CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Will drug-eluting stents bankrupt the healthcare system?

Are Drug-Eluting Stents Cost-Effective?
It Depends on Whom You Ask

Jason Ryan, MD, MPH; David J. Cohen, MD, MSc

Since their commercial introduction in 2003, drug-eluting stents (DES) have rapidly altered the management of coronary artery disease. Before their development, the percutaneous management of coronary artery disease was performed predominantly by implantation of bare metal stents (BMS) made of either surgical stainless steel or metal alloys. Although such stents represented a considerable advance over balloon angioplasty alone, they remained limited by restenosis resulting from neointimal proliferation. As a result, ≈15% to 20% of patients treated with BMS required ≥1 repeat revascularization procedure within the 6 to 12 months after stent implantation. Despite numerous attempts at systemic pharmacotherapy, device modification, and even use of ionizing radiation, the rate of restenosis after BMS implantation remained largely unaffected.

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Over the past 5 years, effective DES have become the first device to substantially reduce the incidence of restenosis after stent implantation. By delivering high concentrations of either antiproliferative or immunomodulatory compounds directly to the site of arterial injury and by controlling this delivery through polymer-based drug release, both sirolimus- and paclitaxel-eluting stents have safely and effectively inhibited the proliferative process that results in in-stent restenosis. In pivotal clinical trials, both sirolimus- and paclitaxel-eluting stents have reduced rates of angiographic restenosis by 70% to 90% compared with conventional BMS designs, with parallel reductions in the need for clinically driven target vessel revascularization (TVR). As a result, in April 2003, DES were approved for use in clinical practice in the United States. Within 9 months of their introduction, DES made up 35% of all stent implantations in the United States, and their use has increased rapidly since that time. At our own institution, DES comprised >85% of all stents implanted during the past year, and national estimates are that >90% of all percutaneous coronary intervention (PCI) procedures currently performed in the United States involve ≥1 DES.

Given current procedural volumes (>1 million PCI procedures were performed in the United States in 2004) and costs (DES are generally 3 to 4 times more expensive than BMS), the rapid growth of this technology has raised important concerns about cost from both a hospital and a societal perspective. Because annual increases in US healthcare expenditures consistently outpace inflation, there is increasing interest in formally evaluating the economic impact of new technologies both before and immediately after their introduction. The aim of the present report is to summarize the economic consequences of current DES use and to explore the possible future impact of DES on US healthcare expenses.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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What Is the Clinical and Economic Impact of Restenosis?

The major benefit of DES is a reduction in the rate of restenosis after PCI. Therefore, to understand the clinical and economic impact of DES, the overall scope and consequences of coronary restenosis must first be appreciated. Unlike native coronary artery stenoses in which plaque rupture and in situ coronary thrombosis can lead to acute myocardial infarction or death, in-stent restenosis is largely a nonfatal condition.10 Luminal narrowing after BMS implantation occurs from neointimal hyperplasia and vascular remodeling mainly at the stent margins.11 This process causes gradual, progressive loss of arterial diameter, resulting most commonly in recurrent myocardial ischemia and anginal symptoms. Given the gradual nature of the disease process, progression to myocardial infarction or sudden cardiac death is very rare.10

Several clinical studies confirm the relatively benign long-term prognosis of patients who experience coronary restenosis. Weintraub and colleagues12 followed-up >3300 patients treated with successful balloon angioplasty who subsequently underwent angiographic restudy to assess for restenosis. Both unadjusted and adjusted comparisons of 6-year survival failed to demonstrate any excess mortality among those patients with restenosis. Similar insights may be derived from randomized comparisons of PCI with bypass surgery.13,14 Although rates of restenosis requiring repeat revascularization are consistently higher among patients treated with PCI in these trials (both balloon angioplasty and BMS implantation), in general, these studies have demonstrated little to no difference in long-term survival. These observations thus confirm that restenosis itself and its subsequent treatment generally do not increase mortality—at least among the vast majority of patients who currently undergo PCI procedures. One may thus infer that, although DES may dramatically reduce restenosis rates for patients treated with PCI, they are unlikely to have a major impact on long-term mortality.

On the other hand, quality of life (QOL) is clearly affected by restenosis. For example, in the Optimum Percutaneous Coronary Angioplasty With Routine Stent Strategy (OPUS-1) trial of universal versus provisionial bare metal stenting, patients without restenosis had less frequent angina, fewer physical limitations, and improved QOL scores at a 6-month follow-up compared with patients with restenosis.15 Similarly, in the Stent Primary Angioplasty for Myocardial Infarction (Stent-PAMI) trial, significant differences in QOL scores at 6 months were observed in BMS patients compared with those who received balloon angioplasty;16 these differences were driven predominantly by lower rates of clinical and angiographic restenosis associated with BMS implantation. Although no studies to date have directly compared QOL scores between DES and BMS patients, one can reasonably assume that lower rates of restenosis associated with DES will result in improved QOL—at least in the short to intermediate term. There are no data, however, to suggest that these benefits will persist beyond the first year of follow-up once the restenosis process has completed its course and any necessary additional revascularization procedures have been performed.

Economic Impact of Restenosis

To fully characterize the economic impact of restenosis on the US healthcare system, one must consider both the frequency of this adverse event and the cost of each episode. The cost of restenosis is not a single value, however, and varies considerably depending on both the setting of care and, in particular, on the underlying patient population. Much of the available data on the cost and frequency of restenosis within the US healthcare system are derived from clinical trials. For example, in the Enhanced Suppression of Platelet Glycoprotein IIb/IIIa Using Integrilin Trial (ESPRIT) of patients undergoing predominantly elective coronary stenting, the mean cost for each TVR event (which occurred in 14% of the study cohort) was $11 913.17 Thus, the economic burden of restenosis within the ESPRIT population was $1675 (ie, $11 913×14%). This value represents the potential savings to the healthcare system that could be derived from a hypothetical intervention that completely eliminated restenosis for this population. Other patient populations have higher costs associated with restenosis. For example, among patients undergoing PCI for in-stent restenosis in the Gamma-1 trial, the overall economic burden of restenosis was ~5-fold higher than in ESPRIT, reflecting both the higher frequency of restenosis in this challenging patient population and the higher treatment costs per episode of restenosis.18 The economic burden of restenosis is similarly high among patients undergoing multivessel PCI.19

Given the substantial variability in both the frequency and cost of restenosis across differing populations of PCI patients, it is clear that population-based data are required to fully characterize the economic burden of restenosis within the US healthcare system. We recently published such an analysis based on data from the Medicare program.20 Among US patients undergoing coronary stent implantation in 1999 (before the introduction of DES), the overall incidence of repeat revascularization in the first year after stent implantation was 16.9%, and the need for repeat revascularization was associated with excess costs (to the Centers for Medicare and Medicaid Services) of $19 074. By assuming, on the basis of previously published data, that 85% of procedures during this time were for treatment of restenosis,21 we estimated that the true frequency of TVR (ie, clinical restenosis) in the Centers for Medicare and Medicaid Services population was 14.4% and that the overall economic burden of restenosis to the US healthcare system during the BMS era was roughly $2500 per PCI patient.

Economic Impact of DES

There are currently no population-based data on the overall clinical or economic outcomes of DES within the US healthcare system. In the absence of such data, the results of the aforementioned Medicare study can provide important pre-
Although the model originally was designed to computer-simulation model of PCI within the US healthcare system, its list price was about $3200 per stent. With increasing competition and volume discounts, many US centers currently pay roughly $2200 per DES (prices are even lower in Canada and Europe, where even more devices are routinely available). Compared with an average acquisition cost of approximately $600 per BMS, the incremental cost of each DES is currently about $1600 per stent. Because many PCI procedures require >1 stent (both to cover long lesions and to treat multiple lesions and vessels), this number does not represent the true incremental cost of DES use. Given current stent use of ≈1.6 per DES procedure,22,23 complete conversion of the current PCI population from BMS to DES would be predicted to increase costs by about $2500 per procedure.

From a population perspective, however, this upfront increase in cost with DES would be offset to some degree by savings from reduced repeat revascularization procedures and other concomitant medically associated costs. To estimate the balance between these 2 effects, we have developed a computer-simulation model of PCI within the US healthcare system.24 Although the model originally was designed to reflect patients undergoing single-vessel PCI, we have recently updated the model to capture the full spectrum of PCI patients, including contemporary outcomes and costs for BMS based on published data from the Medicare program.20 Key model assumptions thus include the overall BMS clinical restenosis (TVR) rate of 14%, an incremental stent cost of $1600 per DES, and average use of 1.6 stents per PCI procedure.

Figure 1 summarizes the results of this model in terms of the relationship between the restenosis relative risk reduction achieved by DES and the net 1-year cost difference between DES- and BMS-based strategies. Unless DES provide restenosis relative risk reductions >95% compared with BMS, our model projects that using DES will increase the aggregate cost of PCI within the US healthcare system. At current levels of efficacy (70% to 75% relative risk reduction),25 the net 1-year cost associated with replacing BMS with DES is estimated to be $600 per PCI patient. Given current procedural volumes of ≈1 million PCI procedures, we project that the overall impact of substituting DES for all US PCI patients is about $600 million in increased annual healthcare spending.

**Distinction Between “Cost Saving” and “Cost-Effective”**

As we have shown, given current stent prices, use patterns, and outcomes, it is unlikely that drug-eluting stents will result in meaningful net cost savings for the current PCI population. This does not necessarily imply that the treatment is not worthwhile. In fact, many new medical procedures and drugs are associated with a net increase in healthcare expenditures. Under these conditions, formal cost-effectiveness analysis can be used to examine the relationship between the costs and clinical benefits of a medical device or procedure and to provide insight into those conditions under which the benefits of the device or procedure justify any long-term increase in costs.26 In formal economic analysis, the “value” of a new medical therapy is expressed in terms of an incremental cost-effectiveness ratio, which is calculated by dividing the net cost of the treatment under evaluation (relative to standard of care) by its net benefits (also relative to standard of care):

\[
\text{incremental cost ratio} = \frac{\text{cost}_{\text{new}} - \text{cost}_{\text{standard}}}{\text{effectiveness}_{\text{new}} - \text{effectiveness}_{\text{standard}}}
\]

In principle, costs are measured in monetary terms, and any valued clinical outcome may be used as a measure of health benefits. The standard approach, however, is to assess long-term health outcomes in terms of quality-adjusted life-years (QALYs),28 a metric that combines years of life and QOL into a single value. Each time interval in a given state of health is weighted by the “utility” of that health state; utility is a theoretical construct that represents an individual’s preference for that health state on a scale ranging from 0 to 1, where 1 represents perfect health and 0 represents death. Thus, years of life in good health yield more QALYs than years when health status is poor.

Once a cost-effectiveness ratio is calculated, it typically is 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 healthcare budget. In the United States, for example, cost-effectiveness ratios <$50 000 per QALY gained are generally viewed as favorable, and ratios between $50 000 and $100 000 per QALY gained are frequently considered to be in a “gray zone.” In contrast, cost-effectiveness ratios...
expandable stent in the treatment of patients with de novo native coronary artery lesions (Cypher; RAVEL) trial. In this trial, sponsored by Cordis, 238 patients undergoing PCI of a single, de novo coronary lesion were randomized to receive either sirolimus-eluting stents or a comparable BMS. Clinical outcomes demonstrated that the sirolimus-eluting stent completely eliminated both angiographic and clinical restenosis among this highly select patient population. Economic analysis from the Dutch healthcare perspective demonstrated that initial procedural costs were increased by 1284 €, whereas follow-up costs were reduced to a similar extent. The net 1-year cost increment with DES was thus only 54 € per patient.

This study is of limited relevance to the US healthcare system, however, because both stent prices and the costs associated with repeat revascularization procedures differ substantially between the Netherlands and the United States. Moreover, the RAVEL economic analysis also is limited by the performance of protocol-mandated angiographic follow-up. This practice is well known to inflate rates of repeat revascularization procedures (and their associated costs) through the “oculostenotic reflex.” As a result, one should be particularly cautious in interpreting the results of economic analyses derived from clinical trials that incorporate a primary angiographic end point.

The first study to examine the economic impact of DES from the perspective of the US healthcare system was performed alongside the SIRIUS trial (a Cordis-sponsored trial of the sirolimus-coated Bx Velocity stent [Cypher]). In this trial, 1058 patients undergoing single-vessel PCI for moderately complex coronary stenoses were randomized to receive either sirolimus-eluting stents or BMS and were followed up for both clinical and economic outcomes for 1 year. Initial hospital costs were approximately $2800 higher with the sirolimus-eluting stent compared with the BMS ($11 345 versus $8464; P<0.001). Much of this difference in initial costs was offset by lower follow-up costs ($5468 versus $8040; P<0.001), however, mainly because of a reduced requirement for repeat revascularization procedures. Thus, at 12 months, the DES strategy cost an average of $309 per patient more than the BMS strategy, yielding cost-effectiveness ratios of $1650 per repeat revascularization avoided and $27 500 per QALY gained (based on externally derived utility weights). These findings suggest that, for patients at moderate to high risk of restenosis (the population selected for the SIRIUS trial), sirolimus-eluting stents are reasonably cost-effective within the context of the US healthcare system. Of note, this study was conducted in 2004 and assumed an incremental cost of $2000 per DES versus BMS. If the study were to be repeated using 2006 US costs (with an incremental cost per DES of $1600), the resulting outcome would most likely be modest cost savings with the DES strategy.

More recently, we completed an economic analysis based on the TAXUS-IV trial of paclitaxel-eluting stents versus...
BMS for patients undergoing planned single-vessel PCI. The general design of the TAXUS-IV trial and its economic analysis were similar to those of the SIRIUS trial. In TAXUS-IV, use of the paclitaxel-eluting stent increased initial hospitalization costs by $2028. This was partially offset by a reduction in 1-year follow-up costs of $1456 in the DES arm, so mean 1-year costs were $572 higher among DES patients ($14,583 versus $14,011; \( P<0.001 \)). The overall cost-effectiveness ratio for the paclitaxel-eluting stent was $4678 per repeat revascularization avoided and $47,798 per QALY gained. In contrast to the previous studies, TAXUS-IV was the first randomized trial to incorporate a large, prespecified cohort of patients who were managed according to standard clinical practice without mandatory angiographic follow-up. In this 582-patient subset, economic outcomes were actually somewhat more favorable than those for the trial as a whole. The net 1-year cost increment for DES versus BMS in this subgroup was only $97 per patient, with a resulting cost-effectiveness ratio of $760 per repeat revascularization avoided and $572 higher among DES patients ($14,583 versus $14,011; \( P<0.001 \)). The overall cost-effectiveness ratio for the paclitaxel-eluting stent was $4678 per repeat revascularization avoided and $47,798 per QALY gained. Thus, these findings confirm that, for patients at moderate to high risk of restenosis who are undergoing single-vessel PCI, use of DES represents an economically attractive investment within the US healthcare environment.

The most recent economic evaluation of DES versus BMS was performed alongside the BAsel Stent Kosten Effektivitäts Trial (BASKET). In BASKET, 826 “unselected” patients undergoing PCI were randomized to receive sirolimus-eluting stents, paclitaxel-eluting stents, or cobalt-chromium stents (BMS). In contrast to both SIRIUS and TAXUS-IV, BASKET enrolled a relatively diverse patient population, including patients undergoing treatment for acute myocardial infarction and patients undergoing multivessel PCI, and used a pragmatic “real-world” design without angiographic follow-up. At the 6-month follow-up, randomization to either DES was associated with a significant reduction in TVR. An economic analysis performed from the perspective of the Swiss healthcare system demonstrated that aggregate 6-month costs were increased by 905 € with DES implantation (10,544 versus 9639 €). The incremental cost-effectiveness ratio was 18,311 € per repeat revascularization avoided or 72,283 € per QALY gained. Given that clinical restenosis after BMS implantation frequently manifests over a 9 to 12 months, however, it is unclear whether these relatively unfavorable results relate primarily to the relatively brief analytic time horizon or to other differences in the patient population and management of restenosis in European versus US practice.

To overcome the limitations inherent in these trial-based economic analyses, we have developed a decision-analytic model to evaluate the cost-effectiveness of DES for patients undergoing PCI from the perspective of the US healthcare system. Although the original model was based on published data from the medical literature, we have recently updated the model assumptions to reflect population-based PCI outcomes and costs from the Medicare database as previously described. Key assumptions of the current PCI model thus include an average TVR rate for BMS of 14%, an incremental cost of $1600 per DES, and average stent use of 1.6 per procedure. Under these baseline conditions and assuming that DES reduce clinical restenosis by 70%, the model projects that 1-year aggregate costs with DES would be $691 per patient higher than with BMS, with an incremental cost-effectiveness ratio of $5422 per repeat revascularization avoided. Sensitivity analyses demonstrated that DES would be cost saving for patient populations in which the expected BMS TVR rate is >19% and economically attractive (at a threshold of $10,000 per repeat revascularization avoided) as long as BMS TVR rates were >11% (Figure 2). These results provide credible evidence that, at least on average, use of a DES rather than a BMS may be considered an economically attractive healthcare investment within the context of the US healthcare system.

Further insights into the optimal patient population for DES implantation may be derived from statistical models to predict restenosis after BMS implantation. Several previous studies have demonstrated that smaller reference vessel diameter, greater lesion length, and the presence of treated diabetes mellitus are consistently associated with higher rates of angiographic and clinical restenosis after BMS implantation. By incorporating the predicted rates of clinical restenosis based on such a statistical model into our population-based economic outcomes model, we can estimate the projected cost-effectiveness of DES versus BMS for treatment of specific patient subsets (Table). If one considers a cost-effectiveness ratio <$10,000 per repeat revascularization avoided to be acceptable within the US healthcare system, our model suggests that DES are reasonably cost-effective for virtually all diabetic patients. On the other hand, despite their proven clinical benefits, for many nondiabetic patients with reference vessel diameters ≥3.5 mm, our model suggests that DES are not particularly efficient healthcare investments given the relatively low rates of clinical and
angiographic restenosis seen with BMS implantation in these subsets. Whether appropriate guidelines and reimbursement policies can be developed to encourage such a tailored approach is currently unknown.

**Hospital Perspective**

It is important to note that our discussion thus far has focused on costs as assessed from a societal (or healthcare system) perspective. From these perspectives, the initial higher cost of DES implantation can be recouped, at least in part, through downstream cost savings resulting from a reduction in the need for subsequent revascularization procedures. The situation is quite different when viewed from the perspective of a typical US hospital, however, which is paid for each episode of care and does not realize any direct financial benefits related to improved long-term outcomes. From the perspective of the hospital, economic attractiveness is simply the difference between reimbursement and the cost of the episode of care. Although the Centers for Medicare and Medicaid Services have provided incremental hospital reimbursement (in the form of diagnosis-related group payments) for implantation of DES since their approval in 2003, the difference in reimbursement rates between DES and BMS implantation is approximately $1800, which is less than the difference in cost for the 2 procedures. Thus, regardless of the specific cost structure of a hospital, it is clear that profitability is diminished by using drug-eluting stents. Moreover, under the current diagnosis-related group–based reimbursement system, the more stents that are required to treat a specific patient, the greater the financial burden is that is imposed on hospitals by DES adoption.

Insufficient third-party reimbursement accounts for only part of the financial challenge faced by hospitals resulting from the introduction of DES, however. Given the benefits of DES in reducing restenosis, hospitals face further loss of revenue resulting from the expected downstream reduction in the need for repeat revascularization procedures. Finally, hospitals have had to face an important loss of revenue resulting from the substitution of less remunerative DES procedures for bypass surgery—traditionally one of the best reimbursed and most profitable procedures for many tertiary hospitals. An analysis based on historical data from Duke University Medical Center projected that the introduction of DES (with 85% penetration over a 5-year period) would reduce overall hospital revenue by more than $5 million per year despite the availability of higher Medicare reimbursements for DES procedures—mainly because of erosion of coronary artery bypass grafting (CABG) volumes.

How Has the Introduction of DES Affected Overall Healthcare Expenditures?

Although our analyses suggest that use of DES compared with BMS is reasonably cost-effective within the context of the US healthcare system, the underlying framework of cost-effectiveness analysis is based predominantly on the concept of economic efficiency and does not directly address the critical issues of the overall impact of technology on healthcare spending (ie, global budget impact) or the source for any incremental funds required to implement the program. As we have outlined above, when the analysis is restricted to the current US PCI population, universal adoption of DES is unlikely to reduce net healthcare costs. In fact, with a projected long-term incremental cost of about $600 per PCI patient, one can readily project that use of DES in 90% of PCI recipients would increase annual PCI-related costs by $500 million.

Nonetheless, it is possible that DES could eventually result in meaningful long-term cost savings to the healthcare system as a whole. In particular, use of DES for patients who currently undergo bypass surgery (at a cost of $30 000) could result in substantial short- and long-term cost savings, provided the long-term outcomes are not compromised by such a strategy. Indeed, recent data from the Arterial Revascularization Therapy Study (ARTS)–1 and ARTS-2 trials demonstrate that, compared with bypass surgery, DES implantation

### Cost-Effectiveness Ratios for DES According to Patient and Lesion Characteristics

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<td>Nondiabetic patients</td>
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The cost-effectiveness ratio is reported in dollars per repeat revascularization avoided.
(with an average of 3.6 DES per patient) led to 1-year cost savings of approximately $5032 per patient compared with bypass surgery ($31 831 versus $36 863; P<0.001). Given these cost savings, it is conceivable that conversion of 20% to 30% of CABG procedures to DES could result in sufficient savings to the healthcare system to offset the higher long-term costs of DES for the PCI population. Whether the clinical results of multivessel PCI with DES can match the long-term angina relief and survival benefits of CABG and whether such volume shifts are achievable in practice remain to be seen. Recent data from our own institution have shown a 14% reduction in the rate of referral from coronary angiography to CABG since the introduction of DES, however.38

Future Considerations

Despite such optimistic projections, much about the overall economic impact of DES remains unknown. It is important to recognize that all of the economic projections and estimates summarized in this report represent at best “educated guesses” based on current use patterns, clinical trial results, and costs. Of these factors, device costs represent the greatest source of uncertainty. Although DES acquisition costs have declined by ~20% over the 3 years since their initial approval, it is likely that further cost reductions will occur in the near future as additional competitors enter the marketplace. In this case, our economic projections would represent a worst-case scenario, and true cost savings might be realized across much of the current PCI population. On the other hand, development of previously unanticipated new technologies (such as bioabsorbable stents) may further advance the field and command additional price premiums.

In addition to changes in pricing or clinical performance, an additional source of uncertainty is the possibility that new indications for DES will emerge. For example, the medical community has recently focused much attention on characterizing and identifying vulnerable plaques.39 Some have speculated that, in the future, cardiologists may be able to identify and treat vulnerable plaques, possibly with DES, to prevent future events, including sudden death and myocardial infarction.40 Obviously, if this were to become common practice, many more DES would be implanted than under the current practice paradigm.

What the sum total effect of these trends will be on US healthcare spending is not yet clear. Most likely, DES will not bankrupt the US healthcare system, especially as stent costs decline over time. Nevertheless, the healthcare marketplace is fluid, and continuous evaluation of outcomes and costs is essential to optimize cost-effectiveness. Only by monitoring use and cost over time can we accurately ascertain the true impact of DES on the US healthcare system.

Disclosures

Dr Cohen received grant support from Cordis Inc and Boston Scientific Inc. Dr Ryan reports no conflicts.

References

5. Tanne JH. Use of drug eluting stents increases in the US but only for some groups. BMJ. 2004;329:1205.
15. Weaver WD, Reisman MA, Griffin JJ, Buller CE, Leimgruber PP, Henry T, D’Haen C, Clark VL, Martin JS, Cohen DJ, Neil N, Every NR. Optimum percutaneous transluminal coronary angioplasty compared with


Response to Ryan and Cohen

Mark J. Eisenberg, MD MPH

Drs Ryan and Cohen nicely summarize the issue of drug-eluting stent (DES) cost-effectiveness. I think that we are in agreement about many points, including the following: (1) Among nondiabetic patients, DES are cost-effective only when reference vessel diameters are small (≤3.0 mm) or when coronary lesions are long; (2) among diabetic patients, DES are not cost-effective when reference vessel diameters are large (≥4.0 mm); and (3) The universal use of DES is associated with high incremental costs per patient and a substantial increase in global healthcare costs. These points make it clear that across-the-board use of DES is not cost-effective. The universal use of DES is expensive at current prices and leads to many patients receiving DES with little, if any, clinical benefit. Reserving DES for patients at high risk of restenosis is financially responsible and will have minimal, if any, adverse clinical consequences. I would like to emphasize 1 further point. The universal use of DES will not, by itself, bankrupt the US healthcare system. The indiscriminate use of expensive healthcare interventions that are only borderline cost-effective cannot be sustained indefinitely, however. Healthcare resources are limited; DES use necessarily competes for funding with other healthcare interventions. Examining the cost-effectiveness of DESs in isolation, without taking into account competing healthcare interventions, is naive. If we are not financially responsible in the use of healthcare technology, we can and will eventually bankrupt the healthcare system.
Drug-Eluting Stents
The Price Is Not Right
Mark J. Eisenberg, MD, MPH

“Does it make economic sense to completely abandon a therapy that works well for 85% to 90% of the population for a new therapy costing four times as much to treat a transient health condition with no impact on either death or myocardial infarction?”

J.M. Brophy and L.J. Erickson

Since Andreas Gruntzig performed the first percutaneous coronary intervention (PCI) in 1977, the cost-effectiveness of this procedure has engendered major controversy. Debates have erupted over the clinical value and cost-effectiveness of each new device or therapy that has become available. Controversies have arisen regarding the cost of atherectomy, bare metal stents (BMS), brachytherapy, distal protection devices, glycoprotein IIb/IIIa inhibitors, and intravascular ultrasound. Drug-eluting stents (DES) are the most recent devices to have their cost scrutinized.

Clinical Effectiveness and DES Penetration
Balloon angioplasty is associated with restenosis rates of 30% to 40%, whereas PCI with BMS is associated with rates of 20% to 30%, and PCI with DES is associated with rates in the single digits. My colleagues and I pooled the results of 11 DES trials involving >5000 patients using a hierarchical Bayesian random-effects model. We found that, compared with BMS, DES reduce angiographic restenosis from 29.3% to 8.9% (Table 1 and Figure 1). There was no difference between DES and BMS in terms of mortality (0.9% versus 0.9%, respectively) or myocardial infarction (2.7% versus 2.9%, respectively). There was a suggestion that restenosis was less with sirolimus-eluting stents (SES) compared with polymeric paclitaxel-eluting stents (PES) (6.2% for SES versus 36.9% for BMS; 7.1% for PES versus 23.5% for BMS), a finding that was subsequently identified in another meta-analysis.

The interventional community quickly embraced the results of the DES trials. DES use has become nearly ubiquitous in the United States, and its use is becoming widespread outside the United States as well. Rather than reserving this high-cost technology for patients who are at high risk for restenosis, many interventional cardiologists are placing these stents in all patients, including those whose baseline risk of restenosis is low. Before the universal use of DES becomes an entrenched practice, we need to know the answer to the following question: Is the clinical benefit associated with DES substantial enough to justify the use of this high-cost technology in all patients undergoing PCI? Several lines of evidence suggest that DES are currently too expensive to be used in an across-the-board manner in all patients undergoing PCI. These data come from a variety of studies comparing the cost-effectiveness of DES and BMS that have been performed in various countries.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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Cost-Effectiveness of DES Versus BMS
A PubMed search for studies comparing the cost-effectiveness of DES versus BMS identified 7 studies from North America (Table 2)\(^{20–26}\) and 6 studies from Australia and Europe (Table 3)\(^{27–32}\). Only studies that reported cost per quality-adjusted life-year (QALY) gained or cost per repeat revascularization avoided were included. Cost per QALY gained is the primary outcome measure of most cost-effectiveness analyses. Using this measure, we can directly compare the cost-effectiveness of different healthcare interventions (Table 4).\(^{33}\) In the United States, an intervention associated with a cost per QALY gained of $50,000 is considered to be cost-effective; one associated with a cost per QALY gained of $50,000 to $100,000 is in the “gray area”; and one associated with a cost per QALY gained of $100,000 is considered unattractive.\(^{34}\) Cost per repeat revascularization avoided is the other measure that is commonly used in DES cost-effectiveness studies. This disease-specific measure allows us to examine whether the incremental cost of DES above that of BMS is offset by the cost savings brought about by a reduction in the need for subsequent revascularization procedures. In the United States, a cost per revascularization avoided of $10,000 is thought to be cost-effective.\(^{20,21}\)

Cost-Effectiveness Studies of DES in the United States
At the time of this writing, only 2 traditional cost-effectiveness studies examining DES in the context of the
TABLE 2. Cost-Effectiveness Studies of DES in North America

<table>
<thead>
<tr>
<th>Location and Author</th>
<th>Source of Efficacy Data</th>
<th>Source of Cost Data</th>
<th>Patient Group, n</th>
<th>Mean Stents, n (type)</th>
<th>Revascularization Rate; DES vs BMS, %</th>
<th>Cost of DES vs Cost of BMS</th>
<th>Cost of PCI vs Cost of CABG</th>
<th>Assumptions</th>
<th>Outcomes at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States (costs in $US)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenberg et al20</td>
<td>BMS data, RAVEL, SIRIUS</td>
<td>Multicenter trials</td>
<td>Single vessel, 6000</td>
<td>1.3 (SES)</td>
<td>3.8 vs 14.0</td>
<td>2700 vs 700</td>
<td>NR vs 25 000</td>
<td></td>
<td>NR 7000*</td>
</tr>
<tr>
<td>Cohen et al21</td>
<td>SIRIUS</td>
<td>Hospital and Medicare rates</td>
<td>Complex, 1058</td>
<td>1.4 (SES)</td>
<td>16.3 vs 35.4</td>
<td>2900 vs 900</td>
<td>4395 (7251) vs NR</td>
<td></td>
<td>27 540 1650</td>
</tr>
<tr>
<td>Canada (costs in $CAN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowen et al22</td>
<td>CCN CARDIACCESS</td>
<td>NR</td>
<td></td>
<td></td>
<td>1.5 (Both)</td>
<td>9.4 vs 10.7</td>
<td>1899 vs 600</td>
<td>−7050 vs 18 799</td>
<td>2 221 692 95 383</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No DM, no MI, 4796</td>
<td></td>
<td></td>
<td>−7050 vs 18 799</td>
<td>1 688 786 69 896</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No DM, post-MI, 1342</td>
<td></td>
<td></td>
<td>−7050 vs 18 799</td>
<td>1 132 426 49 333</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DM, no MI, 1377</td>
<td></td>
<td></td>
<td>−7050 vs 18 799</td>
<td>438 415 17 711</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DM, post-MI, 349</td>
<td></td>
<td></td>
<td>−7050 vs 18 799</td>
<td>58 721 NR</td>
</tr>
<tr>
<td>Shrive et al23</td>
<td>APPROACH</td>
<td>APPROACH, Alberta Health</td>
<td>Complex, 7334</td>
<td>1.4 (SES)</td>
<td>NR</td>
<td>2900 vs 500</td>
<td>15 569 vs 32 009</td>
<td></td>
<td>26 562</td>
</tr>
<tr>
<td>Mittmann et al24</td>
<td>Meta-analysis</td>
<td>RCTs, Ontario Medicare, personal communication</td>
<td>Complex†, 2447</td>
<td>1.5 (PES)</td>
<td>3.3 vs 12.2</td>
<td>2400 vs 608</td>
<td>9761 vs 19 617</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Brophy et al25</td>
<td>Meta-analysis27</td>
<td>Hospital costs, Quebec Medicare</td>
<td>Complex†, 1748</td>
<td>1.5 (SES)</td>
<td>3.5 vs 18.5</td>
<td>2400 vs 608</td>
<td>9761 vs 19 617</td>
<td></td>
<td>NR 12 527</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.7 (NR)</td>
<td>3.3 vs 12.8</td>
<td>2600 vs 700</td>
<td>4507 vs 15 025</td>
<td>23 067§</td>
</tr>
<tr>
<td>Rinfret et al26</td>
<td>C-SIRIUS</td>
<td>CHUM, RAMQ</td>
<td>Single vessel, 100</td>
<td>1.5 (SES)</td>
<td>4.0 vs 22.0</td>
<td>2700 vs 700</td>
<td>4006 vs 14 402</td>
<td></td>
<td>NR 11 275</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; QALY, quality-adjusted life-years; NR, not reported; CCN, Cardiac Care Network of Ontario; CARDIACCESS, patient registry of the CCN; DM, diabetes mellitus; MI, myocardial infarction; APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; RCTs, Randomized Controlled Trials; CHUM, Centre Hospitalier de l’Université de Montréal; and RAMQ, Régie de l’assurance maladie du Québec.

*After follow-up of 2 years.
†Complex includes all patients, including those with diabetes, long lesions, small vessels, and multivessel disease.
‡Cost of BMS PCI (cost of SES PCI) including stent price.
§After follow-up of 9 months.

United States have been published; both are from the same group at the Harvard Clinical Research Institute (Table 2).20,21 Despite these surprisingly limited cost-effectiveness data, DES are being used in the vast majority of PCI procedures now being performed in the United States.19 Greenberg et al20 published a review of the economic impact of restenosis and DES. Embedded within the review was a decision-analytic model examining DES cost-effectiveness. The model used outcome and resource use data from >6000 “real-world” patients undergoing single-vessel PCI procedures.25–37 Costs were based on pooled data from several clinical trials involving >3000 patients. The model used the following assumptions: (1) a BMS repeat revascularization rate of 14%, (2) an 80% reduction in repeat revascularization rates with DES, (3) an incremental cost of $2000 per DES, and (4) a mean use of 1.3 stents per PCI. Over a 2-year follow-up, this model indicated that overall medical care costs are approximately $900 per patient higher with DES than with BMS, with an incremental cost-effectiveness ratio of approximately $7000 per repeat revascularization avoided. Sensitivity analyses suggested that treatment with DES is cost saving for patients with a BMS repeat revascularization rate ˃20% and cost-effective (<$10 000 per repeat revascularization avoided) for patients with a BMS repeat revascularization rate ˃12% (Figure 2). The authors concluded that, compared with BMS, DES are cost saving for only a modest proportion of the current PCI population in the United States. However, they did suggest that DES are economically attractive for virtually all diabetic patients and for nondiabetic patients with small vessels and long lesions. Greenberg et al did not report a cost per QALY gained, but they concluded that the cost-effectiveness of DES is dependent on the target population undergoing PCI and the alternative therapy that might be used (ie, medical therapy, BMS, or coronary artery bypass grafting).

Cohen et al21 reported an economic analysis of the SIRIUS trial.2 Clinical outcomes, resource use, and costs were prospectively collected for 1058 patients who received either an SES or a BMS over a 1-year period. Initial hospital costs were increased by $2881 per patient with DES. During the 1-year follow-up, use of DES versus BMS was associated with reductions in the rates of repeat PCI (12.4% versus 26.9%, respectively) and bypass surgery (1.3% versus 3.0%, respectively). Although follow-up costs were reduced by $2571 per patient with DES, aggregate 1-year costs were still $309 per patient higher. The incremental cost-effectiveness ratios for DES were $27 540 per QALY gained and $1650 per repeat revascularization avoided. The authors concluded that, al-
though the use of SES was not cost saving compared with BMS, for patients undergoing PCI of complex coronary lesions, the use of DES appeared to be reasonably cost-effective within the context of the United States healthcare system.

These 2 studies examining the cost-effectiveness of DES in the context of the United States came to similar conclusions. Both studies suggested that DES are cost-effective in high-risk patients with respect to repeat revascularizations avoided.

In addition, although the study by Greenberg et al did not report a cost per QALY gained, the figure reported by Cohen et al falls within the range that is generally accepted as being cost-effective in the United States ($50 000 per QALY gained) (Table 4). However, the conclusions drawn from these 2 studies must be tempered in view of the assumptions and methodologies used.

Greenberg et al assumed that all patients underwent single-vessel PCI with a mean use of 1.3 DES per procedure. In contrast, other cost-effectiveness studies assumed a mean use of 1.5 DES per PCI; some have even used 1.7 or 1.9 (Tables 2 and 3). Minimizing the number of DES used per PCI minimizes the estimated cost per repeat revascularization avoided. In addition, because DES allow us to treat more complex lesions than were treated previously, it is likely that future PCI procedures will use more rather than fewer stents per case.

Cohen et al performed a textbook-perfect cost-effectiveness study as part of the SIRIUS trial. However, the results of this study were affected by the use of protocol-mandated angiography. Most of the DES trials, including the SIRIUS trial, used protocol-mandated follow-up angiography at 6 to 9 months with subsequent clinical follow-up several months later. Because follow-up angiography was performed in all patients, many cases of angiographic restenosis were identified in patients who were asymptomatic. If restenosis was identified at the time of the protocol-mandated angiography, repeat PCI was frequently performed—often called the oculostenotic reflex. These asymptomatic patients who had angiographic but not clinical restenosis were then identified as achieving one of the predefined end points of the trial: need for repeat revascularization. The effect of protocol-mandated angiography can be seen in the Kaplan-Meier survival curves for the RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent (Cypher; RAVEL) trial (Figure 3). At the time of the mandated

### Table 3. Cost-Effectiveness Studies of DES in Australia and Europe

<table>
<thead>
<tr>
<th>Location and Author</th>
<th>Source of Efficacy Data</th>
<th>Source of Cost Data</th>
<th>Patient Group, n</th>
<th>Assumptions</th>
<th>Outcomes at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (cost in $AUS)</td>
<td>Lord et al</td>
<td>TAXUS, SIRIUS, RAVEL</td>
<td>National Hospital Cost Data</td>
<td>Complex*, 1748</td>
<td>Mean Stents, n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5 (SES)</td>
<td>4.0 vs 20.5</td>
</tr>
<tr>
<td></td>
<td>Ward</td>
<td>Patient registry</td>
<td>Department of Health</td>
<td>Complex*, 1642</td>
<td>1.5 (PES)</td>
</tr>
<tr>
<td>Sweden (cost in SEK)</td>
<td>Ekman et al</td>
<td>TAXUS IV</td>
<td>Hospital Price Lists</td>
<td>Complex*, 13 200</td>
<td>1.4 (PES)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High risk†, NR</td>
<td>1.4 (PES)</td>
</tr>
<tr>
<td>Switzerland (cost in €)</td>
<td>Kaiser et al</td>
<td>BASKET</td>
<td>TARMEDE</td>
<td>Complex*, 826</td>
<td>1.4 (Both)</td>
</tr>
<tr>
<td>United Kingdom (cost in GBP)</td>
<td>Bagust et al</td>
<td>CTC, RAVEL, SIRIUS</td>
<td>CTC and NHS Costs</td>
<td>Elective PCI, 1951</td>
<td>1.9 (SES)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non elective PCI, 933</td>
<td>1.7 (SES)</td>
</tr>
<tr>
<td></td>
<td>NICE</td>
<td>TAXUS II, RAVEL</td>
<td>NR</td>
<td>Single-vessel disease, NR</td>
<td>1.0 (NR)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; QALY, quality-adjusted life-years; NR, not reported; RAVEL, Randomized study with the sirolimus-eluting Bx Velocity balloon-expandable stent (Cypher); BASKET, Basel Stent Kosten Effektivität試験; TARMEDE, Swiss Medical tariff; CTC, cardiothoracic center; NHS, National Health Service; and NICE, National Institute for Clinical Excellence.

*Complex includes all patients, including those with diabetes, long lesions, small vessels, and multivessel disease.
†High risk includes patients with diabetes, small vessels, and/or long lesions.
‡Prices vary depending on the type of DES or BMS used.
§After follow-up of 6 months.
angiographic follow-up, there was a sharp rise in the identification of restenosis and occurrence of repeat revascularization procedures. Repeat revascularization in the BMS group jumped from 6% before angiography to 20% after angiography. Similar increases were seen in other DES trials that used protocol-mandated angiography (Table 5).28,39–41 Although Cohen et al tried to account for the use of protocol-mandated angiography in their analysis, they were overly optimistic in both the clinical effectiveness data that they used in their cost analysis and the subsequent DES cost-effectiveness that they reported.

Cost-Effectiveness Studies of DES Outside the United States

In contrast to the 2 published studies from the United States, 5 studies from Canada suggest that across-the-board use of DES in all PCI patients is not cost-effective. Although the Canadian dollar is worth ≈90 cents American at the time of this writing, the thresholds considered to be cost-effective in Canada are somewhat different than those in the United States. The reason for this is that the costs of repeat PCI and

TABLE 4. Cost-Effectiveness and Use of Selected Interventions in the Medicare Population*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost-Effectiveness†</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine</td>
<td>Cost saving</td>
<td>40%–70%</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Cost saving</td>
<td>55%–65%</td>
</tr>
<tr>
<td>β-Blockers after myocardial infarction</td>
<td>&lt;10 000†</td>
<td>85%</td>
</tr>
<tr>
<td>Mammographic screening</td>
<td>10 000–25 000†</td>
<td>50%–70%</td>
</tr>
<tr>
<td>Colon-cancer screening</td>
<td>10 000–25 000†</td>
<td>20%–40%</td>
</tr>
<tr>
<td>Osteoporosis screening</td>
<td>10 000–25 000†</td>
<td>35%</td>
</tr>
<tr>
<td>Management of antidepressant medication</td>
<td>Cost saving up to 30 000†</td>
<td>40%–55%</td>
</tr>
<tr>
<td>Hypertension medication (diastolic blood pressure &gt;105 mm Hg)</td>
<td>10 000–60 000†</td>
<td>35%</td>
</tr>
<tr>
<td>Cholesterol management, as secondary prevention</td>
<td>10 000–50 000†</td>
<td>30%</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>30 000–85 000†</td>
<td>100 000 cases/y</td>
</tr>
<tr>
<td>Dialysis in end-stage renal disease</td>
<td>50 000–100 000†</td>
<td>90%</td>
</tr>
<tr>
<td>Lung-volume-reduction surgery</td>
<td>100 000–300 000†</td>
<td>10 000–20 000 cases/y</td>
</tr>
<tr>
<td>Left ventricular assist devices</td>
<td>500 000–1.4 million†</td>
<td>50 000–100 000 cases/y</td>
</tr>
<tr>
<td>PET in Alzheimer’s disease</td>
<td>Dominated‡</td>
<td>50 000 cases/y</td>
</tr>
</tbody>
</table>

PET indicates positron-emission tomography.

*Ranges rather than point estimates are provided because the actual cost-effectiveness will vary according to the target populations and the strategies used.

†Calculated as cost/QALY. The calculation was based on 2002 dollars.

‡With the use of this intervention, benefits are lower and costs are higher than with the use of the standard workup.

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coronary artery bypass grafting are much less in Canada.\(^4^2\) Cost-effectiveness thresholds in Canada are \(<\text{Can }50 000\) per QALY gained and \(<\text{Can }12 551\) per repeat revascularization avoided.\(^{26}\)

Bowen et al\(^{22}\) performed a cost-effectiveness analysis of DES for the Ontario Ministry of Health and Long-Term Care. These investigators found that DES were associated with an exceedingly high cost per QALY gained: Can $438 415 to Can $2 221 692, ratios that clearly place this technology in the non–cost-effective range. In addition, the cost per revascularization avoided was also prohibitive: from Can $17 711 for patients with a recent myocardial infarction and diabetes to Can $95 383 for patients without diabetes, SES use was substantially less cost-effective (Can $72 464 and Can $63 383 per QALY gained, respectively). Importantly, the BAsel Stent Kosten Effektivitäts Trial (BASKET) investigators prospectively performed a study in which they examined the cost-effectiveness of DES in a group of patients randomized to DES or BMS.\(^3^0\) As opposed to most other studies, costs were prospectively collected, and patients did not undergo protocol-mandated follow-up angiography. A total of 826 patients were randomized to SES, PES, or BMS. The aggregate costs at 6 months were higher with DES than with BMS, and higher stent costs were not compensated for by lower follow-up costs (overall 6-month costs were still 905 € higher in the DES group). The incremental cost-effectiveness ratio to avoid 1 major adverse cardiac event was 18 311 €, and the cost per QALY gained was more than 50 000 €. The authors concluded that, in a real-world setting, use of DES should be restricted to patients in high-risk groups. Importantly, BASKET also suggested that DES are associated with a significantly higher rate of thrombotic complications compared with BMS during the 6 months following the cessation of clopidogrel.\(^3^3\) Therefore, the need for prolonged treatment with clopidogrel will further reduce the cost-effectiveness of DES.

**Limitations of DES Cost-Effectiveness Studies**

Despite the fact that most studies have not found DES to be cost-effective in an across-the-board manner, many of these studies still painted an overly optimistic picture of the cost-effectiveness of DES. Two limitations of these studies were responsible. First, the true cost of DES procedures was

### TABLE 5. Target Lesion Revascularization Rates With BMS in DES Trials Before and After Protocol-Mandated Angiography

<table>
<thead>
<tr>
<th>Trial</th>
<th>Before Protocol-Mandated Angiography</th>
<th>After Protocol-Mandated Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>TAXUS II</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

Adapted and reproduced from Ward\(^{28}\) with permission from the Australasian Society of Cardiac and Thoracic Surgeons and the Cardiac Society of Australia and New Zealand. Copyright 2005.
underestimated; second, the clinical effectiveness of DES was overestimated.

Although the cost of a single DES is reasonably well established, the published studies used a mean number of stents per PCI between 1.0 and 1.9. The assumption of a lower number of stents per PCI leads to a better cost-effectiveness ratio; the assumption of a higher number leads to a worse cost-effectiveness ratio. With the advent of DES, there has been a trend of performing increasingly complex PCI procedures. This trend will likely lead to an even greater number of stents per patient in the future. Thus, previous studies underestimated the true cost of DES procedures, and this led to an overly optimistic view of DES cost-effectiveness.

Previous studies also overestimated the clinical effectiveness of DES. Most of these studies based their calculations on data obtained from previous DES trials. Unfortunately, most of these trials enrolled patients with solitary de novo coronary lesions and used protocol-mandated angiography. These features led to the observations of low restenosis rates in patients receiving DES and high rates of restenosis and repeat revascularization procedures in patients receiving BMS. The use of inflated estimates of clinical effectiveness led to overly optimistic estimates of DES cost-effectiveness. Studies like the BASKET trial that were performed in real-world settings without the use of protocol-mandated angiography found that the clinical benefit of DES is substantially less than that described in randomized controlled trials. Consequently, the cost-effectiveness studies that relied on the early DES trials were overly optimistic in the clinical effectiveness data that they used.

Conclusions From DES Cost-Effectiveness Studies

Despite their limitations, several important conclusions can be derived from the DES cost-effectiveness studies that have been published. First, DES are not cost saving and they are not cost neutral. A substantial amount of money has to be spent to obtain a modest clinical benefit. Second, if DES are used in place of BMS, some but not all of the initial cost is recouped during the follow-up period as a result of a reduced need for repeat revascularization procedures. Third, because DES have no impact on mortality or myocardial infarction rates and because their effect on quality of life is modest, DES are associated with a high cost per QALY gained. Thus, the sole justification for the use of DES is their ability to reduce the need for repeat revascularization procedures. An across-the-board manner is not an optimal strategy from a cost-effectiveness point of view.

Other DES Cost Studies

Besides the traditional cost-effectiveness studies detailed above, a number of studies have examined the economics of DES from other perspectives. Several studies examined the decline in DES price required for DES to be cost neutral (the break-even price). Several studies examined the impact of DES penetration on hospital budgets, and other studies examined the impact of DES on global healthcare budgets. The conclusions from these studies can be summarized as follows. First, DES prices have to decline substantially before break-even prices are reached. Second, from both hospital and societal perspectives, across-the-board use of DES leads to substantial increases in budgetary costs that are not recouped by a reduced need for subsequent revascularization procedures.

Competing Healthcare Interventions

Another issue should be considered before deciding on a policy to guide our use of DES. Even in affluent societies, resources available for healthcare interventions are not unlimited. In reality, multiple potential healthcare interventions are in competition for the same resources; consequently, some interventions receive funding while others do not. The best way to determine which interventions will be funded is not by individual studies of cost-effectiveness but instead by directly contrasting the cost-effectiveness ratios of alternative interventions. Many healthcare interventions are associated with a cost per QALY gained in the gray area of $50 000 to $100 000. If we funded each of these interventions, we would quickly deplete the budget of every hospital and every healthcare system. The most efficient, and perhaps the most equitable, way of using our limited healthcare resources is by reimbursing for the most cost-effective interventions. Our budget should first be spent on the most cost-effective intervention, followed by the second most cost-effective intervention, and so on until our resources are spent. In this fashion, the most health benefit is obtained for a given amount of limited resources. The current method of comparing healthcare interventions in isolation leads to inequities. Many high-cost but low-yield interventions are currently available, but other low-cost but high-yield interventions are not. With this perspective in mind, an across-the-board use of DES cannot be justified.

When Is DES Use Cost-Effective?

Although DES are not cost-effective in an across-the-board manner, at current prices, DES may well be cost-effective in several subgroups of high-risk patients. These subgroups include patients at high risk for restenosis (eg, diabetics and those with long lesions and small vessels) and patients who would otherwise undergo coronary artery bypass surgery. Other subgroups in which DES may prove to be...
cost-effective include patients with left main lesions, patients with proximal left anterior descending artery lesions, patients with lesions in saphenous vein grafts, and patients with complex lesions who are at high risk for restenosis. However, at this time, few cost-effectiveness data have been derived directly from these high-risk subgroups. The data that are available are mostly extrapolated rather than directly measured. The cost-effectiveness of DES in these high-risk subgroups should be closely explored before the routine use of DES in these patients becomes entrenched.

**Ethical Considerations**

If DES are used in an across-the-board manner in all PCI patients, well over half of the patients who receive these stents will not derive any clinical benefit from them. One has to question whether it is ethical to subject large numbers of patients who are at low risk of restenosis to the small but real risk of late thrombosis known to be associated with DES. Moreover, the widespread use of DES and the ensuing risk of late thrombosis is creating a new clinical phenomenon: long-term dependence on clopidogrel. With an aging population and with the increased bleeding risks associated with clopidogrel, we may need to temper our enthusiasm regarding DES. One also has to question whether it is ethical to use an extremely high-cost technology in many patients who will not derive any clinical benefit while denying more essential care to many patients who do not have the financial resources to pay for it. Although framing the issue in this manner may not be popular, policy makers in many countries have decided that using BMS in patients at low risk of restenosis will free up valuable resources that can be used to improve health care in other arenas. With an increasing realization that limited healthcare resources must be used in an optimal manner, a healthy debate about the ethics of using DES at their current prices in an across-the-board manner should be encouraged.

**Conclusions**

Almost 30 years after Andreas Gruntzig performed the first PCI, the debate about the cost-effectiveness of this procedure still arouses controversy. Interventional cardiology is a constantly changing field, and new devices and therapies are continually being introduced. Some of these devices and therapies find a permanent place; others are eventually discarded. After the initial cost-effectiveness debates, virtually all of these devices and therapies drop in price until the cost-effectiveness debates are scarcely remembered. I anticipate that a similar scenario will occur with DES. As second- and third-generation DES become available and as new companies enter the market, prices will drop. In addition, improvements in stent design, use of different polymers, and the introduction of cheaper and more effective drugs that can be eluted from stents will lead to an increase in DES effectiveness. As prices drop and clinical effectiveness increases, the cost-effectiveness of DES will improve substantially. Our original question was, Is the clinical benefit associated with DES substantial enough to justify the use of this high-cost technology in all patients undergoing PCI? I think that the cost-effectiveness data that we now have available indicate that DES are currently too expensive to be used in all patients undergoing PCI. However, as their prices drop and as their effectiveness increases, DES will become increasingly attractive from a cost-effectiveness point of view, and their use will likely become a permanent addition to the pantheon of interventional cardiology.

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**Disclosures**

None.

**References**


**TABLE 6. Predicted Rates of Clinical Restenosis After BMS Implantation as a Function of Lesion Length, Reference Vessel Diameter, and Diabetes**

<table>
<thead>
<tr>
<th>Vessel Diameter (mm)</th>
<th>Lesion Length, mm</th>
<th>Diabetic patients (%)</th>
<th>Nondiabetic patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Diabetic patients (%)</td>
<td>2.5</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Nondiabetic patients%</td>
<td>2.5</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>7</td>
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<td></td>
<td>3.5</td>
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<td>4.0</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

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28. Pfisterer ME. Late clinical events related to late stent thrombosis after stopping clopidogrel: prospective randomized comparison between drug-eluting versus bare-metal stenting. Presented at: Late-Breaking Clinical Trials, American College of Cardiology, 55th Annual Scientific Session; March 14, 2006; Atlanta, Ga.

Response to Eisenberg

Jason Ryan, MD, MPH; David J. Cohen, MD, MSc

In this issue of Circulation, we and Dr Eisenberg have reviewed the data on the economic impact of drug-eluting stents (DES) and come to seemingly opposite conclusions. In this debate, as in many others, however, the true value lies not in the conclusions themselves but in exploring the reasons for these alternative views. In the case of the DES controversy, 2 fundamental differences largely explain our divergent conclusions. The first is regarding the principle that cost-effectiveness always reflects an incremental analysis. In other words, a device or procedure cannot be evaluated in a vacuum but rather must be compared with an alternative treatment strategy. Taken to its logical conclusion, this concept implies that economic analyses should be focused on specific patient subgroups (based on any number of potential patient characteristics), within the bounds of evidence to distinguish differences in cost and clinical effectiveness. This concept of incremental analysis is the basis for Dr Eisenberg’s assertion that conclusions about cost-effectiveness of DES based on clinical trials reflect only the specific population under investigation. We wholeheartedly agree with this point and acknowledge that this is an important limitation of virtually all trial-based economic evaluations. In an ideal world, it would be most efficient to allocate DES specifically to those patients for whom they are most cost-effective and to withhold them from patients who derive only marginal benefit. Unfortunately, at present, the healthcare reimbursement systems in most countries are not sufficiently sophisticated to accommodate this level of analysis. Indeed, decisions about reimbursement for new medical technologies rarely differentiate between populations that derive different levels of absolute benefit (and, as a result, different cost-effectiveness levels). This contrast between optimal resource allocation at the individual level versus at the population level is 1 of the key differences between Dr Eisenberg’s view and our own. The second key difference between our position and that of Dr Eisenberg is the perspective of the analysis. Virtually all of the data we cite are based on studies conducted within the United States, whereas most of the analyses cited by Dr Eisenberg are derived from studies conducted in other countries such as Canada and Switzerland. In addition to different care patterns, these countries tend to have lower costs for procedures and hospitalizations and spend far less on health care than in the United States, and these factors would tend to minimize the economic benefit of DES. In the case of the debate on DES versus bare metal stents, differences in the country chosen for the analysis may be at least as important as the underlying patient population. In light of these considerations, we believe that there is more agreement than disagreement in this debate. There is little question that DES are more cost-effective for patients at higher risk of restenosis than for patients for whom the restenosis risk is relatively low. Optimal application of DES technology would certainly focus on those patients for whom it is highly cost-effective. Given the realities of our current reimbursement system, however, it seems unlikely that such fine gradations can be reliably enforced. Therefore, if one accepts the concept that DES should be evaluated in aggregate, we believe that the data are clear. At least from the standpoint of the US healthcare system, the balance of costs and benefits currently favors DES implantation for the overall percutaneous coronary intervention population. Given the numerous differences in practice patterns, treatment costs, and cost-effectiveness thresholds, however, it is clear that this conclusion cannot be readily extrapolated to other countries and healthcare systems and that additional population-based analyses are needed.
Drug-Eluting Stents: The Price Is Not Right
Mark J. Eisenberg

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