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An evaluation of drug eluting (coated) stents for percutaneous coronary interventions;

What should their role be at the McGill University Health Centre (MUHC)?

By
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Final Version

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Invitation. *This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.*

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Foreword

In March 2003, the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) received a request from the Chief Operating Officer, Mr. Victor Simon, to provide guidance on the future use of drug eluting (coated) stents for percutaneous coronary interventions. These new devices are expected to cost approximately five times the price of regular stents and it is imperative to fully assess their safety, efficacy and cost-effectiveness. The TAU agreed to proceed to a formal evaluation at the March 13, 2003 Committee Meeting.
The report was first presented to the full TAU committee on May 28, 2003 and accepted following the TAU meeting of June 18, 2003.

It must be acknowledged that this is a very rapidly developing area with an almost continuous influx of new information. Accordingly any recommendation in this document must be re-evaluated periodically as new evidence becomes available. It is suggested that the issue be re-examined in 6 months.

Executive Summary

Coronary angioplasty is a commonly used procedure to reduce the symptoms of coronary artery disease. A persistent complication has been the occurrence of coronary restenosis and consequently the need for repeat revascularizations. The recent introduction of coronary stents has greatly improved the safety of angioplasty and has reduced but not eliminated the problem of restenosis. This report aims to 1) summarize our knowledge regarding drug eluting stents, 2) interpret this scientific evidence in the MUHC context and 3) provide estimates of the expected costs and benefits so as to assist the administration in deciding on the appropriate place of this technology.

There is accumulating and rather compelling evidence that specific drug eluting stents may greatly reduce the magnitude of restenosis. A synthesis of all the randomized trials of drug eluting stents suggests that repeat revascularization rates may be reduced by 65% (OR 0.35, 95%CI 0.27-0.44). For the most promising sirolimus coated stents the revascularization rate was reduced by 83% (OR 0.17, 95%CI 0.11-0.27). An examination of current outcomes from across Quebec and within the MUHC shows that currently 12 of every 100 patients require a repeat angioplasty within 6 months. The adoption of coated stents could therefore eliminate 9 or 10 repeat angioplasties for every 100 performed. Since the average cost for an angioplasty at the Royal Victoria is approximately $4,500, this would be expected to save approximately $405,000 to $450,000 in repeated procedures for each 1000 patients treated with coated stents.

Preliminary data suggest that the acquisition of each coated stent will cost an additional $2,800. Since approximately 1000 procedures are performed annually at the MUHC, with an average of slightly more than 1.5 stents each , a complete switch to coated stents could require additional funding of approximately $3,795,000 ($4,200,000--$405,000) annually. More sophisticated and realistic modeling, accounting for the possibility of more than 1 repeat revascularization, suggests that the replacement of all uncoated with coated stents would increase the hospital budget by approximately $3,400,000 annually. Sensitivity analyses of the most favorable scenarios with decreased coated stent costs, increased baseline restenosis rates and limiting 1 coated stent per case still gives an annual increase in the budget from 1.4 to 2.0 million dollars / year.

What would we have purchased for this additional expense? We would have purchased some improved health for the approximately 90 to100 patients who would have otherwise had restenosis. This strategy would have improved the patients' quality of life (freedom from angina, and avoidance of a second angioplasty), an improvement that is difficult to measure and probably small given that the period of incapacity due to angina, a typically mild disability, is short. Cost-effectiveness ratios can not be reliably calculated in the absence of measures of this disutility.

One frequently proposed approach to the introduction of high priced technology is to try to identify subsets of patients with the expected highest benefit and to reserve the treatment for this subgroup. For DES, this would involve predicting those at greatest risk of restenosis, but this is not yet a clinically reliable science. Even in an idealized situation where it was possible to identify 15 % of the MUHC stent population who were at a 100% increase in the risk of restenosis (relative risk =2, at present more realistic estimates of relative risk for restenosis = 1.3) expenses would still increase by $418,000 in order to save 30 people from the need for a repeat angioplasty.

There are also non-monetary reasons to hesitate before adopting this new technology. No reductions in mortality, myocardial infarction or bypass surgery rates with coated stents have been demonstrated. The safety and efficacy data beyond 1 year follow-up are limited. The small size of these studies has also precluded the reliable identification of any patient subgroups deriving particularly large clinical benefits. Technical issues also remain including the necessity of routine intravascular ultrasound (IVUS) and the generalizability of the results.

However, it is rarely possible to create guidelines that apply to all clinical situations. Thus, even if coated stents are not available for *routine* use there may be individual cases that could benefit from this technology. Accordingly, exceptions should be allowed when, in the Cardiologist's opinion, the risk of restenosis is high, and when there are very high risks associated with a repeat percutaneous intervention (E.g. advanced renal failure, technical difficulties with arterial access, last remaining vessel in a symptomatic patient despite optimal medical management). Each exception in which a coated stent is employed should be approved by two members of the Division of Cardiology. Ideally the two members should be interventional cardiologists who have the greatest knowledge concerning this technology. The records of such review should be maintained within the Division.

The exact number of exceptions is impossible to accurately predict and may be expected to evolve as more experience is acquired and more studies are published. At present 7 coated stents per month have been approved by the Department of Medicine. This represents 6% - 7% of the approximately 1,200 to 1,400 patients predicted to have angioplasty at the MUHC over the next year.

In conclusion, acceptance of a policy of replacing bare metal stents with the new coated versions might avoid the need for a repeat angioplasty for approximately 100 patients per year. It would not prevent any deaths or myocardial infarctions. The net cost to the MUHC of this policy would likely be in the vicinity of $2-3 million per year. Even a policy of restricted use (10-15%) would have a substantial budgetary impact for limited health benefits. The TAU committee believes that in the absence of any fresh budget to meet this demand, the reduction in hospital services that would result from this fresh expenditure would be unjustifiable. TAU therefore recommends:

1. **That despite good evidence supporting the efficacy of coated stents to reduce the rate of restenosis, the current budget of the hospital should not be redistributed to permit the routine acquisition of drug eluting stents. Thus in the absence of a specially dedicated provincial budget for this technology, coated stents should not be provided by the MUHC except for special circumstances.**
2. **The special cases requiring a coated stent should be approved by two members of the Division of Cardiology, ideally two interventional cardiologists.**
3. **The evidence on which this policy recommendation is based is likely to be very time sensitive. The decision should be frequently reviewed and modified if necessary in the light of such evidence. The responsibility for requesting review can be initiated by either the Division of Cardiology or the Technology Assessment Unit.**

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a common intervention primarily employed to reduce the symptoms of angina pectoris. There is no discernible benefit in reducing myocardial infarction or death compared to other treatment modalities[1; 2]. Since its inception approximately 20 years ago, an important limitation of PTCA has been the occurrence of restenosis. Coronary stenting is a percutaneous technique involving the intra-luminal introduction of a metal scaffolding. First introduced in 1989 to treat the acute complications of PTCA[3], the routine use of elective stenting to reduce the incidence of restenosis began in 1994[4; 5] and stents are now employed in the great majority of angioplasties.

Recent studies have demonstrated that the coating of stents with certain drugs is able to substantially lower the rate of restenosis. At present one drug eluting stent (*Cypher* stent, Cordis Corp.) has been approved for clinical use by Health Canada. No formal technology assessments of this technology have been published, although in October 2002, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA)[6] published a bulletin acknowledging the promise of this technology, its potential for rapid diffusion and the need for further clinical and economic studies to best appreciate the future role of this technology. This stent was approved by the FDA on May 5, 2003 and already major centers are planning to implant them as the routine standard of care[7] Progressive introduction of this high cost technology could have a major impact, not only on the budget of the MUHC but of the whole health-care system. The goal of this report is to 1) summarize the extent of our knowledge regarding drug eluting stents, 2) interpret this scientific evidence in the MUHC context and 3) provide estimates of the possible costs and benefits so as to assist the administration in deciding on the appropriate place of this technology.

Background

To fully evaluate the role of coated coronary stents, it is helpful to first appreciate the benefits of regular metallic (uncoated) coronary stents. A systematic overview of uncoated coronary stents has been recently performed[8]. The overview, reflecting its component randomized clinical trials, did not contrast uncoated stents to plain balloon angioplasty, but rather evaluated two different strategies for stent utilization; routine stenting of all arteries during angioplasty, versus an evolving but more restrained or provisional approach which treats not only the acute complications but also increasingly sub-optimal balloon angioplasty results with a coronary stent. This overview examined 29 published randomized trials, involving 9,918 patients with stable and unstable coronary syndromes.

The totality of the evidence from these randomized trials confirmed the safety of routine coronary stenting but did not show any evidence of decreased risk of death, myocardial infarction or coronary artery bypass surgery compared to the provisional (more conservative) approach. Quality of life as measured by the persistence of angina was only marginally improved. What stenting did produce was a large reduction in

angiographic restenosis and repeat angioplasty rates. However, once the rate of stent insertion approaches 40%, less than 4-5 repeat angioplasties per 100 patients are avoided compared to a policy of universal stenting.

Although the benefits of stenting in routine practice have been less often studied than those from randomized trials, intracoronary stents are now widely used. An early population study during a period of rapid adoption of coronary stent technology (1994-1997) in British Columbia did show a corresponding 28% reduction in repeat revascularization but with no changes in overall death or myocardial infarction rates[9]. Despite coronary stents, not only has the problem of restenosis not disappeared but a new iatrogenic problem of in-stent restenosis has developed. To date, most pharmaceutical and mechanical approaches to this problem have met with only limited success. Treatment options for in-stent restenosis include repeat angioplasty with or without another coronary stent or intravascular brachytherapy. Intravascular brachytherapy appears more effective (see Table 1) but is difficult to handle, unpredictably associated with edge restenosis, and associated with long term follow-up complications.

Drug Eluting Stents

General

Before examining the literature on coated stents, some caveats are required for an accurate interpretation of the evidence. First, all published clinical experiences with coated stents have been financed by industry suggesting the possibility of an associated publication bias . Second, randomized trials of conventional stents versus "plain old balloon angioplasty" (POBA) has shown that the accompanying obligatory angiogram at 6 months results in an over estimation of the need for repeat revascularization compared to a clinically driven approach[8; 10]. Therefore it is important when assessing the benefits of reduced repeat revascularizations to use actual local outcomes data and not rely on estimates from randomized trials. Care must be taken to distinguish between reductions in angiographic restenosis and the need for a repeat revascularization since only about 50% of angiographic restenoses necessitate a repeat revascularization procedure[8].

It is also important that enthusiasm for technology should not drive its innovation. In the case of *uncoated* coronary stents, their use was endorsed by some consensus panels even before a large body of high quality evidence was available[11]. Now the promise of a possible major reduction or even elimination of restenosis with drug-eluting stents (DES), has again generated widespread clinical enthusiasm among cardiologists. Given that DES may cost up to 5 times the price of a bare metal stent and with world-wide projections of a potential 5 billion dollar/year industry, there is also considerable enthusiasm for this technology in the device industry[12] .

Any benefits of coated stents will depend on the stent, the carrier and the drug and not all coated stents have been successful. For example, three trials of gold coated stents not only failed to show any reduction in restenosis rates but contrary to expectations, had an exaggerated proliferative neointimal response compared to uncoated stents[13-15]. Also a randomized trial comparing heparin coated stents to conventional bare metal stents in 277 patients found no impact on the in-hospital complications, stent thrombosis or restenosis rates. [16] More recently, the COAST investigators[17] also found

no clinical benefit in a study of 588 patients with small vessel disease randomly assigned to angioplasty (n=195), bare stenting (n=196), or heparin-coated stenting (n=197). In particular, thrombotic events and survival without myocardial infarction or target vessel revascularization were not different between the three groups. The message is nevertheless clear; the generalizability of results from one coated stent group to another is perilous. Therefore stents coated with heparin or gold will not be discussed further and we will concentrate on the studies involving stents eluting antimitotic drugs.

Promising results, with reduced neointimal proliferation, have been observed with the local delivery via coated stents of sirolimus (rapamycin), a natural macrocyclic lactone immunosuppressant that inhibits cytokine and growth-factor–mediated proliferation and migration of lymphocytes and smooth-muscle cells. Sirolimus has been approved by the Food and Drug Administration for the prophylaxis of renal transplant rejection. This drug binds to an intracellular receptor protein and induces cell-cycle arrest in the late G1 phase thereby inhibiting the proliferation of both rat and human smooth muscle cells in vitro.

Sirolimus has been blended with polymers and applied to the surface of a stainless-steel, balloon-expandable stent (Bx Velocity, Cordis, Johnson & Johnson). The stent was loaded with a fixed amount of sirolimus per unit of metal surface area (140 µg of sirolimus /cm^2). A layer of drug-free polymer was applied on top of the drug–polymer mixture as a diffusion barrier to slow drug release. Approximately 80 % of the drug should be released within 30 days after implantation.

Paclitaxel (*Taxol*®), is another antimitotic agent which has been applied to stents in an attempt to reduce restenosis. Paclitaxel is derived from a novel class of anticancer agents known as taxanes derived from the Pacific yew tree and originally developed as a chemotherapeutic agent for the treatment of ovarian, breast, and other cancers. Taxanes exert their cytotoxic effects through a unique action on the microtubular system which are important in cellular multiplication (proliferation) and migration. Theoretically, paclitaxel has the ability to interfere with some of the proposed mechanisms of restenosis. Moreover, its pharmacokinetic lipophilic properties may facilitate cellular uptake. The TAXUS NIRx stent system (Boston Scientific Corp) is a commercial drug-eluting stent system using paclitaxel incorporated into a unique slow-release, hydrocarbon-based elastomer polymer system applied to a metal stent. A taxane analogue of paclitaxel, QP2, a taxol-derived lipophilic microtubule inhibitor has also been evaluated in conjunction with the QuaDS-QP2 stent, (Quanam Medical Corp).

It is expected that many other types of drug eluting stents will be available commercially in the near future. The success of these drug eluting stent systems will depend on stent, drug and polymer characteristics in addition to patient and angiographic characteristics. The complexity of these interactions may well limit any extrapolations beyond the confines of the precise population and stent studied.

SIROLIMUS

Observational studies

The First in Man study involved a total of 45 patients, 30 from Brazil[18] and 15 from Europe[19]. Briefly, patients with short (<15 mm) de novo coronary lesions were eligible and received a single 18-mm sirolimus-eluting Bx-Velocity *Cypher* stent (Cordis Corp). In the Brazilian study 15 patients were randomized to a fast release (FR) formulation (<15-day drug release), and 15 to a slow release (SR) formulation (>28-day drug release). Eight month follow-up of the Brazilian group showed no evidence of restenosis (<20% diameter stenosis by intra-vascular ultrasound (IVUS)) and no clinical events. All 15 European patients received the SR formulation. There was 1 early death and 1 myocardial infarction. At 9 months no further adverse events had occurred and all patients were angina free. In the 38 patients who had a 2 year follow-up, angiography showed no in-stent restenosis and IVUS revealed only minimal neointimal hyperplasia[20; 21]. Two patients did have restenosis at 8 and 12 mm beyond the coated stent[21].

The Rapamycin Eluting Stent Evaluated at Rotterdam Hospital (RESEARCH) Registry[22] consisted of a control group of 434 patients who underwent bare metal stent implantation from October 2001 to April 2002, followed by a treated group of 503 patients assigned to receive the sirolimus-eluting Bx-Velocity *Cypher* stent. The RESEARCH Registry was conducted to evaluate the outcomes of "real world" lesions treated with coated stents compared with bare metal stents. According to investigators, the registry consisted of more complex lesions (type B2/C, calcified, chronic total occlusions, bifurcations, and thrombus-containing lesions) than in previous published studies.

Of the 503 patients, only 376 actually received the coated stent; the others were treated with a bare metal stent when the appropriate size and length of the coated stent was not available. There were no difference in the rate of mortality (treated, 8 [1.6%]; control, 6 [1.4%], $P = 0.8$) or in the rate of subacute thrombosis (treated, 0.6% vs. control, 0.9%). However, there were fewer reinterventions with the coated stent (treated, 5.4% vs control, 9%, $P = .03$).

The first clinical experience[23] with sirolimus-eluting stents for the treatment of in-stent restenosis (ISR) involved 16 patients with objective evidence of ischemia. All procedures involved predilation, and stent deployment guided by IVUS. Stents were 18mm long and varied from 2.5 to 3.5 mm diameter. Three patients had total occlusions, 10 had diffuse proliferative restenosis and only 3 had a focal lesion. Four patients had previously received brachytherapy. At four months follow-up, one patient had died and three patients (20%) had angiographic evidence of restenosis (one in-stent and two in-lesion). At nine months clinical follow-up, three patients had experienced four major adverse cardiac events (two deaths and one acute myocardial infarction necessitating repeat target vessel angioplasty) in addition to the three with recurrent restenosis (who required no further treatment). There was no control group. The authors concluded that sirolimus eluting stents in patients with severe ISR lesions effectively prevents neointimal formation and recurrent restenosis at four months angiographic follow-up.

Sirolimus eluting stents have also been assessed in another observational study of 25 patients with ISR[24]. Nine patients received 2 stents (1.4 stents per lesion) and 68% of

the lesions were diffuse. Patients having had intravascular radiation, ostial, saphenous graft or long (>36 mm) lesions were excluded. At 12 months, all vessels were patent and only one patient developed ISR at 1-year follow-up. There was no evidence of stent malapposition and there were no deaths, stent thromboses, or repeat revascularizations. The authors conclude that this study demonstrates the safety and efficacy of sirolimus coated stents for the treatment of in-stent restenosis.

The RESEARCH registry also examined a sub-group of 57 patients treated with coated stents for ISR[25]. The reintervention rate was 12.3%, but increased to 21.4%, when treating vessels that were previously irradiated. When their results were compared with 66 age-matched controls that were treated at the center during the prior six months with bare metal stents, no significant differences were observed. The authors conclude that (SES) are safe for treatment of in-stent restenosis, but in the real world of day-to-day clinical practice they work no better than bare metal stents.

Randomized trials

RAVEL[26] was the first published randomized, double-blind trial investigating sirolimus coated stents for revascularization of single, primary lesions in native coronary arteries. The trial included 238 patients at 19 medical centers, who were randomized to receive either an 18-mm sirolimus-eluting stent (Bx VELOCITY stent, Cordis) or an uncoated stent. The primary end point was in-stent late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months). Secondary end points included the percentage of in-stent stenosis of the luminal diameter and the binary rate of restenosis (luminal narrowing > 50 %). A composite clinical end point consisting of death, myocardial infarction, and percutaneous or surgical revascularization was also reported at 1, 6, and 12 months.

At six months 88.7% of patients had angiographic follow-up. The degree of neointimal proliferation, as measured by the mean (±SD) late luminal loss, was less with the sirolimus stent (-0.01±0.33 mm) compared to the standard stent group (0.80±0.53 mm, $p<0.001$). None of the patients in the sirolimus-stent group, compared to 26.6% of those in the standard-stent group, had restenosis of > 50% of the luminal diameter ($P<0.001$). Although not pre-specified and involving only small numbers (44), a greater difference between restenosis rates was observed in diabetics (41.7% vs. 0%, $p=0.002$). There were no episodes of stent thrombosis. During a one year follow-up, there were no differences in deaths (2 vs. 2), or myocardial infarctions (4 vs. 5) or CABG (1 vs. 1). However, the rate of repeat target percutaneous revascularization was reduced (27 vs. 0). The combined rate of major cardiac events was therefore 5.8 % in the sirolimus-stent group and 28.8 % in the standard-stent group ($P<0.001$).

Intravascular ultrasound (IVUS) was performed in a subset of 95 patients at 6 months. Neointimal hyperplasia (2±5 versus 37±28 mm3) and percent of volume obstruction (1±3% versus 29±20%) were reduced in the coated stent group ($P<0.001$). The authors concluded that a sirolimus-eluting stent was safe, prevented neointimal proliferation without creating an edge effect and was not associated with evidence of angiographic restenosis nor the need for repeat revascularization.

Despite these impressive angiographic findings, follow-up is only for 12 months, no reduction in deaths or myocardial infarctions was observed and the overall sample size

is small. Also, although a relatively low risk group, the control restenosis rate of 27% is higher than might be expected in routine practice where angiography is not systematically performed at 6 months. Also a substantial number of the repeat angioplasties in the uncoated stent group(at least 11/27) were driven not by clinical symptoms but by the protocol mandated 6-month angiogram. Caution is also mandated by the IVUS results showing that the incidence of incomplete stent appositions was significantly higher in patients with coated stents (20% vs. 4%, p <0.015) at 6-months[27]. Although not associated with adverse clinical events, long-term follow-up is needed to investigate the clinical implication of this IVUS observation.

The SIRIUS trial was another multicenter, randomized, double blind, controlled study designed to evaluate the sirolimus coated stent. This trial has not yet been published but the results are available online at www.clinicaltrialresults.com. The trial appears to have been presented at 2 scientific meetings and the clinical outcomes reported vary slightly. The results presented at Transcatheter Cardiovascular Therapeutics meetings follow. A total of 1101 patients with de novo coronary lesions, 2.5-3.5 mm in diameter and 15-30 mm in length, were randomized to either the coated (n = 545) or bare stent (n = 556). Subsequently, 43 patients were excluded and 85% had angiographic follow-up at 8 months. Clinical follow-up evaluated a primary composite endpoint of cardiac death, myocardial infarction (MI), or target vessel revascularization (TVR).

Compared with control, sirolimus-treated patients had significantly lower rates of in-stent (within the margins of the stent, 3.2% vs. 35.4%, $P < .001$) and in-segment (either within the margins of the stent or 5 mm proximal or distal to the stent, 8.9% vs 36.3%, $P < .001$) restenosis. Late luminal loss was also reduced (0.17 vs. 1.00 mm, p <0.001). The 2 groups exhibited similar stent thrombosis rates (0.4% [n = 2] for sirolimus and 0.8% [n = 4] for control), and there were no differences for in-hospital events. At 9-month follow-up, there was no difference in the rate of death or myocardial infarction. The composite endpoint difference of 8.6% vs. 21.0% was consequently totally driven by the difference in target lesion revascularizations (5.1% vs. 19.7%). In this trial, reductions in restenosis rates for diabetics were not significantly reduced compared to the overall result (65% vs. 75%). There was also no extra gain associated with coated stents when used in smaller compared to larger vessels.

The C-SIRIUS study results were reported at the April 2003 American College annual meeting, In this study 100 patients with de novo coronary lesions, diameter 2.5 – 3.0 mm were randomized to a bare metal stent or a sirolimus eluting stent (http://www.acc03online.org/). At 8 months, there was reduced angiographic restenosis (44% vs. 2%, p<0.001) and fewer repeat revascularizations with the coated stent (9 vs. 3). There was no increase in edge stenosis with the coated stent.

PACLITAXEL

Observational studies

TAXUS III was a single-arm, 2-center study that enrolled 28 patients to evaluate the feasibility and safety of paclitaxel-eluting stent (TAXUS NIRx, Boston Scientific) for the treatment of ISR[26]. Patients had entry criteria of lesion length < 30 mm, 50% to 99% diameter stenosis, and vessel diameter 3.0 to 3.5 mm. Diffuse ISR was present in 64%

but only 1 had a total occlusion. Thirteen lesions received 2 coated stents. All stents were 15 mm long and 3.0 or 3.5 mm in diameter and had a total load of 1.0 ug/mm2 of paclitaxel incorporated into a slow-release copolymer carrier system that gives biphasic release response. The initial release is over the first 48 hours followed by slow release over the next 10 days. Patients completed angiographic (25) and IVUS (17) studies at 6 months. No subacute stent thrombosis occurred, but there was one late chronic total occlusion, and 6 patients (21.4%) had additional target lesion revascularization (TLR) by 6 months. Only three of these patients showed angiographic restenosis, 1 had a less than 50% restenosis but presence of anginal symptoms and 2 underwent TLR as a result of the IVUS assessment at follow-up (1 incomplete apposition and 1 insufficient expansion of the stent). Of the patients with TLR, 1 had restenosis in a bare stent implanted for edge dissection and 2 had restenosis in a gap between 2 paclitaxel-eluting stents. The total major adverse cardiac event rate was 29% (8 patients; 1 non–Q MI, 1 CABG, and 6 TLR). The authors conclude 1) the process is feasible and safe (no sub-acute thrombosis) 2) low rates of late neointimal proliferation (net loss 0.54 mm) 3) low angiographic restenosis rates (4/25 = 16%) 4) low TLR rates.

The first study[28] of the taxol-derived lipophilic microtubule inhibitor (QP2), a taxane analogue of paclitaxel, involved 32 patients treated with the QuaDS-QP2 stent, (Quanam Medical Corp) . Thirteen patients were restudied angiographically and by IVUS and all were patent at 12 months. There was no evidence of significant proliferation. Two reinterventions have been required for either new disease or to distal, small-vessel disease beyond the stent. Based on this data, the randomized SCORE trial (see below) was undertaken. Another study[29] using the same stent was performed in 15 native coronary lesions and at 8 months, no patients showed clinically significant in-stent or edge restenosis. Furthermore, IVUS showed only a minimal amount of neointimal proliferation in the stented segment.

Liistro et al[30] reported the first clinical experience using the QuaDS-QP2 stent to treat ISR in 15 patients. At 6 months, there was minimal intimal hyperplasia (loss=0.47+/-1.01 mm) and three patients (20%) had restenosis (one with stent occlusion). By 12 months 8 of 13 patients (61.5%) had angiographic restenosis. A total of 3 non-Q MI, 1 CABG and 9 TLR were performed by 12 months. The antiproliferative effect was not maintained at the 12-month follow-up, resulting only in delayed occurrence of angiographic restenosis.

Randomized trials

The TAXUS I trial[31] was the first in-human experience evaluating safety and feasibility of the TAXUS NIRx stent system with paclitaxel for treatment of coronary lesions. This was a prospective, double-blind, three-center study randomizing 61 patients with de novo (59) or restenotic (2) lesions (<12 mm) to receive a TAXUS (n=31) versus control (n=30) stent (diameter 3.0 or 3.5 mm). The 30-day major adverse cardiac event rate was 0% in both groups and no stent thromboses were reported at 1, 6, 9, or 12 months. At 12 months, the major adverse event rate was 3% (1 event) in the TAXUS group and 10% (4 events in 3 patients) in the control group (p = NS). Six-month angiographic restenosis rates were 0% for TAXUS versus 10% for control (P = NS) patients. There were significant improvements in minimal lumen diameter, diameter

stenosis, neointimal hyperplasia and late lumen loss with the coated stent (P<0.01). No evidence of edge restenosis was seen in either group.

The ELUTES trial[32] randomized 192 patients in Europe with low-risk lesions in native coronary arteries to receive either an uncoated stent or a paclitaxel-coated stent using 4 different dosages. At 6 months there was no difference in the clinical events rates between the groups (11% in each). The binary restenosis rate was reduced in the highest-dose paclitaxel group compared to the uncoated group (3% vs. 21%, p=0.055). This trial has only appeared in abstract form (2001).

ASPECT (Asian Paclitaxel-Eluting Stent Clinical Trial) was a 3-center, triple-blind, randomized, placebo-controlled trial[33; 34] to evaluate the efficacy of paclitaxel-coated stents in reducing ISR. A total of 177 patients with single *de novo* in-stent restenotic lesions were randomized to receive bare, low-dose (1.28 mcg/mm^2), or high-dose (3.1 mcg/mm^2) pure paclitaxel-coated stents (Cook Cardiology) in a 1:1:1 ratio. Patients were treated with clopidogrel for 6 months following the procedure. The binary restenosis rate was decreased in the high-dose group compared to the uncoated group (4% vs 27%) but not in the low dose group (12% vs. 27%). In an 81 patient IVUS sub-study[35], the authors demonstrated that neointimal hyperplasia was reduced with paclitaxel compared to placebo, although there was no difference between the low and high dose groups. They did not observe any edge restenosis and only 1 case of late stent malapposition. There were no differences in deaths, myocardial infarctions, bypass surgeries or subacute stent thrombosis between the coated and uncoated stents. Most surprising was the fact that the number of additional target-lesion revascularizations for restenosis was similar among treatment groups, despite the significant difference in all angiographic measures of restenosis. This is explained by the fact that reintervention in these centers is predicated not on angiographic restenosis but patient symptoms.

TAXUS-II enrolled 536 patients who were randomized in a double-blind fashion to receive either a paclitaxel-eluting coronary stent (TAXUS) or a bare metal stent for stenting of de novo lesions[36]. The TAXUS patients received either a moderate-release stent or a slow-release stent. The 12-month major adverse cardiac events (MACE) rate was 10.9%, while target lesion revascularization (TLR) was 4.7% for patients treated with slow-release stents. The 12-month MACE rate for the moderate-release stents was 9.9% and the TLR was 3.8%. These numbers contrast with a 21.7% MACE rate and a 14.4% TLR in the patients receiving bare metal stents.

The SCORES trial[14] randomized 266 patients to either a stent coated with a taxane derivative of paclitaxel (QuaDDS-QP2 stent has 5 polymer sleeves that contain QP2) intended to inhibit restenosis (N=128) or bare metal stents (138). While restenosis was reduced there was an *increase* in major adverse cardiac events, particularly increased early and late stent thrombosis (12 vs. 0, p<0.01) and deaths (5 vs. 0, p= 0.02). The trial was stopped early due to these adverse events and has so far only been published as an abstract. Despite the inferior clinical results, the 6 month angiographic component of this study showed a significant reduction in restenosis rates (10.1% vs. 36.9%, p <0.001)[14].

DELIVER was a multi-center, randomized trial of the paclitaxel-eluting stent presented at the ACC meetings in March 2003 (www.clinicaltrialresultr.org). 1,041 patients with de novo lesions in native coronary arteries <25 mm in length and 2.5 to 4.0 mm in diameter, randomized to a multi-link Rx PENTA™ stent (n=519)or an RX ACHIEVE™ stent coated with paclitaxel (n=522). There was slightly less lumen loss

with the coated stent (0.81 mm vs. 0.98 mm, p=0.003) but no difference in binary restenosis (16.7% vs. 22.4%, p=0.15). There were also no clinical differences in target vessel failure (11.7% vs. 14.8%, p=ns), myocardial infarctions (1.0% vs. 1.2%, p=ns) or deaths (1.0% vs. 1.0%, p=ns). Unlike TAXUS II which used polymeric paclitaxel-eluting stent DELIVER used a non-polymeric version.

Summary of the evidence

Non-randomized studies in initially selected[18; 19], and later more diverse populations[22], have shown the safety and efficacy of sirolimus eluting stents for de novo lesions accompanied by low rate of repeat revascularization for restenosis. Two very small studies[28; 29] of de novo lesions with the paclitaxel derivative QP2 also showed promise with low rates of neoinitimal hyperplasia. These studies are limited by small sample sizes and their non-randomized design.

Three non-randomized studies[23-25] with sirolimus and one with paclitaxel[26] concluded that the drug eluting stents are an effective treatment option for in-stent restenosis, although this latter study did have relatively high clinical event rates. Moreover, in a very small study of in-stent restenosis, the paclitaxel derivative QP2 stent was ineffective[30]. Although the absence of late thrombosis as seen with brachytherapy is cause for optimism[37], reservations about coated stents for this indication remain due to the very small sample sizes, limited follow-up, and heterogenous results. Results for ISR have generally been less promising than those undertaken in de novo lesions. Finally without a randomized trial, it is impossible to compare the relative efficacy of DES, bare metal stents or brachytherapy for in-stent restenosis.

Figure 1 gives the results of all published randomized clinical trials of DES. Paclitaxel or its derivatives have been studied in 5 randomized trials[14; 31-34; 36] involving a total of 1232 patients. However, 1 study [32; 33] did not report their clinical outcomes and the trial with the paclitaxel derivative QP2 stent another was stopped for an increased mortality with the coated stent[14]. Among the 3 published trials reporting clinical results (751 patients), there have been a reduction in repeat angioplasty (OR 0.24, 95%CI 0.15,0.40) but no differences in deaths, myocardial infarctions or CABG. Three RCTs[26; 38; 39] have confirmed that sirolimus coated stents decrease the rate of angiographic restenosis and are associated with a large reduction in repeat revascularizations compared to uncoated stents (OR 0.17, 95%CI 0.11-0.27). No other clinical benefits have been demonstrated. Although angiographic and IVUS studies show a consistent pattern of reduced restenosis there remain occasional problems with malapposition or edge stenosis. Parameters such as drug toxicity, optimal drug dosage, and delayed endothelial healing have not been fully resolved.

When interpreting these promising early data in humans, it should not be forgotten that preclinical animal studies with drug eluting stents showed efficacy at one month but lack of benefit by three and six months [40]. In animals with drug eluting stents, normal healing is delayed from 1 month to 3-6 months and restenosis is not prevented, only delayed in a corresponding fashion. Since the human healing response and neointimal formation following a bare metal stent insertion or after brachytherapy is much longer (9 - 12 months) compared to animal models (1 month), the possibility that

restenosis in humans is only delayed and not prevented with drug eluting stents can not yet be discarded.

Therefore there are several reasons that definitive endorsement of coated stents should be delayed. In summary, these are as follows:

1) Doubts exist, based on animal models, as to whether human restenosis is eliminated or merely retarded (although these doubts are decreasing with increasing follow-up)
2) There has been limited follow-up of outcomes beyond 1 year
3) All studies have been sponsored by device companies
4) The largest study (SIRIUS) has yet to appear in a peer review publication
5) There have been significant delays in publishing, especially for the less promising studies. This could influence the overall impression.
6) Results appear less spectacular in more diverse populations, raising questions about generalizability (see RESEARCH, SIRIUS)
7) Study designs, which include the need to carry out angiographic or IVUS studies, favor an over-estimation of the absolute number of revascularizations avoided (how many of repeat revascularized patients were symptomatic)
8) Studies are too small and results too inconsistent to reliably identify any subgroups expected to derive a particularly large advantage
9) Inconsistencies as to the amount or importance of malapposition or edge stenosis
10) it is still uncertain whether IVUS is needed for improved stent deployment, and for how long should clopidogrel should been given
11) Although the enthusiasm is high for the overall concept of drug eluting stents, there are significant inconsistencies in the results between the different coated stent models
12) Most importantly, the absence of any reduction in deaths, myocardial infarctions or coronary artery bypass surgery compared to ordinary stents (perhaps somewhat related to the relatively small sample sizes).
13) Studies have not quantified any quality of life benefits associated with coated stents. This renders cost-effective analyses highly subjective.

However, the biggest obstacle to adopting the use of coated stents may well be financial, as any marginal benefit may come at a prohibitive cost. In the next section, we will consider the cost implications of drug eluting stents at the MUHC.

Estimation of the benefits/costs of DES at the MUHC

Although there have been no reductions in deaths, myocardial infarctions or the need for cardiac surgery with coated stents, there have been impressive reductions in restenosis rates. At present, the repeat angioplasty rate in Quebec and at the MUHC is 12% (see appendix 1). These restenosis rates were determined from the provincial administrative database (MED-ECHO) and apply only to patients having a first angioplasty. They do not include angioplasties repeated on the same day for acute

complications (coated stents have not been shown in trials to reduce the acute complication rates). Since these patients are not routinely examined angiographically during follow-up, no measure of restenosis not requiring a re-intervention is available.

If the results from the clinical trials are applicable to routine practice, one could anticipate an 80% reduction (OR 0.20, 95%CI 0.14-0.27) in the restenosis rate. In other words, the substitution of coated stents for regular stents would avoid approximately 9 repeat angioplasties for each 100 patients treated. The average cost for an angioplasty at the Royal Victoria Hospital is approximately $4,500 (Quality Management) . Therefore the introduction of coated stents would be expected to save $40,500/ 100 treated patients in repeated procedures. Preliminary data suggests that the Cordis Cypher stent will cost about $3,500, while uncoated stents are now available for $700. Therefore treating these 100 patients with coated versions, using on average 1.5 stents per procedure, would increase our stent expenditures by $379,500 (increase/case* # cases – savings = $2,800*1.5 *100 -$40,500). Since approximately 1000 procedures are performed annually at the MUHC (average 1.5 stents per procedure), a complete switch to coated stents would require additional funding of approximately $3,795,000 annually.

The above analysis is simplistic in its deterministic approach and ignores that fact that a certain percentage of patients, particularly those with uncoated stents, will require more than 1 repeat PCI. A more sophisticated model using decision analysis and Markov chains was performed. This allows consideration of the variability in the parameter estimations, the allowance of up to 2 subsequent angioplasties for restenosis, the possibility of a small reduction in the need for CABG (even if not supported by the clinical trial data) and the performance of sensitivity analyses. The rate of restenosis reduction is estimated by the preceding meta-analysis with the accompanying uncertainty. It is assumed that there is a 45% success rate in treating restenosis with bare metal and stents and that this is reduced by 50% with coated stents.

The base case would increase the hospital budget by approximately $3,400,000 annually. Sensitivity analyses of the most favorable scenarios with decreased coated stent costs, increased baseline restenosis rates and limiting 1 coated stent per case still gives an annual increase in the budget from 1.4 to 2.0 million dollars / year. Without a major increase in the hospital budget, the scenario of a total switch to coated stents appears untenable.

One frequently proposed approach to the introduction of high priced technology is to try to identify subsets of patients with the expected highest benefit and to reserve the treatment for this subgroup. For DES, this would involve predicting those at greatest risk of restenosis. Although intellectually and socially pleasing, there are several problems with this approach. Principally, the question becomes “can we reliably predict who is most likely to have restenosis?”

A large number of patient, vessel, lesion and physician characteristics have been associated with restenosis. Among patient characteristics showing a correlation to restenosis are age, sex, diabetes, smoking and extent of disease. Vessel characteristics include native versus vein graft, location and size of vessel. Lesion characteristics are severity of stenosis, length of stenosis, post procedure minimal diameter, acute gain, plaque burden and AHA classification. Physician characteristics include principally the volume of activity. At present, there is no reliable model based on these numerous characteristics to predict an increased risk of restenosis and consequently to identify a

sub-population with an increased level of benefit. Virtually every patient may be expected to have at least one previously identified high risk feature and attempts at predicting high risk patients and assigning them to receive coated may well become a more arbitrary than scientific process. The development of guidelines to select high-risk patients for restenosis would appear very challenging and is presently unavailable. Most studies of DES have concentrated on less complicated lesions as the initial goal is most often proof of concept. Furthermore thresholds of meaningful improvements in restenosis rates have not been established. Moreover, meaningful cost-effectiveness analyses can't be performed until reliable measures of quality of life for restenosis, since there is no improvement in survival, are determined.

Notwithstanding these limitations, suppose that by some method, for example by targeting insulino-dependent diabetics, it was possible to identify a 15% segment of our 1000 patient population with a 100 % increased risk of restenosis. Although a somewhat improbable scenario as we have not as yet identified such a powerful constellation of restenosis predictors, let us examine the effects of reserving DES for this "high risk" population. For these 150 high risk patients, a baseline restenosis rate of 25%, (100% increase over our present 12% rate) might therefore be reduced to 5%, by again assuming a 80% reduction with the DES. Even this idealized scenario would result in a $418,000 increase in expenses.

What would we have purchased for this additional expense? We would have purchased improved health of 30 (150*.25 – 150*.05) patients who would have otherwise had restenosis. The monetary costs to the MUHC of the avoided events have already been accounted. From a societal perspective, this strategy would have the benefits of an improvement in patients' quality of life and no loss of income for those working patients. The quality of life improvement is difficult to measure and probably small given that the period of increased incapacity due to angina is short. At present, patients miss approximately 2 weeks of work following a PCI. Therefore assuming that all patients are working, the investment of approximately $14,000 each may be expected to reduce their work absence by an average of approximately 2-4 weeks, including waiting times.

Since it is not yet possible to predict a subgroup of the population who would be at particularly high risk of restenosis, another scenario might reserve DES only for those patients who do develop in-stent restenosis. Moreover, current therapies for in-stent restenosis are unsatisfactory with a restenosis rate of 45% in those receiving a second stent and approximately 20% for those treated with brachytherapy. Calculating cost-effectiveness for this scenario is highly problematic as there are no comparative studies between DES and uncoated stents or with brachytherapy. Suppose we have a 15% restenosis rate leading to approximately 150 cases annually. If DES were restricted to those cases, our stent acquisition costs would increase by $630,000. Bare metal stents would be expected to lead to 67 cases of recurrent restenosis compared to 18 with DES (12%). Assuming that 50% of these patients would require another revascularization DES would therefore be expected to avoid 20 revascularizations with a savings of $90,000. Under these conditions, the net cost to the MUHC would be $330,000 with the same benefits as estimated above regarding absence from work.

Although the above mentioned benefits are tangible and desirable from a societal viewpoint, without the infusion of new money, the hospital will be obliged to reduce its budget elsewhere by a corresponding amount with presumably some resulting loss in

health benefits. Obviously, care would be necessary to assure that the benefits lost do not exceed those gained by the introduction of coated stents, which at present are limited to reduced repeat revascularizations.

Special Considerations

So far discussion has examined DES as a treatment substitution for conventional stenting. As demonstrated, in this context, any additional health benefits (fewer revascularizations and less loss of work) come at a relatively steep price. However, the possibility of DES as a treatment expansion, in other words the provision of stenting to patients who would otherwise be deprived of angioplasty due to high risks of restenosis should be considered. In this case, some patients who might otherwise be referred for a higher cost CABG might become candidates for lower priced angioplasty with DES. As another example, patients who remain symptomatic with medical therapy but are not surgical candidates, and for whom standard PCI carries too high a risk of a restenotic complication might possibly experience substantial long-term quality of life benefits with DES.

Clinical trials have not and likely will not be able to address this issue of treatment expansion. Consequently, it is very hard to attach any concrete estimates of cost-effectiveness for expansion utilization. Nevertheless one can easily appreciate the clinical desire to have the necessary flexibility to address these rather special situations. Since any benefits from such a treatment expansion program are at present only theoretical, it is not justified to recommend the redistribution of the catheterization or hospital budget to cover the additional costs of coated stents.

One can easily appreciate the clinical desire to have the necessary flexibility to address these rather special situations but to date clinical evidence and cost effectiveness data to support this position is unavailable. However, clinical specialists may well decide to collectively petition the Quebec government for a reserved supplemental fund for coated stents for these special conditions. Although difficult to quantify, it should be appreciated that the greatest health benefits and best cost-effectiveness are potentially available for this group. At present, there are no estimates of the potential number of coated stents required for this indication, although a judicious guess might place the number between 5 to 10%.

Each exception in which a coated stent is employed should be approved by two members of the Division of Cardiology. Ideally the two members should be interventional cardiologists who have the greatest knowledge concerning this technology. The records of such review should be maintained within the Division.

Conclusion

Coronary angioplasty is a commonly used procedure to reduce the symptoms of coronary artery disease. Coronary restenosis and consequently the need for repeat revascularizations have remained the Achilles heel of angioplasty. The recent introduction of coronary stents has greatly improved the safety of angioplasty and has reduced but not eliminated the problem of restenosis. There is accumulating and rather

compelling evidence that specific drug eluting stents may greatly reduce the magnitude of this problem, although the exact clinical benefit in routine practice has not been fully defined.

At the present time, there remain several obstacles to adopting a policy of universal use of coated stents. The number and size of the studies evaluating this technology are relatively small with limited safety and efficacy data beyond 1 year follow-up. The limited size of these studies has also precluded the reliable identification of any patient subgroups deriving particularly large clinical benefits. Questions concerning the equivalency of the different models are as yet unanswered. Technical issues also remain including the necessity of IVUS and the generalizability of the results. No reductions in mortality, myocardial infarction or bypass surgery rates have been demonstrated. However, the principal obstacle to conversion to coated stents is the extremely high cost for the somewhat limited health benefits to be expected.
Based on the synthesis of all available information and while recognizing the innovative nature of drug eluting stents and their potential to reduce the problem of restenosis and consequently repeat revascularizations following coronary angioplasty, the TAU Committee has therefore come to the conclusion that, in the absence of supplementary budget to meet increased costs, the reduction in hospital services that would result from a policy of adopting coated stents would not be justified.

Accordingly, the committee recommends that:

1. **That despite good evidence supporting the efficacy of coated stents to reduce the rate of restenosis, the current budget of the hospital should not be redistributed to permit the routine acquisition of drug eluting stents. Thus in the absence of a specially dedicated provincial budget for this technology, coated stents should not be provided by the MUHC except for special circumstances.**
2. **The special cases requiring a coated stent should be approved by two members of the Division of Cardiology, ideally two interventional cardiologists.**
3. **The evidence on which this policy recommendation is based is likely to be very time sensitive. The decision should be frequently reviewed and modified if necessary in the light of such evidence. The responsibility for requesting review can be initiated by either the Division of Cardiology or the Technology Assessment Unit.**

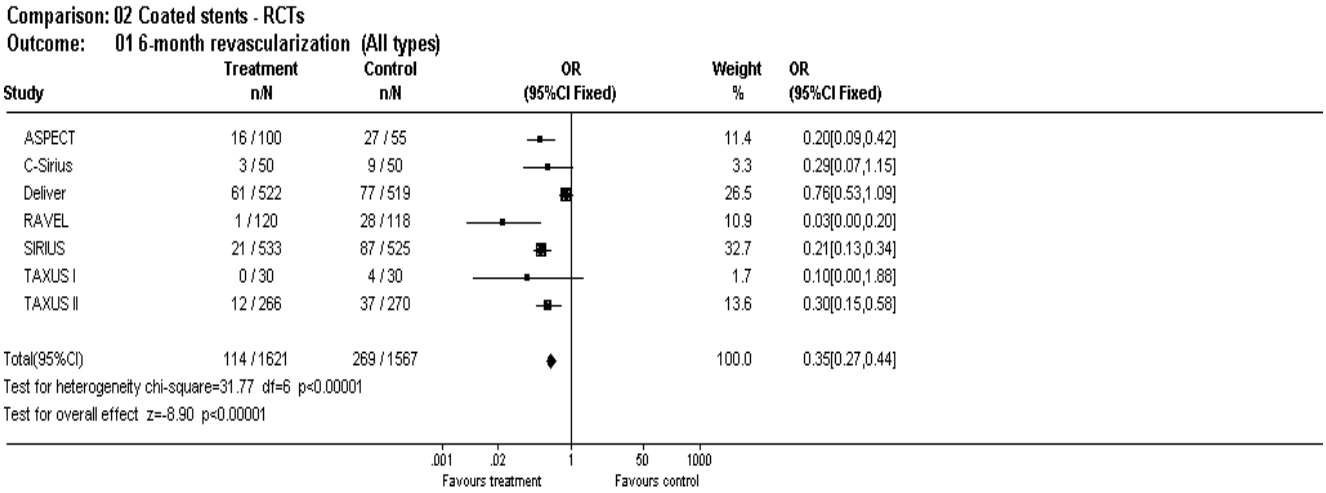
Table 1 Summary of landmark brachytherapy trials[41]

Table 2 Summary of landmark brachytherapy trials

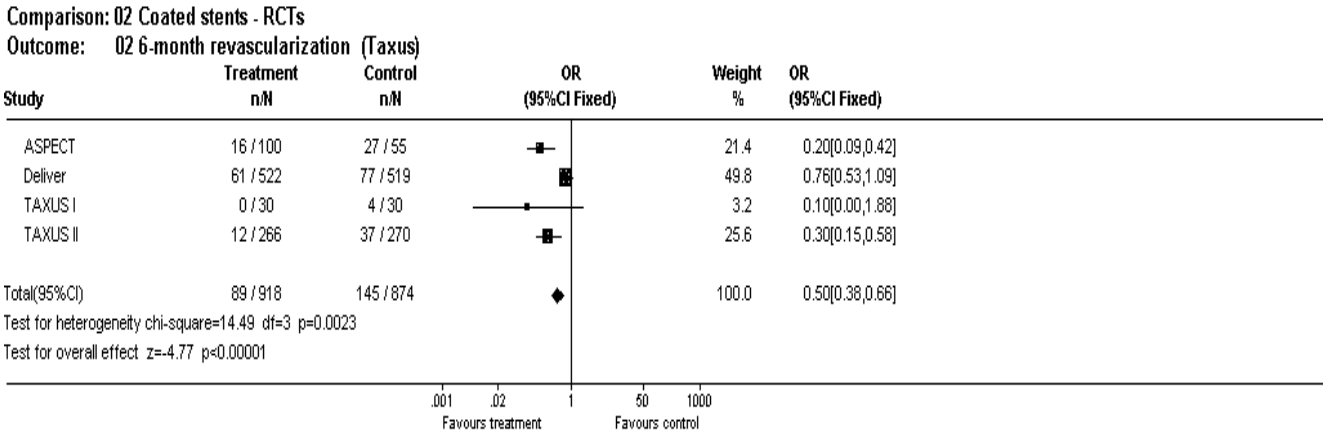
	BERT	SCRIPPS	GAMMA– WRIST	BETA-WRIST	PREVENT	GAMMA-ONE	β Irradiation: the Dose-Finding Study Group
Trial design	Radiation	Radiation v placebo	Radiation v placebo	Radiation	Radiation v placebo	Radiation v placebo	Radiation
Type of radiation	β (strontium/ yttrium 90)	γ (iridium 192)	γ (iridium 192)	β (yttrium-90)	β (phosphorus 32)	γ (iridium 192)	β (yttrium-90)
Number of patients	21	55	130	50	105	252	181
Lesion treated	PTCA sites	Restenosis after PTCA or stenting	In-stent stenosis	In-stent stenosis	De novo or restenosis lesions	In-stent stenosis	Restenosis after PTCA or stenting
Restenosis rates (6 months)	15%	17% v 54%	19% v 58%	22%	22% v 50%	32.4% v 55.3%	15% (for highest dose)
TVR at 6 months	15%	12% v 45% (TLR)	26.2% v 67.7%	34%	6% v 24% (21% v 32% at 12 months)	31.3% v 46.3%	6% (for highest dose)

PTCA, percutaneous transluminal coronary angioplasty; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

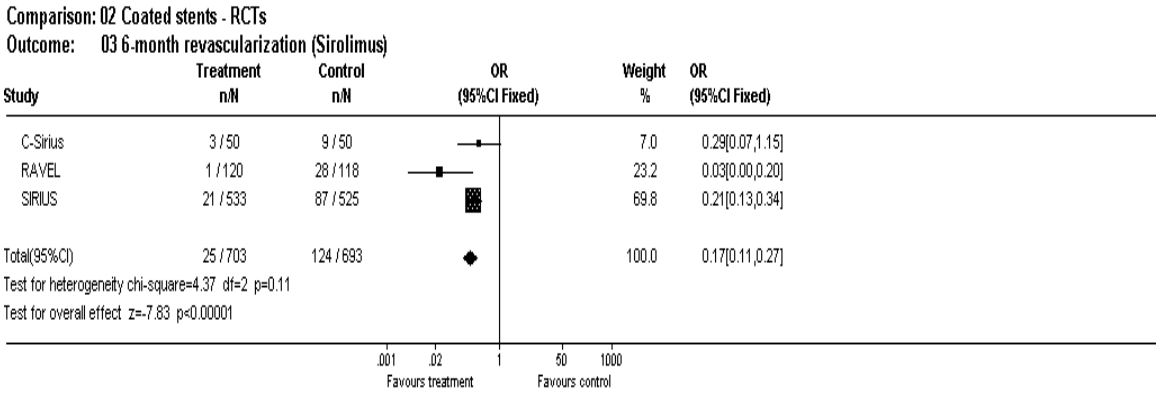
Figure 1 Summary of RCT with drug eluting stents



Paclitaxel coated



Sirolimus coated



Appendix 1

Population use of current angioplasty techniques

The total number of angioplasties in Quebec is increasing annually. Among patients with a new angioplasty (no procedure in the preceding 6 months), the number has grown from 5541 in 1995 to 8279 in 2000. There has been an increase in the use of stents from 8% of the cases in 1995 to 88% in 2000. Similar trends occurred at the MUHC.
Over the period 1998-2000 the need for a second angioplasty in the 6 months following an initial procedure was 11% among those receiving PTCA alone and 8% among patients having received a stent. The absolute reduction in repeated angioplasties avoided is therefore 3 per 100. This represents a 27% reduction in the need for repeat revascularization, similar to what was predicted from the clinical trials. It is important to note the discrepancy between this observed stent restenosis rate (8%) and that reported in the literature (11%). The literature estimates may have been biased by trial mandated 6 month angiographic studies.

Stents and PTCAs in Quebec – 1998 –2000
Only the 15 hospitals that do PTCA included

Number of First Procedures 1996 –2000 (i.e no angioplasty in previous 6 months)

# of Procedures	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**
PTCA alone	5,132 (92%)	4,416 (78%)	3,434 (51%)	2,204 (32%)	1,452 (18%)	960 (12%)
PTCA + Stent	409 (8%)	1,224 (22%)	3,280 (49%)	4,779 (68%)	6,670 (82%)	7,319 (88%)
TOTAL	**5,541**	**5,640**	**6,714**	**6,983**	**8,122**	**8,279**

1995 - 1997 – source: RAMQ / 1998-2000 – source: Med-Echo

Proportion of patients who had a second revascularization procedure within 6 months of the first one

Number (%) of Patients with > 1 Revascularization (range)				
	1998	1999	2000	All Years
PTCA alone	279 (12%)	169 (11.6%)	79 (8.2%)	527 (11%)
PTCA + stent	464 (9.5%)	595 (8.9%)	481 (6.5%	1,540 (8%)

COSTS OF PTCAs / STENTS – 1996 – 2000 (cdn$)

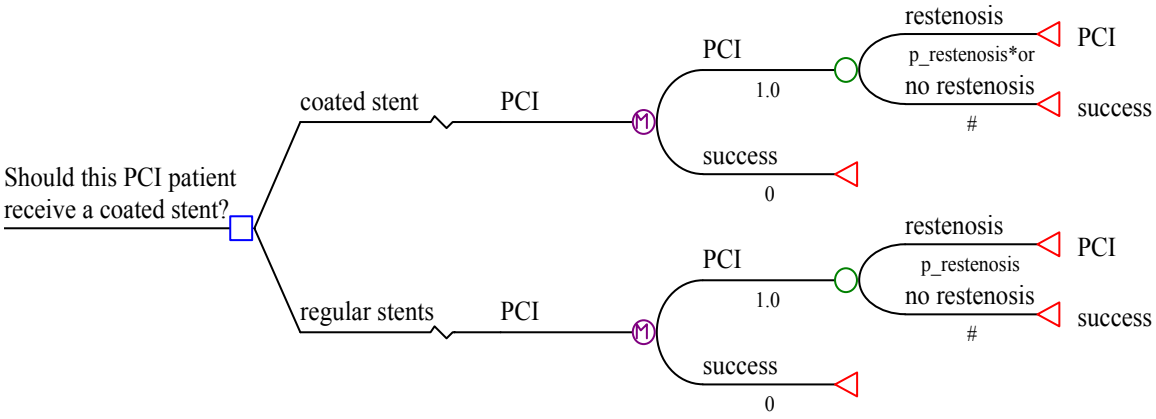
SOURCE: ROYAL VICTORIA QUALITY MANAGEMENT DATA

YEAR	**1996**	**1997**	**1998**	**1999**	**2000**
N / missing*	494 / 5	495 / 30	543 / 82	523 / 117	555 / 62
LOS (Median -IQR)	2 (3)	2 (3)	2 (2)	1 (2)	1 (3)
Total cost (Median -IQR)	4398.2 (2832)	4328.7 (2368)	4598.5 (2806)	4105.6 (2717)	4531.3 (3122)

- Patients whose cath lab cost was zero were excluded
- LOS = length of stay, IQR = interquartile range

Appendix 2

DECISION ANALYSIS for USE of COATED STENTS



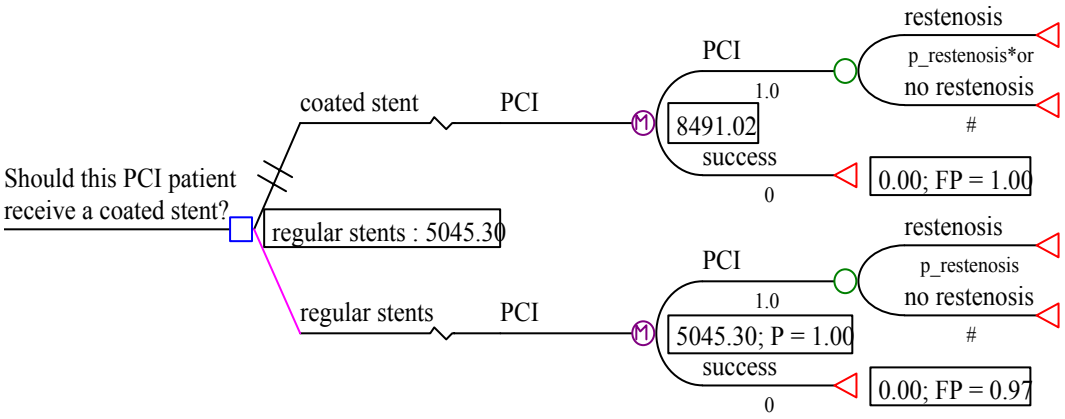
This Markov model considers transitional health states. Specifically, it assumes that following a PCI, a patient is either well or returns with restenosis. The model allows a patient to return for a maximum of 2 additional angioplasties. If there is still a problem of restenosis, the model assumes that 2/3 of the remaining patients are referred for CABG at a cost of $15,000.

Variables in the model and assumed values

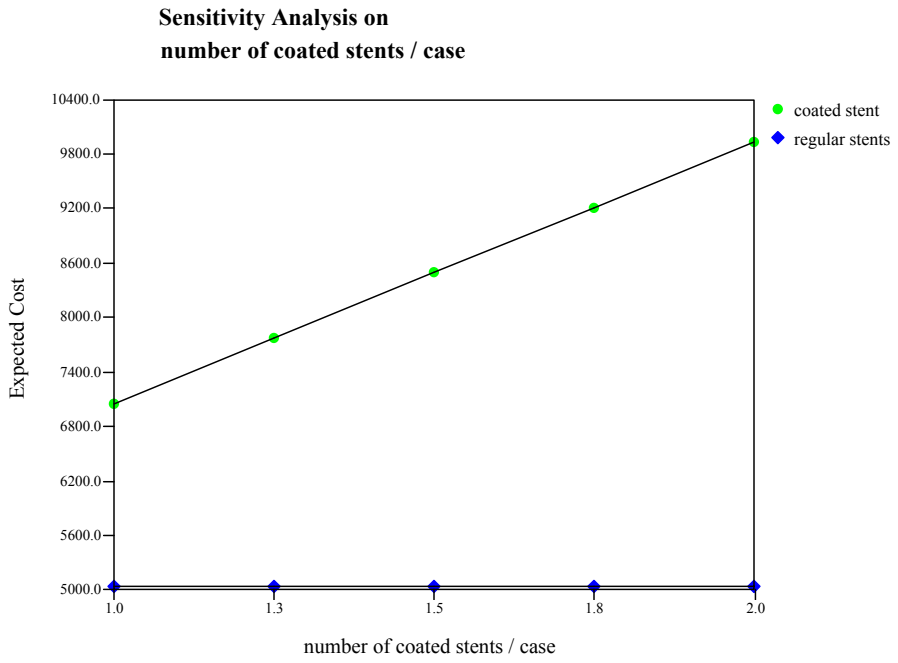
Description	Mean Initial Value	Sensitivity Low	Sensitivity High
<u>Uncoated stents</u>			
Cost of PCI	4531	1500	6000
# stents/case	1.5	1	2
Rate of repeat PCI	0.12	0.08	0.20
<u>Coated stents</u>			
Additional cost / coated stent	2800	2300	2800
Reduction in OR for repeat PCI (1^{st})*	0.2	0.14	0.28
Reduction in OR for subsequent PCI*	0.5		
Disutility of repeat PCI	0.95	0.9	1

* Binomial distributions based on the data from the literature

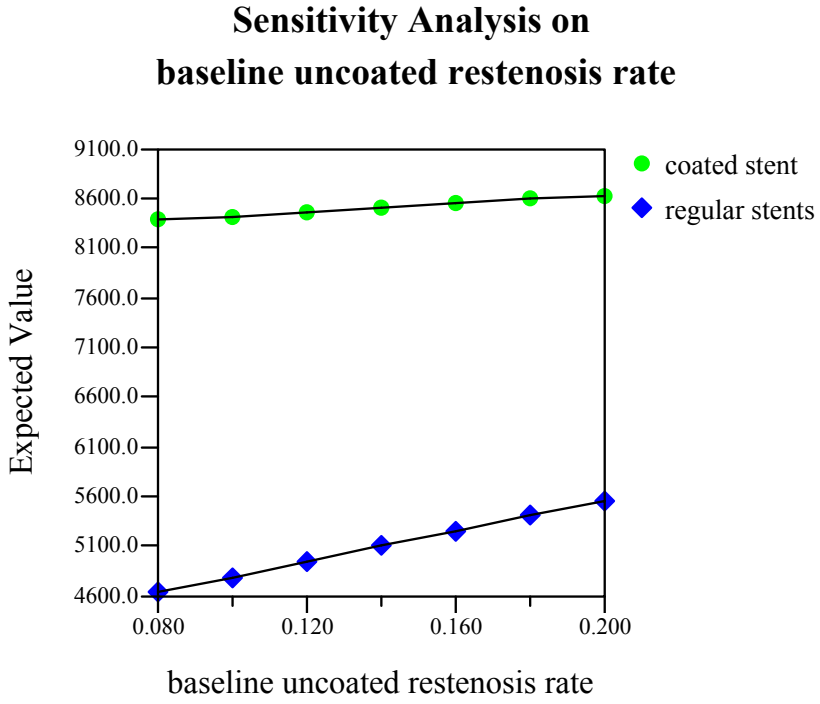
COST CALCULATION



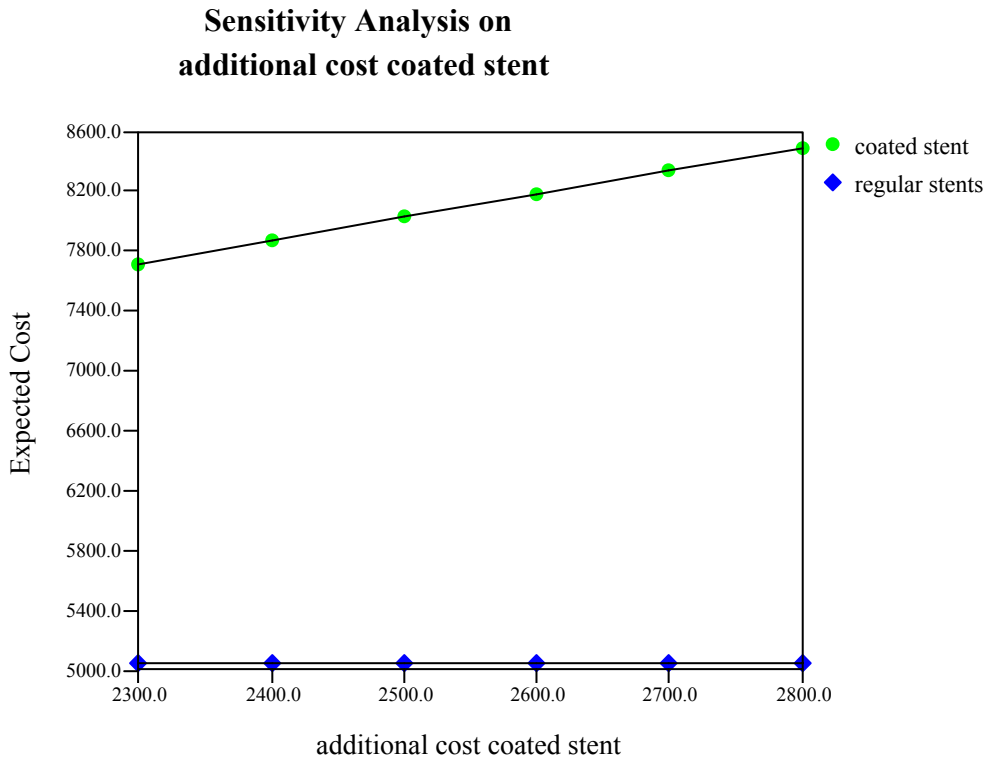
COST CALCULATION WITH SENSITIVITY ANALYSES



number of coated stents / case	1	1.25	1.5	1.75	2
coated stent	7045	7768	8491	9213	9936
regular stents	5045	5045	5045	5045	5045



baseline uncoated restenosis rate	0.08	0.1	0.12	0.14	0.16	0.18	0.2
coated stent	8378	8420	8462	8505	8547	8589	8631
regular stents	4631	4786	4941	5097	5252	5407	5562



additional cost coated stent	2300	2400	2500	2600	2700	2800
coated stent	7716	7871	8026	8181	8336	8491
regular stents	5045	5045	5045	5045	5045	5045

TWO WAY SENSITIVITY ANALYSES

BEST SCENARIO

Additional cost coated stent => 2300.00
Baseline rate of repeat revascularization => 0.20

Cost difference = 7844 – 5562 = $ 2282

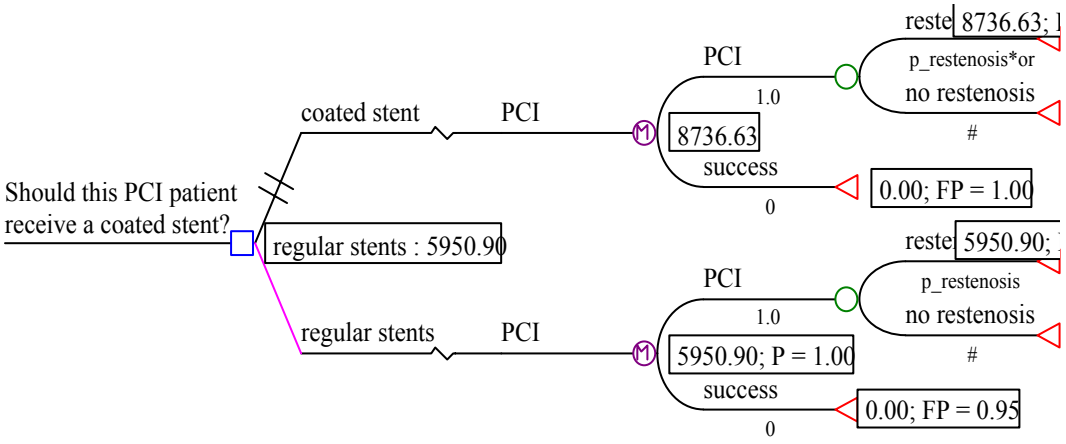
BEST SCENARIO

Additional cost coated stent => 2300.00
Number coated stent / case=> 1

Cost difference = 6529 – 5054 = $ 1475

COST CALCULATION (MARKOV MODEL)

ASSUMING COATED STENTS GIVEN ONLY TO PATIENTS WITH A RR = 2 OF RESTENOSIS (IE BASELINE RESTENOSIS RATE IS 25%)



Assuming that this population represents 15% of the total annual number of cases, i.e. 150 cases.

In this case the additional cost = (8736-5950) * 150 = 417,900

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