Drug-eluting stents (DES) were first approved in the United States in 2003 on the basis of improvement in angiographic and clinical restenosis. The first 2 DES, now referred to as “first-generation” DES, were the sirolimus-eluting stent (SES) (Cypher, Cordis Corporation, Miami Lakes, Florida; approved in 2003) and paclitaxel-eluting stent (PES) (Taxus, Boston Scientific, Natick, Massachusetts; approved in 2004). Within a few months of approval, early signs began to accumulate suggesting that DES were associated with increased risk of sub-acute stent thrombosis and adverse cardiac outcomes. This was followed by indications that the benefits of DES relative to restenosis and target-lesion revascularization (TLR) might have been overestimated and risks relative to stent thrombosis (ST) might have been underestimated in preapproval randomized controlled trials conducted primarily in relatively low-risk patients and lesions, compared with more complex patients and lesions treated in clinical practice (the so-called “off-label use”) (1). Nonetheless, the DES use continued unabated, peaking at nearly 92% of all percutaneous coronary interventions (PCIs) in 2006. Eventually, 2 highly publicized study-level meta-analyses presented at the European Society of Cardiology (ESC) Congress in 2006 (2,3) ignited a firestorm of controversy. As a result, the U.S. Food and Drug Administration Circulatory System Devices Advisory Panel advised against “off-label” use of DES and recommended extending dual antiplatelet therapy (DAPT) to at least 12 months to mitigate the risk of late ST (4).

In 2008, the newer “second-generation” DES, zotarolimus-eluting stent (Endeavor, Medtronic CardioVascular, Santa Rosa, California) and the everolimus-eluting stent (EES) (Xience V, Abbott Vascular, Santa Clara, California), were approved for use on the basis of noninferiority to PES in populations very similar to those in the initial SES and PES trials. Although the drugs and polymer coatings of the first-generation DES are considered biocompatible, they are associated with allergic reactions and chronic inflammation of the vessel wall, which might cause impaired endothelialization and delayed healing leading to slight excess of late ST and higher incidence of remodeling resulting in malapposition, attenuation of antirestenotic efficacy (the so-called “catch-up” phenomenon), and coronary artery aneurysm formation late after device implantation. The newer DES have a stent platform of a cobalt-chromium alloy and are thinner and more flexible than the first-generation DES, thereby rendering them more deliverable. Another advantage is improved biocompatibility resulting in less inflammatory response and more rapid vessel endothelialization or healing. The second-generation DES have quickly replaced SES and PES in most centers, on the basis of the results of the randomized trials and registry experience. Consequently, EES is presently the most commonly used stent in the United States and Europe.

In this issue of JACC: Cardiovascular Interventions, Planer et al. (5) pooled together the individual patient data from 4 prospective randomized trials that compared EES with PES in patients with coronary disease and focused on the comparative efficacy and safety in patients with acute coronary syndromes (ACS) over 2 years of follow-up. The principal finding in the current report is that, compared with PES, the use of EES resulted in superior safety and efficacy in both ACS and stable coronary artery disease, exhibiting substantial reductions in myocardial infarction (MI), ST, and ischemia-driven TLR with no significant difference in total or cardiac mortality. The study provides the best available data, short of a dedicated prospective randomized trial, on outcomes involving the most widely used DES in complex patients presenting with ACS in whom the majority of PCIs are performed in the United States (6).

There are several strengths and limitations of the present dataset that merit consideration. First, with more than 13,000 patient-years of follow-up, including the availability of a large number of ACS patients (2,381 patients), the present pooled analysis is 1 of the largest randomized comparisons between any 2 DES and clearly the largest in patients with ACS.

Second, the availability of individual patient data allows more informative analyses such as the time-to-event and covariate-adjusted analyses leading to more reliable and valid treatment estimates than is possible with trial-level aggregate data.
Third, poolability across the 4 trials was justified by use of common endpoint definitions and absence of statistical heterogeneity. Although a purist might yet argue that these trials nevertheless manifest a substantial amount of residual clinical heterogeneity, important hypothesis-generating insights can be gained by pooling.

Fourth, although pooled results were stratified by clinical presentation (ACS vs. stable coronary artery disease), randomization was not similarly stratified in any of the 4 trials, thereby challenging the interpretability of these data. Stratification can be used to avoid imbalances in prognostic factors, thereby decreasing the chance of a type I error (finding a difference between treatment arms because of chance alone), type II error (not finding a difference if 1 exists), and increasing the validity of subgroup analyses (7). That similar results were obtained with or without covariate adjustment provides reassurance that imbalances in prognostic covariates did not have a material impact on outcomes. Nonetheless, stratified randomization, as was done for assessment of treatment effect in diabetes in 3 of the 4 trials by the same investigators (8), would have yielded more reliable and valid treatment estimates.

Fifth, a 2-year follow-up cannot be considered long enough to fully evaluate the potential of very late ST and “delayed” restenosis observed with first-generation DES. The erosion of the early advantage of SES compared with PES in TLR did not emerge until 5 years of follow-up (9). Indeed, in the SPIRIT II (A Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) trial, the superiority of EES detected at 6 months vanished at 2 years, as demonstrated by late angiographic and intravascular ultrasound catch-up phenomenon (10), suggesting this phenomenon is not unique to first-generation DES. Whether these effects might have a larger impact in more complex lesions than evaluated in the SPIRIT II trial also remains unclear. In addition, although the risk of ST is much lower with EES compared with PES, without comparative data against bare-metal stents (BMS), it is not possible to know that the 2-year rates observed in non-ST-segment elevation myocardial infarction (1.6%) and ST-segment elevation myocardial infarction (1.3%) cohorts are reassuringly low. Longer follow-up is required to better define the risk of late ST and consequently the optimal duration of DAPT required to mitigate this risk. Fortunately, a 5-year follow-up is planned for all 4 trials that will help clarify these issues.

Sixth, it can be argued that the superiority of EES was only demonstrated because it was compared with PES, which historically is regarded as less efficacious and safer than SES. Indeed, a formal meta-analysis of 5 randomized trials including 7,370 patients showed no difference with regard to ST and statistically comparable need for reintervention between EES and SES (11). The surprising decision by Cordis/Johnson & Johnson to abandon manufacture of SES after 2011 has important implications with regard to the choice of the best benchmark against which future-generation DES should ideally be evaluated.

Seventh, in addition to reporting the results of the conventional endpoint that combines safety and efficacy outcomes (target vessel failure or major adverse cardiac event), the authors also report data for the clinically relevant composite endpoint of cardiac death, MI, or ST. Ideally, endpoints such as TLR and MI that do not lie on the same pathophysiologic spectrum should not be combined (12).

Finally, data regarding DAPT at and beyond 1 year are not reported. It is unclear whether differences in duration of DAPT were included in the Cox model used for covariate adjustment. Therefore, to what extent these differences contribute to outcomes cannot be discerned.

The clinical implications of the present study require careful consideration. Should the data be taken to imply that EES is the preferred DES, especially in patients with ACS, given that the zotarolimus-eluting stent has not been shown to be superior to PES and that SES will no longer be available in the near future? The value of EES has been established by comparisons with PES. Without data from randomized trials comparing EES with current-generation BMS, can we reliably recommend EES as the default choice for PCI in all patients with ACS? Previous trials in acute MI suggest that PES offers modest efficacy advantage over BMS in reducing TLR without reducing ST, MI, or death (13). The American College of Cardiology/American Heart Association guideline recommendations indicate that DES are a reasonable alternative (Class IIa, Level of Evidence: B) to BMS in ST-segment elevation myocardial infarction patients at low risk for bleeding, who are likely to be compliant with DAPT and who do not have any planned imminent surgery (14)—all very difficult to assess during the emergency setting of an acute MI. Although, the current results allay the concerns of ST with EES in ACS, the modest albeit statistically significant benefit in clinical restenosis coupled with the increased cost of EES and the attendant prolonged DAPT argues against EES being the default stent choice for PCI in all patients with ACS. A DES, preferably EES, might be considered for clinical and anatomic settings in which the efficacy/safety/cost profile seems favorable as shown below:

Mitigate risk at “acceptable” benefit: avoid DES in patients unable or unlikely to take DAPT or in need of noncardiac procedures; extend antiplatelet therapy beyond 12 months (perhaps indefinitely in patients at low bleeding risk)

Accentuate benefit at “acceptable” risk: judicious, selective, evidence-based use ideally reserved for pa-
tients at highest risk for restenosis (longer lesions >30 mm, smaller vessels <3.0 mm, insulin-treated diabetes).

Recently, a temporal reduction in DES use from an unrestricted use in 92% of all PCIs in the years 2004 to 2006 to a more selective 68% use in 2007 was reported to be associated with a small 1% increase in TLR without any increase in repeat revascularization, death, or MI and a modest reduction in total cardiovascular costs, totaling $401/PCI (15), which translates to a saving of nearly $250 million/year ($401/PCI × 622,000 PCIs in 2007). These findings support the restricted DES treatment strategy endorsed in the United Kingdom and Canada.

One final thought: with baseline event rates now in the range of 6% to 7% for TLR and 2% to 3% for ST and absolute risk reductions in the range of 2% to 3% and 1% to 2%, respectively, we are fast approaching the point of diminishing returns. It is high time for us to acknowledge the limitations of our success and begin restructuring reimbursement strategies to encourage the judicious, selective, and evidence-based use of DES in the United States (16).

References


Key Words: acute coronary syndromes ■ drug-eluting stent(s) ■ percutaneous coronary intervention.