

EDITORIAL COMMENT

Second-Generation Everolimus-Eluting Stents

And the Beat Goes On?*

Michael A. Kutcher, MD

Winston-Salem, North Carolina

The past decade has seen a tremendous evolution in percutaneous coronary intervention (PCI) stent technology (1). The superiority of the first generation of drug-eluting stents (DES) over bare-metal stents (BMS) to reduce restenosis and repeat revascularization was demonstrated with sirolimus-eluting stents (SES) (2) and with paclitaxel-eluting stents (PES) (3). Once approved by the U.S. Food and Drug Administration in 2003, there was unbridled enthusiasm to use DES in increasingly complex lesion and patient subsets. This strategy was subsequently tempered by reports of late stent thrombosis (4) that led to major concerns and a dramatic pullback in the use of DES. A subsequent meta-analysis by Kirtane et al. (5) of randomized multicenter trials and registry data demonstrated the safety and efficacy of DES versus BMS. Nevertheless, lingering worries regarding cost, no clear mortality benefit, and late stent thrombosis continued to affect the use of DES.

See page 1209

To address these clinical issues, potential problems, such as thicker stent struts, inflammation-inducing release polymers, and the mechanisms of antiproliferative agents, prompted the development of second-generation thinner stent architecture and improved polymer and elution dynamics. One such effort has culminated in the current second-generation everolimus-eluting stent (EES), Xience V (Abbott Vascular, Santa Clara, California), also distributed as Promus (Boston Scientific, Natick, Massachusetts). This stent architecture was compared with a PES, Taxus Express in the SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treat-

ment of Patients with de novo Native Coronary Artery Lesions) II (6), III (7), and IV (8) multicenter randomized trials and the Taxus Liberte (Boston Scientific) in the COMPARE (Comparison of the Everolimus Eluting XIENCE-V Stent with the Paclitaxel Eluting TAXUS LIBERTE Stent in All-Comers: a Randomized Open Label Trial) (9). A recent meta-analysis of these 4 trials demonstrated a significant reduction in target lesion revascularization (TLR), myocardial infarction (MI), and stent thrombosis in EES compared with PES at 1-year follow-up (10).

There is great interest in the interventional cardiology community as to the safety and effectiveness of second-generation DES. Foremost is the issue of whether these newer designs translate into a meaningful improvement in long-term outcomes when compared with older first-generation elution platforms, particularly in complex lesions and off-label indications found in contemporary practice.

The study by Claessen et al. (11), in this issue of *JACC: Cardiovascular Interventions*, is a patient-level data analysis pooled from the randomized SPIRIT II, III, IV, and COMPARE trials to investigate the impact of reference vessel diameter (RVD) and lesion length (LL) on the relative safety and efficacy of EES compared with PES. Quantitative angiographic core data were available in 6,183 patients randomized to EES (n = 3,944) or PES (n = 2,239). Long lesions were defined as LL > median (13.4 mm) and small vessels as RVD ≤ median (2.65 mm). Major adverse cardiac events (MACE) assessed at 2 years included: cardiac death, MI, or ischemia-driven TLR. Outcomes according to stent type were analyzed in 3 groups: Group A (n = 1,297): short lesions in large vessels; Group B (n = 2,981): long lesions or small vessels, but not both; and Group C (n = 1,905): long lesions in small vessels.

The authors reported 2-year MACE rates of 5.6% in Group A, 8.2% in Group B, and 10.4% in Group C. Group A 2-year MACE rates were not significantly different between EES (4.8%) and PES (7.0%). However, EES was associated with lower 2-year rates of MACE in Group B (6.6% vs. 11.2%, $p < 0.01$) and in Group C (9.1% vs. 12.7%, $p = 0.008$), as well as lower individual rates of MI and TLR. Of note, stent thrombosis was significantly lower in EES versus PES in the more complex groups—Group B (0.5% vs. 1.4%, $p = 0.005$) and Group C (0.3% vs. 1.9%, $p = 0.0007$). Cardiac mortality was also reduced in the EES arm of Group B (1.0% vs. 2.1%, $p = 0.03$). Multivariable analysis confirmed EES versus PES was an independent predictor of freedom from MACE in Groups B and C.

The investigators reaffirmed that, even in the DES era, longer lesions and smaller vessel diameter continue to be important determinants of long-term outcomes. However, they concluded that in these more complex patients—those with intermediate risk (long lesions or small vessels but not both) and high risk (long lesions in small vessels)—second-

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Department of Internal Medicine (Cardiology), Wake Forest School of Medicine, Winston-Salem, North Carolina. Dr. Kutcher reports his institution receives Interventional Cardiology Fellowship grant support from the Abbott Fund, administered by Rockefeller Philanthropy Advisers.

generation EES appeared to be safer and more effective than first-generation PES. The authors suggest a mechanism may be attributable to the thin struts and a nonthrombogenic fluoropolymer on the EES surface.

So the “beat goes on” about the superiority of EES—or does it? This study demonstrated that the outcomes were similar in the low-risk group of short lesions in large vessels regardless of the generation of stent used. One could extrapolate that any type of DES or even BMS may do just as well in this low-risk group. Even though the pooled analysis was superbly done, the bulk of patients were from the relatively selective SPIRIT trial patients (6–8). Only the COMPARE study (9) was a “real-world” contemporary study. Finally, diabetic patients were not extensively analyzed except for inclusion in the Cox model. The SPIRIT IV study (8) and a post hoc analysis of the COMPARE study (9) demonstrated similar results for EES and PES in diabetic patients.

This is not a “home run” for use of second-generation EES in extremely complex lesions and presentations. However, the investigators do contribute important information on the safety and effectiveness of EES when patients are stratified into higher-risk long lesion and small vessel size subgroups.

The selection of EES for complex lesions in contemporary clinical practice may be a foregone conclusion because of dwindling alternatives in the United States. Johnson & Johnson recently announced the discontinuation of the Cypher SES (Cordis, Miami Lakes, Florida) and have halted further development of the next-generation Nevo SES platform (12). In addition, there is a lack of evidence for any superiority benefits for the first-generation PES compared with other DES (13) and a growing disenchantment in the interventional cardiology community with this elution scheme. So, in the “real world” of off-label use in complex patients and lesions, at least in the United States, the beat goes on for second-generation EES. Nevertheless, subanalysis of multicenter data, as was nicely done by Claessen et al. (11), and long-term post-marketing registries should continue to be used to monitor the appropriate use of EES in expanded complex clinical indications.

Although the beat goes on, lurking in the wings is a newer third generation of DES architecture. However, these newer stent platforms and elution schemes will have to be compared to the ongoing and extensive accumulated body of data regarding the clinical use of EES.

Reprint requests and correspondence: Dr. Michael A. Kutcher, Department of Internal Medicine (Cardiology), Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem, North Carolina 27157-1045. E-mail: mkutcher@wakehealth.edu.

REFERENCES

1. Garg S, Serruys PW. Coronary stents: current status. *J Am Coll Cardiol* 2010;56:S1–42.
2. Moses JW, Leon MB, Popma JJ, et al., for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–23.
3. Stone GW, Ellis SG, Cox DA, et al., for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221–31.
4. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998–1008.
5. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation* 2009;119:3198–206.
6. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention* 2006;2:286–94.
7. Stone GW, Midei M, Newman W, et al., for the SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 2008;299:1903–13.
8. Stone GW, Rizvi A, Newman W, et al., for the SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;362:1663–74.
9. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 2010;375:201–9.
10. Claessen BE, Stone GW, Smits PC, et al. Would SYNTAX have been a positive trial if Xience V had been used instead of Taxus? A meta-analysis of a first-generation vs. second-generation drug-eluting stent system. *Neth Heart J* 2010;18:451–3.
11. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents: pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) randomized trials. *J Am Coll Cardiol Interv* 2011;4:1209–15.
12. Rockoff JD, Kamp J. Stent pioneer J&J to exit business. *The Wall Street Journal*; June 16, 2011.
13. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol* 2007;50:1373–80.

Key Words: complex PCI ■ everolimus-eluting stent(s) ■ paclitaxel-eluting stent(s).