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EDITORIAL COMMENT

Biodegradable Polymer Drug-Eluting Stents

Can a Class Effect Be Assumed?*

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Coronary artery stenting is an established therapy for patients with obstructive coronary artery disease ranging from stable angina to acute coronary syndromes. Clinical trials have demonstrated that durable polymer drug-eluting stents (DP-DES) significantly reduce in-stent restenosis and target lesion revascularization compared with bare-metal stents (1). However, we learned that coatings that persist long after they deliver antiproliferative medications come with a cost: hypersensitivity reactions that can lead to chronic inflammation and poor intimal healing, providing a substrate for neoatherosclerosis and late stent thrombosis (ST) (2). As a result, clinicians are faced with a 2-fold dilemma: what is the most effective way to prevent ST and other late events, and how do we minimize adverse cardiac events when dual-antiplatelet therapy needs interruption (3)?

New stent technologies attempt to address this predicament from different angles. Bioresorbable scaffolds have received a great amount of attention but have not as yet addressed these issues. Polymer-free stents deliver antiproliferative drugs without the possibly problematic polymer carriers and have shown promising results compared with bare-metal stents (4). However, their outcomes compared with second-generation DES have yet to be investigated. Biodegradable polymer drug-eluting stents (BP-DES) are coated with polymers that degrade once the active antiproliferative drug is eluted, thereby leaving only a bare-metal stent behind in the long term. Theoretically, this would mitigate the risk of late ST and potentially reduce the need for prolonged dual-antiplatelet therapy. Multiple randomized clinical trials have been performed studying different BP-DES and have proven to reduce late events compared with first-generation DP-DES (5–7); however, these studies are only powered for non-inferiority analyses, and a definitive advantage of using BP-DES has yet to be demonstrated over the less thrombogenic second-generation DP-DES. In addition, individual studies are not statistically powered to demonstrate differences in very late ST rates, given the current low incidence of these events.

SEE PAGE 462

In this issue of *JACC: Cardiovascular Interventions*, El-Hayek et al. (8) report an important meta-analysis investigating the safety and efficacy of BP-DES compared with current second-generation DP-DES. This analysis included 16 randomized controlled trials comparing BP-DES to DP-DES, containing a total of 19,885 patients. Overall, there were no differences in target vessel revascularization, cardiac death, myocardial infarctions, or ST rates between BP-DES and DP-DES. Furthermore, a landmark analysis for endpoints after 1 year revealed similar rates of very late ST. Thus, despite adequate statistical power, this study failed to demonstrate a clinical benefit of BP-DES implantation over second-generation DP-DES.

Although this analysis offers data supporting the safety and efficacy of BP-DES, this information must be interpreted with caution. An important assumption in generating any meta-analysis is that the data are similar enough to be appropriately aggregated together. However, given the considerable

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differences in stent design, biodegradable polymer kinetics, and drugs eluted, it is currently unclear whether all BP-DES are equivalent or whether it is suitable to combine their data together to determine a class effect of this technology (**Table 1**). Data from these BP-DES were combined in this meta-analysis; however, prior studies suggest these stents do not lead to equivalent outcomes. When compared with durable polymer everolimus-eluting stents in separate trials, the Nobori stent (Terumo, Leuven, Belgium) was not shown to be noninferior in the SORT OUT V (Scandinavian Organization for Randomized Trials With Clinical Outcome V) trial (5), whereas the Orsiro stent (Biotronik, Bülach, Switzerland) was noninferior in the BIOSCIENCE A Randomized Comparison of a Sirolimus-eluting Stent with Biodegradable Polymer Versus an Everolimus-eluting Stent with a Durable Polymer for Percutaneous Coronary Revascularization) trial (6). Furthermore, when compared head to head, the SORT-OUT VII trial demonstrated differences in outcomes between these 2 BP-DES. At 1 year, the Orsiro stent was noninferior to the Nobori stent for target lesion failure. However, definite ST rates were lower with the Orsiro stent (9). In order to address some of the differences found between stent types, El-Hayek et al. (8) performed several subgroup analyses and found that there were similar outcomes regardless of antiproliferative drug (biolimus or sirolimus), stent platform, polymer degradation kinetics, or strut thickness. However, these subgroup analyses cannot account for the complex interplay between all the different stent components, which cannot be predicted and cannot be ignored at this time. Most important is the fact that most of the purported beneficial effects of resorbed polymers would be realized after 1 year. In this analysis, the lion's share of outcomes after 1 year are attributable to studies with thick-strut stents. There are only about 1,000 patients with Orsiro and <200 with the Synergy stent (Boston Scientific, Natick, Massachusetts) with more than 12-month follow-up included. Thus, it is premature to conclude we are observing a class effect at this time.

This study from El-Hayek et al. (8) is an impressive large meta-analysis that provides the power needed to determine the efficacy of BP-DES and supports the safety and efficacy of BP-DES when compared with second-generation DP-DES. Although this meta-analysis did not demonstrate superiority of this new technology over second-generation DP-DES, BP-DES should not be marginalized and disregarded. Recent analysis of the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) data suggests lower long-term thrombosis rates with certain BP-DES. Importantly, there are multiple ongoing studies and follow up of reported studies that will yield valuable insights. The recently reported BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) trial compares 2 BP DES and a second-generation DP DES, and has reported noninferiority at 1 year. The SORT OUT VIII trial, longer-term data from the EVOLVE II trial (EVOLVE II Clinical Trial to Assess the SYNERGY Stent System for the Treatment of Atherosclerotic Lesion[s]), data from a recently completed pivotal U.S. trial with Orsiro, and multiple other ongoing comparative trials will help clarify these issues over the next few years. Furthermore, with preclinical and early optical coherence tomography data suggesting more rapid and complete healing with thin-strut BP-DES (10), the role of this technology in allowing further shortening dual-antiplatelet therapy use is still being defined, and prospective studies are underway. This question was not addressed by this meta-analysis because all the included trials required dual-antiplatelet therapy for 6 to 12 months. Thus, although this meta-analysis provides interesting insights into BP-DES, it is too early for us to generalize about the impact and role of this technology in routine clinical use.

TABLE 1 Stent Characteristics of BP-DES

Stent	Material	Thickness (μm)	Polymer	Resorption Time (Months)	Drug
Biomatrix flex	Stainless Steel	112	PLA	6-9	Biolimus
FIREHAWK	CoCr	86	PLA	9	Sirolimus
MiStent	CoCr	64	PLGA	1.5-2	Sirolimus
Nobori	CoCr	120	PLLA	6-9	Biolimus
Orsiro	CoCr	60	PLLA	12-24	Sirolimus
SYNERGY	PtCr	74	PLGA	3	Everolimus
TIVOLI	CoCr	80	PLGA	6	Sirolimus
Ultimaster	CoCr	80	PDLLA and PCL	3-4	Sirolimus
Yukon Choice PC	Stainless steel	87	PLA	6-9	Sirolimus

CoCr = cobalt chromium; PCL = polycaprolactone; PDLLA = poly(D,L-lactic acid); PLA = poly(lactic acid); PLGA = poly(lactic-co-glycolic acid); PtCr = platinum chromium.

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MARCH 13, 2017:474–6

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