Hippocrates Revisited

The Evidence for Drug-Eluting Stents

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As to diseases, make a habit of two things—to help, or at least do no harm.

—Hippocrates, in The Epidemics

Evidence-based medicine provides proof of efficacy (“to help”) and defines the risk-benefit relationship (“do no harm”) for specific therapeutic intervention. Guidelines provide an algorithm by which evidence-based medicine is incorporated into clinical practice. The cornerstone of evidence-based medicine is the randomized controlled clinical trial. On the basis of carefully constructed and well-executed randomized trials, the US Food and Drug Administration (FDA) has recently approved and released the Cypher sirolimus-eluting Bx VELOCITY coronary stent (Cordis, a Johnson and Johnson Company). Other drug-eluting coronary stent prostheses are currently under investigation. Because of its cost, the clinical benefit demonstrated for Cypher (versus uncoated Bx VELOCITY stents) has been scrutinized. The present cost of Cypher ($3195) is at least 3 times that for a new-generation non–drug-eluting stent (DES) and is not borne by a proportional increment in reimbursement. The average incremental reimbursement provided by the Center for Medicare and Medicaid Services for diagnosis-related group 527 (percutaneous cardiovascular procedure with DES, without acute myocardial infarction) is $1800 (geographically weighted). In societies in which patients are responsible for the large portion of cost increment related to a new technology, utilization of the Cypher stent has been limited. For example, 1 year after the release of Cypher in Europe (April 15, 2002), utilization remains ≤12% of all coronary stent devices. In the United States, we now find ourselves with an expensive new technology and a limited evidence base from which to determine its optimal use.

In the present issue of Circulation, Drs O’Neill and Leon1 and Drs Lemos, Serruys, and Sousa,2 who have pioneered the clinical development of DES, offer their expert opinions on both the merits and the limitations of DES and provide tentative recommendations for their use.

“To Help”

The Cypher stent provides marked clinical benefit by reducing restenosis related to stent deployment. Although more preliminary, the data from trials of a polymer-based paclitaxel-eluting stent (TAXUS; Boston Scientific Corp) suggest similar benefit. However, all DES are not equal. Clinical development has ceased for several DES found not to reduce restenosis during initial clinical trials. Has the “Achilles heel of angioplasty finally been conquered,” as suggested by the introductory comments of O’Neill and Leon1? Or, rhetorically, “Is in-stent restenosis really so bad?” as asked by Lemos et al.2 The truth lies somewhere in between.

First, acknowledging the clinical and angiographic complexity of the patient cohorts evaluated by randomized trials to date, restenosis after Cypher stent deployment has been observed in up to 9% of all patients, 18% of all diabetic patients (35% of insulin-dependent diabetics), and 16% of patients with small-caliber target vessels.3 Furthermore, the restenotic process has not killed anyone. As pointed out by Lemos et al,2 no differences in the incidence of death or nonfatal myocardial infarction was observed in the SIRollimUS-eluting Cypher balloon-expandable stent (SIRIUS) trial (n=1102 patients) and the TAXUS II (n=536 patients) trial of polymer-based paclitaxel elution. A more recent presentation from the...
Europe- (E) SIRIUS randomized trial (n=352 patients) of the Cypher stent (versus uncoated Bx VELOCITY) confirms the absence of differences in death or nonfatal myocardial infarction (J. Schofer, personal communication, March 24, 2003). In the classic hierarchical definition of major adverse cardiovascular events, only the relatively “soft” end points of restenosis (angiographic) and target lesion/vessel revascularization (clinical) have been positively influenced by DES. At what cost is this benefit accomplished? Lemos et al suggest that competition in the marketplace when multiple DES devices are available will drive down the current cost. In the near term, however, the projections by O’Neill and Leon1 for the William Beaumont Hospital ($3.8 million loss with 1.43 stents per patient and only 50% DES utilization) are sobering. These numbers are strikingly similar to those of our own program, The Christ Hospital, Health Alliance of Greater Cincinnati, and thus are likely extrapolatable to most large-volume centers in the United States.

With the assumptions of no incremental stent usage (1.6 stents per patient), reimbursement equal to Center for Medicare and Medicaid Services diagnosis-related group 527 from all payors, and 50% DES utilization, the projected net loss during year 1 after DES availability is $3 041 313. As detailed by O’Neill and Leon,1 the “triple whammy” faced by hospitals includes the additional loss of downstream revenues obtained from repeat revascularization procedures (both percutaneous and surgical) as well as a reduction in elective coronary bypass procedures. These “cost offsets” are enjoyed by payors and patients, not by hospitals or physicians. Moreover, traditional pharmacoeconomic and cost efficacy models have focused on cost per life-year saved or gained. A benchmark precedent threshold for cost efficacy established by US law has been renal dialysis ($50 000/life-year gained). Interventions that cost $≤50 000/life-year gained are considered cost effective, and those costing $≥20,000 are “highly cost effective.” In the absence of lives saved, softer clinical end point analyses for quality of life and individual productivity are used in support of DES.

“At Least Do No Harm”

Despite approval and release of Cypher, the available data from randomized controlled trials are limited. The question is posed succinctly by Drs O’Neill and Leon,1 as follows: “Should standard practice patterns undergo marked immediate changes when fewer than 2000 patients have been studied in 3 clinical trials?” A member of the FDA panel, Mitchell Krucoff, MD, asked a similar question during the panel proceedings on Cypher.6 “What is the β error for a 1000-patient randomized study (SIRIUS)? Could we miss a 1% adverse outcome?” Are these concerns valid? With follow-up now available to 3 years from the first-in-man trial, 2 years from the RAndomized double-blind study with the sirolimus-eluting Bx VELOCITY balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (RAVEL) trial, and 1 year from SIRIUS, concerns regarding the clinical significance of an observed increased frequency of late stent strut malapposition have abated. Similarly, late aneurysm formation, edge restenosis or “catch-up” late lumen loss have not been observed. The relative benefit of Cypher (versus uncoated Bx VELOCITY) in the patient population studied is durable. Recently, 8-month angiographic and 9-month clinical follow-up has been presented from the E-SIRIUS trial, which enrolled a more complex cohort of patients who were randomly assigned to receive either the uncoated Bx VELOCITY stent or the Cypher stent. When compared with SIRIUS, patients enrolled in E-SIRIUS were more often smokers with a history of prior myocardial infarction who had smaller reference vessel diameter and longer target lesion lengths that required the deployment of multiple stents more frequently. Despite the apparent increment in complexity, binary restenosis at 8 months and target vessel revascularization at 9 months were reduced in the Cypher-treated patients by 86% and 81%, respectively.

What limitations remain in the evidence-based support for DES? First, in the randomized trials to date, only E-SIRIUS has allowed direct stenting, and none have permitted the use of atheroablative technologies before Cypher deployment. Hence, Cypher coronary stenting is currently contraindicated in “patients judged to have a lesion which prevents complete inflation of an angioplasty balloon.” Second, the use of ≥2 Cypher stents in the same patient has “not received adequate clinical evaluation. Use of more than 2 Cypher stents will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies.” As sirolimus is a metabolic substrate for the cytochrome p450 (CYP3A4) enzyme, the potential for drug-drug interactions may be enhanced by multiple stents. Thus, coadministered drugs that may increase sirolimus blood concentrations include calcium channel blockers, antifungal agents, macrolide antibiotics, cimetidine, danazol, and others. The effect of more elevated sirolimus levels due to multiple stents and drug-drug interactions on the metabolism of medications (eg, atorvastatin or clopidogrel) that utilize the CYP3A4 metabolic pathway is unknown. The potential for sirolimus to antagonize the conversion of clopidogrel to its active moieties and thus diminish the platelet-inhibitory effects of clopidogrel is clear. The safety and efficacy of Cypher in patients with prior brachytherapy to the target lesion has not been established. Furthermore, brachytherapy for restenosis after Cypher stent deployment has not been evaluated. Does brachytherapy alter the polymer coat in an adverse manner? Despite efficiency of the process, current manufacturers of DES prostheses have avoided use of ionizing radiation for batch device sterilization in part because of concerns regarding polymer degradation. Similarly, the safety and efficacy of Cypher for the treatment of diffuse in-stent restenosis is unclear. Lastly, the relative safety and efficacy of Cypher (versus non-DES) for the treatment of thrombus-containing coronary lesions (including acute myocardial infarction), ostial or bifurcation lesions, saphenous vein bypass graft...
lesions, and vessels <2.5 or >3.5 mm in diameter has not been established. 7

The recommended guidelines for current use of Cypher as proposed by Drs O’Neill and Leon 1 are both thoughtful and progressive based on evidence from randomized controlled trials. Indeed, the Class IIa recommendation for ostial or protected left main lesions as well as parent vessel bifurcation lesions with balloon angioplasty of the side branch may be viewed in the context of available Class IIa guideline recommendations proposed by the American College of Cardiology/American Heart Association Task Force Committee for the treatment of unstable angina and non-ST-segment-elevation myocardial infarction. 8 Platelet glycoprotein IIb/IIIa inhibitors are given a Class IIa recommendation for high-risk patients “in whom an invasive management strategy is not planned” (level of evidence A) and for patients “in whom catheterization and percutaneous coronary intervention are planned.” This recommendation is based on data from >31 000 patients enrolled into randomized clinical trials. Similarly, enoxaparin has received a Class IIa recommendation as being “preferable to unfractionated heparin as an anticoagulant in patients with unstable angina.” This specific recommendation for enoxaparin is based on >7000 patients enrolled into randomized clinical trials in comparison with unfractionated heparin. Furthermore, the hierarchical clinical endpoint reduced by both glycoprotein IIb/IIIa blockade and enoxaparin has been the composite occurrence of death or myocardial infarction in follow-up.

Clearly, the present “guideline for use of DES” proposed by Drs O’Neill and Leon 1 is a guideline in evolution and will require periodic revision based on results of ongoing clinical trials and registries. Our present obligations to our patients are both to provide the best evidence-based therapies and to continuously update our knowledge base in this rapidly evolving field.

References

4. Deleted in proof.