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EDITORIAL COMMENT

The Quest for the Perfect Stent for a Given Patient

Drug-Coated Stents for the Treatment of Coronary Disease*

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Since the initial case of plain old balloon angioplasty by Andreas Grüntzig in 1977, there has been tremendous advancement in the treatment of coronary artery disease. After balloons and bare-metal stents (BMS), the introduction of drug-eluting stents (DES) in 2002 transformed the practice of percutaneous coronary intervention (PCI) by significantly reducing rates of restenosis and repeat revascularization caused by the excessive tissue proliferation seen after BMS (1). The safety concerns raised by the first-generation sirolimus- and paclitaxel-eluting stents (PES) in regard to higher rates of late stent thrombosis (ST) and very late ST prompted changes to DES (2). The second-generation DES employed new stent designs with thinner struts, stronger materials such as cobalt or platinum-chromium with more biocompatible permanent polymers, and new antiproliferative drugs such as everolimus and zotarolimus, which further improved performance with lower rates of restenosis and late ST but still required long-term dual antiplatelet therapy (DAPT) (3). Other DES with bioresorbable polymers were also developed and significantly decreased the late ST phenomenon (4).

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In this issue of *JACC: Cardiovascular Interventions*, Costa et al. (5) report on a novel nonpolymeric drug-coated stent (DCS) that is now being introduced as an alternative to polymeric DES. This stent was designed to possibly accelerate healing and abolish the potential adverse effects of polymers. Polymers are susceptible to cracking and shearing, which affects the integrity of the stent surface and can potentially generate long-term inflammation, delayed endothelialization, hypersensitivity reactions, neoatherosclerosis, and late acquired incomplete stent apposition (6).

The BioFreedom DCS (Biosensors Europe S.A. Corporation, Morges, Switzerland) transfers Biolimus A9, a highly lipophilic sirolimus analogue, into the vessel wall. As described by Costa et al. (5), the DCS is composed of 3 key components, including a 316L stainless steel platform that has been reformed with a proprietary surface treatment, resulting in a selectively microstructured, abluminal surface. This allows Biolimus A9 to adhere to the stent surface and be delivered to the vessel wall over a relatively short time course, with 98% of the drug being released within 28 days (7,8). Overall, this novel stent has been designed to allow normal healing of the artery with the intent of reducing restenosis compared with BMS and to potentially obviate the need for long term DAPT compared with DES.

In a well-designed prospective, randomized, single-blind multicenter feasibility study, Costa et al. (5) compared the performance, safety, and efficacy of a novel standard-dose BioFreedom drug-coated stent (BFD) and low-dose BioFreedom drug-coated stent (BFD-LD) with the Taxus Liberté PES (Boston Scientific, Marlborough, Massachusetts) in the treatment of de novo coronary artery disease in 182 patients. Their primary endpoint was in-stent late lumen loss (LLL) at 12 months as determined by quantitative coronary angiography.

The investigators had several important findings. The study met the primary outcomes of terms of

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noninferiority at 12 months (e.g., in-stent LLL at 12 months: 0.17 mm in the BFD group compared with 0.35 mm in the PES group; $p < 0.001$) with a trend toward superiority ($p = 0.11$). Conversely, the BFD-LD did not reach noninferiority compared with PES.

Although the study was not powered for clinical outcomes, there were no significant differences between the 3 groups in major adverse cardiac events up to 5 years (23.8%, 26.4%, and 20.4% for BFD, BFD-LD, and PES, respectively), and there was an absence of definite or probable ST in all groups (minimum duration of DAPT was 6 months). Clinically indicated target lesion revascularization (TLR) was also not different between the 3 groups at 5 years (10.8%, 13.4%, and 10.2% for BFD, BFD-LD, and PES, respectively).

In general, 2 main features should be considered when assessing the results of a new active stent—efficacy and safety. The new stent should be noninferior or equivalent in terms of TLR compared with a market leader or "gold standard" DES. It should also display similar, if not superior, safety results compared with BMS and current DES. Generally, 12-month results are required to support early safety and efficacy, and longer follow-up, up to 5 years, is important to address the concerns of very late ST and catch-up restenosis.

In terms of efficacy, the BFD was compared with a first-generation PES that was an appropriate control at the time of study enrollment, and did indeed show a nonsignificant reduction in median in-stent LLL from 0.35 to 0.17 mm at 12 months. However, this comparison is now somewhat dated, because several randomized trials (SPIRIT [Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) III, SPIRIT IV, and TUXEDO [The Taxus Element versus Xience Prime in a Diabetic Population]) have demonstrated that the use of permanent polymer EES resulted in consistent reduced angiographic LLL, noninferior rates of target vessel failure, and fewer major adverse cardiac events than PES at 1 year and up to 5 years of follow-up (9–11).

Nonetheless, numerically the in-stent LLL of 0.17 mm seen with BFD was not very different from the in-stent LLL of 0.14 mm seen in the SPIRIT III trial at 8 months (9). This observation also applies to the rate of TLR at 5 years that was 10.8% in the BFD group versus 8.9% in the Xience V (Abbott Vascular, Santa Clara, California) group studied in the SPIRIT III trial (10). Although no real comparison can be made without a randomized study directly comparing the 2 stents, the outcomes of the BFD in this study give reason for initial optimism on the potential effectiveness and safety of the stent.

One of the initial concerns that the study investigators had regarding the stent was the fear that rapid drug elution would affect stent efficacy, as shown with earlier polymer-free stents such as the Yukon stent, which was associated with an in-stent LLL of 0.48 mm (i.e., higher than a PES comparator) (12,13). Importantly, this fear was unfounded. Costa et al. (5) suggest that Biolimus A9 may have optimal pharmacokinetics due to its high lipophilic nature, allowing for a fast but extended treatment effect while counteracting the boost effect (8).

As far as safety of the stent, although no cases of ST occurred, the study was not powered for such rare events.

As noted by Costa et al. (5), the population studied was small and only included a sample of simple, short, and discrete type A lesions with an average of 1 stent/patient. Due to the trends of both the clinical efficacy and safety of the stent in this study, the authors proposed that a potential use for the polymer-free stent, due to its rapid drug elution, would be for patients who require a DES but are unable to receive prolonged DAPT. This potential was studied and recently published in the landmark LEADERS FREE double-blind trial, which compared the safety and efficacy of the biolimus-eluting DCS with the Gazelle BMS (Biosensors International, Singapore) in patients at high risk for bleeding post-PCI (14). A total of 2,432 patients were enrolled and treated with 1-month DAPT only followed by single antiplatelet treatment. The results clearly showed superior safety at 1 year with the DCS versus BMS with regard to cardiac death, MI, and ST (9.4% vs. 12.9%; p for superiority = 0.005). They also documented markedly lower rates of TLR (5.1% vs. 9.8%; $p < 0.0001$) (14).

The field of PCI continues to evolve with the introduction in the last couple of years of new devices, including stents with biodegradable polymers, biodegradable scaffolds, and now, polymer-free stents. Although clinical data have accumulated to support the use of biodegradable polymer stents and to a lesser extent bioresorbable scaffolds, data on polymer-free devices were conflicting and limited until now. When combining this first-in-man study with the results of the LEADERS FREE trial, it appears that the standard-dose biolimus DCS is noninferior to first-generation DES in terms of late lumen loss and is superior in efficacy and safety compared with BMS in patients with high bleeding risk on 1 month of DAPT. Indeed, such patients currently seem to represent the ideal candidates for these polymer-free stents. Whether biolimus DCS

has the same safety and efficacy compared with a second-generation DES in a nonselected population remains to be proven.

This is again an exciting time for coronary intervention, as the quest for the ideal personalized coronary stent seems to become a reality.

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REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.

2. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55; discussion 1455.

3. Garg S, Serruys PW. An update on drug-eluting stents. Curr Treat Options Cardiovasc Med 2013; 15:61–78.

4. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. J Am Coll Cardiol Intv 2013;6: 777–89.

5. Costa RA, Abizaid A, Mehran R, et al. Polymer-free Biolimus A9-coated stents in the treatment of de novo coronary lesions: 4- and 12-month angiographic follow-up and final 5-year clinical outcomes of the prospective, multicenter BioFreedom FIM clinical trial. J Am Coll Cardiol Intv 2016;9:51–64.

6. Abizaid A, Costa JR Jr. New drug-eluting stents: an overview on biodegradable and polymer-free next-generation stent systems. Circ Cardiovasc Interv 2010;3:384–93.

7. Costa RA, Lansky AJ, Abizaid A, et al. Angiographic results of the first human experience with the Biolimus A9 drug-eluting stent for de novo coronary lesions. Am J Cardiol 2006;98:443–6.

8. Ostojic MC, Perisic Z, Sagic D, et al. The pharmacokinetics of Biolimus A9 after elution from the BioMatrix II stent in patients with coronary artery disease: the Stealth PK Study. Eur J Clin Pharmacol 2011;67:389–98.

9. Stone GW, Midei M, Newman W, et al. 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.

10. Gada H, Kirtane AJ, Newman W, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2013;6:1263–6.

11. Kaul U, Bangalore S, Seth A, et al., for the TUXEDO-India Investigators. Paclitaxel-eluting versus Everolimus-eluting coronary stents in diabetes. N Engl J Med 2015;373:1709–19.

12. Mehilli J, Kastrati A, Wessely R, et al. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. Circulation 2006;113:273–9.

13. Costa JR Jr., Abizaid A, Costa R, et al. Preliminary results of the hydroxyapatite nonpolymer-based sirolimus-eluting stent for the treatment of single de novo coronary lesions a first-in-human analysis of a third-generation drug-eluting stent system. J Am Coll Cardiol Intv 2008;1:545–51.

14. Urban P, Meredith IT, Abizaid A, et al., for the LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med 2015;373:2038–47.

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