristics of patients treated with DES in clinical trials included in Babapulle[20] meta-analysis

Trial	Number of DES/Total Stents	Mean Age (years)	% Male	% Diabetic	Restenosis Risk*	% Glycoprotein IIb/IIIa Inhibitors	Lesion Length (mm)	Mean Number of DES Implanted
Ravel[1]	120/238	61.8±10.17	70	16	Low; single primary target lesion in native coronary artery with diameter of 2.5 mm to 3.5 mm (covered by 18 mm stent)	10.1	9.56±3.33	N/A
Sirius[2]	533/1,058	62.1±11.2	73	25	Intermediate; single primary target lesion in native coronary artery with diameter of 2.5 mm to 3.5 mm, length of 15 mm to 30 mm	60	14.4±5.8	N/A
C-Sirius[34] (Canadian trial centres)	50/100	60.3	70	24	Intermediate; single primary target lesion in native coronary artery with diameter of 2.5 mm to 3.0 mm, length of 15 mm to 32 mm	58	14.5±6.3	1.66 (54% had 1)
E-Sirius[35] (European trial centres)	175/352	62.0±11.4	70	19	Intermediate; single primary target lesion in native coronary artery with diameter of 2.5 mm to 3.0 mm, length of 15 mm to 32 mm	14	14.9±5.4	51% had 1 (34% had overlapping)
Taxus I[36]	31/61	66.0±6.8	94	23	Low; single de novo or restenotic coronary lesion with diameter of 3.0 mm to 3.5 mm, length of <12 mm	N/A	10.7±3.27	N/A
Taxus II[37 †] SR MR	 131/536 135/536	 61.5±10.5 59.3±10.1	 70 76	 11 17	Low; single de novo target lesion with diameter of 3.0 mm to 3.5 mm, length of <12 mm	N/A	 10.6±3.9 10.2±4.8	N/A

Trial	Number of DES/Total Stents	Mean Age (years)	% Male	% Diabetic	Restenosis Risk*	% Glycoprotein IIb/IIIa Inhibitors	Lesion Length (mm)	Mean Number of DES Implanted
Taxus IV[19]	662/1,314	62.8±11.8	72.4	23.4	Intermediate; single target lesion with diameter of 2.5 mm to 3.75 mm, length of 10 mm to 28 mm	N/A	13.4±6.3	1.08±0.29 (92% had 1)
Aspect[38] ‡					Low; discrete coronary lesions with 2.25 mm to 3.5 mm diameter, length of <15 mm	N/A		N/A
3.1 μg/mm^2	60/177	58±9	80	18			10.9±3.6	
1.3 μg/mm^2	58/177	60±9	72	24			11.2±3.2	
Elutes[39] **					Low; single de novo lesion <15 mm length in native coronary artery that could be stented; 16 mm long and 3.0 mm or 3.5 mm in diameter	N/A		N/A
2.7 μg/mm^2	37/190	56±11	81	11			11.1±3.1	
1.4 μg/mm^2	39/190	61±10	79	21			10.2±3.7	
0.7 μg/mm^2	39/190	58±9	95	15			10.6±3.1	
0.2 μg/mm^2	37/190	64±10	73	22			11.3±4.4	
Deliver[40]	522/1,041	61.8	70.5	30.7	Low; de novo lesions in native coronary arteries 2.5 mm to 4.0 mm in diameter	64.4	11.7±5.0	N/A
Patency[41]	24/50	N/A	67	25	Low; de novo lesions in native coronary arteries 2.7 mm to 4.0 mm in diameter	N/A	N/A	N/A

*Angiographic restenosis risk based on predictors such as pre-existing restenosis, number of stented lesions, diameter of stented artery, lesion length and diabetic status. Eight out of 11 trials enrolled patients at low risk of angiographic restenosis based on predictive variables listed. Three trials (SIRIUS, C-SIRIUS, E-SIRIUS) with patients at intermediate risk for restenosis based on implanted stent length exceeding actual lesion length, possibly increasing risk of restenosis.

†Two paclitaxel eluting release formulations evaluated against standard stent per release formulation: TAXUS-SR (slow release) (n=131) with an initial burst phase over first 48 hours after implantation followed by low-level release phase for approximately 10 days; and TAXUS-MR (moderate release) (n=135) with an eight-fold higher 10-day drug release.

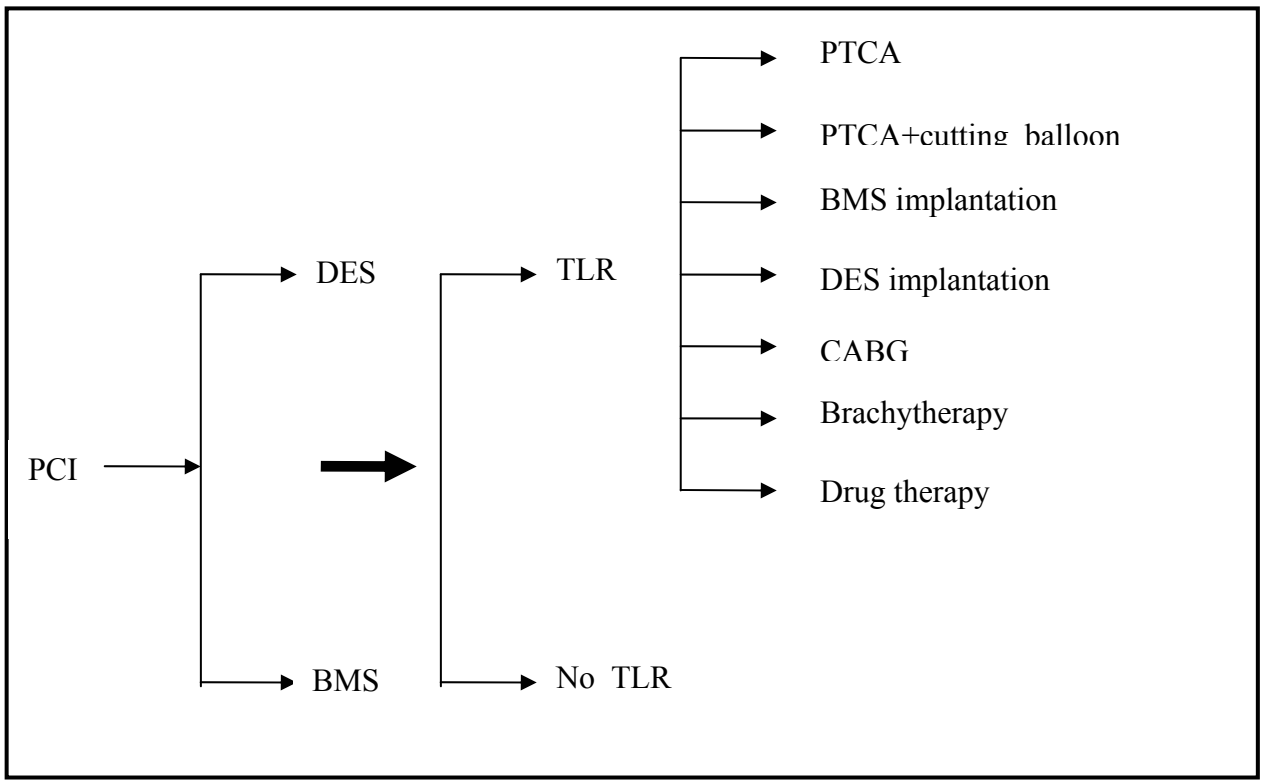
‡Two different doses of paclitaxel eluting coated stents evaluated against uncoated control stent of the same design.

**Four different doses of paclitaxel eluting coated stents evaluated against uncoated control stent.

N/A=not applicable

While it might be presumed that the avoidance of repeat procedures would affect survival (because of the small but finite mortality associated with repeat procedures), there are no long-term clinical data to support this presumption. Clinical trials have been conducted only up to a year's time. Given the low rates of procedure-related mortality, the magnitude of any benefit is likely to be small and the extent to which it could be offset by rare and as yet undetected effects of DES is unknown. An analysis of survival would be based on extrapolation from other sources (e.g., periprocedural MI links to future MI risk and mortality in patients undergoing PCI with or without glycoprotein inhibitors[42]). As a result, a survival analysis was not conducted.

Figure 1: Economic model



4.7 Determination of Clinical Inputs

The inclusion criteria were met by 11 trials that involved 5,090 patients and that compared sirolimus or paclitaxel eluting stents with BMS (Table 2).[1,2,19,34-41]

The meta-analysis was based on a systematic literature search to identify all randomized clinical trials with at least six months of clinical follow-up.[20] An "in press" version of the meta-analysis was made available for this study. Results were pooled using a hierarchical Bayesian random effects model with pre-specified stratification according to drug and carrier type. Outcomes of interest were rates of death, myocardial infarction (MI), target lesion revascularization (TLR), major adverse cardiac events (MACE) (composite of death, MI and TLR), angiographic restenosis, stent thrombosis, edge restenosis and late incomplete stent apposition (Table 3).

Results from the meta-analysis indicated that there were no differences in MI or death rate associated with BMS or DES. Significant differences arose, however, when comparing the TLR rates (Table 3). Results were stratified by type of DES (sirolimus and paclitaxel polymer) and by pooling all DES.

Table 3: Clinical inputs from meta-analysis[20]

Variable	Pooled DES Point Estimate (%)	Pooled BMS Point Estimate (%)
Sirolimus		
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
Paclitaxel (polymeric)		
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
Sirolimus+paclitaxel (polymeric and non-polymeric)		
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

The number needed to treat (NNT) was calculated separately based on the pooled trial data, the sirolimus data and the paclitaxel data, using the formula NNT=1/absolute risk reduction (ARR). Pooled results showed that 6.7 individuals with the sirolimus DES and 11.2 with the paclitaxel DES needed to be treated to avoid one TLR. The NNT was influenced by the control group event rate in the relevant randomized trials.

NNT= 1/ARR

$NNT_{DES\ pooled}=1/(0.142-0.048)=10.6$

$NNT_{sirolimus}=1/(0.185-0.035)=6.7$

$NNT_{paclitaxel}=1/(0.122-0.033)=11.2$

Table 4 presents the adverse events post-PCI and after stent implantation. In terms of adverse events or complications, the consequences of DES thrombosis are the same as those of BMS thrombosis. Edge restenosis has the same clinical features as in-stent restenosis. Late incomplete stent apposition has no clinical correlate according to the clinical trials. These results were used as clinical inputs for the decision analytic model.

Table 4: Adverse events

Variable	Pooled DES Point Estimate (%)	Pooled BMS Point Estimate (%)
Sirolimus		
Stent thrombosis	0.6	0.6
Edge restenosis	3.6	1.3
Late incomplete stent apposition	13.3	1.9
Paclitaxel (polymeric)		
Stent thrombosis	0.7	0.5
Edge restenosis	2.9	2.5
Late incomplete stent apposition	8.6	6.9
Sirolimus and paclitaxel		
Stent thrombosis	0.7	0.5
Edge restenosis	3.0	1.9
Late incomplete stent apposition	8.5	5.1

Two interventional cardiologists and one non-interventional cardiologist, who perform angioplasty and stent implantation at health centres across Canada, were surveyed. Table 5 presents their estimates of the proportion of clinical procedures that occur after a TLR.

4.8 Perspective and Determination of Cost Inputs

The perspective of the analysis determines the cost components included looking at the direct medical costs. Only costs incurred after the original stent implantations were considered.

Costs were presented in hospital and provincial health system perspectives. The analysis conducted from a hospital perspective included stent acquisition costs, drug acquisition costs, hospitalization costs (incorporating, where applicable, the costs of repeat revascularization procedures) and rehabilitation costs. The analysis from a provincial payer perspective included stent acquisition costs, drug acquisition costs, hospitalization costs, rehabilitation costs, physician fees and costs for laboratory and diagnostic tests.

Primary cost sources included stent manufacturers, the SWCHSC's drug formulary, the Ontario Drug Benefit formulary, the Ontario Case Costing Initiative (OCCI) and personal communications. Costs were presented in 2002 to 2003 Canadian dollars. No discounting was applied.

Table 5: Survey of post-TLR interventions based on expert opinion of three cardiologists

Post-TLR Intervention Variables	**Expert 1 (Quebec) Based on 50,000 Angioplasties from 1995 to 2000**	**Expert 2 (Ontario) Based on Upcoming 12 Months in Sunnybrook Catheterization Laboratory**	**Expert 3 (Nova Scotia) Based on Upcoming 12 months in QEII Catheterization Laboratory**	**Mean**
	JB, personal communication, 2004 Feb 16	EC, personal communication, 2004 Feb 16	LT, personal communication, 2004 Feb 16	
PTCA combined	84%	no data	no data	84%
PTCA alone (balloon)	no data	5% to 10%, mean point estimate of 7.5%	PTCA alone-1.8% (mean point estimate 7.5%*.25)	4.7% (range 1.8% to 10%)
PTCA (cutting balloon)	no data	25%	PTCA cutting balloon-5.6% (mean point estimate 7.5%*.75)	15.3% (range 5.6% to 25%)
Balloon predilatation before stent	no data	50% of stent cases	no data	50%
DES implantation	no data	25%	35% to 40% (mean point estimate of 37.5%)	31.3% (range 25% to 40%)
BMS implantation	no data	0%	0%	0%
Brachytherapy	Reserved for minority of cases after failing ≥1 PTCA attempts at treating restenosis	30%	25% (with cutting balloon)	27.5% (range 25% to 30%)
CABG	16%	10% to 15% (mean point estimate 12.5%)	20% (after failure of 1 TLR treatment)	16.2% (range 10% to 20%)
Death	no data	0%	0%	0%
Medical (drug)	no data	no data	10%	10%
Does original type of stent affect post-TLR intervention?	I think it is reasonable to assume that TLR treatment is independent of BMS or DES	Treatment of ISR may vary depending on type of initial stent; while DES implant may be effective for ISR of a bare stent (there are some observational data and randomized trials underway), there are no data on DES implanted to treat DES restenosis	I think that the type of stent put in originally will have an impact on treatment for ISR. If a DES was put in originally, implanting a second DES is unlikely, unless it was for uncovered disease (proximal or distal to original DES) or for disease progression. Not a lot of data about performing brachytherapy after DES failure. For DES failures, I suspect that a larger group of patients may cross over to surgery (perhaps as much as 50%)	

4.8.1 Stent costs

The hospital acquisition costs for DES and BMS were often unclear, as complex purchasing matrices based on the volumes of stents and other products that were used, were negotiated with stent manufacturers. The manufacturer's list price of CYPHER in Canada is C$3,500 per unit (David Duerr, Cordis/Johnson & Johnson Medical Products, Toronto: personal communication, 2004 Mar 2). The DES cost from Boston Scientific was unavailable. An informal survey of cardiologists indicated that the price of DES has dropped since their release into the market. Point estimates for costs were unavailable because of confidential contract negotiations between hospitals and stent manufacturers. Consequently, personal communications were used as the primary source for device acquisition costs. For this analysis, Ontario stent costs were unavailable or not provided. A generic Quebec cost of C$2,400 for DES was used for the sirolimus and paclitaxel eluting stents (JB, personal communication, 2004 Mar). Current prices in most high volume centres may be significantly lower for both types of DES.

The manufacturer's list price for the Bx Velocity^{TM} stent (a BMS) in Canada is C$1,690 per unit (David Duerr: personal communication, 2004 Mar 2). Cardiologists indicated that the price of BMS has dropped since their release into the market several years ago, particularly since multiple manufacturers have entered the market. The previous analysis of glycoprotein IIb/IIIa inhibitor drugs used a cost of $780 for BMS, based on the costs of SWCHSC's cardiac catheterization laboratory (as of financial year 2001 to 2002), although bare stent costs have fallen further since then. Table 6 outlines the costs used in the economics and budget analyses.

Table 6: Stent costs

Stent	Cost	Source
DES		
Cordis sirolimus CYPHER	$2,400	JB, personal communication, 2004 Mar
Boston Scientific paclitaxel TAXUS	$2,400	JB, personal communication, 2004 Mar
BMS		
Generic BMS (Cordis, Boston Scientific, Medtronic, Guidant)	$608	JB, personal communication, 2004 Mar

4.8.2 Drug costs

Glycoprotein IIb/IIIa inhibitors (eptifibatide and abciximab) are used during and after angioplasty procedures. The costs for each drug, based on standard dosages, are $409.75 and $1,609.95 respectively (Table 7). The mean cost of eptifibatide and abciximab ($1,009.85) was used as a model input only when individuals underwent a repeat PTCA. It was not considered for the original BMS or DES procedure. This analysis only looked at the downstream costs associated with the initial implantation. Table 8 lists the cost of clopidogrel, which is prescribed for one year as long-term medication management in this patient population.

Table 7: Dosage and cost (2003) calculations for eptifibatide and abciximab

Drug	Bolus Dose	Infusion Dose	Bolus Cost (20 mg/10 mL bolus vial=$38)*	Infusion Cost (75 mg/100 mL infusion vial=$111.25)*	Total Cost
Eptifibatide	180 µg/kg x 2	2 µg/kg/min for 18 hours	Bolus=30.24 mg so 2 bolus vials =$76 needed	Infusion=181.44 mg so 3 infusion vials=$333.75 needed	$409.75
Drug	**Bolus Dose**	**Infusion Dose**	**Bolus and Infusion Costs (10 mg/5 mL vial=$536.65)***		**Total Cost**
Abciximab	0.25 µg/kg	0.125 µg/kg/min for 12 hours	21 mg+7.560 mg = 28.560 mg, so 3 vials needed		$1,609.95
Mean drug costs					$1,009.85

*Source: PPS pharma publication.[43] Based on ESPRIT clinical trials, median weight of patients given eptifibatide=84 kg. Same weight used in abciximab calculations.

Table 8: Drug therapy costs used in model

Drug	Cost
Glycoprotein IIb/IIIa inhibitors (average of eptifibatide and abciximab)	$1,009.85
Clopidogrel for one year	$806.88*

*Source: Ontario drug benefit formulary/comparative drug index: no. 38.[44]

4.8.3 Hospitalizations

Aggregate level costs for hospitalizations relating to revascularization and CABG were obtained from the OCCI. All ICD-9-CM codes submitted to OCCI when requesting cost data were confirmed with an expert interventional cardiologist (EC, personal communication, 2003 Feb 11).

Created by the MOHLTC, the OCCI continues the work started by the Ontario Case Costing Project (OCCP). The OCCI's primary objectives are the collection of case costing data in support of improved management decision making and the development of hospital funding methods. Participating hospitals implemented a standardized case costing method developed by the OCCI and participated in a series of milestone audits to ensure the quality of the data. The OCCI collects case cost data for acute in-patient, day surgery and ambulatory care. A search of all hospitalizations between April 1, 2000 to March 31, 2001 inclusive was conducted for patients older than 18 years, based on the ICD-9-CM codes submitted. For the 2000 to 2001 data set, OCCI collected patient-specific cost records from eight hospitals in the province: Arnprior & District Memorial Hospital Corporation, Lakeridge Health, London Health Sciences Centre, Mount Sinai Hospital, The Ottawa Hospital General Site, St. Michael's Hospital, Trillium Health Centre and the University Health Network. Table 9 summarizes the OCCI's data for the relevant patient population.[45] Although SWCHSC was excluded from this group, five of the eight hospitals included would have contributed costing data specific to angioplasties performed by their catheterization laboratories.

Table 9: OCCI's data (2000 to 2001) for coronary angioplasty and CABG hospitalizations

Type of Hospitalization	Number of Cases	% Male	% Stented	% Glycoprotein IIb/IIIa	Average Length of Stay (days)	2000 to 2001 Total Average Cost Per Patient
PTCA	3,076	72	90.9	19.2	2.28	$4,903
CABG	2,921	79	N/A	N/A	9.88	$13,822
MI or death	3,977	64	N/A	N/A	8.28	$7,863

N/A=not applicable.

Table 10 summarizes the adjustments made to ensure actual hospital costs were used without the duplicate costs associated with the BMS and glycoprotein inhibitor drug therapies. The second column in Table 10 lists the 2000 to 2001 total average costs, while column 3 shows the 2003 inflated costs based on the Bank of Canada's inflation rate. To arrive at the hospitalization component of the PTCA procedure, the costs of stent and glycoprotein IIb/IIIa inhibitor drug therapy (weighted by proportion) were subtracted (column 4). Among patients, 90.9% received a stent and there were 1.5 stents per person.[46]

Table 10: Corrected total average costs for hospitalizations included in decision analytic models

Type of Hospitalization	2000 to 2001 Total Average Cost	Inflated 2003 Cost*	Deduction Components	Corrected 2003 Cost
PTCA	$4,903	$5,208	Stent=90.9% x $608 X 1.5=$829.01 ($608 cost taken from Table 6) Drug=19.21% X $1,009.85=$193.99 ($1,009.85 cost taken from Table 8)	$4,185
CABG	$13,822	$14,683	N/A	$14,683
MI or death	$7,863	$8,353	N/A	$8,353

*The Bank of Canada provides an online inflation calculator[47] that uses monthly consumer price index (CPI) data from 1914 on to show changes in cost of a fixed "basket" of consumer purchases. Results generated by the inflation calculator are based on the most recent month for which CPI data are available (approximately two months before month accessed).
N/A=not applicable

4.8.4 Brachytherapy

Bracytherapy costs of $3,000 were based on $2,500 for the catheter plus $500 for the technician's time in the catheterization laboratory (Nancy Cooper, Sunnybrook and Women's

College Health Sciences Centre, Toronto: personal communication, 2003 spring). The overall cost of $3,057.10 also includes $57.10 for the cardiologist's billing.

4.8.5 Rehabilitation

A cost of $1,500 for cardiac rehabilitation was obtained from the Cardiac Care Network of Ontario (CCN).[48]

4.8.6 Physician visits and diagnostic testing

Provincial health ministries are responsible for the costs associated with physician billing and diagnostic testing. These costs can be divided into in-patient and out-patient costs (Table 11). Physician visit and diagnostic procedure costs were obtained from the Schedule of Benefits for Ontario[49] and were used to represent the costs for the rest of Canada. The physician billing codes, diagnostic procedure codes and laboratory codes were validated by interventional cardiologists (EC, personal communication, 2003 spring. LT, personal communication, 2003 spring).

Table 11: Physician plus testing and costs per outcome

Outcome	Physician Billing Code	Physician Costs	Test	Total Test Costs
CABG	In-patient cardiology consultation Cardiac surgeon repair of 1 vessel Cardiac surgeon repair of 2 vessels Cardiac surgeon repair of additional vessel Out-patient cardiac surgeon assessment Out-patient GP visit x 2	$112.35 $2,002.86 $2,303.81 $184.00 $40.40 $108.20	Stress test X 2	$182.90
PTCA	In-patient cardiology consultation In-patient PTCA procedure In-patient PTCA additional vessel In-patient stent procedure In-patient angiogram + catheterization Out-patient cardiologist assessment x 2	$112.35 $427.10 $192.30 $71.45 $268.03 $114.20	Routine blood work X 2 Stress test Myocardial perfusion	$32.05 $91.45 $934.00
Complication	Same as PTCA			
MI or death	In-patient CCU physician (first day) In-patient CCU physician (second and third days) Out-patient cardiologist assessment Out-patient GP visit	$207.00 $179.40 $57.10 $54.10	N/A	N/A

N/A=not applicable; CCU=critical care unit; GP=general practitioner

To determine the physician cost of a PTCA, Dr. Eric Cohen (EC, personal communication, 2003 fall) was asked to provide his expert opinion as an interventional cardiologist regarding the percentage breakdown for the number of vessels requiring angioplasty (Table 12).

Table 12: Vessels requiring angioplasty

Number of Vessels	Proportion of Individuals (%)
1	70
2	25
3	5
4	0
5	0

The physician cost of a CABG was also weighted by the number of vessels. Dr. Stephen Fremes was asked to provide his expert opinion as a cardiothoracic surgeon regarding the percentage breakdown for the number of vessels requiring CABG (Table 13). (Dr. Stephen Fremes, Sunnybrook and Women's Health Sciences Centre, Toronto: personal communication, 2003 spring).

Table 13: Vessels requiring CABG

Number of Vessels	Proportion of Individuals (%)
1	5
2	20
3	50
4	20
5	5

4.8.7 Laboratory costs

Table 14 lists the out-patient laboratory tests conducted (each unit has a fixed rate of $0.517).

Table 14: Laboratory test costs during out-patient care in 2003

Laboratory Test	Units	Total Cost (1 unit = $0.517)
Complete blood count	16	$8.272
Triglycerides	5	$2.585
Total cholesterol	5	$2.585
Random glucose	5	$2.585
Creatinine	5	$2.585

The troponin test was excluded as it is not covered by OHIP because it is not listed on the Schedule of Benefits for Laboratory Services and Fees with a unique L-code. It is a cardiac-related blood test that is usually ordered in a hospital. Consequently, it is covered in a hospital's global budget.

4.8.8 Cost inputs for clinical pathways

Table 15 outlines each costing equation associated with the clinical pathways used in the decision analytic model. Each equation combines components such as stent and drug acquisition costs, hospitalization costs, physician billing, diagnostic and laboratory testing costs and rehabilitation costs.

Table 15: Description of costing equations for each clinical pathway

Description of Population	Costing Equation	Cost Components
No TLR	Stent (BMS or DES) Complication (stent thrombosis) Rehabilitation (provincial perspective only)	$608 or $2,400 $9,761.37 $1,500
TLR ordinary balloon	Stent (BMS or DES) Ordinary balloon PTCA (PTCA hospital-PTCA out-patient±brachytherapy) Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $250 $9,761.37 $9,761.37 $1,500
TLR cutting balloon	Stent (BMS or DES) Cutting balloon PTCA Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $750 $9,761.37 $9,761.37 $1,500
TLR brachytherapy	Stent (BMS or DES) Brachytherapy Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $3,057.10 $9,761.37 $1,500
TLR BMS implantation	Stent (BMS or DES) BMS PTCA Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $608 $9,761.37 $9,761.37 $1,500
TLR DES implantation	Stent (BMS or DES) DES PTCA Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $2,400 $9,761.37 $9,761.37 $1,500
TLR CABG	Stent (BMS or DES) CABG (hospital+out-patient) Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $19,617.52 $9,761.37 $1,500
TLR drugs	Stent (BMS or DES) Medications (clopidogrel for one year) Complication Rehabilitation (provincial perspective only)	$608 or $2,400 $806.88 $9,761.37 $1,500
TLR death	Stent (BMS or DES) MI or death (hospital+out-patient) Rehabilitation (dependent on perspective)	$608 or $2,400 $8,850.60 $1,500

4.9 Determination of Resource Utilization Elements

Resources related to the intervention and the comparator are used in previous treatment, supportive therapies, clinical investigations (e.g., laboratory and diagnostic tests such as INR and myocardial perfusions), out-patient visits and hospitalizations. It is not always possible to obtain data on resource utilization or the proportions needed to populate the trees from the

published literature, especially for a Canadian population. Population rates for procedures are available in Canada (e.g., CCN of Ontario, APPROACH in Alberta, BC Cardiac Registry in British Columbia), but the databases contain limited information on the clinical management pathway for patients undergoing PCI. No resource allocation differences are assumed in the use of DES compared to BMS, as all costs associated with the index procedure, including those for drugs, laboratory tests, physician billing, nursing time and disposables (apart from the costs of the stents) are considered to be identical for the DES and BMS groups. Although this is thought to be the most reasonable assumption based on current practice, it is conceivable that if DES became widely adopted, then routine post-PCI surveillance for restenosis (i.e., the use of stress testing or nuclear perfusion scanning) would diminish.

4.10 Incremental Analysis

An incremental analysis is conducted when there is no dominance associated with one of the treatments. In this analysis, costs and outcomes are considered. The primary outcome of interest is avoidance of TLR. The ratios of the increments of the average expected costs and the average expected outcomes when DES are compared to BMS are calculated using the following formula:

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

where ICER=incremental cost-effectiveness ratio.

4.11 Subgroup Analysis

No subgroup analysis was conducted as stratified data were unavailable. ICERs from $5,000/TLR avoided to $20,000/TLR avoided were used to determine the incremental cost for DES and BMS.

4.12 Assumptions

- Clinical outcomes are mutually exclusive.
- No resource allocation differences are associated with the use of DES compared to BMS (drugs, laboratory tests, physician billing, nursing time and procedures will all be considered identical in the two groups).
- There is no incremental difference after the first year for out-patient resource utilization.
- The cost of death is the same as the cost of MI.
- Stent thrombosis always results in acute MI.
- The consequences of DES thrombosis are the same as those of BMS thrombosis.
- Edge restenosis has the same clinical features as in-stent restenosis.
- Late incomplete stent apposition has no clinical correlate according to the clinical trials; this is an angiographic finding only.
- Only patients with ISR will undergo another revascularization procedure

- A stent thrombosis results in another PTCA procedure. Patients may undergo additional revascularization procedures, but procedures that are unrelated to the index lesion (and hence to ISR) would not differ as to whether a DES or BMS was used for the index lesion.
- The average number of stents (1.5) implanted per patient is the same for a DES and a BMS.
- Only the paclitaxel polymer DES were examined as the non-polymer version is unavailable.
- Since the non-polymer version is unvailable, only the paclitaxel polymer DES were examined.

4.13 Sensitivity Analysis

Simple univariate sensitivity analysis was conducted by varying the cost of DES from $608 (the cost of BMS) to the original DES list price of $3,500.

To assess the impact of uncertainty on all other variables, a probabilistic sensitivity analysis was done using Crystal Ball™ software. Probabilistic analysis, through Monte Carlo simulation, has been considered to be appropriate to address uncertainty with model inputs in the evaluation of health care interventions.[50] In a Monte Carlo simulation, different estimates of outcomes such as costs and life expectancies are obtained by re-running a decision model using different values for each data input.[51] Values for each data input are randomly selected from specified probability distributions. Based on several such replications, a set of outcomes can be obtained. There is no rule governing the appropriate number of replications, as this is a function of the level of uncertainty for the outcomes of interest. The greater the number of replications conducted, the more precise the estimate of the outcomes.

The probabilistic analysis focused on the comparison of DES and BMS, based on the pooled data. For this analysis, the authors adopted a simulation with 5,000 replications.

It is necessary to specify probability distributions for three sets of parameters: the probability of TLR with BMS and DES, the probability of stent thrombosis with BMS and DES and the probabilities of the consequences of TLR. For the first two sets of parameters, uncertainty is characterized by a beta distribution based on data from the Babapulle[20] meta-analysis. For the consequences of TLR, data are not empiric, but based on clinical opinion.

To characterize the uncertainty, a Dirichlet distribution covering all probabilities was adopted, assuming a lot of uncertainty using a small sample size of 10 (Table 16).[52]

Data were required for the costs of stents and the costs of associated complications and TLR. The costs of stents were assumed to be fixed in the probabilistic sensitivity analysis. For other costs, it was assumed that uncertainty would be characterized by a normal distribution. Given that data were based on clinical expert opinion, the method in previous studies was followed by assuming a standard deviation equivalent to 50% of the mean (Table 16).[53]

In the deterministic analysis, it was assumed 1.5 stents would be used per procedure. For the probabilistic analysis, we incorporated uncertainty regarding the number of additional stents required. This was characterized by a gamma distribution (0.5, 1).

Table 16: Probability distributions for Monte Carlo simulation

		Expected Value	Probability Distribution*
Costs			
DES		$2,400	Fixed
BMS		$608	Fixed
Stent thrombosis or PTCA		$6,995	Normal ($6,995, $3,497)
Rehabilitation		$1,500	Normal ($1,500, $750)
Ordinary balloon		$250	Normal ($250, $125)
Cutting balloon		$750	Normal ($750, $375)
Brachytherapy		$3,112	Normal ($3,112, $1,556)
CABG		$18,600	Normal ($18,600, $9,300)
Medications		$807	Normal ($807, $403)
MI		$8,851	Normal ($8,851, $4,425)
Number of stents		1.5	1 + gamma (0.5, 1)
Probabilities			
Stent thrombosis	DES	0.007	Beta (19, 2628)
	BMS	0.005	Beta (12, 2444)
TLR	DES	0.048	Beta (127, 2520)
	BMS	0.142	Beta (349, 2107)
Ordinary balloon		0.01875	Dirichlet (0.1875, 0.5625, 2.5, 3.75, 2, 1)
Cutting balloon		0.05625	
Brachytherapy		0.25	
DES implantation		0.375	
CABG		0.2	
Medications		0.1	

* Normal distributions are characterized by means and standard errors of the mean. Beta distributions are characterized by number of events and number of non-events. Gamma distributions are characterized by their shape and scale. Dirichlet distributions are characterized by number of each type of event.

The cost-effectiveness of treatment options is presented in terms of the incremental cost per TLR avoided (ICER), which is the ratio of the mean incremental costs and incremental benefits.[54] The cost-effectiveness is also expressed as the expected value of net monetary benefit, which is a function of the maximum willingness to pay for a unit of outcome (λ).[55]

Uncertainty regarding the cost-effectiveness of DES relative to BMS was assessed through credible intervals for the incremental costs; effects and cost-effectiveness and cost-effectiveness acceptability curves.[56,57] Credible intervals are similar to confidence intervals and present the lower and upper limit of a 95% interval for outcomes. Cost-effectiveness acceptability curves show the probability that treatment is cost-effective given the available data.

The contribution to the uncertainty regarding the cost-effectiveness of stents was assessed through an estimation of the expected value of perfect information (EVPI) for distinct parameter groups (trial-based probabilities, consequences of TLR and costs), assuming a range of values for avoiding a TLR to be from $0 to $50,000.[58,59]

5 RESULTS: ECONOMIC EVALUATION

"SIRIUS (sirolimus)" included the nine-month data from the SIRIUS trial published by JW Moses *et al.,* in NEJM 2003 Vol 349, 1315-23.[2] "TAXUS IV (paclitaxel polymer)" included the nine-month data from the TAXUS IV trial published by GW Stone *et al.,* in NEJM 2004 Vol 350, 221-31.[19] "Sirolimus pooled" included data from clinical trials RAVEL, SIRIUS, C-SIRIUS and E-SIRIUS; and was based on the Babapulle meta-analysis results.[20] Paclitaxel (polymer) pooled" included trial data from TAXUS I, II and IV; and was based on the Babapulle meta-analysis results.[20]

5.1 Hospital Perspective

The expected costs during one year ranged from $4,350 to $4,430 per patient for DES and $1,939 to $2,505 for the BMS group (Table 17). Patients receiving DES had significantly lower rates of TLR than those in the BMS group (Table 18). Therefore, DES were associated with a higher cost but significantly better outcomes. ICER were between $12,527 and $29,048 per TLR avoided (Table 19).

5.2 Provincial Perspective

The expected costs per patient during one year ranged from $4,702 to $4,797 for DES and $2,404 to $3,072 for the BMS group (Table 20). Patients receiving DES had a significantly lower rate of TLR (8.3% to 15.0% absolute risk reduction) than those in the BMS group (Table 21). DES were associated with a higher cost, but significantly better outcomes. ICER were between $11,133 and $27,687 per TLR avoided (Table 22).

5.3 Simulation Analysis for ICERs and Cost Differentials

A simulation exercise was done to determine what DES to BMS cost differences were needed to attain particular ICERs. For sirolimus, there would need to be a $750 difference between BMS and DES acquisition costs to obtain an ICER of $5,000 per TLR. At the $20,000 per TLR avoided level, the difference in acquisition cost was $3,000. In contrast, for paclitaxel, there would need to be a $445 difference between BMS and DES acquisition costs to obtain an ICER of $5,000 per TLR. At the $20,000 per TLR avoided level, the difference in acquisition cost was $1,780 (Appendix 2).

Table 17: Average annual expected costs per patient associated with DES (hospital perspective)

Comparator	SIRIUS (sirolimus) ($)	TAXUS IV (paclitaxel polymer) ($)	Sirolimus Pooled ($)	Paclitaxel (polymer) Pooled ($)
DES	4,430	4,350	4,384	4,374
BMS	2,355	1,939	2,505	2,009
Difference (DES−BMS)	2,075	2,411	1,879	2,365

Table 18: Average expected TLR rates (hospital perspective)

Comparator	SIRIUS (sirolimus) (%)	TAXUS IV (paclitaxel polymer) (%)	Sirolimus Pooled (%)	Paclitaxel (polymer) Pooled (%)
DES	4.1	3.0	3.5	3.3
BMS	16.6	11.3	18.5	12.2
Difference (DES−BMS)	−12.5	−8.3	−15.0	−8.9

Table 19: Incremental analytical results (hospital perspective)

Comparators	Incremental Ratio
SIRIUS (sirolimus) BMS	$16,600 per TLR avoided
TAXUS IV (paclitaxel polymer) BMS	$29,048 per TLR avoided
Sirolimus pooled BMS	$12,527 per TLR avoided
Paclitaxel (polymer) pooled BMS	$26,562 per TLR avoided

Table 20: Average annual expected costs per patient associated with DES (provincial perspective)

Comparator	SIRIUS (sirolimus) ($)	TAXUS IV (paclitaxel polymer) ($)	Siroliumus Pooled ($)	Paclitaxel (polymer) Pooled ($)
DES	4,797	4,702	4,742	4,730
BMS	2,898	2,404	3,072	2,487
Difference (DES−BMS)	1,899	2,298	1,670	2,243

Table 21: Average expected TLR rates (provincial perspective)

Comparator	SIRIUS (sirolimus) (%)	TAXUS IV (paclitaxel polymer) (%)	Sirolimus Pooled (%)	Paclitaxel (polymer) Pooled (%)
DES	4.1	3.0	3.5	3.3
BMS	16.6	11.3	18.5	12.2
Difference (DES–BMS)	−12.5	−8.3	−15.0	−8.9

Table 22: Incremental analytic results (provincial perspective)

Comparators	Incremental Ratio
SIRIUS (sirolimus) BMS	$15,192 per TLR avoided
TAXUS IV (paclitaxel polymer) BMS	$27,687 per TLR avoided
Sirolimus pooled BMS	$11,133 per TLR avoided
Paclitaxel (polymer) pooled BMS	$25,202 per TLR avoided

5.4 Sensitivity Analysis Results

One-way sensitivity analyses were conducted using a range of costs for DES. The threshold value describing the point at which the cost of a DES provides a similar average expected cost compared to the cost of a BMS is provided in Table 23.

Table 23: One-way sensitivity analysis

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

The one-way sensitivity analysis indicated the cost of a DES in the TAXUS and paclitaxel trials would need to be lower than the DES cost in the SIRIUS and sirolimus trials, because the difference in clinical outcomes comparing paclitaxel and placebo were not as large as those from the sirolimus studies. Consequently, the cost had to be lower to overcome any differences in efficacy.

For the probabilistic sensitivity analysis, Table 24 reports the expected value of costs and TLRs for BMS and DES. DES are more costly with an expected incremental cost of $1,848 (95% credible interval $510; $5,278) and an absolute reduction in TLR of 9.4% (95% credible interval 7.8%; 11.0%). DES were more costly in 99.94% of replications and led to a reduction in TLRs in 100% of replications (Figure 2). The incremental cost per TLR avoided with DES was $19,640 with a great degree of uncertainty as characterized by the 95% credible interval, which ranged from $5,177 to $57,420.

The uncertainty about the cost-effectiveness of DES is illustrated in the cost-effectiveness acceptability curve (Figure 3). At a value of $50,000 for each TLR avoided, the probability that DES is cost-effective is 93.56%. For values <$1,000 for each TLR avoided, the probability that DES is cost-effective is <10%. There is no commonly accepted value for a TLR avoided.

Analysis of the EVPI (expected value of perfect information) found that uncertainty regarding the costs contributed most to the overall uncertainty regarding the cost-effectiveness of DES (Figure 4).

Table 24: Expected values for costs and effects from Monte Carlo simulation

	BMS	**DES**	**Difference**
Cost	$2,544 ($1,473, $4,281)	$4,392 ($2,975, $10,287)	$1,848 ($510, $5,278)
Probability of TLR	14.2% (12.8%, 15.6%)	4.8% (4.0%, 5.6%)	−9.4% (−11.0%, −7.8%)
Cost per TLR avoided			$19,640 ($5,177, $57,420)

Figures in parentheses are 95% credible intervals.

Figure 2: Incremental Costs and Effects for DES from Monte Carlo Simulation

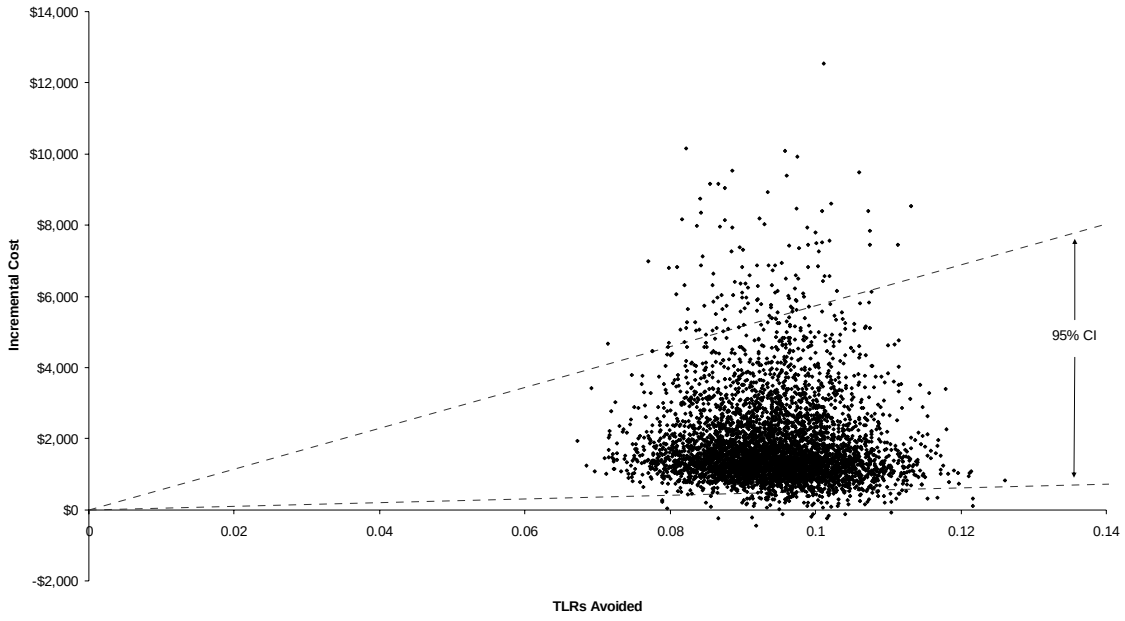


Figure 3: Cost-effectiveness acceptability curve for DES compared to BMS

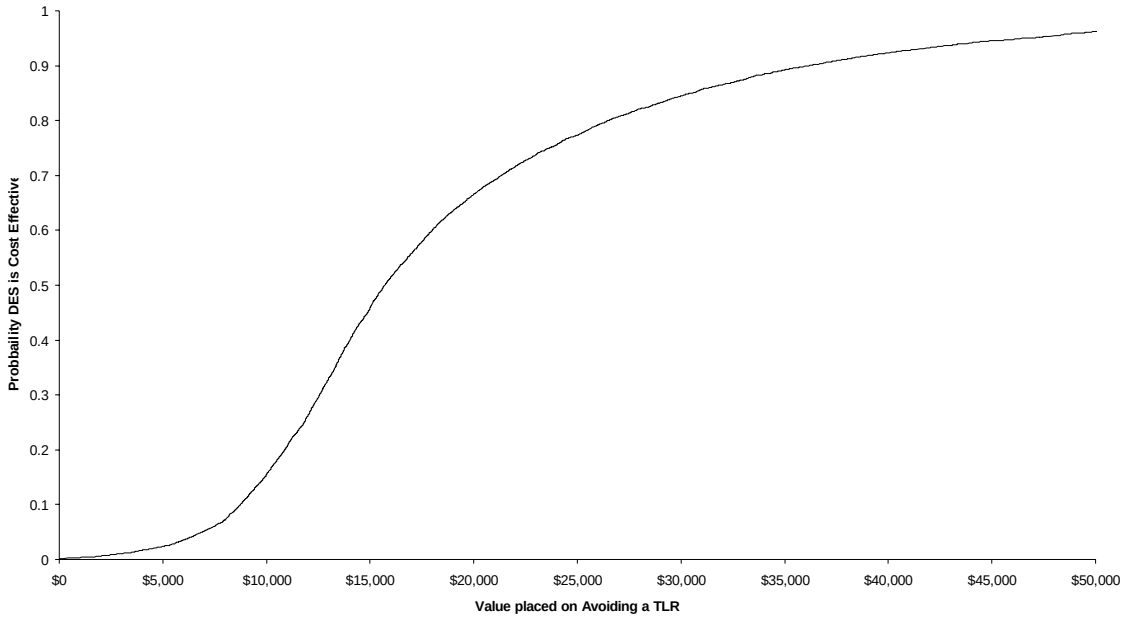
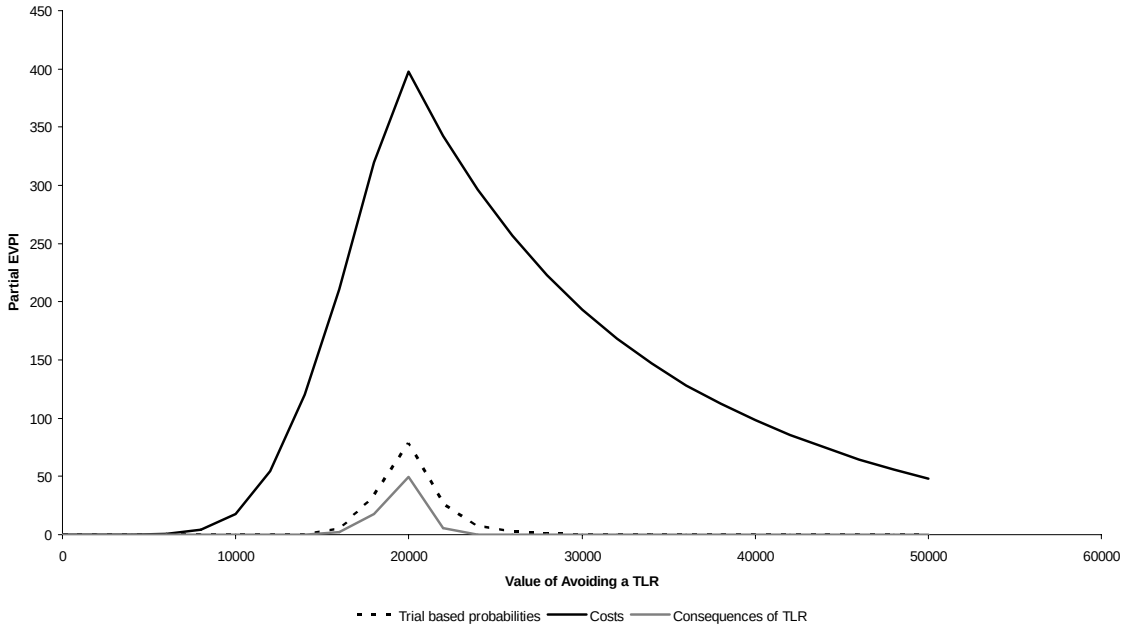


Figure 4: Partial EVPI for parameter groups by value of avoiding a TLR



EVPI=expected value of perfect information

6 METHODS: BUDGET IMPACT ANALYSIS

6.1 Objective

The purpose of this budget impact analysis was to examine the potential impact of the introduction of DES at a macroeconomic level from a hospital and provincial payer perspective.

6.2 Perspective

Hospital and provincial perspectives were used. Sunnybrook and Women's College Health Sciences Centre (SWCHSC) was used as the base case site for the hospital perspective. SWCHSC is a large tertiary care centre with approximately 400 acute care beds. It is one of 12 hospitals providing PCI services in Ontario and treats about 12% of the angioplasty patients in the province. SWCHSC started implanting DES in July 2003 at the same time as the other 11 CCN sites.[60]

Ontario was used as the base case from the provincial perspective, as it was the first province to receive funding for DES. The Ontario MHLTC allocated $12 million for DES in 2003 to 2004.[46] Hospitals were instructed to target DES use for patients considered to be at high risk for restenosis. It is assumed that funding will continue into 2004 to 2005. Based on the average monthly number of angioplasty procedures for April 2002 to September 2003, reported by the CCN, there were 13,774 angioplasty procedures performed annually across Ontario (Table 25).

Table 25: Angioplasty procedures conducted in Ontario and SWCHSC

Time Horizon	Average Angioplasty Procedures per Month in Ontario[3]	Average Angioplasty Procedures at SWCHSC per Month (proportion of total in Ontario)[3]
April to June 2002	1,161	156 (13.4%)
July to September 2002	1,068	148 (13.8%)
October to December 2002	1,128	149 (13.2%)
January to March 2003	1,154	139 (12.0%)
April to June 2003	1,118	119 (10.6%)
July to September 2003	1,258	147 (11.7%)
Combined period from April 2002 to September 2003	1,148 (13,774 per year)	143 (1,716 per year)

6.3 Type of Analysis

For the budget impact analysis, the cost was disaggregated for high risk of restenosis patient groups. The CCN reported that patients who constituted the upper 40% of the restenosis "risk spectrum" were likely to benefit sufficiently from DES and that it would be reasonable to provide funding for this group. The immediate and three-year cost impacts were considered in this analysis.

We examined the potential impact that using DES would have on provincial drug plan costs. We postulated that if funding were provided for DES, then DES could replace BMS.

The budget impact was calculated in 2003 Canadian dollars for the base case analysis, because we obtained angioplasty and stent information for that year. The results for Ontario were extrapolated to give a result for Canada. The base case analysis included several scenarios with varying DES utilization from 0% to 100%.

Switch rates from BMS to DES were unavailable from published peer-reviewed literature. However, in the CCN Working Group on Drug Eluting Stents Report on Initial Utilization Strategy,[21] eligibility criteria indicate that an estimated 40% of BMS stents could be switched to DES.

Site-specific and province-specific utilization data were obtained from SWCHSC and CCN Ontario. The cost of a DES varied in the published literature and personal communications. We used a DES cost of C$2,400 for the sirolimus and paclitaxel stents. A BMS was priced at C$608.

We examined only the impact of DES on the hospital and provincial systems. All other costs associated with stent implantation were assumed to be identical between the BMS and DES groups. Our analysis can be considered to be an upper bound for the budget impact, as it does not estimate potential savings from DES use due to a possible reduced need for restenosis testing and possible reduction in expensive revascularization procedures such as CABG.

6.3.1 Hospital

Several analyses were conducted. In the first, the 2003 SWCHSC statistics from the cardiac catheterization laboratory were used. The number of angioplasty procedures, proportion of stents implanted and the number of stents implanted were collected. The mean number of stents implanted per angioplasty procedure was calculated. A second analysis calculated the total hospital costs based on variable DES and BMS utilization. The rate of DES utilization at SWCHSC was varied between 0% and 100%. The total hospital costs based on the number of angioplasty procedures were calculated by multiplying the mean number of stents by the number of angioplasty procedures. This number was then multiplied by the cost of a DES or BMS. In a third analysis, the DES cost was reduced from 0% to 80%, in 10% increments. Here, the DES cost was multiplied by the mean number of stents per procedure.

Several subanalyses were conducted. We calculated the cost to each Ontario hospital conducting angioplasty procedures for patients at high risk of restenosis (considered to be 40% of the population). The costs were calculated by multiplying the annual number of angioplasty procedures per site by the proportion of patients who received stent implantation. This value was then multiplied by the proportion of patients considered to be at high risk of restenosis and then multipled by the mean number of stents. The DES stent cost was used to determine the total cost to the hospital. We calculated the cost to each Ontario hospital conducting angioplasty procedures for all stented patients. The costs were calculated by multiplying the annual number of angioplasty procedures per site by the proportion of patients who received stent implantation. This value was then multiplied by the mean number of stents. The DES cost was then used to determine the total cost to the hospital for a total conversion of BMS to DES.

"Budget impact" (or the total additional cost to the hospital)
= number of DES stents used X incremental cost per DES
= total PCI procedures x stent rate X number of stents per case X DES conversion rate X (DES cost – BMS cost)

6.3.2 Province

Ontario was used as the base case, but the budget impact analysis was extrapolated to Canada. The Ontario statistics for the number of angioplasty procedures from 1994 to 1995 and 2002 to 2003 were obtained from the CCN. We approached other provinces in Canada for their angioplasty rates. The proportion was used to calculate the number of angioplasty procedures. The population-weighted number of angioplasty procedures was multiplied by the number of stent implantations and the proportion of patients considered to be at high risk of restenosis. This value provided us with the number of stent implantation procedures per province, which was then multiplied by the average number of stents per procedure and the cost of DES. For the sensitivity analysis, the cost of a DES was reduced by 50% ($1,200) and reduced to the cost of a BMS ($608). The same calculation was done for 100% of patients receiving DES implantations.

Three-year projections were calculated by linear regression based on the Ontario angioplasty procedure numbers. The best fit curve was also used to predict utilization and then costs.

6.4 Results: Budget Impact Analysis

6.4.1 Utilization statistics for hospital perspective

SWCHSC was used as the base case hospital for this analysis. From July to September 2003, SWCHSC conducted an average of 11.7% of angioplasty procedures in Ontario (Table 26). This rate is similar to other centres across Ontario including the Hamilton Health Sciences Centre, University of Ottawa Heart Institute and the University Health Network (Toronto).[3]

SWCHSC's department of cardiology reported that 1,674 patients underwent a PCI in 2003. Of angioplasty patients, 90% (N=1,520) received stent implantation. A total of 2,582 stents were

implanted during this time. A mean of 1.7 stents per patient was originally used in calculations for SWCHSC. Several clinical experts and reviewers considered this to be higher than the average number of stents per patient at other facilities. As a result, the lower value of 1.5 was used to represent the mean number of stents per patient in this analysis.

Since the introduction of DES utilization in the hospital (July 2003) to the end of the year, 409 or 29% of the 1,418 stents were DES (Table 26).

Ontario provided DES funding for patients who were at high risk of restenosis and who would be able to respond to DES treatment (40% of the population). Using SWCHSC as the base case hospital, 608 patients would be theoretically appropriate for DES implantation.

In Table 28, the proportion of BMS to DES implanted was varied from no use (0%) to only DES (100%) utilization. Using SWCHSC as the base case, there were 2,582 stents implanted in 2003. Using a BMS price of $608, the cost to the hospital would be almost $1.6 million if all stents implanted were BMS. If 40% of the stents implanted were DES with a cost $2,400, then the total cost to the hospital would be $3.4 million. If all stents implanted were DES, with a cost of $2,400, then the total cost to the hospital would be $6.2 million (Table 27).

In the results of the previous analysis (Table 27), we considered the number of stents used regardless of the patients who were considered to be at high risk of restenosis. According to the annual statistics compiled by CCN, 1,520 patients had angioplasty procedures that required stent implantation, so based on the 40% at high risk of restenosis criterion for DES eligibility, 608 of these patients would be considered to be eligible for DES implantation.

In Table 28, we varied the population at risk of restenosis and therefore requiring DES implantation. If 100% of patients are at risk of restenosis, all 2,582 DES used would cost $6.2 million. In terms of budget increases to provide DES for 40% of patients at risk for restenosis, the BMS stent budget ($627,942) would have to increase by 295% to cover the additional cost of DES ($2,478,720).

As the cost of DES is not fixed in Canada, we evaluated the cost to the hospital if the DES acquisition cost was reduced in increments of 10% in a sub-analysis. We assumed the cost of DES would decrease, based on the market shift since their introduction. Only when the DES cost was reduced by 75% of the base case did the cost approximate that of a BMS (Table 29). The number of stents (N=2,582) was obtained from the base case scenario (SWCHSC). We assumed that all BMS were converted to DES.

Table 30 is another sub-analysis of the number of angioplasties per catheterization laboratory in Ontario (based on July to September 2003 data) as listed on the CCN web site. The monthly average number of angioplasties (column 2) was translated into an annual number of angioplasty procedures (column 3). Among angioplasty patients, 90% received stent implantations (column 4). Of these patients, 40% are considered to be at high risk of restenosis and consequently suitable for DES implantation (column 5). The number of DES cases (column 6) for the high risk population was based on multipliying the number of high risk patients by 1.5 stents/patient for each site and for the Ontario total. The cost of implanting DES in 40% of the population at risk of restenosis in Ontario was calculated to be $19.6 million, which is an increase of $14.6 million from the cost of BMS ($4.96 million).

Table 26: Hospital statistics for 2003, based on SWCSHC data

2003	PTCAs	PTCAs with Stent	Unplanned PTCAs	Unplanned PTCAs with Stent	Total PTCAs	Total PTCAs with Stent (Proportion of Patients with PTCAs+Stent and PTCAs)	Total Number of Stents	Number of Stents per Patient	Number of BMS (Percentage of total stents)	Number of DES (Percentage of total stents)
January	12	92	4	35	143	127 (88.8%)	212	1.7	212 (100%)	0
February	8	100	1	21	130	121 (93.1%)	189	1.6	189 (100%)	0
March	4	95	10	34	144	129 (89.6%)	229	1.8	229 (100%)	0
April	3	34	6	24	67	58 (86.6%)	106	1.8	106 (100%)	0
May	8	82	14	42	146	124 (84.9%)	199	1.6	199 (100%)	0
June	7	87	5	44	143	131 (91.6%)	229	1.7	229 (100%)	0
July	4	91	7	37	139	128 (92.1%)	229	1.8	220 (96.1%)	9 (3.9%)
August	8	88	3	39	138	127 (92.0%)	218	1.7	185 (84.8%)	33 (15.1%)
September	9	95	5	55	164	150 (91.5%)	237	1.6	177 (74.7%)	60 (25.3%)
October	7	99	7	63	176	162 (92.0%)	282	1.7	141 (50.0%)	141 (50.0%)
November	5	87	9	38	139	125 (89.9%)	224	1.8	165 (73.6%)	59 (26.3%)
December	2	87	5	51	145	138 (95.2%)	228	1.7	121 (53.1%)	107 (46.9%)
Statistics										
Annual Total	77	1037	76	483	1674	1520	2582	20.5	2173 (84%)	409 (16%)
Mean	6.4	86.4	6.3	40.3	139.5	126.7 (90.6%)	215.2	1.7	181.1	68.7

Table 27: Total hospital cost of 2,582 stents implanted based on variable utilization of BMS and DES

Percentage of BMS	BMS Subtotal ($608 each) ($)	Percentage of DES	DES Subtotal ($2,400 each) ($)	Cost to Hospital of BMS+DES ($)
100	1,569,856	0	0	1,569,856
90	1,412,870	10	619,680	2,032,550
80	1,255,885	20	1,239,360	2,495,245
70	1,098,899	30	1,859,040	2,957,939
60	941,914	40	2,478,720	3,420,634
50	784,928	50	3,098,400	3,883,328
40	627,942	60	3,718,080	4,346,022
30	470,957	70	4,337,760	4,808,717
20	313,971	80	4,957,440	5,271,411
10	156,986	90	5,577,120	5,734,106
0	0	100	6,196,800	6,196,800

Table 28: Hospital cost of 1,520 angioplasty procedures (2,582 stents in total) with variation in DES use for patients at risk of restenosis

Population at Risk of Restenosis	Number of BMS	Total Cost to Hospital with Cost of BMS=$608
All BMS and no DES	2,582	$1,569,856
Angioplasty Population at Risk of Restenosis	**Number of DES**	**Variable Cost to Hospital for DES with Cost of DES=$2,400 ($)**
0% stent population (N=0)	0	0
10% stent population	258	619,200
20% stent population	516	1,238,400
30% stent population	775	1,860,000
40% stent population	1033	2,479,200
50% stent population	1,291	3,098,400
60% stent population	1,549	3,747,600
70% stent population	1,807	4,336,800
80% stent population	2,066	4,958,400
90% stent population	2,324	5,577,600
100% stent population	2,582	6,196,800

Table 29: All BMS converted to DES (N=2,582)
stratified by reducing DES cost

Reduction	Reduced DES Cost	Total Cost to Hospital
0% reduction (base case)	$2,400	$6,196,800
10% reduction in DES cost	$2,160	$5,577,120
20% reduction in DES cost	$1,920	$4,957,440
30% reduction in DES cost	$1,680	$4,337,760
40% reduction in DES cost	$1,440	$3,718,080
50% reduction in DES cost	$1,200	$3,098400
60% reduction in DES cost	$960	$2,478,720
70% reduction in DES cost	$720	$1,859,040
75% reduction in DES cost	$600*	$1,549,200
80% reduction in DES cost	$480	$1,239,360

* Considered to be approximate cost of a BMS.

Table 31 shows full DES adoption in Ontario as per the number of angioplasties per catheterization laboratory in the province from July to September 2003.[3] There would be an increase in cost of $36.5 million from the $12.4 BMS cost to cover the DES cost of $48.9 million. The number of DES cases for the overall population was based on multiplying the number of all angioplasty patients by 1.5 stents/patient for each site and for the province in total.

6.4.2 Utilization statistics for provincial perspective

CCN's annual report for 2002 to 2003[61] indicated that the annual number of angioplasty procedures has increased since 1994 to 1995 (Table 32) and that in 2002 to 2003, 13,539 angioplasty procedures were conducted in Ontario.[61] The authors are aware that in Section 6.4.1 of this report, the annual number of angioplasty procedures is higher, with 15,096 as the total number of angioplasty procedures performed in 2002 to 2003. This difference is attributed to the absence of results from one catheterization laboratory (Kitchener).[61] Consequently, 15,096 is a more accurate figure for the number of angioplasties conducted in Ontario. According to SWCHSC data, 90% of patients received stent implantation and the number of stents used was assumed to be 1.5 per patient. Using these percentages, the total number of stents used in Ontario would be 20,379.

Table 33 presents the total cost associated with the use of DES in high risk of restenosis patients (considered to be 40% of the Ontario population). The number of angioplasty and stent implantations was weighted by the provincial sample size (using a 0.1%). If 40% of patients are considered to be at high risk for restenosis, then Canada would be expected to pay $50.7 million for DES (at a cost of $2,400 per DES). This is $37.9 million higher than the cost of BMS ($12.8 million at $608 per BMS). If all BMS patients were converted to DES (Table 34), the cost to the Canadian system is projected to be $126.8 million (at a cost $2,400 per DES). This is $94.7 million higher that the cost of BMS ($32.1 million at $608 per BMS).

Table 30: Hospital costs associated with DES for high risk of restenosis patients

	Monthly Average of Angioplasty Procedures	Annual Number of Angioplasty Procedures	Number of Patients with Stent Implant (90% of angioplasties)	Number of Patients at Risk for Restenosis (40% of stent implants)	Number of DES (1.5 stents per procedure)	Cost of DES ($2,400 each)
Sudbury	89	1,068	961	384	576	$1,382,400
Ottawa Heart Institute	153	1,836	1,652	661	992	$2,380,800
Kingston General	105	1,260	1,134	454	681	$1,634,400
University Health Network	159	1,908	1,717	687	1,031	$2,474,400
SWCHSC	147	1,764	1,588	635	953	$2,287,200
St. Michael's Hospital	124	1,488	1,339	536	804	$1,929,600
Rouge Valley	20	240	216	86	129	$309,600
Trillium Health Centre	149	1,788	1,609	644	966	$2,318,400
Kitchener-St. Mary's	60	720	648	259	389	$933,600
Hamilton	143	1,716	1,544	618	927	$2,224,800
London	110	1,320	1,188	475	713	$1,711,200
Total for Ontario	1,258	15,096	13,586	5,434	8,151	$19,562,400

6.4.3 Three-year projections

We used Ontario data to project angioplasty rates out three years to 2006. We attached trend lines to graphs using linear analysis first. We also calculated the trend line using an exponential curve for Ontario based on the actual data points for the number of angioplasty procedures (Tables 35 and 36). Table 36 shows, from a provincial perspective, if the number of angioplasty procedures increases and the high risk patients are implanted with DES, the cost to Ontario in 2006 would be between $22 million and $27 million (linear and exponential increases respectively) using a DES price of $2,400. In comparison, the cost to the province for BMS at $608 each, using the same linear and exponential projections, would be $5 million and $7 million. By 2006, there would be an additional annual cost of $17 million to $20 million associated with DES utilization in this high risk of restenosis group.

Table 37 shows if all BMS stents were replaced with DES, then the cost to the province by 2006 would be between $54 million to $67 million if DES were priced at $2,400. Three-year projections for BMS show a cost of $14 million to $17 million. The province would need to pay an additional $40 million to $50 million for all patients undergoing DES implantation compared with BMS by 2006.

Table: 31: Catheterization laboratory costs associated with 100% adoption of DES

	Monthly Average of Angioplasty Procedures	Annual Number of Angioplasty Procedures	Number of Patients with Stent Implantation (90% of angioplasties)	Number of DES (1.5 Stents per procedure)	Cost of DES ($2,400 each)
Sudbury	89	1,068	961	1,442	$3,460,800
Ottawa Heart Institute	153	1,836	1,652	2,478	$5,947,200
Kingston General	105	1,260	1,134	1,701	$4,082,400
University Health Network	159	1,908	1,717	2,576	$6,182,400
SWCHSC	147	1,764	1,588	2,382	$5,716,800
St. Michael's Hospital	124	1,488	1,339	2,009	$4,821,600
Rouge Valley	20	240	216	324	$777,600
Trillium	149	1,788	1,609	2,414	$5,793,600
Kitchener-St. Mary's	60	720	648	972	$2,332,800
Hamilton	143	1,716	1,544	2,316	$5,558,400
London	110	1,320	1,188	1,782	$4,276,800
Ontario Total	1,258	15,096	13,586	20,379	$48,909,600

Table 32: CCN of Ontario angioplasty and stent statistics

	1994-1995	1995-1996	1996-1997	1997-1998	1998-1999	1999-2000	2000-2001	2001-2002	2002-2003
Number of angioplasty procedures in Ontario	5,047	5,386	5,977* 6,176*	6,562	7,537	8,574	10,363	12,529	13,539
Proportion of stents	N/A	N/A	N/A	73%	82%	N/A	N/A	N/A	N/A
Number of stents per patient	N/A	N/A	N/A	N/A	1.41	N/A	N/A	N/A	N/A

*Two different values reported in 1996-1997 annual report and 1997-1998 annual report
CCN=Cardiac Care Network; N/A=not applicable.

Table 33: Total cost associated with DES use in high risk of restenosis angioplasty patients (40% of stented population in Ontario)

	Population (Statistics Canada, October 2003)	Number of Angioplasty Procedures	Patients Receiving Stent Implantation (90% of angioplasties)*	High Risk of Restenosis patients (40% of stent implants)	Number of Stents (1.5 per procedure)	Overall Cost with Cost of DES= $2,400	Overall Cost with Cost of DES= $1,200	Overall Cost with Cost of BMS=$608	Overall Cost Difference DES=$2,400; BMS=$608	Source of Angioplasty Information
Ontario	12,096,627	15,096	13,586	5,434	8,151	$19,562,400	$9,781,200	$4,955,808	$14,606,592	CCN-Ontario
Canada	31,361,611	39,136	35,222	14,089	21,134	$50,721,600	$25,360,800	$12,849,472	$37,872,128	Calculation

*Proportion of angioplasty patients who received stent implantation is 90%, based on SWCSHC statistics.

Table 34: Total cost associated with DES use in all stent implantation patients

	Population[62]	Number of Angioplasty Procedures	Patients Receiving Stent Implantation (90% of angioplasties)	Number of Stents (1.5 per procedure)	Overall Cost with Cost of DES=$2,400	Overall Cost with Cost of DES=$1,200	Overall Cost with Cost of DES=Cost of BMS=$608	Overall Cost Difference DES=$2,400; BMS=$608	Source of Angioplasty Information
Ontario	12,096,627	15,096	13,586	20,379	$48,909,600	$24,454,800	$12,390,432	$36,519,168	CCN-Ontario
Canada	31,361,611	39,136	35,222	52,833	$126,799,200	$63,399,600	$32,122,464	$94,676,736	Calculation

Table 35: CCN of Ontario angioplasty and stent statistics

	1994-1995	1995-1996	1996-1997	1997-1998	1998-1999	1999-2000	2000-2001	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006
Number of angioplasty procedures in Ontario	5,047	5,386	5,977* 6,176*	6,562	7,537	8,574	10,363	12,529	13,539	14,287 (linear)† 15,615‡ (exponential)	15,504 (linear) 17,938 (exponential)	16,722 (linear) 20,607 (exponential)

*Two different values reported in 1996-1997 annual report and 1997-1998 annual report. CCN=Cardiac Care Network

† Based on the formula 1217.5x+3329.6

‡ Based on the formula $4481.3e^{0.1387x}$

Table 36: Three-year cost projections for Ontario for 40 percent high risk of restenosis population

Year	Number of Angioplasty Procedures	Patients with Stent Implantation (90% of angioplasties)	High Risk of Restenosis Patients (40% of stent implants)	Number of DES (1.5 per procedure)	Cost of DES with Cost of DES=$2,400	Cost of DES with Cost of DES=$1,200	Cost of DES with Cost of DES=Cost of BMS=$608
2003 (actual)	13,539	12,185	4,873	7,310	$17,544,000	$8,772,000	$4,444,480
Based on linear projections							
2004	14,287	12,858	5,143	7,715	$18,516,000	$9,258,000	$4,690,720
2005	15,504	13,954	5,582	8,373	$20,095,200	$10,047,600	$5,090,784
2006	16,722	15,050	6,020	9,030	$21,672,000	$10,836,000	$5,490,240
Based on exponential projections							
2004	15,615	14,054	5,622	8,433	$20,239,200	$10,119,600	$5,127,264
2005	17,938	16,144	6,458	9,687	$23,248,800	$11,624,400	$5,889,696
2006	20,607	18,546	7,418	11,127	$26,704,800	$15,133,200	$6,765,216

Table 37: Three-year cost projections for Ontario for the entire stent population

Year	Number of Angioplasty Procedures	Patients with Stent Implantation (90% of Angioplasties)	Number of DES (1.5 per procedure)	Cost of DES with Cost of DES=$2,400	Cost of DES with Cost of DES=$1,200	Cost of DES with Cost of DES=Cost of BMS=$608
2003 (actual)	13,539	12,185	18,278	$43,687,200	$21,933,600	$11,113,024
Based on linear projections						
2004	14,287	12,858	19,287	$46,288,800	$23,144,400	$12,054,816
2005	15,504	13,954	20,931	$50,234,400	$25,117,200	$12,726,048
2006	16,722	15,050	22,575	$54,180,000	$27,090,000	$13,725,600
Based on exponential projections						
2004	15,615	14,054	21,081	$50,594,400	$25,297,200	$8,544,832
2005	17,938	16,144	24,216	$58,118,400	$29,059,200	$14,723,328
2006	20,607	18,546	27,819	$66,765,600	$33,382,800	$16,913,952

7 DISCUSSION

7.1 Background

This is the first economic evaluation for DES that includes a Canadian hospital and provincial perspective. DES are expected to reduce the number of revascularization procedures, but they will increase hospital and provincial expenditures. We calculated the incremental cost-effectiveness analyses to be $10,000 to $30,000 per revascularization avoided. Possible cost savings, not considered in the economic evaluation and budget impact analysis, could arise from using DES procedures for some CABG patients. There is also the possibility of fewer diagnostic tests for restenosis being done.

Cohen *et al.,* conducted the first study that applied the principles of economic evaluations to new devices in coronary revascularization. Coronary stenting (BMS) and glycoprotein IIb/IIIa inhibitors were associated with significant acquisition costs. Separate economic evaluations of stents and abciximab suggested that these were cost-effective. A study performed in the US, based on EPIC, suggested that the costs associated with abciximab use would be offset by the savings in medical care for cardiac events that were avoided.[42] Coronary stenting was projected to have a reasonable incremental cost-effectiveness ratio of <$20,000 per life year gained compared with balloon angioplasty.[63] Cohen outlined cost-effectiveness threshold values pertaining to angioplasty restenosis and stent restenosis rates. Using the studies baseline assumptions, an acceptable cost-effectiveness ratio was $40,000 per quality adjusted life-year (QALY). Incremental ratios, however, were presented as the cost per QALY, not the cost per revascularization avoided.[63]

There is no long-term evidence for the effects of DES on morbidity and mortality. The primary outcome reported in studies has been the rate of target lesion revascularization (TLR). There needs to be some clarification regarding revascularization outcomes used in the interventional cardiology clinical trials. Stone *et al.* define the target vessel revascularization (TVR) and the TLR. A TVR is the need for repeat revascularization (percutaneous or surgical) for re-narrowing anywhere in the treated (target) coronary vessel. In contrast, a TLR was defined as repeated revascularization for recurrent narrowing anywhere in the stent or within the 5 mm border proximal or distal to the stent.[19] The rate of TVR will likely be greater than that of TLR, given that a TLR occurs in and around the implanted stent and a TVR revascularization may occur anywhere in the vessel.

All DES studies reported outcomes in terms of TLR, because the focus of the analysis was to compare DES and BMS. It made sense to investigate the only stent-associated restenosis and subsequent revascularization. In contrast, the clinical trials reporting on brachytherapy and intravascular ultrasound often reported results in terms of TVR or repeat revascularization. Babapulle *et al.* defined TLR as the rate of PCI or surgical revascularization of the stented lesion in and around the stent.[20] TLR is considered to be the most appropriate outcome for a study examining differences in stents. We assumed that any difference in TLR rate between DES and BMS would be similar to the TVR difference for both stents. Consequently, the cost per TLR avoided would be similar to the cost per TVR avoided. This assumption was based on the fact that nothing other than the type of stent was different in the treatment regimen.

Since DES implantations are not associated with differences in MI or mortality, we cannot calculate a cost per life-year gained. The cost per QALY is difficult to measure. For a cost-effectiveness analysis, the typical outcomes reported are the QALYs gained and the incremental cost-effectiveness ratio (ICER). Table 38 provides incremental ratios (cost per revascularization avoided calculated using results from several cardiology studies). If the economic outcome is presented in terms of a cost per event avoided, then it is difficult to make comparisons to other cardiology studies where survival and QALYs are determined. Depending on the relative value of new therapeutic interventions in cardiology, some may think that spending an extra $5,000 to avoid a TLR is acceptable or reasonable, while others may be willing to spend as much as $20,000 per TLR avoided. There is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective, in contrast to outcome measures such as cost per life-year or cost per QALY gained, where ranges for cost-effectiveness are implicit.[64,65]

It is difficult to place the results of this analysis using "cost per event avoided" in context with those of other cardiology analyses using "cost per death avoided," given that we do not have accepted thresholds for the value of a revascularization event avoided. Consequently, the results of this analysis were examined in light of those from other cardiology studies of accepted technologies such as brachytherapy, intravascular ultrasound and stenting versus balloon. These technologies have a minimal effect on mortality and morbidity, but they do affect repeat revascularization. Incremental ratios based on these studies ranged from US$1,333 per TVR avoided for intravascular ultrasound to US$18,619 per repeat revascularization avoided with brachytherapy.

Table 38: Revascularization rates

Source	Revascularization Rate for Comparator A	Revascularization Rate for Comparator B	Cost of Comparator A	Cost of Comparator B	ICER
Other therapies					
Brachy-therapy[72]	0.374 (1 year repeat revascularization combined for brachytherapy)	0.471 (1 year repeat revascularization combined for placebo)	US$28,543	US$26,737	$18,619/ repeat revascu-larization avoided
Brachy-therapy[72]	0.328 (updated 1 year repeat revascularization combined for brachytherapy)	0.471 (updated 1 year repeat revascularization combined for placebo)	US$26,352 updated	US$26,729 Updated	$2,636/ repeat revascu-larization avoided updated
Intra-vascular ultrasound (IVUS)[73]	0.174 (2 year TVR for stenting with IVUS+balloon catheter)	0.291 (2 year TVR for stenting with angiographic guidance only)	US$15,947	US$16,103	$1,333/TVR avoided
Stenting versus balloon in acute MI[74]	0.131 (1 year repeat revascularization combined for stented)	0.225 (1 year repeat revascularization combined for balloon)	US$20,571	US$19,595	$10,383/ repeat revascu-larization avoided
Stenting versus CABG in multivessel disease[75]	0.21 (1 year repeat revascularization combined for stenting)	0.038 (1 year repeat revascularization combined for CABG)	US$10,665	US$13,638	$17,285/ repeat revascu-larization avoided
Stenting versus balloon in single vessel disease[63]	0.20 (baseline estimates for angiographic restenosis rate in de novo lesion for stenting)	0.37 (baseline estimates for angiographic restenosis rate in de novo lesion for PTCA)	US$7,900	US$5,400	$14,706/ restenosis avoided
DES using model costs (province and hospital)					
Sirolimus pooled (province)[20]	0.035 (TLR) (sirolimus)	0.185 (TLR) (BMS)	$4,730 (province) $4,374 (hospital)	$3,002 (province) $2,443 (hospital)	$11,520/ TLR (province) $12,873/ TLR (hospital)

Source	Revascularization Rate for Comparator A	Revascularization Rate for Comparator B	Cost of Comparator A	Cost of Comparator B	ICER
Paclitaxel polymer pooled[20]	0.033 (TLR) (paclitaxel polymer)	0.122 (TLR) (BMS)	$4719 (province) $4,364 (hospital)	$2,463 (province) $1,969 (hospital)	$25,596/ TLR avoided (province) $26,910/ TLR avoided (hospital)
DES Pooled[20]	0.048 (TLR) (DES)	0.142 (TLR) (BMS)	$4,851 (province) $4,476 (hospital)	$2,617 (province) $2,118 (hospital)	$23,766/ TLR avoided $25,085/ TLR avoided
SIRIUS only[2]	0.041 [TLR during 270-day follow-up (f/up) for sirolimus stent]	0.166 (TLR during 270 day f/up for standard stent)	$4,730 (province)	$3,002 (province)	$13,824/ TLR
TAXUS IV[19]	0.047 (TVR for 9-month f/up for paclitaxel polymer	0.12 (TVR for 9-month f/up for BMS)	$4,719 (province)	$2,441 (province)	$31,205/ TLR
DES abstracts					
SIRIUS (based on results from 400/1,100 patients with DES/total stents)[26]	0.068 (1 year repeat revascularization of target vessel for sirolimus stent)	0.176 (1 year repeat revascularization of target vessel for BMS)	US$14,245	US$13,646	$5,546/ TVR avoided assumed DES cost=$3,000
Sirolimus in Brazil (N=58)[69]	0.912 (6-month restenosis-free survival for sirolimus stent)	0.708 (6-month restenosis-free survival for BMS)	US$5,594	US$4,390	$5,902/ restenosis avoided
Paclitaxel-polymer (TAXUS II)[70]	0.0536 (model estimates for repeat revascularization rates for paclitaxel stent) 0.07 (model estimates for repeat revascularization	0.1643 (model estimates for repeat revascularization rates for BMS) 0.2145 (model estimates for repeat revascularization	US$20,170 US$20,467	US$19,327 US$20,238	$7,615/ repeat revascu-larization avoided $1,585/ repeat revascu-

Source	Revascularization Rate for Comparator A	Revascularization Rate for Comparator B	Cost of Comparator A	Cost of Comparator B	ICER
	rates in diabetic paclitaxel stent)	rates in diabetic BMS)			larization avoided in diabetics (assumed DES cost=$3,000, BMS= $1,1100)

Our results indicate that the incremental ratio of $11,133 to $15,192 per TVR avoided for the sirolimus eluting stent falls in the range of ICER of other cardiovascular procedures considered to be acceptable by some investigators in the US. It is unclear, however, what the norms for these procedures in a Canadian context would be. Other results from our analysis fall on the high end of the range. The paclitaxel data show a higher cost per revascularization avoided, suggesting a potentially less favourable cost-effectiveness result. There is an unexpectedly high TVR rate in the BMS treatment arm in one of the pivotal sirolimus studies. Stone *et al.* presented only TVR rates and TLR rates for their paclitaxel eluting study. We calculated the ICER per TVR avoided for this study to be $31,205.

An analysis varying the allowable difference in price between BMS and DES to achieve an acceptable ICER was conducted. For example, if one is willing to accept $5,000/TLR avoided, then the maximum price premium for a DES over a BMS that one would be willing to pay would be $750. If $20,000/TLR avoided is accepted, then one would be willing to pay a $3,000 premium.

Results from the economic evaluations are based on the clinical inputs and model assumptions. The same case could be made for DES-BMS comparisons in which the higher overall costs of DES over BMS is the dominant factor. This would result in high ICERs even though DES offers lower TLR and repeat revascularization rates. Only if the DES costs decrease or the difference between TLR and repeat revascularization rates widens (through patient populations such as diabetics) can the ICER for DES be lowered to facilitate DES utilization on a wider scale.

The differences in DES and BMS costs for a range of ICER values indicate that sirolimus is associated with higher incremental costs than paclitaxel because of better clinical outcomes with paclitaxel.

7.2 Other Economic Evaluations of DES

A few economic evaluations for DES in other jurisdictions have been conducted. Shrive *et al.* conducted an economic evaluation of sirolimus eluting stents from an Alberta provincial perspective using the APPROACH data base.[66] Using a quality adjusted life-year approach, investigators determined that sirolimus eluting stents compared to BMS in patients undergoing

PCI had an incremental value of $58,721/QALY. This ICER decreased in patients with diabetes ($44,135/QALY) and those individuals 75 years or older ($40,129/QALY). Limitations include the fact that DES have not shown to decrease the rate of MI, CABG or mortality.[67] Galanaud *et al.* calculated the theoretical break-even cost for sirolimus eluting stents in France, the Netherlands and the US. The costs of the DES ranged from 2,100 euros to 3,150 euros and 60 euros to 800 euros for BMS. The clinical results were based on the RAVEL study of sirolimus. The perspective of the analysis was the health system. The break-even price was defined as the cost of a BMS plus avoided revascularization costs all divided by the number of stents per procedure.[68] Results showed that the break-even price was approximately 1,400 euros in France (21% to 39% lower than the actual DES cost), 2,000 euros in the Netherlands (12% lower than the actual DES cost) and 2,700 euros in the US (14% lower than the actual DES cost). A sensitivity analysis indicated that DES were cost-neutral or resulted in savings when the number of stents per procedure was decreased and the reduction in revascularization rate approached 25%. The results were limited by the fact that the results of only RAVEL were used for the clinical inputs and that there was no single price for DES. An incremental value was not calculated.

Some abstracts on the economics of DES have been presented. Polanczyk *et al.,* presented the results of their cost-effectiveness analysis for sirolimus from a Brazilian health care perspective in an abstract presented at the Transvascular Cardiovascular Therapeutics conference in 2003. A cohort of 58 patients was evaluated. The authors assumed a 70% relative reduction in TLR rates and applied the total costs between DES and BMS. The ICER was US$5,887 per restenosis avoided. There was limited information available from the abstract in terms of sources for the information.[69] Lacey conducted a cost-effectiveness analysis for paclitaxel from a US perspective. A decision analytic model was constructed for a year time horizon. Clinical events were obtained from a health maintenance organization (HMO) database, the literature and TAXUS II results. The calculated ICER was $7,615 per revascularization avoided in the general population and $1,585 per revascularization avoided in diabetic patients.[70] Morneault *et al.* evaluated the economic impact of DES from an American hospital system perspective.[71] The study assumed 100% conversion from BMS to DES. The reimbursement and expenses for DES were examined. Results, which are presented in an abstract, indicated that there would be an increase of >US$10 million in one year after DES approval for use in the hospital system. Authors used a readmission reduction rate of 25%, but did not present the source of the data or conduct sensitivity analysis. The authors concluded that the widespread adoption of DES over BMS would result in severe financial hardship. An economic evaluation to determine the "value" of DES was not conducted.

Morton *et al.,*[76] used stent dimensions and diabetes as predictors of restenosis. Criteria for DES utilization were applied to patients who were stratified according to stent and comorbidity. Results showed that DES was considered to be the most "cost-effective" in patients considered to be at high risk and that this required an increase in budget by 44%. In contrast, when low risk patients were converted to DES, the stent budget increased 229%. A formal economic evaluation was also not conducted. Cohen *et al.* presented the results of a cost-effectiveness analysis based on the SIRIUS trial.[77] The DES cost was evaluated at $3,000 per stent. Results showed that the total one-year costs were higher in the DES group (US$14,245 per patient) than the BMS group ($13,642) despite the 62% decrease in TVR. The incremental cost from a

societal perspective was $5,542 per repeat revascularization avoided.[26] The incremental value is similar to those calculated in this study and for BMS implantation and brachytherapy.

7.3 DES and New Clinical Evidence

In a systematic review of DES conducted by Hill *et al.,*[78] 14 randomized controlled published and unpublished studies were used. The search strategy included MEDLINE®, EMBASE® and the Science Citation Index between 1990 and 2002 for studies comparing DES (paclitaxel, sirolimus, actinomycin, everolimus) to non-DES. Bibliographies, meeting abstracts and the Internet were also examined. Outcomes evaluated included death, MI, revascularization, event rate and restenosis. Results showed no differences in death and MI rates.With respect to event rates, paclitaxel had an odds ratio (OR) of 0.30 and sirolimus OR 0.63 at one year. Limitations of the meta-analysis included the heterogenous studies (single vessel, multiple vessel, stable angina, acute coronary syndrome, differential vessel size), early DES studies with differential follow-up periods and unpublished studies. In addition, the analysis was based on several different types of paclitaxel DES.

7.4 Diabetics and DES

There is limited information on the effect of DES in diabetic patients who are at high risk for vascular events post-procedure.[79] While diabetic patients were eligible to be included in the randomized controlled trials, the analyses did not stratify results for diabetic patients only. One study examined the effect of DES in a diabetic population only.[80] The results of that study are based on the diabetic population in the RAVEL study and show a 0% restenosis rate for diabetic patients with DES compared with a 42% restenosis rate in diabetic in the BMS population. There was a significant difference in major adverse cardiac events (MACE), in that more BMS diabetic patients had higher MACE rates ($p<0.01$). The RAVEL study used a BMS that may be associated with a higher rate of restenosis, thus increasing the restenosis rate between the two types of stents. Moreover, a small sample size was used.

7.5 Stents Now and in the Future

While sirolimus has been clinically tested in one type of stent with a uniform type of coating in a fixed dose (CYPHER), different DES systems are available for paclitaxel eluting stents. A European analysis[81] was published using six RCTs with 3,319 patients [TAXUS-I (n=61), TAXUS-II (n=536), ASPECT (n=177), ELUTES (n=190), DELIVER-I (n=1041) and TAXUS IV (n=1314)]. In the TAXUS series, paclitaxel released from the stent was controlled by the Translute polymer and the dose density of 1 $\mu g/mm^2$ significantly reduced the angiographic parameters of restenosis and improved clinical outcomes. In the other studies, however, no polymer carrier was used. In ASPECT and ELUTES, there was a dose-dependent effect on the angiographic parameters of restenosis with the best results for a paclitaxel dose density of approximately 3.0 $\mu g/mm^2$. Clinical outcomes at six and 12 months, however, were not improved in these studies without coating. The studies unanimously showed the paclitaxel eluting stents are safe, if clopidogrel is added to ASA for three to six months. The safety of paclitaxel eluting stents is independent of the

stent design, the dose density and the presence of a polymer carrier system. For paclitaxel eluting stents using a polymer carrier, the dose density of 1 $\mu g/mm^2$ is effective, whereas for paclitaxel eluting stents without a polymer carrier, the minimal effective dose density is higher (3 $\mu g/mm^2$). Despite their improvement of angiographic parameters, paclitaxel eluting stents without a polymer carrier did not demonstrate a positive effect on clinical outcome. In contrast, polymer-based paclitaxel elution produced a significant clinical benefit. Colombo *et al.* also published data assessing the effectiveness of slow and moderate release polymer-based paclitaxel eluting stents (TAXUS) compared to control stents.[37]

Different devices made by various manufacturers will soon be available to include everolimus in the FUTURE study;[82] angiopeptin in the SWAN study[83] and cytochalasin D.[84] Results have been encouraging. We suspect that all types will be made available and that the choice will depend on the size of the vessel. There is no evidence to suggest that one DES is superior to another.

At the American College of Cardiology's scientific session in New Orleans, March 2004, B. Meier presented initial data from the REALITY trial, which is a prospective, randomized study of the first head-to-head comparison of the CYPHER sirolimus eluting stent and the TAXUS paclitaxel eluting stent (sponsored by Cordis, the manufacturer of CYPHER). There were 1,386 patients at 90 centres in Europe, Asia and Latin America enrolled with 1,941 lesions treated and 32% of the patient population being diabetic.[85] Principal investigator Marie-Claude Morice has stated that, "Although the two arms of the investigation remain blinded at this point, we know the rate of successful stent delivery for the two arms – 98% and 99% – which are virtually equivalent," and that deliverability relates to the ability to cross the lesion with the stent in the targeted vessel. Stent lengths up to 33 mm are being used in the trial.[86]

The availability of different products may introduce competition and ultimately decrease the price of DES.

The tacrolimus eluting stent has an integral Carbofilm thromboresistant coating combined with the capability to load the drug and release it from deep sculptures made on the external surface of the stent. The advantages of this design are the possibility to load higher amounts of drug; to selectively deliver it to the vessel wall without loss in the blood stream and to improve the biocompatibility and thromboresistance of the stent. Preclinical studies, using tacrolimus as the biological agent, showed excellent vessel tissue response and mild inflammation scores. A significant reduction of intimal proliferation was observed in comparison with a control stent. The enrollment in a safety first-in-man evaluation has been successfully completed. A randomized, double-blind, multicentre study is expected to start at the completion of the "safety" evaluation.[87]

The Medtronic Endeavor DES[88] utilizes the drug ABT-578, which blocks the cell cycle regulatory protein mTOR from functioning, so smooth muscle cell proliferation is inhibited and ultimately, restenosis cannot occur. Medtronic Inc. received conditional approval from the US Food and Drug Administration (FDA) in February 2004 to begin its third clinical trial to support global product approval of its drug-releasing coronary stent. The US-based trial, to be conducted at 30 sites, seeks to compare the safety and effectiveness of Medtronic's Endeavor Drug Eluting Coronary Stent with the Cypher stent, which was first to market, sold by Johnson & Johnson's

Cordis Corp. Although both are made with similar laser micromachining processes, the stents contain different drugs that are released from special polymers to reduce renarrowing in arteries. Medtronic seeks to have its stent approved for sale in Europe in 2004 and in the US by 2005.

7.6 Adverse Events

Health Canada has received no voluntary reports of thrombosis associated with sirolimus or paclitaxel eluting stents. Thrombosis is a rare complication of coronary stenting procedures. There is no denominator available to indicate the number of DES implanted in Canada. As the use of DES is limited across Canada, however, we may be able to estimate the number of individuals who have received these stents.

In completed and ongoing clinical trials of the sirolimus eluting stents worldwide, the rate of thrombosis seems to be similar to that associated with BMS. The meta-analysis outcomes used in this analysis indicate that there are no differences in thrombosis rate between DES and BMS.[20]

On July 23, 2003, when Health Canada posted a medical device safety warning[14] for the Cypher stent, it was estimated that 900 sirolimus stents had been implanted since November 2002. Health Canada stated that, "the FDA has received 34 reports of thrombosis in 47 stents." A denominator of 50,000 angioplasties was used, indicating a <0.1% rate of thrombus in the angioplasty population. We are confident about the estimated denominator, given the devices' limited use and the early time horizon. There is no evidence to suggest that the rate of thrombosis differs between BMS and DES.

In January 2004, the FDA's Center for Devices and Radiological Health reported 41 adverse events (total of 54 stents) involving the Taxus Express^2 paclitaxel stent, despite the fact that paclitaxel is not yet marketed in the US. Almost half of the patients (N=20) had a product-related problem and 32 percent reported adverse events. Among the adverse event cases, 14 reported thrombus and occlusion.[89] This analysis presents the costs and outcomes for sirolimus and paclitaxel eluting stents separately and pooled. There was no head-to-head comparison of sirolimus and paclitaxel eluting stents.

On July 2, 2004, Boston Scientific Corporation announced a voluntary recall of an estimated 200 units of its Taxus Express^2 paclitaxel eluting coronary stent systems due to "characteristics in the delivery catheters that have the potential to impede balloon deflation during a coronary angioplasty procedure. Impeded balloon deflation can result in significant patient complications, including coronary artery bypass graft surgery and death."[90] The stents had been shipped to 99 hospitals in the US and three Canadian hospitals. Boston Scientific emphasized the recall applied to specific lots and did not affect patients who had already received a Taxus stent, because the difficulty involved the delivery system, so it occurred during insertion not afterward.

On July 16, 2004, the recall was expanded to involve about 85,000 Taxus stent systems and 11,000 Express^2 stent systems. (Overall, the company has shipped >500,000 Taxus stent systems and >600,000 Express^2 stent systems.[91])

On August 5, 2004, Boston Scientific announced an additional 3,000 Taxus stent systems would be recalled, mainly in the US. The company was aware of one death and 22 serious injuries associated with the balloon deflation problem for the Taxus stent system, but it was reiterated that "patients who have already received stents are not at risk, because any difficulty associated with non-deflation occurs during the implantation procedure."[92]

The recall has led to speculation that the relative market shares of the Taxus and Cypher stents would be affected.[93] As Cypher stents tend to be more expensive, the total number of DES that can be used may be affected. DES use, however, is likely to continue to rise in the US and Canada, with relative market share being affected by factors such as recalls and new product introductions.

7.7 Caveats to Analysis

Because of the paucity of published information related to DES use, some of the model inputs were based on assumptions rather than true values. For example, data on DES to treat ISR are still being accumulated. There are several ways to address the uncertainty resulting from decision analytic modeling including sensitivity analysis, sub-analysis, population criteria and prospective economic evaluation. There is likely variation in the use of treatments for ISR. For example, brachytherapy is only available in some hospitals and DES use varies between provinces. These factors will influence the treatment of ISR. Sensitivity analysis is used to explore the impact of the model inputs. The treatment of ISR may vary depending on the type of initial stent. For example, while DES implantation may be effective for ISR of a bare stent, there are no data to support this.

There are limitations when estimating the "real world" clinical benefit of DES from the existing RCTs. For example, in the RAVEL and SIRIUS trials, the angiographic restenosis rate and TLR rates were higher than was seen in the Taxus studies. This could have an effect on the calculated ICER. It has been speculated that the BMS (Bx Velocity) used in the RAVEL study was inferior in preventing restenosis compared with later generations of the stent. In clinical practice, the TLR rate has been reported to be 50% of the angiographic restenosis rate. This relationship was not seen in RAVEL, where the TLR rate for DES was higher than predicted. One can speculate whether the TLR rate was driven by the study protocol, namely angiographic procedures leading to the discovery of a restenosis rather than for the treatment of recurrent ischemia. This difference in clinical benefits between the two types of DES has a greater influence on the ICER, because the cost of the devices are equal (even though there is a spread of several hundred dollars among the prices at most catheterization laboratories in Canada).

There may be significant differences between event rates in RCTs and in the "real world." Large prospective registries are being established to evaluate the actual rate of restenosis and revascularization among stent patients.

This analysis does not consider the accessibility to angioplasty and stent implantation procedures. In Ontario, 76% of cardiac sites offer angioplasty and stent implantation procedures. Alberta has four cardiovascular hospital sites and British Columbia has four sites that conduct angioplasty and stent implantation. In provinces where patients have limited access to such procedures, DES may not have a substantial impact on the health care system.

The long-term benefits associated with DES are unknown. The data do not support any differences in mortality when DES are compared to BMS. Short-term morbidity differences are evident in the reduced TLR rates. Avoiding a TLR will result in fewer PCI procedures. As a result, incremental cost-effectiveness ratios using a cost/QALY or cost per life-year gained are not calculable.

7.8 Budget Impact Analysis

The addition of DES will have a sizable impact on provincial and hospital systems. For our base case scenario at one hospital (SWCHSC) with an annual rate of 1,764, angioplasty procedures (Table 31), we estimate a total cost of $2.2 million if DES were used in 40% of the population. This analysis used the Ontario provincial angioplasty and hospital-based DES implantation rates for the high risk population. These rates could be applied to other Canadian provinces when they are weighted by the relevant population. The impact on Canada was calculated to be $50.7 million when applied to the high risk population only. With 100% adoption of DES, the impact to Canada would be $126.8 million at $2,400 per DES; $63.4 million at a DES cost of $1,200 and $32.1 million if the cost of DES was equivalent to that of BMS.

One challenging issue in interventional cardiology and cardiac care is whether DES are affordable. Provinces and hospitals can expect to see large annual changes to their budgets after the adoption of these devices. Policy decision makers, who are contending with limited budgets and allocation issues, may be reluctant to embrace DES. Any new policy will be associated with up-front costs, but there may be savings associated with the decreased number of repeat procedures. The establishment of strict inclusion criteria, based on clinical evidence for specific populations, (e.g., high risk of restenosis patients) may provide targeted availability with cost containment.

In May 2004, the CCN's consensus panel on target setting released its final report, which indicated that the 2002 to 2003 rate of PCI (149 per 100,000 adults) exceeded the previous target rate (140 per 100,000 adults) by 6.4%.[46] Projections for 2005 to 2006 show that there are increases in PCI rates (221 per 100,000 adults). These increases will affect the overall numbers of DES used in PCI procedures.

7.9 DES and Funding

There is no funding strategy for DES across Canada. The provinces have made different funding commitments, ranging from an envelope of dedicated funds in Quebec and Ontario to no funding in some provinces. In comparison, the US Department of Health and Human Services (HHS) provided some accelerated incremental reimbursement to hospitals for newly established diagnosis related groups (DRG). These DRG codes were assigned before FDA approval.[94] A report indicated that sirolimus had a 60% share of the stent market, but that the paclitaxel DES was still unavailable in the US. FDA approval for the Taxus Express^2 paclitaxel eluting stent system was subsequently received in March 2004.

In the UK, each National Health Service hospital negotiates with manufacturers to get the best deal possible. DES are funded from the general resources of the cardiac directorate. No separate funding is available and patient co-funding is not allowed. It is different in the UK private sector where DES are billed as a separate item (Dr. Alan Haycox, Liverpool University, Liverpool (UK): personal communication, 2004 Mar 15).

Society is already paying for BMS implantation in approximately 90% of PCI procedures in Canada. This amounts to more than $29 million. In comparison, DES in all patients undergoing stent implantation would amount to more than $126 million when DES cost $2,400 each. The actual price of a DES can be lower than the suggested list price. Decreases in DES acquisition price could decrease the incremental cost for DES and BMS.

7.10 DES and Cost-Benefit Analyses

A formal cost-benefit analysis was not conducted here. Using the clinical trial results for the change in events for the SIRIUS (−12.5%) and TAXUS IV (−8.3%) studies, one could hypothesize a beneficial effect on the hospital and the province in terms of fewer repeat procedures and fewer hospitalizations. For example, using an average number of PTCA procedures conducted at the base case hospital (N=1,520), there would be a reduction of 190 and 126 post-procedural TLR events for SIRIUS and TAXUS IV respectively. Using the incremental costs for SIRIUS ($2,075) and TAXUS IV ($2,411) would result in a net savings of $394,250 and $303,786 per base case site. A benefit may occur in terms of reducing CABG and additional PTCAs, but "free" hospital beds will be filled with those patients waiting for angioplasty procedures, thereby increasing the cost to the system.

7.11 DES and Availability of Information

It was difficult during this analysis to determine the actual costs per DES and those for some cardiac procedures. The DES price used in the analysis was obtained through personal communication. An informal survey of interventional cardiologists indicated that the cost of DES had decreased since their listing and the acquisition cost was lower than the cost used in this analysis. Prices for these devices were generally negotiated with manufacturers and were affected by the volume of DES and other products bought. The lack of transparent cost information will impede any accurate analysis of the economic value of these devices.

8 LIMITATIONS

- The analysis takes a short to medium-term time horizon (one year), because the key outcomes (TRL) and costs occur within that time. Longer-term survival data are unavailable for DES interventions.
- The price estimates for DES and BMS came from expert opinion. The manufacturers and hospitals did not make the discounted prices available to the authors of this report.
- The cost-effectiveness results had a high degree of uncertainty, especially regarding costs.

- Some resource use and cost estimates came from expert opinion. Ideally, an economic evaluation is done prospectively to capture actual resource utilization.
- The clinical outcome information was based on trial results (directly from the SIRIUS and TAXUS IV trials or pooled in a meta-analysis). Clinical trial data cannot be directly extrapolated to "real world" practice.
- The economic evaluation did not directly compare the paclitaxel eluting stent (Taxus Express^{2}™) and the sirolimus eluting stent (Cypher™), because the clinical trials did not compare the two head-to-head and there were different BMS comparators in the trials.
- Costs used in this analysis were based on Ontario costs and may vary from province to province. Some costs used in this analysis were based on those of the SWCHSC and may vary from hospital to hospital.

9 CONCLUSIONS

Drug eluting stents (DES) were developed to reduce the incidence of in-stent restenosis that persist with the use of bare metal stents (BMS) in the treatment of coronary artery disease. While DES do not offer a mortality benefit, they are associated with a significant decrease in restenosis and the need for repeat target lesion revascularization (TLR). While some health care costs may be avoided with the use of DES, they are more expensive than BMS.

This report examined the cost-effectiveness of sirolimus and paclitaxel DES relative to BMS from the perspectives of a university-affiliated, tertiary care hospital and a provincial ministry of health. A decision analytic model was developed to conduct a cost-effectiveness analysis using a cost per TLR avoided. A budget impact analysis to examine the impact on hospital and provincial expenditures, if DES were to become widely adopted, was also carried out. The authors assumed a DES acquisition cost of $2,400 and a BMS acquisition cost of $608.

For the paclitaxel eluting stent, the economic evaluation found that from a hospital perspective, there was an additional cost relative to a BMS of $2,365 to $2,411, but the 8.3% to 8.9% reduction in TLR yielded an incremental cost-effective ratio (ICER) of between $26,562 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, from a hospital perspective, there was an additional cost relative to a BMS of $1,670 to $1,899, but the 12.5% to 15.0% reduction in TLR yielded an incremental cost-effective ratio (ICER) of $12,527 to $16,600 per TLR avoided. From a provincial health ministry perspective, the ICER was $11,133 to $15,192 per TLR avoided. The lower cost per TLR of a sirolimus eluting stent 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. Some reports available have suggested a cost-effectiveness threshold of $10,000 to $15,000 per TLR avoided may be acceptable. Most of this literature, however, cannot be used in a Canadian context and is based on BMS data.

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

While DES are more costly than BMS, they are associated with a significantly lower incidence in the one-year rate of restenosis. Long-term survival data are unavailable. 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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Appendix 1: Funding Status of DES Across Canada as of July 30, 2004

Province	DES Funding	Source
DES funding available		
Alberta	Regional health authorities (RHAs) receive global funding allocation for hospital and other health services provision; RHAs for Edmonton (Capital Health) and Calgary (Calgary Health) receive an additional targeted allocation to provide specialized services or provincewide services. In 2004-2005, Alberta provided $43.5 million specifically for angioplasty, an increase of 13.8% over 2003-2004. Additional device cost for DES is expected to be covered from these targeted dollars or supplemented by RHAs' global funding (i.e., Alberta Health & Wellness does not specifically provide an amount for DES). Calgary Health and Capital Health are responsible for providing services and setting standards for patient eligibility. While the two regions are using DES, the Province Wide Services department does not routinely collect data on the type of stents used	Sean M. Delaney, Alberta Health & Wellness, Edmonton: personal communication, 2004 Aug 3
British Columbia	Funding from BC Health Ministry made available in amount of $500,000 for four catheterization laboratories ($125,000 each)	Dr. Christopher E. Buller, University of British Columbia, Vancouver: personal communication, 2004 May 6
Manitoba	DES implantation at St. Boniface General Hospital (Winnipeg) is done on per patient basis with no stock of DES in hospital; each drug eluting stent must be ordered and paid for by hospital's catheterization laboratory	Bev Humphries, St. Boniface General Hospital, Winnipeg: personal communication, 2004 Mar 3
New Brunswick	DES utilization decisions made at a clinical level at Saint John Regional Hospital; no provincial guidelines established by New Brunswick Department of Health and Wellness (NBHW). DES utilization rates at Saint John Regional Hospital lower than initial estimates; funding for projected cost differential between BMS and DES reimbursed by Hospital Services Branch of NBHW through base budget amendment	Dr. Jean-Louis Thibodeau, New Brunswick Department of Health and Wellness, Fredericton: personal communication, 2004 Mar 30
Newfoundland	For 2004-2005, an increase in funding from $400,000 to $500,000 has been requested for a planned 20% to 25% DES utilization.	Dr. Barry Rose, General Hospital (Health Care Corporation of St. John's), St. John's: personal communication, 2004 July 7

Province	DES Funding	Source
Ontario	Ministry of Health and Long-Term Care provided $12 million for DES utilization	EC, personal communication, 2004 Feb 19
Quebec	In June 2004, Quebec government approved funding for 20% utilization of DES, representing $13 million addition to budget	JB, personal communication, 2004 July 7
Saskatchewan	Several specialized programs funded as provincewide services. Saskatoon and Regina Qu'Appelle Regional Health Authorities receive funding for cardiac catheterization services as a provincewide service. Both regions able to allocate some of this funding in 2003-2004 fiscal year to support use of DES for narrowly defined patient population. On a provincial basis, in March 2004, DES used in approximately 12% of cases involving stents	Diane Tucker, Saskatchewan Health, Regina: personal communication, 2004 May 27
DES funding under consideration		
Nova Scotia	Under consideration by provincial government	LT, personal communication, 2004 Feb 16
No DES funding		
Prince Edward Island	As residents of Prince Edward Island who require angioplasty are transferred to hospitals in Saint John NB or Halifax NS, there is no DES utilization and no DES funding.	Dr. Jean-Louis Thibodeau: personal communication, 2004 Mar 30

Appendix 2: Simulation Analysis for ICERs and Cost Differentials

	Difference in TLR Rate between DES and BMS	**Calculated Difference in Cost between DES and BMS based on ICER Value**
SIRIUS		
ICER value= $5,000/TLR avoided	0.125 (0.166 to 0.041)	ICER value allows for difference of $625 in device acquisition cost for DES and BMS
ICER value= $10,000/TLR avoided	0.125 (0.166 to 0.041)	ICER value allows for difference of $1,250 in device acquisition cost for DES and BMS
ICER value= $15,000/ TLR avoided	0.125 (0.166 to 0.041)	ICER value allows for difference of $1,875 in device acquisition cost for DES and BMS
ICER value= $20,000/ TLR avoided	0.125 (0.166 to 0.041)	ICER value allows for difference of $2,500 in device acquisition cost for DES and BMS
TAXUS IV		
ICER value= $5,000/TLR avoided	0.083 (0.113 to 0.03)	ICER value allows for difference of $415 in device acquisition cost for DES and BMS
ICER value= $10,000/TLR avoided	0.083 (0.113 to 0.03)	ICER value allows for difference of $830 in device acquisition cost for DES and BMS
ICER value= $15,000/TLR avoided	0.083 (0.113 to 0.03)	ICER value allows for difference of $1,245 in device acquisition cost for DES and BMS
ICER value= $20,000/TLR avoided	0.083 (0.113 to 0.03)	ICER value allows for difference of $1,660 in device acquisition cost for DES and BMS
Sirolimus pooled		
ICER value= $5,000/TLR avoided	0.15 (0.185 to 0.035)	ICER value allows for difference of $750 in device acquisition cost for DES and BMS
ICER value= $10,000/TLR avoided	0.15 (0.185 to 0.035)	ICER value allows for difference of $1,500 in device acquisition cost for DES and BMS
ICER value= $15,000/TLR avoided	0.15 (0.185 to 0.035)	ICER value allows for difference of $2,250 in device acquisition cost for DES and BMS
ICER value= $20,000/TLR avoided	0.15 (0.185 to 0.035)	ICER value allows for difference of $3,000 in device acquisition cost for DES and BMS

	Difference in TLR Rate between DES and BMS	Calculated Difference in Cost between DES and BMS based on ICER Value
Paclitaxel pooled		
ICER value= $5,000/TLR avoided	0.089 (0.122 to 0.033)	ICER value allows for difference of $445 in device acquisition cost for DES and BMS
ICER value= $10,000/TLR avoided	0.089 (0.122 to 0.033)	ICER value allows for difference of $890 in device acquisition cost for DES and BMS
ICER value= $15,000/TLR avoided	0.089 (0.122 to 0.033)	ICER value allows for difference of $1,335 in device acquisition cost for DES and BMS
ICER value= $20,000/TLR avoided	0.089 (0.122 to 0.033)	ICER value allows for difference of $1,780 in device acquisition cost for DES and BMS