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EDITORIAL COMMENT

Newer Generation Drug-Eluting Stents for Revascularization of Chronic Total Occlusions*

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Newer generation drug-eluting stents (DES) have improved device safety and efficacy compared with early-generation DES. Although new-generation DES differ widely in terms of metallic backbone, strut design and thickness, loaded drug, and type of polymer, cardiovascular outcomes were comparable in numerous recent head-to-head investigations (1-3). In the majority of trials, all-comers populations were enrolled, and devices were not tested in specific patient or lesion subsets. Thus, the evidence on differential DES safety and efficacy in individual clinical subgroups is currently limited to stratified analyses of head-to-head DES trials. The study by Teeuwen et al. (4) in this issue of *JACC: Cardiovascular Interventions* advances our knowledge by testing 2 newer generation DES platforms in chronic total occlusions (CTO).

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The PRISON (Primary Stenting of Occluded Native Coronary Arteries) IV investigators should be congratulated on this exemplary effort in a very challenging patient subset. The angiographic efficacy of the thin-strut biodegradable-polymer sirolimus-eluting stent (BP-SES) was compared with that of the durable-polymer everolimus-eluting stent (DP-EES). CTO lesions are increasingly treated percutaneously, with growing evidence of the associated clinical benefit, increasing operator experience, and technological improvements facilitating procedural success. On the basis of the commonly encountered excessive lesion length, high calcium burden, and subintimal recanalization, the angiographic efficacy of DES in CTOs is considerably attenuated, and the rate of clinically relevant restenosis is increased compared with non-CTO lesions. Testing newer generation DES under such challenging circumstances could potentially unravel device-related differences not apparent in simple to moderately complex lesions.

WHAT WAS KNOWN BEFORE THIS STUDY?

The 81-μm cobalt chromium DP-EES represents the gold-standard platform for percutaneous coronary intervention on the basis of consistent and robust evidence. The BP-SES is a 60-μm (for devices <3 mm in diameter; otherwise 80-μm) cobalt chromium stent with a biodegradable poly-L-lactic acid polymer coating that degrades over a period of 12 to 24 months. The BP-SES showed similar angiographic 9-month efficacy compared with the DP-EES (0.10 ± 0.04 mm vs. 0.11 ± 0.04 mm, p = 0.37) in 452 patients with stable coronary artery disease treated in the BIOFLOW-II (BIOTRONIK—Safety and Clinical Performance of the Drug Eluting Orsiro Stent in the Treatment of Subjects With Single de Novo Coronary Artery Lesions II) study (5). The findings applied also to long (>20-mm) lesions. Clinically, the BP-SES was noninferior to the DP-EES in an all-comers trial including 2,119 patients with regard to the primary endpoint, target lesion failure at 1 year, and a subanalysis suggested no interaction between lesion length and stent type (2). The BP-SES was further compared against a variety of newer

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generation DES and has been consistently found to be noninferior (1,3).

WHAT DID THE STUDY SHOW?

A total of 330 patients undergoing percutaneous coronary intervention of CTOs were randomly allocated to receive BP-SES or DP-EES. Given its low attrition rate, this angiographic study was well conducted. Baseline and procedural characteristics were balanced, with the exception of the J-CTO (Multicenter CTO Registry in Japan) score, which was lower in the BP-SES group. The primary endpoint of in-segment late loss at 9 months was 0.13 ± 0.63 mm in BP-SES-treated patients and 0.02 ± 0.47 mm in patients allocated to DP-EES. The mean difference amounted to 0.11 mm (95% confidence interval: −0.01 to 0.25 mm). The primary angiographic endpoint did not meet the criteria of noninferiority, as the upper bound of the confidence interval (0.25 mm) was higher than the pre-specified margin of 0.20 mm ($p_{noninferiority} = 0.11$). No significant difference in in-stent late lumen loss was observed (0.12 ± 0.59 mm with BP-SES vs 0.07 ± 0.46 mm with DP-EES, p = 0.52). There was also no difference in total reocclusions. Nevertheless, more patients with in-segment binary restenosis (i.e., diameter stenosis >50%) were observed in the BP-SES group (8.2%) compared with the DP-EES group (2.1%) (p = 0.028). This was echoed by a numerically higher rate of clinically driven target lesion revascularizations (9.2% with BP-SES vs. 4% with DP-EES, p = 0.08). No other difference in cardiovascular events was observed.

WHAT IS THE CLINICAL IMPACT OF THE STUDY?

The key issue is whether the study should be considered conclusive and BP-DES no longer be used for CTO revascularization. The reported mean difference in late lumen loss was small (0.11 mm; 95% confidence interval: −0.01 to 0.25 mm), even when considering the upper bound of the confidence interval, and the cumulative distribution curves were largely superimposed. According to a previous systematic evaluation (6), the observed change in late lumen loss is not expected to translate into a reduction in the rate of target lesion revascularization. The observed angiographic potency of the BP-DES is consistent with the results of the BIOFLOW-II study (5), despite increased lesion complexity. In contrast, the observed late lumen loss in DP-EES patients is at variance with all data previously reported, including the large SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V® Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) angiographic study (0.14 ± 0.41 mm, n = 669), which included far less complex lesions (7). The increased risk for binary restenosis and a tendency toward a more frequent occurrence of clinically indicated target lesion revascularization, though in the context of routine repeat angiography, is notable, as this endpoint is clinically relevant. However, the study was not powered to address these secondary endpoints. Thus, caution is warranted when concluding on a potential clinical benefit of DP-EES over BP-SES, as the play of chance cannot be excluded.

ARE THE RESULTS APPLICABLE TO AN ALL-COMERS CTO POPULATION?

The prevalence of several baseline characteristics suggests a selected CTO population: <20% of patients had diabetes, <7% had undergone previous coronary artery bypass grafting, and the mean occlusion length was relatively short (<20 mm). Likewise, procedural characteristics such as the low prevalence of antegrade dissection and re-entry (<2%) and retrograde approach (<10%) indicate less complex lesions compared with a contemporary European CTO cohort (8). Therefore, the unprecedented low late lumen loss observed in the DP-EES group may be related to patient selection. Accordingly, Markovic et al. (9) reported in-stent late lumen loss of 0.50 ± 0.71 mm in 50 DP-EES-treated patients with CTOs at 8 months and, more strikingly, Kotsia et al. (10) observed in-segment late lumen loss of 0.88 ± 0.81 mm in 100 DP-EES-treated patients with CTO examined at 9 months. It remains speculative whether and how the observed small difference in minimal late lumen loss between the 2 devices would be affected by the inclusion of a more representative CTO cohort.

QUESTIONS UNANSWERED BY THE STUDY

The addition of serial documentary intracoronary imaging, preferably optical coherence tomography, would have represented a relevant enrichment of the study, by unravelling mechanisms involved in binary restenosis such as neointima formation versus recoil. In their discussion, the investigators mention that the thinner strut design of the BP-SES may be associated with a lower radial force due to the lower strut thickness and hence a higher risk for recoil and restenosis. The notion regarding lower strut thickness (and associated lower radial force) holds true only for BP-SES with diameters <3 mm, whereas for larger diameters, both devices have the same strut

thickness. The presented angiographic data speak against differences in acute recoil, as the post-procedural minimal luminal diameter was identical between the "ultrathin" and thin-strut group. Thus, to further elucidate the aspect of radial strength, serial stent area assessment by intracoronary imaging in both groups would be required. Although angiographic efficacy represents the main objective of this study, safety cannot be adequately addressed. Accordingly, although the low occurrence of stent thrombosis in both arms is reassuring, the follow-up time was short and the sample size small. Arterial healing is impaired in complex lesions, and the impact of strut thickness in this setting remains unknown. Large regions of malapposed or uncovered struts were recently correlated with very late stent thrombosis (11) and thus represent a meaningful surrogate for assessing device safety by means of optical coherence tomography.

It is likely that the present study will not change clinical practice. In the absence of data supporting clinically relevant differences among devices, any newer generation DES should be considered for CTO procedures. It remains speculative whether the signal in favor of DP-EES for binary restenosis is due to the play of chance or whether this finding would be potentiated in a larger cohort of patients with more complex CTO lesions.

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