Drug-Eluting Stents
Costs Versus Clinical Benefit
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Since the advent of coronary angioplasty in 1977, the procedure has changed from an uncommonly used method of treating simple discrete lesions to one that challenges surgical revascularization. Step by step, major anatomic obstacles have fallen as this procedure has been applied to an expanding patient population. Technical breakthroughs including steerable and movable guidewires, low-profile balloon shafts, atherectomy devices, and ultimately stent implantation have made percutaneous coronary intervention (PCI) more successful, safer, and more durable. Unfortunately, 2 major obstacles have limited PCI: these are chronic total occlusions and restenosis. The year 2002 will be remembered as the year in which one of these remaining obstacles fell. The recent publication of the RAVEL study (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) and the presentation of the SIRIUS (a multicenter randomized double-blind study of the SIRolImUS-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions) and TAXUS II studies provide optimism that the “Achilles heel of angioplasty” has finally been conquered. As we embark on this new era of PCI, all clinicians are grappling with which patients and lesions are most appropriately treated using these effective and expensive new stents. We will attempt to briefly review the initial clinical data and formulate guidelines for rational use of drug-eluting stents (DES) that would be relevant to clinical practice in the immediate future.

Anatomy of a DES
A DES is an advanced biotechnology platform consisting of a 3-component system, as follows: (1) a stent with catheter-based deployment and optimized features for enhanced deliverability to the lesion site, (2) a drug-carrier vehicle that permits elution of the drug or biologic into the vessel wall at the required concentrations and kinetic profile, and (3) a pharmacological agent possessing specific properties that interfere with local neointimal formation. Most DES systems utilize current-generation commercial stents and delivery systems. In the near future, stent design features and balloon catheter delivery systems will be importantly modified to accommodate the specialized needs of homogeneous site-specific drug delivery into the subjacent vessel wall. The spectrum of drug-carrier vehicles ranges from known biocompatible polymers to multiple innovative newly engineered modalities, including biomimicry with phosphorylcholine coverings and nanoporous ceramics. Most importantly, the drug carrier should not significantly alter the mechanical and deliverability characteristics of the stent and should facilitate precise drug delivery without inducing independent pathobiological effects such as inflammation or thrombosis. Several different classes of pharmacological agents are being closely scrutinized, starting with cell culture studies, progressing to porcine coronary models, and culminating in phase I safety, first-in-human clinical experiences. The drug classes can be divided into antiproliferative agents, anti-inflammatory (or immunomodulating) agents, antimigratory agents that affect extracellular matrix properties, and prohealing agents that encourage more rapid endothelializa-
tion of the injured vessel wall. Many of the more exciting agents have multifunctional properties, influencing several components of the pathophysiologic cascade leading to restenosis. Second- and third-generation drug systems are also being explored favoring multidrug approaches and either disease state-specific or lesion-specific targets (eg, diabetes).

The clinical imperatives that drive DES development efforts require a substantial (>50%) reduction in restenosis (both angiographic end points and the clinical surrogate end points, such as target lesion revascularization) in all patient cohorts and lesion subsets. At the same time, DES therapies must be completely safe relative to bare metal stents, without early or late thrombosis, late aneurysms, hyperproliferative effects, or late “catch-up” phenomena (ie, delayed restenosis). Finally, the DES system must be user friendly, with facilitated entry into a catheterization laboratory milieu and without logistic deterrents (eg, shelf-life limitations). Undoubtedly, the rigorous standards imposed on present DES systems will result in many failures, either in the preclinical experimental phase of testing or in early proof-of-concept clinical trials. A successful DES system, after completion of the Food and Drug Administration approval pathway, will be a strikingly efficacious, safe, and practical multicomponent drug-device combination that provides enormous clinical benefit to patients with coronary artery disease.

**Major Clinical Trials**

Initial first-in-human clinical experience with the sirolimus-eluting stent (Cypher, Cordis Corp) was obtained in Sao Paolo, Brazil, and Rotterdam, the Netherlands. These small pilot studies demonstrated an astonishing reduction in restenosis, based on angiographic and intravascular ultrasound assessments, with durability of the results for up to 2 years after the initial procedure. Thereafter, a double-blind multicenter randomized trial (RAVEL) in 238 patients corroborated these early observations with a reduction in angiographic binary restenosis at 6 months follow-up from 26% in the bare metal stent control to 0% in the sirolimus-eluting stent group. Importantly, there were no significant angiographic or clinical complications associated with the sirolimus-eluting stent; thus, patient safety was not sacrificed to achieve this profound reduction in restenosis frequency. The RAVEL patient cohort represented a relatively simple lesion substrate—focal native coronary lesions in vessels 2.5 to 3.5 mm in diameter, covered by a single 18-mm-long stent.

Therefore, the RAVEL outcomes are difficult to extrapolate to more complex lesion subsets, including ostial lesions, bifurcations, chronic total occlusions, acute myocardial infarction (MI) lesions, saphenous vein graft lesions, and diffuse disease.

More recently, a large US multicenter (53 sites), phase III, double-blind study (SIRIUS) has been completed, randomizing 1101 patients to either bare metal control stents or sirolimus-eluting stents. Patients and lesions were more complex in SIRIUS, including more cardiac risk factors (especially diabetes), longer lesions (15 to 30 mm), and frequent overlapping stents (28% of patients). Angiographic restenosis at 8 months was reduced by 75% in the sirolimus treatment group ($P<0.001$), and the primary end point, target vessel failure at 9 months, was similarly reduced by 59% ($P<0.001$). Stent thrombosis, major clinical events (death and MI), and aneurysms were similar in the 2 treatment groups. Again, although the lesions were somewhat more complex than those in RAVEL, many lesion subgroups were still excluded from SIRIUS, making generalizations to the overall “real-world” PCI population problematic.

Finally, the TAXUS II randomized double-blind trial, utilizing paclitaxel incorporated within an encapsulating polymer over a stent (NIRx Conformer, Boston Scientific), has also recently been completed. Two sequential randomized studies, testing first the slow-release and then the moderate-release formulations, were compared with control bare metal stents. A total of 536 patients were randomized, and the primary end point, in-stent percentage volume obstruction assessed by intravascular ultrasound at 6 months, was reduced by 60% ($P<0.001$) in the paclitaxel-treated patients. There appeared to be no significant differences in objective outcomes between the slow- and the moderate-release paclitaxel formulations, and there were no important angiographic or clinical complications that could be attributed to the paclitaxel treatment arms.

In aggregate, these studies clearly demonstrate that intimal hyperplasia within a stent can be virtually eliminated by integrating commercially available stents with nonreactive polymer drug carriers that contain appropriate doses of potent antiproliferative and immunomodulating drugs. Although potential safety issues still must be clarified in more complex patients and lesions, thus far, there have been infrequent untoward clinical consequences. Based on the aforementioned studies and on the unanimous approval recommendation by the Food and Drug Administration (FDA) advisory panel on October 22, 2002, commercial access of the sirolimus-eluting stent to the US interventional community occurred in May, 2003. Clinicians are now faced with the important challenge of properly selecting lesions and patients to apply this new breakthrough technology.

**Coping With DES Euphoria**

Given the dramatic reduction in restenosis observed in these major clinical trials, rapid and widespread adoption of DES is anticipated in the United States. Would this exuberance be “irrational” or scientifically and economically justified? Should standard practice patterns undergo marked immediate changes when fewer than 2000 patients have been studied in 3 clinical trials? This controversial question has engendered heated debate among clinical practitioners, hospital administrators, and healthcare economists. Admittedly, a 70% reduction in restenosis frequency, especially among our most challenging patient and lesion cohorts (eg, those with diabetes or diffuse disease), represents an important advance in the
management of patients with symptomatic ischemic heart disease. Reduced recurrent symptoms, reduced repeat hospitalizations, and reduced repeat PCI procedures constitute worthwhile forward steps in establishing catheter-based coronary intervention as a long-lasting and durable procedure. Some would argue that DES are potentially a “disruptive” technology, in that the full impact will extend beyond interventional cardiology—affecting the practice of medical treatment of coronary disease, surgical revascularization procedures, and the general management of all vascular disease states.

The counterarguments fall into 3 categories as follows: (1) long-term safety and efficacy of DES, (2) the extrapolation of restrictive clinical trial results to literally all patient populations, and (3) the financial implications of this very costly technology. In perspective, it is important to note that restenosis has long been considered a “soft” noncatastrophic clinical end point, and preventing restenosis will likely not change patient survival or prevent major MIs. In both the Bypass Angiography Revascularization Investigation (BARI) and the Emory Angioplasty versus Surgery Trial (EAST), long-term survival was similar for the percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft groups, even though repeat revascularization was much higher for percutaneous transluminal coronary angiography. Although initial safety reports with DES are encouraging, there are very limited long-term data, and lingering questions remain. Late thrombosis has been reported in patients treated with complex in-stent restenosis lesions. The frequency and clinical importance of incomplete stent apposition (by intravascular ultrasound), due to vessel wall remodeling and possibly resulting in late aneurysm formation, must be resolved. The occurrence of delayed restenosis (beyond the traditional 6-month time frame) must be evaluated in more patient subgroups by angiographic follow-up studies.

Unfortunately, the initial euphoria stimulated by the remarkable results from RAVEL has not been sustained in subsequent studies involving more complex lesions. Absolute restenosis rates with DES have been higher in diabetics and in small vessels, in-stent restenosis lesions, and bifurcation lesions. Moreover, we have only anecdotal reports in saphenous vein graft lesions, left main coronary artery disease, heavily calcified lesions, total occlusions, acute MI and other thrombus-containing lesions, and vascular brachytherapy failures.

Most assuredly, the principal driver of controversy in this debate centers on health economic issues. The DES systems are projected to cost between $2000 and $3000 per device, which will dramatically skyrocket in-hospital procedural equipment costs, thus threatening the economic viability of interventional cardiology programs. At William Beaumont Hospital, the following assumptions were used in an economic model for the fiscal year 2003 budget: (1) April 2003 commercial availability, (2) stent availability in 2.5- to 4.0-mm diameters, (3) 1.43 stents per case (current usage), (4) diagnosis-related group revenue increase of $1800 US for DES codes, (5) 10% reduction in surgical volume, and (6) 50% reduction in coronary restenosis interventions. Assuming a cost of $3500 US per stent and 50% usage, the hospital will lose $3.8 million with this transition. If DES usage approaches 70% or 80%, costs will escalate proportionately. Although patients and insurance carriers benefit by having fewer repeat interventions and fewer bypass operations, hospitals face a “triple whammy.” Fewer repeat procedures and fewer bypass operations will cause less revenue to be generated, and the higher DES cost will cause enormous increases in supply costs. Until a more comfortable equilibrium is established between costs and reimbursement, cogent arguments have been forwarded suggesting more restricted use of DES, even to the point of strict rationing. Clearly, these very real economic concerns are the immediate “dark side” of DES euphoria. In fact, the slow acceptance of these stents in Europe is overwhelmingly related to the prohibitively high cost.

### Guidelines and Recommendations

To alleviate the confusion and anxiety associated with widely varying and physician-dependent or hospital-mandated decisions regarding DES use, some general guidelines for indications for use may be helpful. The American College of Cardiology/American Heart Association Task Force on Practice Guidelines has published such recommendations since the 1980s. Using this format, an initial attempt at formulating indications for DES is presented in the Table. Class I indications are obtained from the inclusion criteria of the 3 randomized clinical trials. Classes II and III are derived from subgroup analyses of these trials and from soon-to-be-

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**Recommended Guidelines for DES**

<table>
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<th>Class</th>
<th>Condition</th>
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| I     | 1. Lesions 15 to 30 mm in length and 2.5 to 3.5 mm in diameter, with 50% to 99% obstruction preprocedure*  
2. Diabetes†  
3. Lesions <15 mm in length and 2.5 to 3.5 mm in diameter† |
| IIa   | 1. Ostial RCA, LAD, LCX, or protected left main lesions‡  
2. Parent vessel bifurcation lesion with PTCA of side branch |
| IIb   | 1. Recanalized CTO  
2. Lesions >30 mm in length and 2.5 to 3.5 mm in diameter  
3. In-stent restenosis—focal pattern  
3. Unprotected left main lesions |
| III   | 1. SVBG disease  
2. In-stent restenosis—diffuse pattern |

RCA indicates right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PTCA, percutaneous transluminal coronary angiography; CTO, chronic total occlusion; and SVBG, saphenous vein bypass graft.

*Level of evidence A, entry criteria for SIRIUS, RAVEL, and TAXUS II trials.  
†Level of evidence B.  
‡In 2003, registry data from the Guidant Corp Randomized Paclitaxel-Coated Stent trial (DELIVER II) and the SIRIUS studies will be available.
published registries. Evidence level A is derived from multiple randomized trials, and level B is from single randomized trials or registries. Special consideration should be given to diabetic patients. Angioplasty and stent implantation are known to be associated with more restenosis, more late occlusions, and worse mortality. Thus, the profound risk reduction of restenosis in subgroup analysis of diabetics treated with DES mandates special consideration for these patients. It must be emphasized that only relatively small numbers of diabetic patients and even fewer insulin-treated diabetics have been studied. Furthermore, although restenosis is significantly decreased compared with bare metal stents, absolute levels of restenosis of >20% may still occur. Because many trials are completed but unpublished, these criteria may dramatically evolve over the next year.

In summary, DES promise to revolutionize the field of interventional cardiology. It is incumbent on industry to sponsor clinical trials that address the gaps in safety and efficacy. It is incumbent on investigators to conduct rigorous, properly designed, and adequately powered studies to address gaps in knowledge. And, most important, it is incumbent on clinicians to carefully weigh the evidence to judiciously apply this new technology in the best interests of our patients.

References
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