

Narrative Review: Drug-Eluting Stents for the Management of Restenosis: A Critical Appraisal of the Evidence

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Interventional cardiologists have quickly replaced bare metal stents with intravascular drug-eluting stents for treating and preventing restenosis, largely on the basis of empirical evidence that shows profound reduction in angiographic and clinical restenosis. A critical reassessment of the published evidence, however, suggests that the putative superiority of intravascular drug-eluting stents is founded on questionable premises, including 1) overestimation of restenosis benefit, 2) underestimation of the risk for stent thrombosis, 3) overreliance on “soft” rather than “hard” outcomes (need for

repeated revascularization vs. death or myocardial infarction), and 4) the attendant overestimation of cost-effectiveness. Because the long-term incremental risks, benefits, and costs of drug-eluting stents have not yet been optimally evaluated in a broad spectrum of patient and lesion cohorts, the rational role of these devices in clinical management warrants reappraisal.

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Since their approval in April 2003, drug-eluting stents have revolutionized the practice of interventional cardiology. Currently, more than 85% of all coronary interventions in the United States are performed with drug-eluting stents (1). Two pivotal trials, Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) (2) and Treatment of De Novo Coronary Disease Using a Single Paclitaxel Eluting Stent (TAXUS)-IV (3), demonstrated striking reductions in angiographic restenosis and revascularization rates with sirolimus- and paclitaxel-eluting stents, respectively. The current U.S. Food and Drug Administration–approved indication for drug-eluting stents is for discrete, de novo lesions in native vessels with reference vessel diameters of 2.5 mm to 3.5 mm (4). Nevertheless, the unrestricted implementation of drug-eluting stents seems to be widely accepted in contemporary interventional clinical practice. This widespread adoption has largely been driven by nonrandomized registry experience and has been fueled by enthusiastic dissemination and acceptance of data, aggressive marketing, and unbridled expectations of patients. At our institution (Cedars-Sinai Medical Center, Los Angeles, California), 2975 drug-eluting stents were used in a 2-year period (May 2003 to April 2005), representing nearly 95% of all coronary interventions.

While drug-eluting stents are clearly effective in reducing the “knotty” problem of restenosis, they cost nearly 3- to 4-fold more than bare metal stents. The unrestricted, off-label use of drug-eluting stents has important implications for health care delivery systems. The benefits of this new technology must be appraised for optimal utilization in clinical practice. Accordingly, we searched the MEDLINE database for articles published from January 1999 to November 2005 by using the following terms: *drug-eluting stents*, *bare metal stents*, *restenosis*, *stent thrombosis*, and *cost-effectiveness*. We focused on pivotal randomized trials and pertinent registry studies to explore key issues relating to drug-eluting stents. We offer a critical appraisal that challenges the mainstream interpretation of the data on several grounds (Table 1).

HAVE TRIALS OVERESTIMATED THE CLINICAL BENEFITS OF DRUG-ELUTING STENTS?

The impressive results on restenosis and repeated revascularization in the pivotal drug-eluting stent trials may have been overestimated for many reasons.

First, careful examination reveals inordinately high restenosis or target vessel revascularization rates in the bare metal stent control group—nearly 50% higher than that observed in contemporary randomized trials and in real-world clinical experience (Table 2). The inferior performance of bare metal stents may be explained by the use of thick-strut stents: Bx VELOCITY (140 μm ; Cordis Corp., Miami Lakes, Florida) in the SIRIUS trial and Express (130 μm ; Boston Scientific, Natick, Massachusetts) in the TAXUS-IV trial, both of which are associated with a high restenosis rate. Use of thick-strut stents that yield a higher risk for restenosis (17), in small-diameter lesions (<3.0 mm in SIRIUS) where the risk for restenosis is often magnified, may have inflated the restenosis and revascularization rates with bare metal stents in these trials. Had the trials used the best available benchmark—thin-strut stents, such as PALMAZ-SCHATZ (62 μm ; Cordis Corp.) used in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) and Stent-Primary Angioplasty in Myocardial Infarction (Stent-PAMI) trials or MULTI-LINK DUET (91 μm ; Guidant Corp., Santa Clara, California) used in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study, instead of a suboptimal bare metal stent—they may have determined a more reliable estimate of the true restenosis reduction rate with a drug-eluting stent. Thus, the impressive restenosis reduction rate observed in the pivotal trials may, in fact, be exaggerated because of the

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Table 1. Summary of Critical Appraisal

Overestimation of clinical benefit with drug-eluting stent
Inferior performance of suboptimal thick-strut control bare metal stent (a "straw man")
Protocol-mandated angiography bias ("oculostenotic" reflex)
Failure of angiographic surrogate outcomes to consistently translate into clinical benefit
Attenuation of restenosis benefit in high-risk cohorts
Underestimation of risk for stent thrombosis with drug-eluting stent
Increased risk for stent thrombosis in current clinical practice settings (2- to 3-fold more than that in clinical trial data)
Unacceptably high complication rate of death or myocardial infarction associated with stent thrombosis (approximately 50%)
Prolonged dual antiplatelet therapy required for preventing stent thrombosis
Optimal time of interruption of antiplatelet therapy or type of short-term "bridging" therapy during elective procedures unknown
Overreliance on "soft" rather than "hard" outcomes
Benefit driven primarily by "soft" outcome of target vessel revascularization (the most prevalent component of the composite end point)
Numeric trends in wrong or neutral direction in "hard" outcomes of death or myocardial infarction
Questionable validity of composite end point (dissimilar clinical importance, frequency, and therapeutic responsiveness of the individual components)
No statistically significant difference in weighted end point analysis
Underestimation of costs of drug-eluting stent
High cost of drug-eluting stent (3- to 4-fold higher than that of bare metal stent)
Underestimation of stent utilization rates in clinical trials compared with clinical practice
Overestimation of restenosis benefit with drug-eluting stent in clinical trials
Underestimation of duration and cost of antiplatelet therapy in clinical trials
Recommendations for judicious and cost-effective use of drug-eluting stents
Selective initial use in cohorts at high risk for restenosis (<20% of stent-eligible patients)
Provisional ("bailout") use in patients with restenosis after bare metal stenting (<10% to 15% of patients)
Strict avoidance in patients who cannot or are unlikely to adhere to long-term antiplatelet therapy
Long-term follow-up necessary to assess overall safety and efficacy

"inferior performance" of the control bare metal stent compared with the "superior performance" of the drug-eluting stent.

Second, protocol-mandated angiography in drug-eluting stent trials may have overestimated the need for revascularization. The analysis of event-free survival on the basis of target lesion revascularization in the SIRIUS trial (Figure 1) demonstrates a sudden increase of 8.3 percentage points immediately after angiography at 8 months in the bare metal stent group (from 13.1% at 7.5 months to 21.4% at 9 months) compared with 2.9 percentage points in the sirolimus-eluting stent group (from 6.0% at 7.5 months to 8.9% at 9 months). In contrast, no such increase was observed in patients who did not undergo protocol-mandated angiography (18). The 6-month target vessel revascularization rate of 7.8% in the Basel Stent Kosten Effektivitäts Trial (BASKET) (6), which did not allow protocol-driven angiography, provides additional evidence

that supports this. Thus, protocol-mandated angiography may have biased revascularization against the bare metal stent group through the well-described "oculostenotic" reflex, thereby contributing to an overestimation of benefit with drug-eluting stents.

Third, the clinical relevance of surrogate angiographic outcomes, such as binary restenosis or late lumen loss (a surrogate for neointimal proliferation), which primarily account for the superiority of drug-eluting stents, is unclear. While a mean late loss of 0.17 mm or 0.39 mm reported with drug-eluting stents (2, 3) is an incremental advantage over the late loss of 0.6 mm to 1.2 mm reported with bare metal stents (16, 19), the clinical relevance of this difference is not known. Figure 2 depicts data from the 4 largest randomized drug-eluting stent trials to point out several important facts.

Despite a more than 2-fold difference in late loss with the TAXUS stent (Boston Scientific) compared with the CYPHER stent (Cordis Corp.), rates of restenosis (8.9% vs. 7.9%) and target lesion revascularization (3.0% vs. 4.1%) did not differ. Ellis and colleagues (20) have attributed this to a possible curvilinear relationship between late loss and target lesion revascularization. Late loss of 0.0 mm to 1.0 mm may lie on a relatively flat portion of the curve, with high revascularization rates (>15% to 20%) not expected until late loss values appear on steeper parts of the curve (>1.2 mm to 1.5 mm); these are seldom seen with optimal clinical-grade bare metal stents (16, 19).

A steep gradient (>4-fold difference) in late loss between the ACHIEVE stent (Guidant Corp.) (used in the Drug-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Lesions [DELIVER]) and CYPHER was not associated with substantial differences in major adverse cardiac events (10.3% vs. 7.1%) or target vessel failure (11.9% vs. 8.6%), suggesting a curvilinear relationship between late loss and clinical outcomes as well. These findings highlight a lack of consistent translation of "cosmetic" angiographic benefits to improvement in clinical outcomes.

Bare metal stent late losses of 1.0 mm in SIRIUS and 0.92 mm in TAXUS-IV reflect a mean minimum lumen diameter (postprocedural minimum lumen diameter – late loss) of 1.69 mm and 1.74 mm, respectively, or diameter stenosis ($1 - [\text{minimum lumen diameter}/\text{reference vessel diameter}] \times 100$) of 36% and 35%, respectively. These values are unlikely to be associated with flow-limiting stenosis causing angina or ischemia, which typically occurs at a minimum lumen diameter less than 1.0 mm to 1.5 mm or diameter stenosis greater than 70%. Given the near-normal distribution of late loss with bare metal stents (19), these numbers are difficult to reconcile with the high proportion (>75% to 80%) of revascularizations that were performed because of anginal symptoms in SIRIUS (18) or because of ischemia in TAXUS-IV (3).

Fourth, the revascularization benefit with drug-eluting stents is attenuated in high-risk patients and lesion cohorts (diabetes; the acute coronary syndromes, including ST-seg-

Table 2. Target Vessel Revascularization Rates with Bare Metal Stents in Recent Trials*

Trial, Year Performed (Reference)	Stent Type†	Strut Thickness, μm	Time, mo	Target Vessel Revascularization (Binary In-Segment Restenosis), % (%)
Drug-eluting stent trials				
SIRIUS, 2001 (2)	Bx VELOCITY	140	9	18.9 (36.3)
TAXUS-IV, 2002 (3)	EXPRESS	132	9	12.0 (26.6)
DELIVER, 2003 (5)	MULTI-LINK PENTA	91	9	11.3 (22.4)‡
BASKET, 2004 (6)§	MULTI-LINK VISION	81	6	7.8
TAXUS-V, 2004 (7)§	EXPRESS II	130	9	17.3 (33.9)
Contemporary bare metal stent trials				
EPISTENT, 1997 (8)	PALMAZ-SCHATZ	62	6	8.7
EPISTENT, 1997 (9)	PALMAZ-SCHATZ	62	12	15.2
Stent-PAMI, 1998 (10)	PALMAZ-SCHATZ (heparin-coated)	62	6	7.8
Stent-PAMI, 1998 (11)	PALMAZ-SCHATZ (heparin-coated)	62	12	10.5
CADILLAC, 1999 (12)	MULTI-LINK DUET	91	6	5.2
CADILLAC, 1999 (13)	MULTI-LINK DUET	91	12	7.2
ESPRIT, 2000 (14)	Mixed types		6	8.6
ESPRIT, 2000 (15)	Mixed types		12	8.9
Real-world registry				
RESEARCH, 2002 (16)	Mixed types		6	6.0
			12	10.9

* BASKET = Basel Stent Kosten Effektivitäts Trial; CADILLAC = Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; DELIVER = Drug-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Lesions; EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integridin Trial; RESEARCH = Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital; SIRIUS = Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions; Stent-PAMI = Stent-Primary Angioplasty in Myocardial Infarction; TAXUS = Treatment of De Novo Coronary Disease Using a Single Paclitaxel Eluting Stent.

† All stents are made of stainless steel except MULTI-LINK VISION, which is made of cobalt–chromium. Bx VELOCITY and PALMAZ-SCHATZ are manufactured by Cordis Corp. (Miami Lakes, Florida); EXPRESS and EXPRESS II are manufactured by Boston Scientific (Natick, Massachusetts); and MULTI-LINK PENTA, MULTI-LINK VISION, and MULTI-LINK DUET are manufactured by Guidant Corp. (Santa Clara, California).

‡ Only target lesion revascularization rates are available for DELIVER.

§ BASKET and TAXUS-V used a more complex patient and lesion cohort compared with other drug-eluting stent trials (diabetes, acute coronary syndrome, smaller-diameter vessels, longer lesions, and multiple stenting).

|| Target vessel revascularization rates in EPISTENT and CADILLAC are shown for bare metal stents plus abciximab group.

ment elevation myocardial infarction [MI]; left main disease; bifurcation lesions; smaller-diameter lesions and longer lesions; several stents or overlapping stents; chronic total occlusions; and vein grafts). For example, the risk reduction in target vessel revascularization decreases from 67% in SIRIUS (19.2% to 6.4%) (2) and 60% in TAXUS-IV (12.0% to 4.7%) (3) in non–high-risk cohorts to 41% in BASKET (7.8% to 4.6%) (6) and 30% in TAXUS-V (17.3% to 12.1%) (7) in high-risk cohorts. Similar attenuation of reductions in target lesion revascularization (73% to 45%) and major adverse cardiac events (43% to 29%) is also observed with drug-eluting stents in TAXUS-V compared with TAXUS-IV (Figure 2). Despite these reduced benefits with drug-eluting stents, avoiding repeated procedures or bypass surgery may be clinically worthwhile in high-risk patients.

Finally, disease progression (which may be responsible for more than one third of repeated revascularizations at 1 year and 4 times the number of adverse clinical outcomes beyond the first year compared with clinical restenosis [21]) may substantially mitigate the long-term benefits of drug-eluting stents.

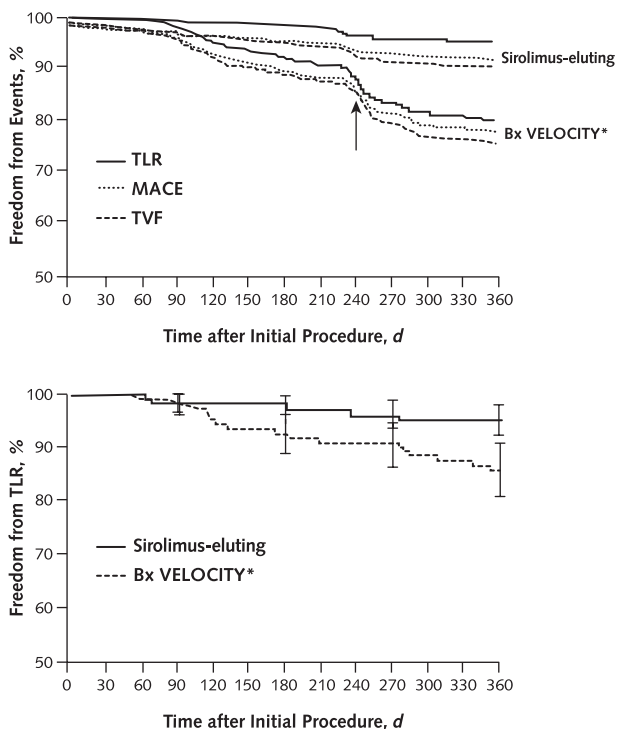
HAVE TRIALS UNDERESTIMATED ADVERSE EVENTS, SUCH AS STENT THROMBOSIS?

Unlike restenosis, thrombosis is a rare but potentially life-threatening complication of coronary stents (22–26).

Stent thrombosis usually occurs before reendothelialization (healing) has been completed. Stent thrombosis rarely occurs (and, therefore, dual antiplatelet therapy is rarely required) beyond 2 to 4 weeks for bare metal stents. Sirolimus- and paclitaxel-eluting stents effectively reduce restenosis by inhibiting neointimal hyperplasia, but they also delay the healing process far beyond the time period usually required with bare metal stents (a potential liability of a nonselective antiproliferative approach to prevent restenosis), thereby warranting prolonged antiplatelet therapy with aspirin and clopidogrel for at least 6 months or, in some cases, for longer or perhaps indefinitely.

In clinical trials, the 9- to 12-month cumulative incidence of stent thrombosis with drug-eluting stents has ranged from 0.4% to 0.6%, which is roughly similar to that with bare metal stents (2, 3). However, these trials, either individually or pooled together, were not adequately powered to detect or exclude rare events, such as stent thrombosis (22, 26). By contrast, the rate has been reported as 2- to 3-fold higher than that in routine clinical practice as mirrored by registry data (6, 23). In a large observational study of drug-eluting stent use in real-world settings, the incidence of stent thrombosis was 1.3% (29 of 2229 cases) at 9 months (23), which is substantially higher than that observed in major trials. Nearly half of the episodes were subacute (<30 days), with 13 cases (45%) re-

Figure 1. Influence of protocol-mandated angiography on target lesion revascularization.



Event-free survival for target lesion revascularization (TLR), major adverse cardiac event (MACE), and target vessel failure (TVF) for patients undergoing protocol-mandated angiography ($n = 850$) in the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial (*top*) and TLR rates in patients without protocol-mandated angiography ($n = 208$) (*bottom*) are shown. Adapted from Holmes et al. (18). *Bx VELOCITY manufactured by Cordis Corp., Miami Lakes, Florida.

sulting in death. The strongest independent predictor of stent thrombosis was premature discontinuation of antiplatelet therapy. A recent report suggested an even higher rate of stent thrombosis (4.5%) associated with more complex bifurcation stenting with the crush technique (24). These findings highlight the increased risk for stent thrombosis associated with drug-eluting stents in more complex lesions and patients than those evaluated in the initial trials, the unacceptably high mortality rate associated with stent thrombosis, and the danger of early discontinuation of antiplatelet therapy.

A 2004 research letter described 4 cases of late stent thrombosis, 2 each with the CYPHER and TAXUS stents, occurring over a year after stent implantation and shortly after discontinuation of antiplatelet therapy (25). All 4 cases resulted in MIs. Similar cases have been reported promptly (4 to 9 days) or several months (8 to 26 months) after discontinuing antiplatelet therapy or even while the patients were receiving stable therapy (26). The estimated incidence of late stent thrombosis with drug-eluting stents was 0.35% to 0.72% (23, 26). Mechanisms of late stent

thrombosis with drug-eluting stents may include delayed reendothelialization and impaired intimal healing, enhanced inflammatory response, and delayed hypersensitivity reaction to polymer coatings (27).

Thus, late stent thrombosis is a rare but potentially life-threatening complication of drug-eluting stents that is especially likely to occur when antiplatelet therapy is discontinued either by accident (nonadherence) or by necessity (elective procedures or surgeries and bleeding episodes). More data are clearly needed to address the optimal duration of antiplatelet therapy, the optimal time of interruption (if at all), and the choice of short-term “bridging” antithrombotic treatment during elective surgical procedures in patients with drug-eluting stents.

HAVE TRIALS OVERRELIED ON “SOFT” RATHER THAN “HARD” CLINICAL OUTCOMES?

Design and evaluation of interventional trials involve combining the “hard” outcomes of death or MI and the “soft” outcome of revascularization into a composite end point commonly called “major adverse cardiac event” or “target vessel failure.” A composite end point improves trial efficiency by overcoming insufficient power and addresses the issue of competing risks where, for example, a patient who has died is no longer at risk for adverse effects. However, for the composite end point to be clinically relevant, its components should be of equal or comparable importance, frequency, and therapeutic responsiveness. This condition is seldom fulfilled.

Thus, in a Bayesian meta-analysis of 11 trials (22), the results predominantly favored drug-eluting stents with respect to the composite end point of death, MI, and target lesion revascularization (odds ratio, 0.42 [95% CI, 0.32 to 0.53]). The most prevalent “soft” component of target lesion revascularization decreased substantially (odds ratio, 0.26 [CI, 0.14 to 0.45]), MI was not very affected (odds ratio, 0.92 [CI, 0.66 to 1.25]), and mortality rate increased, although not statistically significantly, in the drug-eluting stent group (odds ratio, 1.11 [CI, 0.61 to 2.06]).

Utility ranking or weighted schemes may be a viable approach to combining end points of different clinical importance and may provide a solution for overinterpretation of composite end point results (28). For example, death may be given the highest weight of 1.0, followed by an intermediate weight for MI (0.5) and the least weight for revascularization (0.1 to 0.2). **Figure 3** shows the results of a post hoc, weighted end point analysis applied to the pivotal SIRIUS trial. We derived the weights from a brief survey of 40 physicians at our institution. The data show no statistically significant difference between the 2 groups with respect to the weighted composite end point. A sensitivity analysis demonstrates a statistically significant difference in favor of drug-eluting stents only at a revascularization weight of 0.5 or more, that is, only when

revascularization is considered half as important as death—an arguably implausible conjecture.

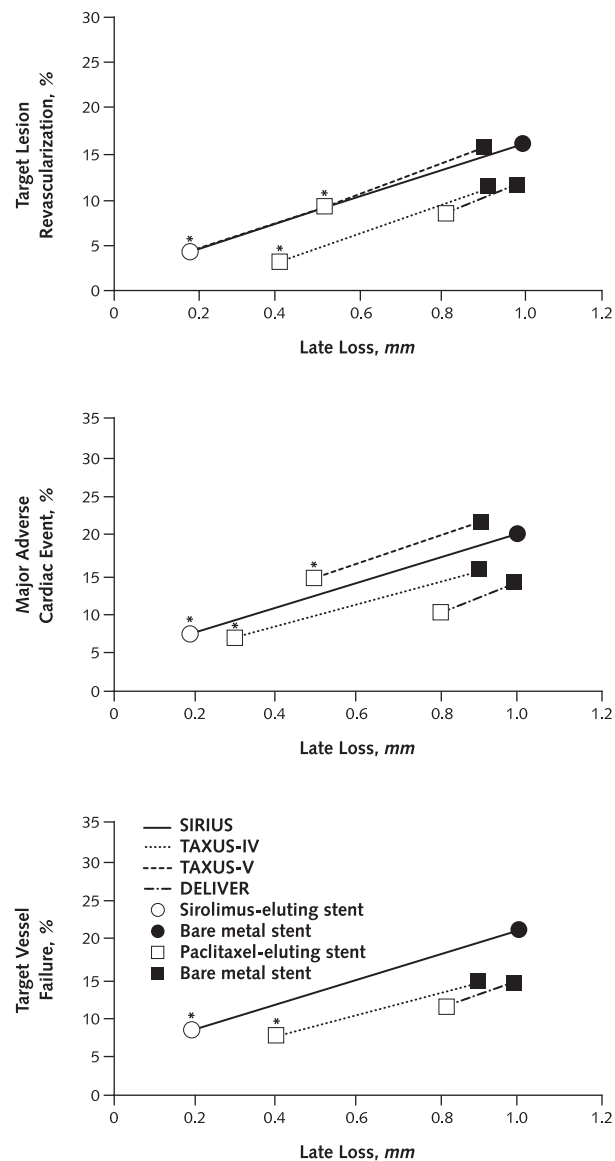
The non-statistically significant but higher mortality and MI rates observed with drug-eluting stents (7, 22) are particularly concerning. This may reflect a chance finding or the increased risk for stent thrombosis inherent to drug-eluting stents. The low frequency of postmortem studies performed in the United States probably precludes an accurate assessment of the overall rate of stent thrombosis as the cause of death, especially sudden death. The 3-year follow-up data recently reported for the SIRIUS trial offer interesting insights (29). Six additional deaths (21 deaths vs. 15 deaths; odds ratio, 1.39 [CI, 0.71 to 2.74]), 4 additional Q-wave MIs (7 Q-wave MIs vs. 3 Q-wave MIs; odds ratio, 2.32 [CI, 0.60 to 9.00]), and 86 fewer target lesion revascularizations (odds ratio, 0.24 [CI, 0.16 to 0.35]) were reported with drug-eluting stents. While the differences in the rates of mortality or Q-wave MIs were not statistically significant, the increased trend nonetheless raises an important question: How many deaths or MIs (stent thrombosis) are we willing to accept in return for a benefit in a relatively benign outcome (restenosis)?

HAVE THE COSTS OF DRUG-ELUTING STENTS BEEN UNDERESTIMATED?

A major impediment to the widespread adoption of drug-eluting stents is cost, which is nearly 3- to 4-fold higher than that of bare metal stents. The cost-effectiveness of drug-eluting stents has been the subject of several studies (6, 30–33). With the exception of 3 independent studies (6, 31, 32), the analyses have generally favored more widespread use of drug-eluting stents. However, most of these studies have been funded by stent manufacturers and have methodologic weaknesses, including interpretive biases due to conflicts of interest with industry (31).

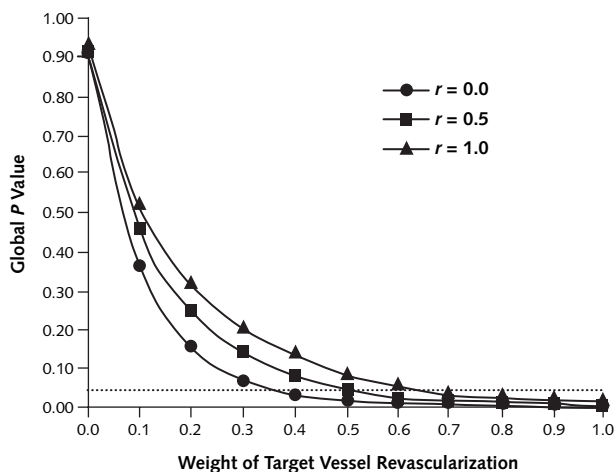
Cohen and colleagues (30) estimated the incremental cost-effectiveness ratio of drug-eluting stents, on the basis of the SIRIUS trial, to be \$27 540 per quality-adjusted life-year (QALY) gained or \$1650 per repeated revascularization avoided (<\$10 000 per repeated revascularization avoided is the generally accepted criterion for incremental cost-effectiveness [33]). They concluded that the use of CYPHER drug-eluting stents was “reasonably cost-effective” but was not cost-saving. This conclusion has several problems. First, extrapolating QALY data from a previous trial of bare metal stents for reperfusion therapy for MI (Stent-PAMI) to the SIRIUS cohort of elective stenting is not clearly applicable. Second, the restenosis benefit and, therefore, the cost-effectiveness of drug-eluting stents in patients who were excluded from SIRIUS (up to 50% of patients undergoing elective stenting, according to the National Heart, Lung, and Blood Institute Dynamic Registry estimates [34]) remain unclear. Third, their model was based on a stent utilization rate of 1.4 per patient (single-vessel procedure), a bare metal stent target vessel revascu-

Figure 2. Relationship between angiographic variables and clinical outcomes.



“Late loss” refers to late lumen loss. Target lesion revascularization (*top*), major adverse cardiac outcomes (*middle*), and target vessel failure (*bottom*) are shown for 4 randomized trials of drug-eluting stents: 1 trial with sirolimus-eluting stent (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions [SIRIUS] [$n = 1058$]) and 3 trials with paclitaxel-eluting stent (Treatment of De Novo Coronary Disease Using a Single Paclitaxel Eluting Stent [TAXUS]-IV [$n = 1314$], TAXUS-V [$n = 1156$], and Drug-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Lesions [DELIVER] [$n = 1041$]). Mean (range) reference vessel diameter and lesion length are as follows: SIRIUS, 2.8 mm (2.5 mm–3.5 mm) \times 14.4 mm (15.0 mm–30.0 mm); TAXUS-IV, 2.75 mm (2.50 mm–3.75 mm) \times 13.4 mm (10.0 mm–28.0 mm); TAXUS-V, 2.69 mm (2.25 mm–4.00 mm) \times 22.9 mm (10.0 mm–46 mm); DELIVER, 2.77 mm (2.50 mm–4.00 mm) \times 11.1 mm (<25.0 mm). The following bare metal stents were used: Bx VELOCITY (Cordis Corp., Miami Lakes, Florida) in SIRIUS; Express (Boston Scientific, Natick, Massachusetts) in TAXUS-IV; Express II (Boston Scientific) in TAXUS-V; and MULTI-LINK PENTA (Guidant Corp., Santa Clara, California) in DELIVER. * $P \leq 0.05$ vs. bare metal stent.

Figure 3. Weighted composite end point analysis for the SIRIUS trial.



P values are derived from a global z statistic under assumptions of perfect ($r = 1.0$), partial ($r = 0.5$), or no ($r = 0$) correlation among the components of the composite end point (28). A sensitivity analysis across a target vessel revascularization weight is also shown (the weight of death and myocardial infarction was fixed at 1.0 and 0.5, respectively). Only target vessel revascularization weights ≥ 0.5 achieve statistical significance ($P \leq 0.05$) (values below dotted line). SIRIUS = Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions.

larization rate of 14%, and a projected 80% reduction in target vessel revascularization by drug-eluting stent (30, 33). These values exceed the contemporary interventional practice estimates by nearly 50%, as demonstrated in BASKET (6). In this first and only prospective randomized trial assessing the cost-effectiveness of open-label drug-eluting stent use in a routine clinical practice setting, BASKET found that an average of 1.9 stents were used per patient, the target vessel revascularization rate in the bare metal stent group was 7.8%, and the target vessel revascularization reduction rate with drug-eluting stents was only 41% (from 7.8% to 4.6%; $P = 0.08$). The trial reported an incremental cost-effectiveness ratio of \$32 149 per major adverse event avoided and a cost of more than \$95 828 to \$128 744 per QALY gained (6). A major limitation, however, was that the cost savings secondary to avoidance of bypass surgery, repeated clinic visits, stress testing, and avoidance of complications from repeated procedures were not captured in BASKET. Nonetheless, underestimation of the stent utilization rate (which is expected to increase even further with migration to multilesion and multivessel stenting), together with overestimation of the control bare metal stent revascularization rate and overestimation of the reduction in revascularization by drug-eluting stents, may amplify the cost-effectiveness of drug-eluting stents (31). Finally, consideration of cost associated with long-term antiplatelet therapy (averaging at least \$1000 annually) for preventing late stent thrombosis may further reduce the cost-effectiveness of drug-eluting stents. The optimal dura-

tion of such therapy is currently unknown. Thus, extrapolation of cost-effectiveness from clinical trial data to clinical practice remains uncertain.

From these data, we conclude that a strategy of ubiquitous substitution of bare metal stents with drug-eluting stents is not cost-worthy. The clinical and economic consequences of inappropriate application of drug-eluting stents are not trivial. One can reasonably argue (on the basis of BASKET data of utilization of 2 stents per patient, a 6-month target vessel revascularization difference of 3.2 percentage points, and a stent cost differential of \$1600 to \$2000) that spending \$3.2 million to \$4.0 million (\$1600 to \$2000 \times 2 \times 1000) to prevent 32 repeated revascularizations per 1000 patients, representing an incremental cost-effectiveness ratio of \$100 000 to \$125 000 per repeated revascularization avoided, may not be a good value for the money. The most acceptable strategy now seems to be selective initial use of drug-eluting stents in patients who are at high risk for restenosis (<20% of stent-eligible patients) (31–33), provisional (“bailout”) use in those who present with clinical restenosis after bare metal stents (<10% to 15% of patients), and strict avoidance in those who cannot or are unlikely to adhere to long-term dual antiplatelet therapy. This restricted strategy is judicious, evidence-based, and fiscally responsible.

SUMMARY AND CONCLUSIONS

Drug-eluting stents are a quantum advance in interventional cardiology, rivaling the impact of angioplasty and stenting. However, in a rush to judgment, drug-eluting stents are now being used in patients and lesion types beyond those evaluated by randomized trials, prompting a concern that the enthusiasm may be exceeding the evidence. Our analysis of the clinical trial and registry data suggest tempering the initial enthusiasm with cautious optimism. Drug-eluting stents show promise in reducing angiographic and clinical restenosis, but they do not confer any benefit in hard clinical outcomes and may even predispose to stent thrombosis, a rare but potentially life-threatening adverse outcome. Other potential issues, such as drug-loading capacity, drug-release pharmacokinetics, polymer durability and biocompatibility, malapposition, wall thinning, aneurysm formation, and delayed restenosis, are beyond the scope of our analysis.

In conclusion, it makes little clinical, economic, or common sense to forsake a therapy that works well for most patients (bare metal stent) in favor of a costly new therapy (drug-eluting stent) that has no effect on important clinical outcomes but increases the risk for stent thrombosis, a life-threatening complication. Thus, drug-eluting stents symbolize a double-edged sword for cutting the Gordian knot of restenosis.

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