Sirolimus-Eluting Cypher Stent

A standard of comparison for drug-eluting stents.

BY COLIN M. BARKER, MD, AND DAVID E. KANDZARI, MD

Compared with bare-metal stents (BMS) in randomized clinical trials, treatment with drug-eluting stents (DES) is associated with statistically significant and clinically meaningful reductions in angiographic restenosis, as well as the need for repeat revascularization. Across varied trial designs, ranging from randomized trials with more restrictive enrollment criteria to observational studies evaluating outcomes in less controlled and more complex cohorts, the consistent benefit of DES observed in clinical trials has enabled clinicians to safely and routinely extend the use of DES to a broader percutaneous coronary intervention (PCI) population (Figure 1).

BACKGROUND

Since the initial approval in April 2003 by the Food and Drug Administration (FDA) for the use of the sirolimus-eluting Cypher stent (Cordis Corporation, Warren, NJ) as part of treatment for coronary artery disease, physicians have extended the use of DES to patient and lesion complexities beyond those studied selectively in early pivotal, randomized trials. In many instances, decisions regarding DES treatment exceeded the supportive evidence for a specific indication and instead were based on extrapolations of the treatment effect of DES in other clinical settings, consistent positive reports from subgroup analyses of subsequent trials, and shared anecdotal experience. Application of DES in this context of patient care beyond the studied (and approved) indications was termed off-label, yet represented at least 60% of clinical practice patterns in contemporary PCI.

In parallel with the increasing use of sirolimus- and paclitaxel-eluting stents emerged a concern that this newly adopted therapy may be associated with an infrequent but higher incidence of late-stent thrombosis, and possibly increased rates of myocardial infarction (MI) and death. Although the pivotal trials evaluating DES were not statistically powered to identify differ-
ences between DES and BMS, the observation that stent thrombosis, in particular late-stent thrombosis, was uniformly associated with death and/or MI4,7-12 prompted caution from both clinicians and regulators, leading to an overall decline in the use of DES. Because of these safety concerns, the FDA convened an expert advisory panel in December 2006, concluding that, although approved DES were associated with a small but measurable increase in stent thrombosis compared with BMS, “the concerns about thrombosis do not outweigh the benefits [of drug-eluting stents].”2 In addition, the panel also agreed that, due to safety concerns, the DES labels should state that when such stents are used in off-label indications, patient outcomes may not be the same as those observed in the more narrowed patient populations of randomized trials used for approval, stating that in off-label use, “the safety and effectiveness of DES as compared with those of alternative treatments deserve continued study.”2 Accordingly, evidence-based conclusions regarding DES safety and efficacy must be derived from well-designed trials performed on large study populations, a broad array of patient and lesion complexities, and with systematic long-term follow-up.

Despite the benefit of DES in reducing the need for repeat revascularization, continued concern has persisted whether this benefit is outweighed by a higher risk of late-stent thrombosis. Furthermore, uncertainty has been raised regarding the relative efficacy of DES in real-world practice, given that differences in the need for repeat revascularization between DES and BMS may be lessened in the absence of protocol-specified angiographic surveillance.3,13,14 As patient and lesion complexity increase, differences in outcome between DES may also become more apparent, refuting a “class effect” among approved DES.15 Accordingly, more recent investigations have focused on evaluating long-term outcomes after DES treatment in population-based studies involving large-study cohorts of appropriate size to examine potential differences in low-frequency events, including death, MI, and stent thrombosis. Investigations have also included re-examinations of patient level data from pivotal, approval-based randomized trials with BMS,3,4,14,16 industry and independently supported observational studies,6,17,18 and randomized comparisons among differing DES.19-22 To this purpose, it is notable that the sirolimus-eluting Cypher stent remains the most extensively evaluated DES across varied trial designs, among broad and diverse patient populations, and for the longest duration of follow-up.

**CLINICAL TRIALS COMPARING THE CYPHER STENT WITH BMS AND ALTERNATIVE DES**

Several large, multicenter, randomized trials have established the long-term safety and efficacy of the Cypher stent compared with BMS across wide-ranging lesion complexities and clinical indications. In a pooled analysis of the RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS trials (N=1,748) comparing the Cypher stent with bare-

Figure 2. In a systematic overview of 14 randomized trials comparing Cypher and BMS, treatment with Cypher was associated with a significant reduction in the composite clinical endpoint of death, MI, or need for reintervention. (Adapted from Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007;356:1030-1039.14)

“As patient and lesion complexity increase, differences in outcome between DES may also become more apparent, refuting a ‘class effect’ . . .”
metal stents through 5-year follow-up, treatment with sirolimus-eluting stents was associated with similar rates of death (8.9% Cypher vs 8.2% BMS; \(P = 0.57\)) and MI (7.9% Cypher vs 6.8% BMS; \(P = 0.44\)) against the background of a sustained and significant reduction in the need for repeat target lesion revascularization (TLR) (9.8% Cypher vs 23.9% BMS; \(P < 0.0001\)). Overall stent thrombosis rates, according to the Academic Research Consortium definition of definite and probable events, were nearly identical in the Cypher and BMS cohorts, with event rates of 2% and 2.1%  
\(P = 0.99\), respectively. Thus, regarding on-label use, and in comparison with BMS, these data reaffirm the durable efficacy and favorable safety profile associated with the Cypher stent and over the longest duration of comparative DES and BMS evaluation.

Similarly, the long-term safety and efficacy of sirolimus-eluting stents have also been demonstrated in off-label indications representing higher-risk clinical settings and lesion complexities. In a systematic overview of 14 randomized trials comparing Cypher and BMS, the overall risk of death (hazard ratio [HR], 1.03; 95% confidence interval [CI], 0.8–1.3) and the combined risk of death or MI (HR, 0.97; 95% CI, 0.81–1.16) did not statistically vary between patient groups. Stent thrombosis, evaluated through a follow-up duration ranging from 1 to 5 years, was also similar between Cypher and BMS cohorts (HR, 1.09; 95% CI, 0.64–1.86; \(P = 0.75\)). In addition, comparable to the relative benefit of Cypher to BMS in on-label use, treatment with Cypher was associated with a significant reduction in the composite clinical endpoint of death, MI, or need for reintervention (HR, 0.43; 95% CI, 0.34–0.54; \(P < 0.001\)) (Figure 2). A subsequent patient-level analysis of the 13 off-label randomized trials included in this analysis also showed no significant differences or trends for increased stent thrombosis (0.88; 95% CI, 0.51–1.52) or death (0.97; 95% CI, 0.7–1.33) between the Cypher and BMS.

Favorable late clinical outcomes with the Cypher stent have also been recently demonstrated in the most comprehensive meta-analysis to date of randomized trials comparing sirolimus-eluting (Cypher), paclitaxel-eluting (Taxus, Boston Scientific Corporation, Natick, MA), and BMS. Representing 38 randomized trials (N=18,023) with follow-up extending to 4 years, this analysis demonstrated similar rates of survival for all three stent groups, yet an approximate 20% relative reduction in MI with the Cypher stent (vs BMS, HR, 0.81; 95% CI, 0.66–0.97; \(P = 0.03\); vs Taxus stent, HR, 0.83; 95% CI, 0.71–1; \(P = 0.45\)). Overall, there were no significant differences in the risk of definite stent thrombosis through 4-year follow-up for either DES relative to BMS, although the risk of definite late-stent thrombosis (\(>30\) days to 4 years) was significantly higher with the Taxus stent compared with bare-metal and Cypher-stent patient groups (vs BMS, HR, 2.11; 95% CI, 1.19–4.23; \(P = 0.017\); vs Cypher stent, HR, 1.85; 95% CI, 1.02–3.85; \(P = 0.041\)) (Figure 3). Similar differences in the occurrence of stent thrombosis between sirolimus- and paclitaxel-eluting stents have been reported in a recent meta-analysis of randomized trials, in addition to observational registries. Furthermore, although rates of repeat TLR were significantly lower for both DES relative to BMS in the Swiss Collaborative Network study, treatment with the Cypher stent was associated with an incremental, statistically significant reduction in TLR.
compared with the Taxus stent (HR, 0.70; 95% CI, 0.56–0.84; \(P=0.0021\)). These data, representing direct, randomized comparative evaluations in broad and varied patient populations, not only support the long-term safety of sirolimus-eluting stents, but also demonstrate the efficacy of the Cypher stent relative to both bare metal and alternative DES.

Recent observational studies having the advantage of generalizability, lack of prespecified angiographic follow-up, and larger data sets that increase statistical power have also contributed to our understanding of the outcomes with the Cypher stent across a broad range of practice. Overall, these studies have reaffirmed the reductions in clinical restenosis demonstrated in randomized trials without an increase in death or MI. Furthermore, although adverse events may be more common after PCI in the setting of off-label versus on-label clinical settings,29,30 in trials in which BMS and Cypher outcomes have been included, treatment with the Cypher stent has been associated with similar, if not lower, rates of death and MI against the background of consistent restenosis benefit.31-35 In a recent analysis of 76,525 Medicare beneficiaries undergoing percutaneous revascularization with either Cypher or BMS, treatment with the Cypher stent was associated with significant reductions in both mortality and repeat revascularization after risk adjustment and propensity score modeling.35

**FUTURE DIRECTIONS**

Despite considerable reductions in clinical restenosis with the Cypher stent and its favorable safety relative to BMS, the continued attention to the safety and efficacy of currently available DES has motivated the development of newer stent designs, with the objective of retaining the clinical efficacy associated with sirolimus while improving upon mechanical features (eg, stent composition, polymer, and deliverability) and possibly enhancing late safety (eg, reduction in late-stent thrombosis and obligatory long-term, dual-antiplatelet therapy). The Cypher Elite stent is the next version of the Cypher stent system and combines the same drug and polymer found on the current stent, along with added improvements in the stent design and delivery system. Like the approved Cypher stent, the Elite stent is a stainless steel platform, yet is redesigned to enhance flexibility and conformity upon deployment. Modifications to the stent delivery system, including a hydrophilic coating, will also optimize deliverability. The forthcoming Elite trial is a randomized, noninferiority design study intended to compare the primary endpoint of 1-year target lesion failure (composite endpoint of cardiovascular death, target vessel-related MI, and/or target lesion revascularization) between the Cypher BX Velocity and Elite stent designs.

Aside from the Cypher Elite stent design, a reservoir-based stent designed for controlled and directional (ie, luminal and/or abluminal) drug delivery is also under current investigation (Figure 4). Initially based upon the Conor stent (Cordis Corporation) design, this modified design cobalt-alloy stent localizes drug and a biodegradable PLGA polymer to reservoir channels within the stent struts, thereby minimizing tissue/polymer contact by 75% compared with conventional surface coating. This biodegradable polymer is designed to completely resorb in 90 to 120 days. The ongoing international RES-ELUTION trial is a randomized trial comparing the primary endpoint of 6-month angiographic in-stent late loss between patients treated with the sirolimus-eluting Nevo stent (Cordis Corporation) and...
COVER STORY

the paclitaxel-eluting Taxus Liberté stent (Boston Scientific Corporation). Potential future applications of the reservoir technology include clinical indication-specific stents for particular patient subgroups, for example, antithrombotic DES for patients with acute coronary syndromes, or DES that may be specific to a disease state, such as acute MI or diabetes.

SUMMARY

Clinical success with the Cypher stent has transformed the practice of interventional cardiology, enabling therapeutic options to patients who might previously have not been considered for percutaneous revascularization. At present, more than 100,000 patients have been included in Cypher-related clinical trials, in addition to approximately 3 million patients treated in routine clinical practice. Compared with BMS, treatment with the Cypher stent is associated with a significant reduction in the need for repeat revascularization, improved quality of life, and similar rates of death and MI. Furthermore, comparative DES data highlight emerging differences in both safety and efficacy between sirolimus-eluting and alternative DES. Though both investigational and clinical experience in a broad array of patient complexities, and with long-term follow-up, the Cypher stent represents a benchmark for angiographic and clinical outcomes for the development of newer-generation drug-eluting stents. Forthcoming developments are intended to improve upon existing favorable clinical outcomes with sirolimus-eluting stents by expanding indications with potential disease-specific DES, and improving stent design for both deliverability and safety.

Colin M. Barker, MD, is an interventional cardiology fellow at Scripps Clinic Torrey Pines, Division of Interventional Cardiology, La Jolla, California. He has disclosed that he holds no financial interest in any products or manufacturers mentioned herein. Dr. Barker may be reached at (858) 554-9905, barkercolin@scrippshealth.org

David E. Kandzari, MD, is Director of Interventional Cardiology Research, Cardiovascular Division, Scripps Clinic Torrey Pines, La Jolla, California. He has disclosed that he holds no financial interest in any products or manufacturers mentioned herein. Dr. Kandzari may be reached at (858) 554-9905; kandzari.david@scrippshealth.org

23. Kirtane AJ. Pooled analysis from 5-year follow-up of 4 randomized, controlled Cypher versus bare metal stent trials. Presented at the annual Transcatheter Therapeutics (TCT); October 22, 2007, Washington, DC.