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Cost-effectiveness of drug-eluting coronary stents in Quebec, Canada

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Objectives: The aim of this investigation was to assess the incremental cost-effectiveness of replacing bare metal coronary stents (BMS) with drug-eluting stents (DES) in the Province of Quebec, Canada.
Methods: The strategy used was a cost-effectiveness analysis from the perspective of the health-care provider, in the province of Quebec, Canada (population 7.5 million). The main outcome measure was the cost per avoided revascularization intervention.
Results: Based on the annual Quebec rate of 14,000 angioplasties with an average of 1.7 stents per procedure and a purchase cost of $2,600 Canadian dollar (CDN) for DES, 100 percent substitution of BMS with DES would require an additional $45.1 million CDN of funding. After the benefits of reduced repeat revascularization interventions are included, the incremental cost would be $35.2 million CDN. The cost per avoided revascularization intervention (18 percent coronary artery bypass graft, 82 percent percutaneous coronary intervention [PCI]) would be $23,067 CDN. If DES were offered selectively to higher risk populations, for example, a 20 percent subgroup with a relative restenosis risk of 2.5 times the current bare metal rate, the incremental cost of the program would be $4.9 million CDN at a cost of $7,800 per avoided revascularization procedure. Break-even costs for the program would occur at DES purchase cost of $1,161 for 100 percent DES use and $1,627 for selective 20 percent DES use for high-risk patients for restenosis (RR = 2.5). Univariate and Monte Carlo sensitivity analyses indicate that the parameters most affecting the analysis are the capacity to select patients at high risk of restenosis, the average number of stents used per PCI, baseline restenosis rates for BMS, the effectiveness ratio of restenosis prevention for DES versus BMS, the cost of DES, and the revascularization rate after initial PCI. Sensitivity analyses suggest little additional health benefits but escalating cost-effectiveness ratios once a DES penetration of 40 percent has been attained.
Conclusions: Under current conditions in Quebec, Canada, selective use of DES in high-risk patients is the most acceptable strategy in terms of cost-effectiveness. Results of such an analysis would be expected to be similar in other countries with key model parameters similar to those used in this model. This model provides an example of how to evaluate the cost-effectiveness of selective use of a new technology in high-risk patients.

Keywords: Cost-effectiveness, Cardiology, Coronary stents

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Percutaneous transluminal coronary angioplasty is a common procedure that is used primarily to reduce the symptoms of angina pectoris; it has no discernible benefit for reducing rate of myocardial infarction or death when compared with other treatments (4). An important limitation of coronary angioplasty has been the occurrence of restenosis, which has been partially palliated with the introduction of coronary stenting (3), a percutaneous technique involving the intraluminal introduction of metal scaffolding and now known as percutaneous coronary intervention (PCI).

Restenosis after PCI with stenting occurs primarily within the stent and is almost entirely due to neointimal hyperplasia (9;12;15). Several recent studies have demonstrated reduced angiographic restenosis rates with stents coated with anti-mitotic drugs (drug-eluting stents [DES]) compared with conventional bare metal stents (BMS). A meta-analysis (1) of 11 trials involving 5,090 patients has confirmed an important reduction in both the angiographic restenosis rate (8.9 percent vs. 29.3 percent; odds ratio [OR], 0.18; 95 percent confidence interval [CI], 0.06–0.40) and in the need for a repeat revascularization procedure (4.2 percent vs. 13.2 percent; OR, 0.26; 95 percent CI, 0.14–0.45) with DES compared with BMS but with no impact on mortality or myocardial infarction.

A major obstacle to the widespread adoption of this technology may be its higher purchase cost. Despite numerous trials demonstrating the clinical efficacy of DES, few rigorous independent cost-effectiveness evaluations of this technology have been published in the peer review literature and such evaluations are a necessary prerequisite for informed decision making regarding the role of this new technology.

METHODS

General Overview

This analysis modeled the clinical pathways of patients using BMS and DES to determine the need for repeat interventions (PCI and coronary artery bypass graft [CABG]). Unitary and total incremental costs for required interventions were calculated for each scenario to determine the incremental total program cost and the cost per avoided revascularization intervention. Multiple sensitivity analyses with various percentages of penetration of DES and varying levels of patient selection were also explored to examine their impact on cost-effectiveness parameters and to determine the robustness of the conclusions.

Input parameters for the efficacy model have appropriately come from a systematic review of all randomized trials comparing DES to BMS. While randomized clinical trials provide the most reliable information on the efficacy of the new drug-eluting stents, an estimate of the current true rate of restenosis with bare metal stents and the choice of the repeat revascularization procedure is best obtained from actual practice patterns. The Quebec provincial administrative databases that were developed in the context of the universal health insurance program provided to all residents of Quebec, Canada, and capture all physician visits, procedures, hospitalizations, and vital status provide such an opportunity. The databases were linked through the use of a unique and anonymous identifier, thereby creating a longitudinal history of each patient's clinical outcome after their initial revascularization procedure. The reliability of the hospital administrative databases in recording the number of coronary revascularizations has been validated previously (7). These databases reflect real-world contemporary practice patterns and are not influenced by the artificial constraints of clinical trials.

Clinical Model

Based on the administrative data, a clinical pathway was constructed to model the current clinical outcomes of patients with BMS in Quebec (Figure 1). The model assumed that any repeat intervention within 9 months of the original dilatation was due to restenosis and allowed a maximum of three repeat interventions per patient, either PCI or CABG. It is acknowledged that this strategy is a simplified model in that repeat PCI may actually involve a variety of different options, including ordinary balloon angioplasty, stenting, cutting balloon angioplasty, or brachytherapy. However, as most cases of restenosis are treated with repeat stenting and as there are only relatively minor costs differences between the other modalities, these alternatives have been grouped together as repeat PCI. Also because a systematic review (1) has shown that there are no differences in mortality, subacute thrombosis, or myocardial infarctions between DES and BMS, these outcomes are not included in the model. This approach has been endorsed by others (11).

The reduction of risk by using DES instead of BMS for the base model was based on a summary value from the meta-analysis (1). The baseline BMS revascularization rate and the choice of revascularization modalities for restenosis were determined from Quebec administrative databases (1995–2000) and included both angioplasty and bypass surgery. Following the logic of allowing observed data to drive our economic model, a reduction in cardiac surgeries as a consequence of the expected overall reduction in repeat revascularizations associated with drug-eluting stents was permitted in the model, although no such effect was seen in the published trials.

Economic Model

The health benefits of medical interventions in cost-effectiveness analyses are most usefully recorded as quality-adjusted life years (QALY) where this metric includes both length and quality of life and allows ready comparisons with existing therapies. However, for coronary stenting, the avoidance of repeat interventions is associated with only a very short-term disutility; therefore, we have elected to measure health benefits primarily in terms of cost per revascularization procedures avoided. Moreover, the difficulty in assigning

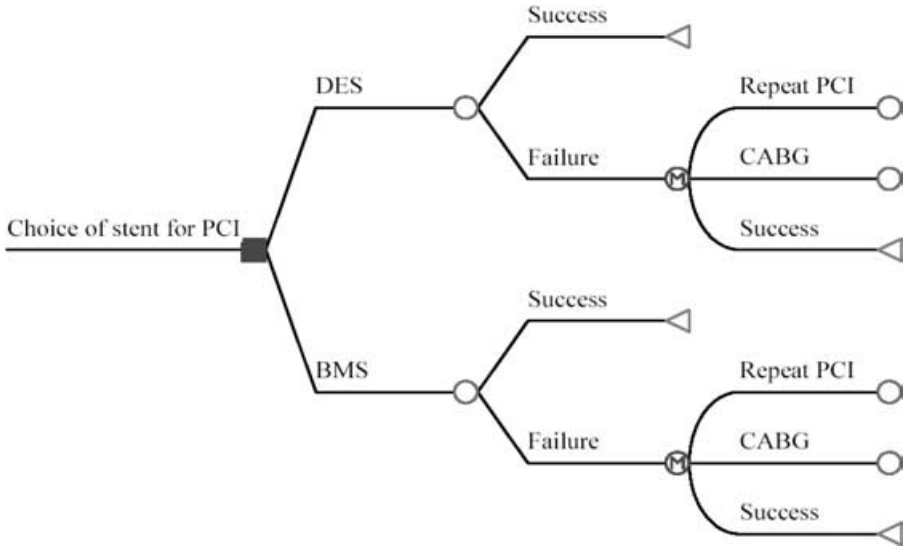

Figure 1. Decision model for the choice of stent for percutaneous coronary intervention (PCI). Note: Since the rates of deaths or nonfatal myocardial infarctions have been shown to be identical for both arms in the published randomized trials, these outcomes have not been considered in the model.

QALYs for patients with restenosis risks compromises the transparency of the model.

All costs were based on data from our local hospital and are expressed in 2003 Canadian dollars. These costs were similar to the cost of cardiovascular procedures reported from other Canadian sources (6;19). The economic model calculated changes in stent purchase cost and repeat interventions (PCI and CABG) of various scenarios of DES penetration compared with BMS use. Savings from avoided revascularization interventions were subtracted from the additional purchase costs of DES to calculate the total incremental cost of each potential program. This cost was divided by the number of avoided revascularization interventions for each scenario to calculate the cost per avoided revascularization intervention. Discounting was not applied, as the outcomes occurrence was determined only up to 9 months, the mean average follow-up time in the clinical trials.

Univariate sensitivity analyses were first applied to model input parameters and on DES penetration to examine their impact on incremental program cost and cost per avoided revascularization intervention. A multivariate sensitivity analysis using a probabilistic Monte Carlo simulation (Crystal Ball, Decisioneering, 2000) was also performed using triangular distributions from the base case value to extreme values with 1,000 trials per simulation.

Specific additional analyses were conducted to examine the impact of potentially higher baseline restenosis rates (up to 20 percent), differing scenarios of DES penetration, the various degrees of success in selecting high-risk patients, and much higher revascularization costs that may be the reality in other countries. The perspective adopted in all instances is that of a universal payer, in this case the Quebec Ministry of Health and Social Services.

RESULTS

Baseline Characteristics

The data sources, base model estimates and ranges utilized for sensitivity analysis are presented in Table 1. Our baseline efficacy parameter has been taken from a recent systematic review (1) showing that the repeat target vessel revascularization rate (generally 6 to 9 months after intervention) was reduced by 74 percent with the drug-eluting stents (OR, 0.26; 95 percent CI, 0.11–0.52). The decision model in Figure 1 was complemented by the observations recorded in the Quebec administrative databases involving 16,746 incident PCI cases treated with BMS and a minimum 9-month follow-up period. The population demographics revealed a mean age of 71.4 years and 61 percent being men. The 9-month re-intervention rate of 12.8 percent (95 percent CI, 10.4–16.0) was used in the baseline analysis. In clinical trials, the rates of CABG for complications or restenosis after a PCI are exceedingly low and no reductions in CABG rates have been observed with DES. However, in our database of actual angioplasty cases, 18 percent of repeat procedures in the 9 months after PCI were CABG and this has been included in the model as a restenosis therapy.

To gain insight into the differential restenosis rates among higher risk patients, we examined diabetic patients from this administrative database as a representative case study. The rate of re-interventions among diabetics had an OR of 1.53 (95 percent CI, 1.37–1.71) compared with non-diabetics.

Economic Impact of Full DES Substitution

Based on a current costs and practice patterns (see Figure 1 and Table 1), the complete substitution of DES for BMS

Table 1. Values of Input Parameters in Economic Model, Sources, and Ranges of Values Used in Sensitivity Analyses

Parameter	Value in base model	Range for sensitivity analysis	Source(s)
Annual number of angioplasties in Quebec	14,000	14,000–15,000	Provincial administrative database
Repeat revascularization rate bare stents (following 1st intervention)	12.8%	9.7%–20%	Provincial administrative database
Repeat revascularization rate, bare stents (following 2nd intervention)	13.9%	12%–16%	Provincial administrative database
Repeat revascularization rate, bare stents (following 3rd intervention)	15.0%	10%–20%	Provincial administrative database
Repeat revascularization risk reduction, drug-eluting stents (following 1st intervention)	0.74	0.48–0.89	Published meta-analysis[a]
Repeat revascularization risk reduction, drug-eluting stents (after PCI #2 and after PCI #3)	0.5	0.2–0.8	Expert opinion
% of patients going to PCI vs CABG after 1st PCI	83%	78%–88%	Provincial administrative database
2nd PCI	74%	69%–79%	
3rd PCI	69%	64%–74%	
Average number of stents per procedure (all interventions)	1.7	1.2–2.2	Expert panel
Average cost of angioplasty (stent costs are excluded)	$4,507	$4,000–$5,000	Local hospital costs
Cost of BMS	$700	$600–$800	Local hospital costs
Cost of DES	$2,600	$2,000–$2,800	Local hospital costs
Cost of CABG	$15,025	$9,825–$17,025	Local hospital costs
RR for restenosis of high-risk patients selected to receive DES	2.5 (for 20% DES implementation)	1–6	Large range based on theoretical model

[a]Babapulle et al., 2004 (1).
PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BMS, bare metal coronary stents; DES, drug-eluting stents; RR, relative risk.

would require an additional $44.9 million in the annual Quebec health-care budget. However, this would be associated with savings in repeat revascularization of $9.7 million leading to a net incremental cost of $35.2 million. This amounts to an expense of approximately $23,000 for each revascularization procedure avoided.

Economic Impact from Partial DES Substitution

Gains in cost-effectiveness may be expected by partial DES implementation, as presumably the highest risk patients would be preferentially targeted for this therapy. Due to the depletion of susceptibles, these gains will diminish as the percentage of DES implementation rises. The selection of high-risk patients involves an assessment of both clinical and angiographic characteristics. Lesion length, diameter, and the presence of diabetes are often quoted as being associated with an increased risk. The key factor then becomes how effectively these high-risk patients can be identified.

Based on the increased risk associated with diabetes, it seems plausible that, by combining a constellation of other clinical and angiographic characteristics, identification of high-risk patients with a relative risk of at least two to three times that of remaining patients could be achieved. However, actual capacity to select a group of higher risk patients varies not only with clinical acumen but also according to the percentage of patients offered DES, and the baseline restenosis rate. To consider the advantages of various different percentages of DES penetration, it is instructive to examine the maximum theoretical risk ratios that could ideally be obtained by clinicians. To determine these maximal values we can consider, for a group of 100 patients receiving an initial PCI and a 10 percent restenosis rate, the ideal case in which the 10 patients who would develop restenosis in the cohort were in the group selected to receive DES. In concrete terms, this ideal scenario can be compared with the scenario in which there is random selection of patients for DES (RR = 1), illustrated in Table 2. This exercise clearly illustrates that, due to the low 10 percent restenosis rate, the impact of patient selection is potentially very high at lower

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Table 2. Maximum Possible Ratios of Cases in DES Cohorts with Perfect Selection of High-Risk Patients (10% Restenosis Rate, Reference Group of 100 Patients)[a]

% DES	Baseline number of cases with restenosis, random patient selection	Maximum possible number of cases	Difference	Ratio of cases in DES cohort in ideal scenario compared to baseline random selection
10%	1	10	9	10
20%	2	10	8	5
30%	3	10	7	3.3
40%	4	10	6	2.5
50%	5	10	5	2.0
60%	6	10	4	1.7
70%	7	10	3	1.4
80%	8	10	2	1.25
90%	9	10	1	1.11
100%	10	10	0	1

[a] In the ideal scenario, there would be identification of all 10 patients with restenosis.
DES, drug-eluting stents.

levels of DES penetration, decreasing necessarily to zero as DES implementation reaches 100 percent. In terms of risk ratios for selection of high-risk patients, this finding suggests a decrease from RR = 2.5 in the scenario with 20 percent DES implementation declining to RR = 1 for 100 percent DES implementation. For simplicity, we can account for this in the economic model by using a linear decline in RR as percentage of DES implementation increases. This method is illustrated in Figure 2, which shows the reduction of cost per avoided revascularization intervention gained by selection of high-risk patients disappearing as DES implementation rates exceed 70–80 percent.

A penetration of 20 percent DES applied preferentially to patients with a 2.5 relative risk for restenosis results in an incremental budget increase of $4.8 million CDN after accounting for $4 million in savings from reduced revascularizations. This finding amounts to an additional cost of $7,800 per revascularization avoided. With 40 percent DES use again applied preferentially to higher risk patients, the incremental cost is $11.9 million or $12,800 per avoided revascularization (Figure 2). At 60 percent DES use, the incremental cost is $19.7 million or $17,300 per avoided revascularization. At higher levels of DES, the cost per avoided procedure approaches the unselected scenario of $23,000.

Break-even Cost for DES

A hypothetical break-even purchase cost of DES was calculated at which benefits of avoided treatment would offset the increased cost of DES implementation. In the scenario

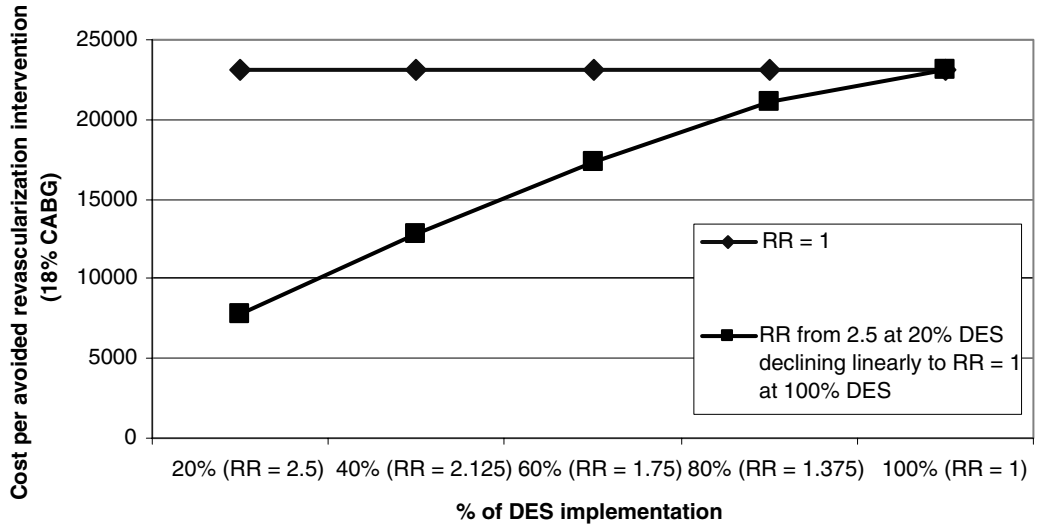

Figure 2. Impact of selection of high-risk patients for drug-eluting stents (DES) versus percentage of DES implementation and relative risk (RR) of selected patients on cost per avoided revascularization event. CABG, coronary artery bypass graft.

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of a 20 percent penetration applied to patients at medium to high risk of restenosis (RR = 2.5), the break-even cost for DES was $1,626. For 100 percent DES implementation, the purchase cost must be over $500 lower, at $1,161.

Sensitivity Analyses

As the parameters in this economic model are not exactly known, their variability may influence the impact on incremental cost and the cost of avoided revascularizations. The impact of varying the input parameters in Table 1 on the outcomes was examined. The five most important factors influencing cost per avoided revascularization intervention and the incremental cost of the program for this model were the ability to select high-risk patients, cost of DES, cost of BMS, the baseline restenosis rate and the efficacy rate for DES (see Figure 3).

Here are some illustrative examples of the impact of outcomes. In the scenario of 100 percent DES implementation, the net incremental cost would fall to $30 million from of $35 million if the restenosis rate were 20 percent instead of the baseline 12.8 percent rate, and the cost per avoided revascularization would decrease from $23,100 to $12,400. At a 20 percent DES implantation rate applied to patients with an increased risk (RR = 2.5) and a 20 percent baseline restenosis rate, the cost per avoided revascularization would be $4,000.

In our model, the variation in cost of a repeat procedure did not strongly influence outcomes. However, in other regions, revascularization costs may be much higher; therefore, we calculated the cost per avoided revascularization at the significantly higher PCI and CABG costs of $25,000 and $100,000, respectively. Under these conditions, the incremental cost of the program would disappear, becoming a net savings of $14 million for 100 percent DES use and of $15.5 million with 20 percent DES implementation applied to higher risk patients (RR = 2.5).

DISCUSSION

This cost-effectiveness analysis suggests that totally replacing BMS with the new DES in the Quebec environment would lead to a substantial increase in costs that would only partially be offset by savings generated by reductions in the need for repeat revascularizations for restenosis. Considerable gains in cost-effectiveness are attained from a selective policy providing this new technology only to patients at an increased risk for restenosis, an example of diminishing returns with generalized use of a more effective, yet more expensive health technology. Within the realm of clinical capability, the cost per revascularization avoided may be expected to fall from $23,000 with universal use to $7,800 when restricted to high-risk patients. This study has also identified the main variables likely to influence this cost-effectiveness ratio.

Others have also proposed a selective approach to the use of DES (14) due to unanswered clinical questions without consideration of the financial issues. This selective approach also appears a justifiable option from an ethical as well as economic point of view, and in fact generally represents the clinical reality in countries using DES. For example, in Europe in 2003, DES procedures were used in an estimated 11 percent of procedures (2). Clinicians should reasonably be able to identify subgroups of patients at an increased risk of restenosis and as implantation of DES increases over 30–40 percent, the risk of restenosis in these residual lower risk patients treated with BMS is similar to the restenosis risks seen with DES in the clinical trials.

An important question is whether this analysis is applicable to other health-care jurisdictions. Perhaps the most controversial baseline parameter was our estimation of the revascularization rate attributed to BMS. Although appearing low, it has been observed previously that randomized trials with their protocol driven mandatory follow-up angiograms tend

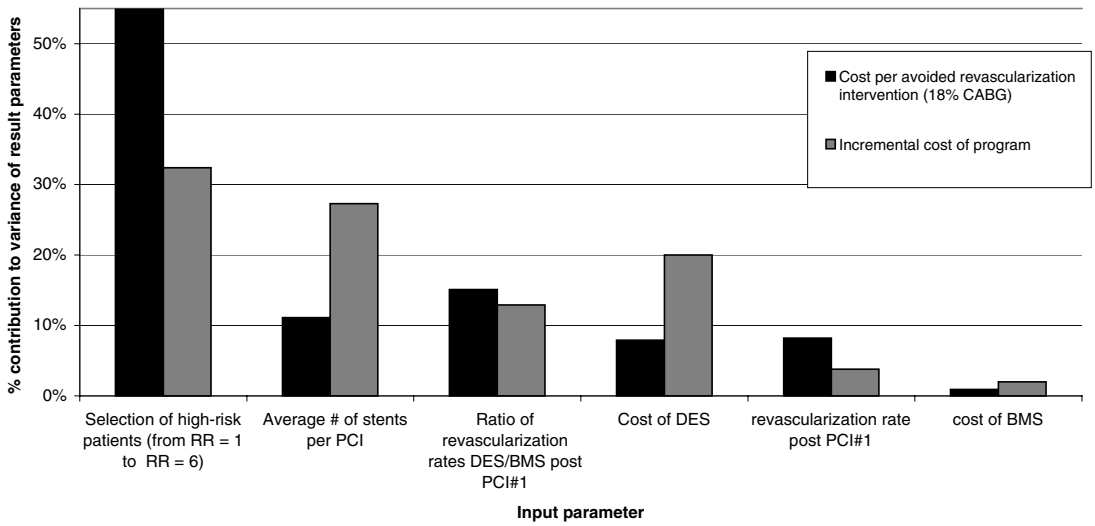

Figure 3. Results of Monte Carlo sensitivity analysis. Impact on incremental cost of program and cost per avoided revascularization, 20% drug-eluting stents (DES).

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to overestimate the need for revascularization (3;21). A recent editorialist has also suggested that, with the arrival of DES, clinicians have begun to overevaluate the clinical impact of restenosis while underevaluating the efficacy of BMS (14). An 10.9 percent re-intervention rate has been observed in another registry (16), lending further credibility to our baseline re-intervention rate with BMS. Moreover, the general nature of our model and the relatively wide range of values examined in the sensitivity analyses suggest that the conclusions may be applicable to many other different jurisdictions.

Although the number of full cost-effectiveness reports of this technology in the peer review literature is limited, it must be acknowledged that our conclusions favoring a selective use of DES is unique. With the exception of an independent Canadian study presented in abstract form (18), most other analyses have favored the more widespread use of this technology. For example, the National Institute of Clinical Excellence technology assessment of coated stents contains four economic models favorable to DES utilization but all were developed by stent manufacturers and all were judged to have methodological weaknesses (11). Two other abstracts (17;22) have been presented recently that appear to favor the cost-effectiveness of DES. However, it is impossible to assess the validity of any model assumptions or the existence of interpretative biases (13) due to possible conflicts of interest with industry from abstract publications alone. An American report (5) has concluded that DES should be reasonably cost-effective (and possibly cost-saving) for most patients who currently undergo PCI, but substantial differences in the economics of interventional cardiology exist between the United States and other countries, including Canada, notably in the very high cost of PCI, so the incremental cost of DES plays a less significant role. Indeed sensitivity analyses with our model did suggest that DES implementation can become cost-saving in the presence of high revascularization costs.

Nevertheless, authors generally acknowledge that, for patients with a low risk of restenosis, DES may not be a cost-effective choice (10). To summarize simply, does it make economic sense to completely abandon a therapy (BMS) that works well for 85–90 percent of the population for a new therapy (DES) costing four times as much to treat a transient health condition with no impact on either death or myocardial infarction?

Our analysis has several strengths, including the use of a systematic measure of DES efficacy based on the clinical trials and of actual outcomes data with realistic expected variability ranges. As mentioned previously, clinical trials with their mandatory protocol angiograms have been shown to inflate the need for repeat revascularizations compared with ordinary clinical practice (21) and, thereby, may falsely improve DES cost-effectiveness ratios.

The limitations of this study should not be neglected, particularly the uncertainty regarding the baseline rate of restenosis. Obviously, actual restenosis rates cannot be measured from this administrative database but revascularization rates remain a clinically pertinent outcome. Although our revascularization estimate is derived from actual observed data on repeat procedures, there is no guarantee that it is not biased by either the inclusion of procedures for disease progression rather than restenosis or by the exclusion of restenosed patients receiving only medical treatment. However, recent studies have shown that disease progression rather than restenosis is responsible for most interventions beyond 1 year and even for a sizable minority (approximately 35 percent) of those performed before 1 year (8). This finding suggests that any bias due to our inability to conclusively measure restenosis rates may be possibly biasing our results in favor of DES.

Also our analysis, like most cost-effectiveness analyses, does not consider the importance of opportunity costs. Finally, this study does not include quality of life measures in the evaluation of health benefits. Although recent measures of the disutility of restenosis have been reported (20), the short period of time living with this disutility will lead to only minor improvements and very high cost/quality-adjusted life year ratios. These potential measurement errors were believed to lead to unreliable estimates for this metric; therefore, they have not been used. Although the cost per procedure avoided is easier to measure and more transparent, there is the difficulty that there exists no societal value or consensus as to an appropriate threshold level. Because long-term efficacy of DES has not been established, we have not constructed our models to examine cost-effectiveness beyond 1 year.

The emergence of competing DES products with potentially lower prices, the possibility of further DES expansion to those not presently eligible for a percutaneous intervention, particularly in patients now undergoing CABG, as well as improved identification of high-risk patients may further improve the cost-effectiveness of this new technology and permit its wider long term inclusion into publicly funded health programs. This model can be updated to reflect changes in various parameters over time and can also be adapted for economic evaluation of this intervention in other countries for which appropriate data are available. The approach presented is a useful example of economic evaluation of selective use of an expensive technology, which can be used in other areas of health technology assessment.

POLICY IMPLICATIONS

For publicly funded health-care systems with costs similar to those currently in Canada, this analysis validates a policy of selective use of DES for high-risk patients. However, significant differences in key parameter estimations could produce different results and policy implications. Given the large potential impact of this technology, if other jurisdictions decide to use our model, they should populate it with their own local parameter estimates to best guide decision making regarding optimal use of DES. Like many economic

evaluations, this analysis is limited by imperfect current and long-term data on outcomes of health interventions. Due to the rapid evolution of this technology, any model must be updated regularly. Despite these limitations, this type of analysis using a mix of clinical efficacy from randomized trials and real-world practice patterns can contribute valuable information to the promotion of rational health policy decision making.

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