Can We Afford to Eliminate Restenosis?

Can We Afford Not To?

Dan Greenberg, Phd,*† Ameet Bakhai, MD, MRCP,*†‡ David J. Cohen, MD, MSc*†

Boston, Massachusetts; and London, United Kingdom

Over the past decade, coronary stenting has emerged as the dominant form of percutaneous coronary revascularization. However, bare metal stents remain limited by a high incidence of restenosis, leading to frequent repeat revascularization procedures and substantial economic burden. Antiproliferative drug-eluting stents (DES) have recently demonstrated dramatic reductions in rates of restenosis, compared with conventional stenting, but important concerns about their costs have been raised. In this article, we summarize current evidence on the economic impact of restenosis and explore the potential benefits and economic outcomes of DES. In addition to examining the long-term costs of this promising technology, we consider the potential cost-effectiveness of DES from a health care system perspective and the impact of specific patient, lesion, and provider characteristics on these parameters. (J Am Coll Cardiol 2004;43:513–8) © 2004 by the American College of Cardiology Foundation

Since it was first introduced in 1977, percutaneous coronary intervention (PCI) has revolutionized the treatment of patients with coronary artery disease (CAD) (1). Despite ongoing technologic advances resulting in improved safety and predictability (2), the “Achilles heel” of PCI has remained restenosis. Although coronary stenting has reduced the rates of angiographic and clinical restenosis, compared with conventional balloon angioplasty (3–5), in-stent restenosis continues to occur in ~15% to 20% of ideal coronary lesions and in as many as 30% to 60% of patients with more challenging characteristics (e.g., small vessels, diffuse disease, bifurcation lesions). When it occurs, in-stent restenosis may be difficult to treat and has a high recurrence rate (6). Thus, there is a considerable impetus for the development of new therapies to reduce the rate of restenosis after coronary stenting.

Drug-eluting stents (DES) represent one of the most innovative developments in interventional cardiology today. Studies involving several different stent platforms and antiproliferative drug coatings have recently demonstrated dramatic reductions in restenosis rates, compared with conventional bare metal stents (BMS) (7–11). Although the clinical benefits of DES are increasingly evident, important concerns about their costs have been raised (12). The aims of this report are to summarize the current evidence on the economic impact of restenosis and to explore the potential benefits and economic outcomes of using DES in patients undergoing PCI.

Clinical and economic burden of restenosis. Since the major proven benefit of DES is to reduce coronary restenosis, it is important to appreciate the clinical and economic outcomes associated with restenosis to better understand the expected benefits of its prevention.

RESTENOSIS AND MORTALITY. To date, no studies have demonstrated a convincing link between restenosis and either short- or long-term mortality. Unlike patients with de novo lesions, where plaque rupture and local thrombus formation may lead to acute myocardial infarction and death, clinically significant coronary restenosis is the result of progressive lumen narrowing due to neointimal hyperplasia and vascular remodeling and generally presents as a gradual recurrence of anginal symptoms that only rarely results in myocardial infarction.

Several lines of clinical evidence confirm the generally benign prognosis of coronary restenosis. Although rates of repeat revascularization after percutaneous transluminal coronary angioplasty are 5- to 10-fold higher than after coronary artery bypass graft surgery (CABG), most randomized trials have failed to demonstrate differences in long-term survival between these alternative forms of revascularization (13,14). Moreover, in a study of more than 3,300 patients, Weintraub et al. (15) failed to identify any differences in six-year mortality between patients with and those without restenosis. Taken together, these findings suggest that even dramatic reductions in restenosis by DES are unlikely to substantially improve survival for patients undergoing PCI.

RESTENOSIS AND QUALITY OF LIFE (QOL). In contrast, restenosis clearly has an adverse impact on QOL. In the OPUS-1 trial, patients without restenosis had less frequent angina, less physical limitations, and improved QOL, compared with patients with restenosis (16). Moreover, in the Stent-PAMI trial, Rinfret et al. (17) found that compared...
To fully understand the economic burden of restenosis, one must consider both the frequency of clinically important restenosis and the additional health care costs associated with its diagnosis and treatment. Most data regarding the impact of restenosis on long-term costs after PCI are based on clinical trials (18–21) or single-center series (22). Although these studies have limited generalizability to the overall PCI population, they nonetheless provide several important insights. For example, in the ESPRIT trial, the mean cost for a hospital admission to treat clinical restenosis was $11,913 (vs. $10,430 for an index hospitalization). On a population basis, treatment of restenosis added an average of $1,675 to each patient’s cost of care during the first year after stenting (21). This value may be considered the direct “economic burden” of restenosis in the ESPRIT trial population. Similar findings were noted in the Stent-PAMI trial of patients with acute myocardial infarction (19). Higher costs for each episode of clinical restenosis have been noted in several distinct populations, including patients undergoing PCI for in-stent restenosis (23) and patients undergoing multivessel PCI (22). These diverse studies demonstrate that just as there is no single “restenosis rate” for all patients who undergo PCI, there is no single cost or economic burden of restenosis; these values vary substantially according to the specific patient population under consideration.

We have recently performed a study to determine the cost and economic burden of restenosis within the U.S. Medicare program (24). In this population, we found that the incidence of repeat revascularization between one month and one year after initial PCI was 16.3%. When one considers that 10% to 15% of repeat revascularization procedures during the first year after PCI are related to treatment of other coronary lesions and not restenosis, these population-based data indicate that the “real-world” clinical restenosis rate in contemporary PCI patients is ~14%. In this study, we found that the direct one-year cost of clinical restenosis was ~$19,000 per episode, and the economic burden of restenosis was thus ~$2,500 per PCI patient (i.e., 1.6% × 0.85 × $19,000).

These data provide an important set of insights into the expected economic impact of DES within the U.S. health care system. The current list price for one Cypher (Cordis Corp., Miami Lakes, Florida) sirolimus-eluting stent in the U.S. is $3,195. With volume discounts to many centers, the average acquisition cost (as of November 1, 2003) is currently ~$2,700/stent. Thus, when compared with an average cost of $700 per BMS, the incremental cost of each DES is currently about $2,000. To estimate the impact of DES on initial treatment costs, one must also consider that many stent procedures require more than one stent. In some cases, this is due to limitations in stent length, requiring implantation of multiple stents to cover a coronary lesion that is longer than the longest stent available. In addition, additional stents may be required to treat complications of the initial stent implantation (e.g., edge dissection), diseased side branches, or multivessel CAD.

Although national estimates are not readily available, data from several contemporary studies indicate that mean stent use is ~1.4 per procedure (20,25). Thus, conversion of the current PCI population from BMS to DES would be expected to increase initial hospital costs by an average of ~$2,800/patient treated (i.e., 1.4 stents/procedure × $2,000/stent). This value may represent an underestimate of the true increase in procedural costs associated with conversion to DES, however. Preliminary data suggest that the long-term results of DES may be optimized by implanting somewhat longer stents than is common with current BMS technology (9). If this approach results in an increase in mean stent utilization per procedure, the net increase in initial hospital cost might be even >$2,800 per procedure.

Based on these projections, it is evident that uniform conversion of all current BMS procedures to DES will not result in net cost savings to the U.S. health care system. Even if DES were to eliminate coronary restenosis, the resulting savings (~$2,500/patient treated) would not fully offset the higher cost of the stents themselves. Given current levels of efficacy (~75% to 80% relative risk reductions), however, more modest cost offsets are likely. Thus, the decision to adopt DES into standard clinical practice must consider whether the benefits of this technology are “worth the costs.”

**Optimizing the use of DES: insights from cost-effectiveness analysis.** No single criterion can define the optimal patient population and utilization rate for DES. At a minimum, patient selection for DES implantation should be based on careful assessment of therapeutic efficacy, short- and long-term side effects, generalizability of the available clinical trials to additional patient subsets, and cost-effectiveness. Currently, the only DES approved for clinical
use in the U.S. is the CYPHER stent. Based on data from randomized, controlled trials, the Food and Drug Administration (FDA) has approved the use of this stent in patients with symptomatic ischemic heart disease due to discrete, de novo lesions ≤30-mm long in native coronary arteries with a reference vessel diameter of 2.5 to 3.5 mm. Long-term follow-up, as well as experience with more complex lesions and in-stent restenosis, is now accumulating in ongoing clinical trials and registries and may expand these indications considerably in the near future.

From the patient’s perspective, DES would ideally be used to treat all lesions for which there was even a small expectation of benefit. However, in the short term, it is likely that the high cost associated with this technology may force hospitals and interventional cardiologists to limit utilization of DES to those high-risk patients who would be expected to derive the greatest absolute clinical benefit (12). Cost-effectiveness analysis provides an important framework that can be used to support the development of such guidelines.

To assess the economic value of any new medical technology, it is essential that the new technology be compared with the current standard of care (26). Cost-effectiveness analysis is a method of comparing the expected benefits of a medical technology with the net cost of the technology (27). This relationship is expressed in terms of an incremental cost-effectiveness ratio, which is calculated by dividing the net cost of the treatment being evaluated (relative to standard of care) by its net benefits (also compared with standard of care):

\[
\text{Incremental cost-effectiveness ratio} = \frac{\text{Cost}_{\text{New}} - \text{Cost}_{\text{Standard}}}{\text{Effectiveness}_{\text{New}} - \text{Effectiveness}_{\text{Standard}}}
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In general, costs are measured in monetary terms, whereas any valued clinical outcome may be used to measure health benefits. Although any clinically relevant outcome measure can be used, the standard approach is to assess long-term health outcomes in terms of quality-adjusted life-years (QALY). The QALY concept uses years of life in perfect health as a common metric to value both life expectancy and QOL. One can calculate QALY by weighting each time interval in a given state of health by its “utility”—a value between 0 and 1 that reflects the individual’s preference for that health state relative to perfect health (utility = 1) and death (utility = 0) (27).

Once a cost-effectiveness ratio is calculated, it is typically compared with cost-effectiveness ratios for other therapies in a “league table.” The threshold for determining whether a therapy is economically attractive varies with the available health care budget. In the U.S., for example, cost-effectiveness ratios <$50,000 per QALY gained are viewed as favorable, and cost-effectiveness ratios between $50,000 and $100,000 per QALY gained are frequently considered to be in a “gray zone.” In contrast, a cost-effectiveness ratio >$100,000 per QALY saved is viewed as economically unattractive in virtually all health care systems (including the U.S.) (28).

Although the use of QALY as an outcome measure in cost-effectiveness analysis is widely accepted, several pragmatic issues limit the attractiveness of this end point for valuing treatments whose principal benefit is preventing restenosis after PCI. Because there is no evidence that restenosis affects survival, one would not expect treatments whose sole benefit is a reduction in restenosis (such as DES) to improve population-level life expectancy. Although it is well recognized that restenosis is associated with reduced QOL (4,16,17), empiric data as to the overall impact of restenosis on quality-adjusted life expectancy are limited.

Given these limitations, several recent studies have used a disease-specific cost-effectiveness ratio: cost per repeat revascularization avoided (5,19,23). The advantages of this end point are that it is simple to measure, can be easily integrated into standard data collection for clinical trials or registries, and is readily interpreted by both clinicians and patients. The primary limitation of this end point is that it is specific to the field of coronary revascularization and cannot be compared with cost-effectiveness ratios for other conditions or against cost-effectiveness analyses using different outcome measures. Thus, determination of an appropriate cost-effectiveness threshold may be challenging.

Within a specific health care system, however, a comparison with other established (and reimbursed) technologies that can prevent coronary restenosis may serve as a useful benchmark. For example, within the U.S. health care system, several technologies with cost-effectiveness ratios <$10,000 per repeat revascularization avoided (e.g., brachytherapy for in-stent restenosis, elective coronary stenting vs. balloon angioplasty) have been widely adopted and are currently reimbursed by most third-party payers (5,19). These observations suggest that therapies with cost-effectiveness ratios <$10,000 per repeat revascularization avoided may be considered reasonably attractive within the U.S. health care system.

COST EFFECTIVENESS IN CLINICAL TRIALS. To date, prospective economic analyses have been conducted alongside two randomized clinical trials comparing DES with BMS. The first such study was performed in conjunction with the RAVEL trial (18). The economic analysis was based on resource utilization from the trial, with unit costs from the Netherlands (in euros), and assumed a cost of 2,000 euros for each sirolimus-eluting stent. In RAVEL, initial procedural costs were 1,284 euros higher for patients treated with DES, but reductions in follow-up costs offset most of the additional expenses. As a result, at 12-month follow-up, the sirolimus-eluting stent was associated with an additional cost of only 166 euros per patient.

More recently, we have reported preliminary results from a prospective economic evaluation performed in conjunction with the U.S. SIRIUS trial (20). For this study, costs were
assessed from a U.S. health care system perspective over a one-year time horizon. Based on current national averages, we assumed that each DES would cost $2,700 and each BMS would cost $700. Initial hospital costs were $2,800 higher with the sirolimus-eluting stent than with the BMS ($11,345 vs. $8,464, p < 0.001). However, much of this difference in initial costs was offset by lower follow-up costs ($5,468 vs. $8,040, p < 0.001), mainly due to a reduced requirement for repeat revascularization procedures. Thus, at 12 months, the DES strategy cost an average of $309/patient more than the BMS strategy, yielding cost-effectiveness ratios of $1,650 per repeat revascularization avoided and $27,500 per QALY gained.

It is important to recognize that the results of these trial-based economic studies cannot necessarily be extrapolated to the conditions of routine clinical practice. For example, although both studies incorporated adjustments or event adjudication to limit the extent to which protocol-driven costs affected the economic outcomes, it is difficult to fully account for the impact of the “oculostenotic reflex” on clinical outcomes in a trial that incorporates routine angiographic follow-up. Moreover, patients enrolled in clinical trials are highly selected and are often treated in high-volume medical centers, thus limiting the generalizability of trial results.

COST-EFFECTIVENESS MODELS. To overcome these limitations, we have developed a decision-analytic model to evaluate the cost effectiveness of DES for patients undergoing single-vessel PCI (29,30). The model’s perspective is that of the U.S. health care system. Data for the model were derived from a database that currently contains one-year outcomes on more than 6,000 patients undergoing PCI with conventional stent implantation (31). Costs for revascularization procedures, their associated complications, and treatment of restenosis were based on pooled economic data from several multicenter trials of contemporary PCI involving more than 3,000 patients (29). Key assumptions of the model were based, to the extent possible, on empirically derived data and included an average target vessel revascularization (TVR) rate for BMS of 14% (24,31,32), an 80% reduction in TVR with DES (7,8), an incremental cost of $2,000 per DES, and mean utilization of 1.3 stents per single-vessel stent procedure (25).

Over a two-year follow-up period, this model projected that overall medical care costs with DES would be $900/patient higher than with BMS, with an incremental cost-effectiveness ratio of $7,000 per repeat revascularization avoided. Sensitivity analyses demonstrated that treatment with DES would be cost saving for patients with a BMS TVR rate <20% and cost effective (i.e., cost-effectiveness ratio <$10,000/repeat revascularization avoided) for patients with a BMS TVR rate <12% (Fig. 1).

Further insight into the ideal patient population for implantation of DES may be derived from statistical models to predict restenosis after BMS implantation. Most studies have identified a smaller reference vessel diameter, a greater lesion length, and the presence of diabetes as consistent predictors of both angiographic and clinical restenosis after conventional stent implantation. Table 1. Predicted Rates of Clinical Restenosis After Bare Metal Stenting as a Function of Lesion Length, Reference Vessel Diameter, and Diabetes*

<table>
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<tr>
<th>Vessel Diameter (mm)</th>
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*Based on a logistic regression model of 4,227 patients undergoing bare metal stent implantation and clinical follow-up only (31).
implantation (31,33). A predictive model for clinical restenosis after stent implantation based on these three predictive factors is displayed in Table 1 (31). By combining these predicted restenosis rates with the previously described cost-effectiveness model, it is possible to estimate the cost effectiveness of DES for a variety of specific patient and lesion characteristics. This approach demonstrates that compared with conventional stents, DES would be cost saving for only a modest proportion of the current PCI population. On the other hand, these models also indicate that DES should be economically attractive (i.e., cost-effectiveness ratio <$10,000 per repeat revascularization avoided) for virtually all-diabetic patients and for non-diabetic patients with smaller vessels (reference vessel diameter <3.0 mm) and longer lesions (lesion length >15 mm).

**What is the expected budget impact?** As we have outlined, when the analysis is restricted to the current U.S. PCI population, universal adoption of DES is unlikely to reduce net health care costs. In fact, with an expected incremental two-year cost of ~$900 per treated patient, the use of DES in 80% of the current PCI population would be expected to increase annual U.S. health care costs by almost $500 million. Nonetheless, it is possible that DES could eventually result in meaningful long-term cost savings to the health care system. In particular, the use of DES for patients who currently undergo CABG (at a cost of ~$25,000) could result in substantial short- and long-term cost savings. If the need for repeat revascularization after multivessel DES implantation were comparable to that after bypass surgery, with similar long-term survival and angina relief, cost savings of $5,000 to $10,000 per converted patient might be achieved. Given these cost savings, it is conceivable that conversion of 20% to 30% of the current U.S. CABG volume to DES could result in sufficient savings to the health care system to offset the higher long-term costs of DES for the current PCI population. Whether the clinical results of multivessel PCI with DES can match these benchmarks and whether such volume shifts are achievable given current practice patterns await future investigation.

Finally, it is important to recognize that the current economic impact of DES is likely to be mitigated in the future by price reductions due to market competition. During the first five years after introduction of BMS in the U.S., prices fell ~25%. Comparable price reductions for DES would render them cost neutral (or cost saving) for the vast majority of the current PCI population.

**Alternative perspectives.** The preceding discussion has focused on the economic impact of DES from a health care system perspective. When considering the overall economic impact of DES, however, it is important to recognize that alternative perspectives may be more relevant to different stakeholders.

**THE HOSPITAL PERSPECTIVE.** In a landmark decision, the Center for Medicare and Medicaid Services established two new diagnosis-related groups (DRGs) for PCI to reimburse hospitals for DES procedures before their FDA approval. As of August 2003, the average reimbursement for DES implantation was ~$1,800 higher than that for a comparable hospitalization involving only BMS implantation. Given the current price of the CYPHER stent and the expected utilization of 1.4 (or more) stents per procedure, it is unlikely that the new reimbursement will fully cover the incremental cost to the average U.S. hospital. Although this reflects a scenario for the “typical” U.S. hospital, it is important to recognize that the incremental reimbursement is also affected by a variety of hospital characteristics (e.g., geographic location, teaching status) and will thus be higher or lower than the average for most institutions. Thus, the profitability of DES procedures for each hospital reflects a complex interplay between the DRG payment rate, the number of stents used per procedure, and the acquisition cost of DES. Currently, using DES for lesions that can be treated with one stent is the only option that will minimize a hospital’s financial loss.

Insufficient third-party reimbursement accounts for only part of the financial shortfall that hospitals will face with widespread adoption of DES, however. Given the benefits of DES in reducing restenosis, hospitals will face further loss of revenue due to the expected downstream reduction in the need for repeat revascularization procedures. Finally, and most importantly, hospitals will face a loss of revenue due to the expected substitution of less remunerative DES procedures for CABG—a highly lucrative and profitable procedure for many hospitals. At least one study, performed from the perspective of a large, tertiary medical center, projected annual losses of $3.8 to $6 million during the first five years after the introduction of DES (34).

**Conclusions.** The development of DES has been hailed as a true breakthrough in interventional cardiology. Although the use of DES is unlikely to reduce already low rates of in-hospital death and myocardial infarction in patients receiving PCI, substantial reductions in restenosis and repeat revascularization should be apparent within the first 6 to 12 months after their introduction. As a result, the demand for these devices by both the clinician and patient is high and, in the short term, has actually exceeded DES supplies by many accounts.

Currently there is no single answer to the question: “Are drug-eluting stents cost effective?” The cost effectiveness of DES depends on the target population and the specific treatment comparator (e.g., BMS, CABG, or medical therapy), as well as on the perspective of the analysis. Nonetheless, at least for the patient population that currently undergoes PCI in the U.S., simulation models as well as prospective analyses from clinical trials suggest that DES will be reasonably cost effective for the majority of patients and even cost saving for a large subgroup of patients who are at relatively high risk of clinical restenosis with conventional PCI techniques. In the future, lower incremental costs for DES should render this technology cost saving for a much
larger subgroup of PCI patients and broaden the ideal target population.

Reprint requests and correspondence: Dr. David J. Cohen, Cardiovascular Division, Beth Israel–Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215. E-mail: dcohen@caregroup.harvard.edu.

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