Centre universitaire de santé McGill
McGill University Health Centre

**Technology Assessment Unit of the McGill University Health Centre (MUHC)**

# Drug Eluting Stents

## What should be the indications for their use at the MUHC?

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**Report prepared for the Technology Assessment Unit (TAU)**

**of the McGill University Health Centre (MUHC)**

**by**

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**Approved by the Committee of the TAU on 31 October, 2011**

## TAU Committee



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| | |
|---|---|
| BMS | Bare metal stent(s) |
| CTO | Chronic total occlusion |
| DES | Drug-eluting stent(s) |
| ESRD | End-stage renal disease |
| MA | Meta-analysis |
| MI | Myocardial infarction |
| PCI | Percutaneous coronary intervention |
| RCT | Randomized controlled trial |
| SES | Sirolimus-eluting stent(s) |
| SR | Systematic review |
| STEMI | ST-segment myocardial infarction |
| TLR | Target lesion revascularization |
| TVR | Target vessel revascularization |

# EXECUTIVE SUMMARY

## Background

Stents are widely used to maintain patency following coronary angioplasty. In recent years, to reduce the rate of in-stent stenosis, bare metal stents (BMS) have been largely replaced by stents that slowly release anti-fibrotic medication, called drug-eluting stents (DES). Since the cost of a single DES is approximately $900 higher than that of a BMS the choice of which stent is used, is a matter of concern to hospital administrators. As a result of a recently observed increase in stent use, the TAU was requested to develop a list of indications for the use of drug-eluting stents (DES) at the MUHC.

## Method

The indications for using DES are the presence of increased risk of restenosis, or the presence of a lesion in which restenosis might have a particularly grave outcome. A literature search was undertaken with the three objectives of

- identifying the health benefits of substituting DES for BMS in the management of coronary artery disease,
- identifying predictors of increased risk of restenosis, and
- identifying any other indications for the use of DES.

In addition, in order to identify the current reasons for use of DES in the MUHC the reports of the last 115 stent procedures were reviewed. Also, the level of usage was ascertained and compared with that of other Québec University hospitals. Finally, estimates were made of the budget impact of the present level of usage of DES.

## Conclusions/Recommendations

### 1. Indications for use of DES

**It is recommended that the recently introduced practice of recording the indications for the use of DES in each procedure be maintained.**

**Although the evidence supporting some of the following indications is inconclusive, the preponderance of evidence suggests that use of DES at the MUHC should be restricted to patients with the following indications:**

- **Patients exhibiting two or three of the following risk factors: diabetes, small vessels (<3 mm diameter), and long lesions (≥20 mm).**
- **Relief of total chronic coronary occlusion.**

- **Patients undergoing repeat procedures to relieve in-stent stenosis.**
- **Patients undergoing multiple stent insertions.**
- **Interventions in the presence of multivessel disease and/or proximal left main stenosis.**

**2. Current usage of DES at MUHC.**

- **The indications currently in effect for the use of DES at the MUHC are largely consistent with the above indications.**
- **Of 2016 stents used in the budget year 2010-2011, 34% were DES. This is lower than in any other Quebec academic Hospital.**

**3. Cost Issues**

- **The gross cost of this intervention in the past budget year was approximately $607,250.**
- **Assuming this use of DES resulted in a 5.9% reduction in repeat angioplasty, the net budget impact would be $448,293, and the cost of each repeat procedure would be $10,934.**

# SOMMAIRE

## Contexte

Les endoprothèses vasculaires (EV) sont largement utilisées pour maintenir la perméabilité des vaisseaux suite à une angioplastie coronarienne. Au cours des dernières années, les EV purement métalliques ont été largement remplacées par les EV qui libèrent lentement un médicament anti-fibrinogène qu'on appelle EV à élution médicamentée (EVEM). Puisque le coût d'une seule EVEM est environ 900$ plus élevé que l'EV métallique, la sélection d'une endoprothèse est un sujet de préoccupation pour les administrateurs. Suite à une récente augmentation de l'implantation d'endoprothèses, l'Unité d'évaluation des technologies (« Technology Assessment Unit ») fut sollicitée pour élaborer une liste d'indicateurs pour l'utilisation des EVEM.

## Méthodologie

L'utilisation des EVEM est indiquée lorsqu'il y a un risque élevé de resténose ou en présence d'une lésion où une resténose pourrait avoir un impact important sur la santé. Ainsi, une revue de la littérature fut menée selon trois objectifs :

- Identifier les avantages pour la santé de remplacer les EVEM par les EV métalliques dans le management de la maladie coronarienne,
- Identifier les indicateurs d'un risque élevé de resténose,
- Identifier tout autre indication pour l'utilisation d'une EVEM.

De plus, afin d'identifier les raisons actuelles pour l'utilisation des EVEM au Centre universitaire de santé McGill (CUSM), les dossiers des 115 dernières implantations d'une endoprothèse furent révisés. De même, la justification de l'implantation fut notée et comparée à celles d'autres centres hospitaliers universitaires québécois. Enfin, l'impact budgétaire actuel de l'utilisation des EVEM fut calculé.

## Conclusions/Recommandations

### 1. Indications pour l'utilisation des EVEM

**Il est recommandé de maintenir la pratique récente d'enregistrer les indications concernant l'utilisation des EVEM.**

**Même si les évidences supportant quelques unes des indications ne sont pas concluantes, la prépondérance de ces évidences suggère que l'utilisation des EVEM au CUSM soit restreinte aux patients présentant les profils suivants:**

- **Les patients où l'on a identifié les risques suivants : le diabète, la présence de petits vaisseaux (<3 mm de diamètre) et la présence de longues lésions (> ou = 20 mm).**
- **Le soulagement complet de l'occlusion coronarienne chronique.**
- **Les patients subissant des angioplasties répétées pour corriger la resténose des endoprothèses.**
- **Les patients subissant l'implantation de plusieurs endoprothèses.**
- **Les interventions en présence de la maladie de plusieurs vaisseaux et/ou d'une sténose proximale de la coronaire gauche.**

**2. Utilisation présente des EVEM au CUSM**

- **Les indications actuellement considérées pour l'implantation des EVEM au CUSM sont largement conformes aux indications précédentes.**
- **Parmi les 2016 endoprothèses considérées dans le budget de l'année 2010-2011, 34% étaient du type EVEM. Ce pourcentage est inférieur à celui de tout autre centre hospitalier universitaire au Québec.**

**3. Enjeux budgétaires**

- **Le coût brut de cette intervention était environ 607 250$ dans le dernier budget annuel.**
- **Si l'on présume que l'utilisation des EVEM se traduisait par une réduction de 5,9% des angioplasties pour resténose, l'impact budgétaire net serait de 448 293$ et le coût de chaque procédure pour resténose serait de 10 934$.**

# Drug Eluting Stents.

# What should be the indications for their use at the MUHC?

## 1. BACKGROUND

It has been common practice since 1994 to place stents in the coronary artery to maintain vessel patency following angioplasty[1]. Angiographic studies subsequently showed that approximately 20% of stents become reoccluded within the first year. Around 2002, coated or drug-eluting stents (DES) were introduced, which incorporate a slow-release coating of drug that inhibits the restenotic process.

A report and systematic review published in 2003 by TAU[1] found that there was good evidence that use of DES could reduce restenosis rates within the first year, but there was no evidence that this would result in any reduction in mortality or the rate of myocardial infarction. Thus, the sole proven health benefit of use of DES was avoidance of the need to undergo a repeat revascularisation procedure in patients who develop ischaemic symptoms.

A risk of late thrombosis (for more than a year post-procedure) has now been identified with DES[4, 5], which prompted a 2006 FDA clinical practice guideline recommending at least 12 months double antiplatelet treatment following stent implantation[6] to reduce this risk. Furthermore, the unit cost of a single DES is currently approximately $900 higher than that of a single uncoated or bare metal stent (BMS). Thus, the choice of which stent is used, and the impact of this choice on budget, is a matter of considerable concern.

The 2003 TAU report concluded that this health benefit was insufficient to justify the budget required to completely replace BMS by DES, and recommended that DES be employed only when there was reason to believe there was an increased risk of restenosis. At that time the identification of increased risk was very imprecise. However, there has subsequently been further study of the health benefits and costs of use of DES and there has been considerable progress in identifying the presence of increased risk of restenosis. A brief follow-up on the issues raised by the TAU report is set out in Appendix 1.

On May 31, 2011, the Technology Assessment Unit (TAU) was asked by Mr Gary Stoopler, Administrative Director of the Medical Mission of the McGill University Health Centre (MUHC), to respond to the request of Dr Nadia Giannetti, acting Head of the Cardiovascular Division, to develop a response to the question “What should be the

accepted indications for drug eluting stents in our practice?" The following Report develops a response to this request.

# 2. OBJECTIVES

The principal indication for using DES is the presence of increased risk of restenosis. A secondary indication is the presence of a lesion in which restenosis might have a particularly grave outcome. Our study therefore had four objectives.

1. To identify the health benefits of substituting DES for BMS in the management of coronary artery disease.
2. To identify predictors of increased risk of restenosis.
3. To identify other indications for the use of DES.
4. To identify the current indications for use of DES, the number used, and the budget impact of their use at the MUHC.

# 3. METHODS

## 3.1. Literature search

To identify relevant publications we searched the Cochrane Collaboration, DARE, EMBASE(Ovid; includes Medline) and PubMed. Topic-specific search terms were "drug-eluting stents", "sirolimus-eluting", "paclitaxel-eluting" (the drugs most commonly used in DES), both mapped to subject headings, and as text words. Truncation with wildcards (eg, "stent*" used to search for "stent", "stents", and "stenting" and other variants) was also used. In the bibliographic databases, articles that discussed implantation of stents other than in coronary arteries were excluded by either restricting articles to those with "coronary" as a text word, or subject headings pertaining to coronary artery disease, or excluding those with "saphenous", and combining the searches.

To retrieve systematic reviews, we initially used the systematic reviews filter in both PubMed and Ovid, but found that these gave an excess of commentaries and non-systematic reviews discussing the SR literature. We therefore used article type "meta-analysis" to filter the results, combined with title words "meta-analysis", "systematic review", with wildcards and variations.

We also reviewed the citation lists of recent (last 5 years) systematic reviews of meta-analyses, and commentaries or narrative reviews whose topic was meta-analyses.

To identify predictors of increased risk of target vessel restenosis in a population similar to that at the MUHC we used a substantial Ontario prospective observational study[5].

We considered other potential predictors of increased restenosis rates, namely the presence of complete coronary occlusion, repeat procedures, multi-vessel disease, multiple stent placement, and acute myocardial infarction, using a non-systematic review based on MEDLINE, and Google Scholar, and studies cited by reviewers.

### 3.2. Use of DES in the MUHC

In order to determine whether stent utilisation at the MUHC was consistent with the indications listed above, one of us (MMcG) reviewed the records of all stent procedures carried out between June 1 and July 20, 2011 .(Detailed reports of each procedure are completed by the cardiologist at the end of each procedure. Since July 20 these reports have included specific reasons for the selection of DES or BMS.). Data on stent utilisation and costs were provided by Madame Christiane Bérubé (Manager, Haemodynamic and cardiac catheterisation laboratories). For costs related to repeat coronary angioplasty we are indebted to her and to Mr N. Robert (Department of Financial Services, MUHC). We summarized stent use according to indication and calculated gross and net costs.

## 4. RESULTS

### 4.1. Health benefits resulting from the use of DES?

To identify the health benefits that might be expected from use of DES we depended heavily on a comprehensive recent Cochrane systematic review by Greenhalgh et al[2] of articles published up to the beginning of 2009. These authors found 47 RCTs comparing DES with BMS used in the treatment of angina or acute coronary syndromes, involving 14,500 patients followed up for up to 5 years. For objective outcomes such as the rates of mortality, myocardial infarction, or thrombotic stent occlusion, they found no statistically significant difference between BMS and DES (all stents). However, the rate of target vessel revascularisation (TVR) at one year was reduced by use of DES compared to BMS by an average 55.25% (95% CI 47.8%, 61.64%), for all stents.

These results were consistent with those of another substantial network meta-analysis covering publications up to March 2007[3] in which no difference was found in mortality or the frequency of myocardial infarction, but a reduction in TVR with DES (sirolimus-eluting) compared to BMS (HR 0.70, 95% credibility interval 0.56, 0.84).

The extent of this benefit is probably an over estimation. Since TVR is an outcome largely driven by the patients' symptoms and the treating physicians' opinion that

angiography is indicated, a completely unbiased result would require adequate blinding of the patient and the treating physician. However, in 17 of the 47 studies included in the Cochrane review[2] there was either no blinding or no mention of any blinding, and in 13 studies only single blinding was reported[2]. In the 15 studies that reported "double blinding", concealment of treatment allocation was rarely mentioned. Since it is widely believed that restenosis is more likely to occur in BMS than in DES, there was potential bias of the treating physician in favour of initiating angiography (with more frequent discovery of stent restenosis) whenever it was known that BMS had been used. Though the effect of any such bias cannot be quantified, it is probable that it leads to some over-estimation of the actual benefit of DES.

By contrast with RCTs, observational studies frequently find lower rates of mortality and myocardial infarction with use of DES. Thus, a 2009 meta-analysis of 34 observational studies found that DES was associated with significant reductions in all cause mortality (HR 0.78 95% CI, 0.71, 0.86), and myocardial infarction (HR 0.54 95% CI 0.78, 0.97)[7]. However, in view of the recognised difficulties in controlling confounding in observational studies and the abundance of evidence from RCTs, we will give preference to the RCT evidence for overall health benefit.

## 4.2. Predictors of increased risk of restenosis

Since the cost of DES is significantly greater than that of BMS it is desirable to restrict use of DES to those patients in whom the probability of reocclusion is increased. The index of reocclusion most frequently used is the performance of target vessel or target lesion revascularisation (TVR or TLR). Restenosis is detected by angiography, carried out either as a routine post-operative procedure, or in response to recurrence of symptoms. It is important to note that in the latter situation reocclusion rates are substantially lower. Unless specifically noted we will use throughout this report the rates of TVR initiated by recurrence of symptoms of ischemia as the basis of comparison of different interventions

To identify predictors of increased risk of target vessel restenosis in a population similar to that at the MUHC we used a substantial Ontario prospective observational study based on a well-balanced cohort consisting of 8,247 patients who received BMS and 5106 who received DES, carefully matched on the basis of propensity score[8] (3751 pairs)[9].

The risk of restenosis has been reported to be increased in several clinical situations. These include, the presence of diabetes[10], and the presence of unusually long or unusually narrow stenotic lesions[10-12]; interventions on chronically totally occluded vessels[10]; performance of repeat procedures on previously stented vessels; and implantation of multiple stents. These are considered below.

### *4.2.1. Presence of diabetes, lesion length, and lesion diameter*

For over a decade it has been realised that the probability of restenosis is increased in the presence of diabetes, or when the atherosclerotic narrowing is very constricted or very long[13-15]. In 2007 the risk of restenosis associated with these three characteristics was quantified in a unique study based on the Cardiac Care Network of Ontario's population-based clinical registry of all patients undergoing PCI in that Province[9]. These authors studied a well balanced cohort consisting of 8,247 patients who received only BMS and 5106 who received only DES during a PCI procedure between December 1, 2003 and March 31, 2005. (Patients with a previous angioplasty or those with left main coronary disease were excluded). Samples of patients who received DES alone or BMS alone were carefully matched in terms of risk of restenosis using propensity scores, and the analysis was done on 3751 pairs. The authors found that use of drug-eluting stents was associated with significant reductions in the rate of target vessel revascularisation (TVR) in those patients exhibiting *two* or *three* of the following risk factors: presence of diabetes, small vessels (<3 mm diameter), and long lesions (≥20 mm)[9, 16]. The absolute differences in the percent TVR, the Hazard Ratio, and the 95% Confidence Interval observed with various combinations of risk factors were as follows (see Table 1).

**Table 1 Effect of patient/lesion characteristics on revascularization**

| Lesion | | % TVR | | | HR (95% CI) |
|---|---|---|---|---|---|
| | N | BMS | DES | BMS-DES | |
| Diabetes + small vessel + long lesion | 347 | 17.6 | 7.2 | 10.4% | HR 0.38 (0.2, 0.60) |
| Diabetes + small vessel | 253 | 13 | 4.7 | 8.3% | HR 0.34 (0.17, 0.66) |
| Diabetes + long lesion | 295 | 10.5 | 6.1 | 4.4% | HR 0.55 (0.32, 0.95) |
| Small vessel + long lesion | 782 | 12.3 | 8.6 | 3.7% | HR 0.66 (0.48, 0.91) |
| Weighted Average | | 13.2 | 7.3 | 5.9 | |

N, number of matched pairs

Small vessel = lesion < 3 mm diameter

Long lesion = lesion ≥20 mm length

Importantly, in the absence of these risk factors, or when they occurred alone, there was *no significant difference* in TVR rates with use of BMS or DES. The presence of these factors in the combinations indicated above constitutes good evidence of increased risk of restenosis and DES is clearly associated with better outcomes than BMS in the presence of the above risk factors. See Table 1 and Appendix 2.

#### *4.2.2. Interventions in chronically totally occluded vessels.*

We have not found direct comparisons of TVR rates in chronically totally occluded coronary arteries versus rates for other coronary lesions. However, reported rates of TVR in cases of total coronary occlusion are significantly higher than overall average TVR rates. Thus, in a recent meta-analysis including 13 studies and 4206 patients with total coronary occlusion, TVR was reported in 24%[17] of patients who received BMS. This is twice the overall TVR rate of 10.7%[3] - 12%[1, 16]. In addition, there is consistent evidence of substantial clinical superiority of DES over BMS following recanalisation of totally occluded vessels. (See Appendix 3)

#### *4.2.3. Repeat procedures for procedures for in-stent restenosis*

It has been proposed that restenosis lesions have a different substrate from that of primary lesions, which may predispose to a higher incidence of second restenosis[14]. Certainly the TVR rate following repeat revascularisation procedures is relatively high, as reported in the meta analysis of Dibra et al (21%)[18], and two studies have found higher restenosis rates after restenting of previously stented lesions[19, 20]. However, others have not confirmed this relationship[13, 14]. Thus, while it is quite probable that restenosis occurs more frequently following repeat procedures, the evidence must be considered inconclusive. The available literature does not provide comparisons of the efficacy and safety of DES versus BMS in this indication. However, the superiority of DES over non-stent modalities is established (See Appendix 4)

#### *4.2.4. Implantation of multiple stents*

It is reasonable to anticipate that the risk of restenosis will increase with the number of stents implanted, and such a relationship has been reported[14, 19, 21]. The need to insert multiple stents therefore appears to be a reasonably supported predictor of increased risk of TVR.

## 4.3. Other indications for the use of DES

In addition to the increased probability of restenosis (as indicated by the above risk factors) there are other circumstances in which DES might be preferable to BMS. To identify these, we principally used, a 2011 systematic review prepared for the French National Authority for Health[22], supplemented by the references used in this and other meta-analyses.

The authors carried out an evaluation of the efficacy and safety of DES compared with BMS, by patient category[22], based on a systematic review of two health technology assessments, 11 meta-analyses, 11 RCTs, and 16 prospective cohort studies, supplemented by the views of a panel of experts. They identified two situations in which

they recommended that use of DES be considered in addition to the predictors of restenosis listed above:

### *4.3.1. Patients with proximal left main coronary artery (LMCA) stenosis or diffuse severe coronary artery disease*

The rationale for the use of stents in the presence of such lesions is that the consequence of a subsequent restenosis could be so grave (death or extensive myocardial infarction) that operators wish to do everything possible to avoid restenosis. Accordingly, it is usual to employ DES in such patients. There is some evidence to support this approach.

Two meta-analyses considered DES versus BMS in left main coronary artery stenosis. Biondi-Zoccai et al (2007)[23] included 16 studies, none of which were RCTs. Pandya et al (2010)[24] included 9 studies with either randomization (one RCT) or adjustment. Both analyses showed a significant difference in outcomes, favouring drug eluting stents. In Biondi-Zoccai et al, there was a significant difference in major adverse cardiac events (OR 0.34, 95% CI 0.16, 0.71). In Pandya et al[24], at three years, there was a significant difference in MI (OR 0.49, 95% CI 0.26, 0.92), death (OR 0.70 95% CI 0.53, 0.92), and revascularization rates (TLR/TVR, OR 0.46 95% CI 0.30, 0.69). The single RCT (n=103)[25] found lower major adverse cardiac event-free survival with BMS compared to DES (70% vs 87%; p=0.036). Thus the available evidence supports the use of DES in the presence of proximal LMCA stenosis.

The same rationale for use of DES (the severity of the consequences of restenosis) underlies the recommendation of the French reviewers[22] for the use of DES for the relief of diffuse severe coronary disease. However, use of DES in this context is as yet unsupported by direct experimental evidence.

### *4.3.2. ST-segment elevated myocardial infarction (STEMI)*

Schapiro-Dufour and colleagues also suggest that the presence of STEMI (acute myocardial infarction with ST elevation) should constitute an indication for use of DES[22], on the basis of evidence that DES is more effective in such patients[22]. We retrieved ten meta-analyses examining DES versus BMS in STEMI[26-35], the three most recent[26, 27, 29] synthesizing data from 13 RCTs involving sirolimus and paclitaxel. Results from all three meta-analyses found a significant difference in OR or RR for revascularization favouring DES for revascularization.

However, acute myocardial infarction has been found to not be associated with any increase in restenosis[21], and in light of the data from the Ontario registry study, it is probable that the observed benefit of DES is confined to those patients with the risk factors for restenosis listed above. The presence of STEMI should therefore not, of itself, be considered an additional indication for use of DES.

# 5. USE OF DRUG-ELUTING STENTS AT THE MUHC

## 5.1. Stent use at the MUHC, 2010-2011

In the budget year 2010-2011, 694 DES and 1332 BMS were used at the MUHC, with three different types of DES (Table 2).

**Table 2 Stent use at the MUHC, 2010-2011**

| Stent | Manufacturer | Drug | Patients (%) |
|---|---|---|---|
| All drug-eluting | | | 694 (34%) |
| Cypher® | Cordis, Johnson and Johnson | Sirolimus | 537 |
| Xience V® | Abbot Vascular | Sirolimus | 100 |
| BioMatrix Flex® | Biosensors international | Biolimus | 57 |
| Bare metal | | | 1322 (56%) |

DES use as a percentage of all stents used at the MUHC was 34%. This is a lower utilization rate than in other Quebec University Hospitals (Sacre Coeur 45%, CHUM 50%, Laval QC 48%, Institut de Cardiologie 47%, Sherbrooke 45% [Source: Christiane Bérubé, Manager Haemodynamics Laboratory, MUHC]).

## 5.2. Indications for DES used at the MUHC

Of the last 116 patients who received a stent between June 1 and July 20, 2011, 36 received only DES (31%), 74 received only BMS (64%) and 6 (5%) patients received both. Of the 176 stents used for these patients, 61 were DES (35%) and 115 (65%) were BMS. In the 42 patients who received DES the principal recorded indications were as follows:

- small vessel diameter, 5.
- long lesion, 6.
- long lesion + small vessel diameter, 10.
- long lesion + diabetes, 3.
- small vessel diameter + diabetes, 1.
- total occlusion, 8.
- repeat procedure, 7.
- multivessel disease, 1.

Severe diffuse disease or proximal main left lesion was a frequent additional factor.

In 11 patients the recorded reasons (small diameter only, length of vessel only) might be questioned, but it is probable that this is more often a defect of recording rather than

of practice, eg, diabetes was only recorded in three patients but is present in 20% of stented patients (Dr. L Bilodeau, Director Haemodynamics Laboratory, MUHC). Thus current practice at the MUHC is largely consistent with the indications listed under "Conclusions" (Section 6), below.

## 5.3. Cost considerations

**Table 3 Estimated cost of stent use at the MUHC**

| | Unit cost (avg) | Repeat TVR/TLR | Gross cost | Net cost |
|---|---|---|---|---|
| DES | $1,287 | 7.3% | | |
| BMS | $412 | 13.2% | | |
| Difference | $875 | 5.9% | $607,250 | $448,293. |

In the fiscal year 2010-11, the average unit price for a DES was approximately $1287 and for a BMS, $412, leading to a price difference of approximately $875 per stent. In the same year, 694 DES were used, which translates to an additional total cost of $607,250.

The cost offsetting due to the avoidance of TVR resulting from the use of these 694 stents cannot be estimated directly. However, these patients were selected for stent implantation on approximately the same criteria as developed by Tu et al[9]. If we assume the same mix of lesion characteristics and comorbidities, we estimate that the percent TVR with BMS and DES would be 13.2% and 7.3% (weighted average, see Table 1) respectively, for a difference of 5.9% (see Table 3). Accordingly, the use of 694 DES would be expected to lead to 41 fewer TVR procedures (assuming one stent per patient). The average cost of angioplasty is estimated to be $3,877 (see Appendix 5), and thus the net cost of using 694 DES would be $607,250 – (41 x $3877) = $448,293. However, since some proportion of TVRs are carried out in the context of acute myocardial infarction, the cost of angioplasty alone is an underestimate of the costs associated with TVR.

Based on the above calculation, the cost-effectiveness of the use of DES in a calendar year in question was approximately $448,293/41 = $10,934 for each repeat procedure avoided. The calculation did not include the costs of double antiplatelet treatment, as this is not part of the MUHC budget.

# 6. CONCLUSIONS/RECOMMENDATIONS

**1. Indications for use of DES**

**It is recommended that the recently introduced practice of recording the indications for the use of DES following each procedure be maintained.**

**Although the evidence supporting some of the following indications is inconclusive, the preponderance of evidence suggests that use of DES at the MUHC should be restricted to patients with the following indications:**

- **Patients exhibiting two or three of the following risk factors: diabetes, small vessels (<3 mm diameter), and long lesions (≥20 mm).**
- **Relief of total chronic coronary occlusion.**
- **Patients undergoing repeat procedures to relieve in-stent stenosis.**
- **Patients undergoing multiple stent insertions.**
- **Interventions in the presence of multivessel disease and/or proximal left main stenosis.**

**2. Current usage of DES at MUHC.**

- **The indications currently in effect for the use of DES at the MUHC are largely consistent with the above indications.**
- **Of 2016 stents used in the budget year 2010-2011, 34% were DES. This is lower than in any other Quebec academic Hospital.**

**3. Cost Issues**

- **The gross cost of this intervention in the past budget year was approximately $607,250.**
- **Assuming this use of DES resulted in a 5.9% reduction in repeat angioplasty, the net budget impact would be $448,293, and the cost of each repeat procedure would be $10,934.**

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## Appendix 1 Update of issues raised in the TAU report of 2003

The 2003 TAU report indicated that for several reasons definitive endorsement of coated stents should be delayed. These included the limited follow-up beyond 1 year at the time of the 2003 TAU report, the lack of information about the risk of late restenosis, and the absence of reduction in deaths, myocardial infarction, or CABG rates in follow-up to date.

The 2009 Cochrane review by Greenhalgh et al[2] found that the reduction in the overall event rate observed DES at 6 months follow-up, persisted out to 5 years. Data were derived from 12 trials of SES at 6 months (11 trials in an analyses restricted to stents approved for marketing as of 2009) and 2 trials at 5 years. This reduction was driven by a significant reduction in revascularization, whether measured as target lesion or target vessel revascularization.

The 2003 TAU report also noted that revascularization rates were potentially influenced by protocol-mandated angiography and use of angiographic rather than clinical definitions of assessment. Recent reviewers[36] have indicated this may still be a concern, since the longest follow-up comes from early studies with angiographically determined endpoints, although the difference in outcomes persists to later time-periods. Observational data, in which angiography is clinically determined, also shows a significant difference in overall events and reinterventions[7].

For the endpoints of mortality, myocardial infarction, and late thrombosis (a concern not yet identified at the time of the previous reports), there continued to be no observed difference between DES and BMS at interim time-points up to five years[2]. A risk of late thrombosis (more than a year post-procedure) has been identified with DES[4, 5], which prompted a 2006 FDA review and clinical practice guidelines recommending at least 12 months double antiplatelet treatment following stent implantation[6] to reduce the risk.

The 2003 TAU report[1] indicated that the early registration trials were conducted in selected populations, and that the early data suggested less favourable outcomes in other populations. The dataset in use in, patients at increased risk of restenosis or thrombosis is now substantial[2, 22, 37], and analysis has not identified a population in which DES are associated with poorer outcomes. Conversely, the increased risk of restenosis in certain patients may make them more appropriate candidates for DES implantation, as discussed above and below. Need for assessment of individual patient risk, particularly those risks associated with prolonged clopidogrel use, is well documented[2].

## Appendix 2 Evidence for use of DES in patients with diabetes and complex lesions

*Patients with diabetes*

We found six meta-analyses examining the use of drug-eluting versus bare metal stents in patients with diabetes[2, 32, 38-41], in addition to the systematic review with narrative synthesis by Shapiro-Dufour et al[22].

In a subgroup analysis of their Cochrane review, Greenhalgh et al[2] synthesized data from the 4 RCTs of SES and bare-metal stents in diabetic patients (DECODE, DESSERT, DIABETES, and SCORPIUS). They found a significant effect favouring SES on a combined endpoint representing combined death, myocardial infarction, revascularization and stent thrombosis, OR 0.21 (95% CI 0.09, 0.47), at 2 years follow-up. Of the individual endpoints, only target-vessel/lesion revascularization showed a significant difference, OR 0.07 (95% CI 0.02, 0.15). The numbers of deaths, MIs, and stent thromboses were small. A random-effects meta-analysis with the same 4 RCTs produced similar results[38].

In a large (35 RCTs) network meta-analysis with indirect comparisons of 35 RCTs that included diabetic patients, Stettler et al[42] found similar rates for TLR for diabetic and non-diabetic patients for both sirolimus-eluting stents (SES) and paclitaxel-eluting stents. For TLR, the HR for SES in diabetic patients was 0.29 (95% CrI 0.22, 0.39), and for non-diabetic patients was 0.29 (95% CrI 0.22, 0.38).

Therefore in the subgroup of patients with diabetes, DES produced a similar benefit in revascularization to all patients and patients without diabetes, without evidence of an effect on mortality, MI, and stent thromboses.

*Effect of lesion characteristics*

Both Greenhalgh et al[2], and Stettler et al[42], raised the possibility that the increased risk of restenosis in patients with diabetes was not associated with the diabetes itself, but with the lesion characteristics found more frequently in diabetics: long lesions, and lesions in small diameter vessels.

Greenhalgh et al presented a subgroup meta-analysis of 5 RCTs which recruited patients with long lesions/small vessels/complex lesions. On a composite measure of event-rate comprising death, MI, revascularization and thrombosis, DES were significantly better. This difference was driven by revascularization rates (TLR at 4 years, OR 0.27, 95% CI 0.19, 0.40 for SES), with no significant difference in mortality, MI, or thrombosis, at any time-point.

Schapiro-Dufour et al[22] reported that both Cypher® (sirolimus-eluting stent, currently in use at MUHC) and Taxus® (paclitaxel-eluting stent, not currently used at MUHC) were significantly more effective than BMS in patients with lesions at high risk of restenosis (>15 mm long or in a vessel <3 mm in diameter). Over a 3-year follow-up, the RR for TLR for Cypher® was between 0.08 and 0.33.

## Appendix 3 Evidence for use of DES in patients with chronic total coronary occlusion

Four individual meta-analyses examined the use of drug eluting stents in patients with chronic total occlusion[17, 43-45], in addition to the systematic review with narrative synthesis by Shapiro-Dufour et al[22]. All four included both RCTs and non-RCTs, with the majority of studies being non-RCTs. The stents involved were coated with sirolimus or paclitaxel. A fifth systematic review of off-label uses of drug-eluting stents[37] did not include a formal meta-analysis, but produced summaries of the rates of deaths, MI, and revascularization. The results of the meta-analyses were consistent with each other and with meta-analyses of unselected patients: a significant difference favouring DES in the composite endpoint of major cardiac events (variously defined), which was driven by revascularization. Other individual endpoints of death, myocardial infarction, and thrombosis did not show a significant difference.

Long term clinical follow-up data from the individual RCTs are consistent with the findings of the meta-analyses, in that the composite endpoint of major adverse cardiac events (however defined) shows a significant difference favouring DES (PRISON II at 3 years, n=200, p<0.001[46]; GISSOC II-GISE at 2 years, n=152, p<0.001; CORACTO at 2 years, n=95, p<0.001[47]; SCANDSTENT at 3 years, n=115, p<0.001[48]). The only consistently significant individual endpoint was revascularization.

## Appendix 4 Evidence for use of DES in patients with repeat procedures for in-stent restenosis

In a meta-analysis of four RCTs involving 1230 patients undergoing procedures for the relief of in-stent restenosis, the risk of TLR was markedly lower in patients treated with DES balloon angioplasty or vascular brachytherapy (9.5% versus 21.2%; OR 0.36, 95% CI 0.27, 0.49)[18].

## Appendix 5 Calculation of cost of an individual revascularization procedure at the MUHC

Calculation of cost of an individual revascularization procedure, assuming all patients receive DES, and the average number of DES implanted is 1.8 DES/patient. Costs of antiplatelet therapy are not included as these are not incurred by the MUHC.

| Component | Cost |
|---|---|
| PCI supplies (excluding stents) | $700 |
| DES (Unit cost $1,547, average 1.8 per patient) | $2,317 |
| Personnel | $150 |
| Post-procedure care | $60 |
| CCU (1 day) | $650 |
| *Total* | *$3,877* |