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EDITORIAL COMMENT

Farewell to Drug-Eluting Balloons for In-Stent Restonsis?

Appropriate Technique of Drug-Eluting Balloons Implantation Matters*

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Because of the burden of additional metal layers in the treatment of in-stent restenosis (ISR), various modalities instead of drug-eluting stents (DES) have been suggested, such as drug-eluting balloons (DEB), plain balloon angioplasty, vascular brachytherapy, and rotablation. Although DES and DEBs have shown the best efficacy and safety to date (1), it has been hypothesized that the new-generation DES will be superior to DEB, especially for the treatment of DES ISR. In 1-year results of the RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent) trial, which is the first randomized controlled trial on this topic, everolimus-eluting stents (EES) demonstrated better angiographic and clinical outcomes than DEBs (2). Similar results were found in 1-year outcomes from the Korean multicenter ISR registry (3). However, there is a paucity of data regarding the comparative outcomes of new-generation DES and DEBs beyond 1 year. Indeed, the long-term follow-up results are highly relevant, considering that occurrence of the late catch-up phenomenon or very late stent thrombosis could have a significant impact on patients' long-term prognosis.

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In this issue of *JACC: Cardiovascular Interventions*, Alfonso et al. (4) present the 3-year outcomes of the RIBS IV trial. They found that the device-oriented composite outcome, a composite of cardiac death, myocardial infarction, or target lesion revascularization, was significantly lower with EES (12.3%) than DEBs (20.1%) ($p = 0.04$). This difference was driven mainly by target lesion revascularization rates, and the results showed that the initial difference at 1 year was sustained until 3 years. The landmark analysis at 1 year showed that evidence suggesting late catch-up was not apparent. The thrombotic event rate at 3 years was twice as high in the DEB group as in the EES group, with myocardial infarctions occurring in 7 and 4 patients, and definite or probable stent thrombosis occurring in 4 and 2 patients, respectively. In summary, this trial provided the following clinical insights: 1) both EES and DEBs were identified as safe and durable treatment modalities for DES ISR; 2) in terms of long-term target lesion revascularization, EES showed significantly better results than DEBs; and 3) the late catch-up phenomenon did not occur, while the DEB group might have presented worse outcomes in terms of long-term thrombotic events.

Although this trial provides valuable evidence as expected, there are some issues to be discussed. First, the primary endpoint of this trial was in-segment minimal luminal diameter, and the statistical power was not sufficient to show meaningful differences in clinical outcomes. Furthermore, the fact that DEBs were inferior to DES only in terms of repeat revascularization could have resulted from procedural repeatability, which is rather considered an advantage of DEBs. Importantly, DEBs were not inferior to EES in terms of hard endpoints. Thus, the favorable clinical endpoints achieved with EES need to be further proved in subsequent trials.

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Differences in the study protocol should also be mentioned. The RIBS IV investigators made considerable efforts with a high quality of procedure-related factors during DEB treatment, including sufficient lesion coverage, the use of high-pressure noncompliant balloons, large balloon-to-artery ratios, and prolonged DEB inflation duration of 60 s. However, there were a few factors that could have adversely affected the DEB arm regarding the criteria for bailout stenting and duration of dual-antiplatelet therapy (DAPT).

The RIBS IV trial allowed crossover to EES only for residual percentage diameter stenosis (%DS) >50% or major residual coronary dissection. This criterion is actually very tight, because recent consensus recommends using DES instead of DEBs for residual %DS >30% after lesion preparation (5). This difference suggests that lesions unsuitable for DEBs could have been treated with DEBs in this trial, resulting in worse outcomes. Of course, the high rate of bailout stenting per se may reflect the inferior generalizability of DEBs compared with EES. However, we should bear in mind that a DEB is a balloon and does not leave any additional metal layers behind. Therefore, DEBs remain a reasonable treatment option for DES ISR, as long as satisfactory outcomes are guaranteed.

The DAPT in this trial was maintained for 1 year in EES arm and for 3 months in the DEB arm. This is a major difference from other trials that maintained DAPT for the same length of time (6 to 12 months) in both DEB and DES groups. Currently, the optimal DAPT duration after ISR treatment has not been determined, and the evidence supporting short-term DAPT in this group has been limited. ISR itself is well known as a complex lesion that increases the risk for thrombosis. In addition, because more than one-half of patients presented with unstable angina in the RIBS IV trial, the participants in this trial could be considered to be at high thrombotic risk. Notably, in the recent DARE (Drug-Eluting Balloon for In-Stent Restenosis) trial, which presented comparable outcomes between DEBs and EES, both groups maintained DAPT for 1 year (6). This difference may have had a significant impact on the results of this trial, including the numerically higher rates of thrombotic events in the DEB arm.

The 3-year outcomes of the RIBS IV trial demonstrated that EES had favorable outcomes compared with DEB, but this should not be a reason to bid farewell to DEBs. Because both DEBs and EES have shown excellent long-term safety, the simple rivalry between the 2 arms is no longer meaningful. Instead, it is time to find ways to improve the efficacy of DEBs. Unlike DES, the efficacy of DEBs is proportional to the amount of antiproliferative drug delivered to the target lesion. In this regard, the device delivery time (time delay to inflation of DEB) would correlate with the amount of drug loss into the bloodstream, and the lesion preparation status would affect the distribution and absorption of the drug. By affecting the contact area and time of DEB, a sufficient balloon-to-artery ratio and DEB inflation duration could maximize the absolute drug amount delivered. Although expert consensus recommends lesion preparation until residual %DS is ≤30%, DEB inflation duration >30 s, and a balloon-to-artery ratio of 0.8 to 1.0 (5), these factors varied widely in the previous randomized controlled trials. Using a dedicated cohort of patients with DES ISR treated with DEBs, we studied the impact of procedure-related factors (7). Three procedure-related factors were identified as independent predictors of target lesion failure: 1) residual %DS after lesion preparation; 2) balloon-to-stent ratio; and 3) DEB inflation time. Dividing into the fully optimized (residual %DS <20%, balloon-to-stent ratio >0.91, and inflation time >60 s), partially optimized, and nonoptimized groups, the rates of target lesion failure at 2 years were 8.3%, 19.2%, and 66.7%, respectively. The excellent efficacy in the fully optimized DEB group was even comparable with that of the new-generation DES reported to date. Future trials are warranted to directly compare the fully optimized DEB technique and new-generation DES.

In addition, further studies are required to determine appropriate DAPT duration after ISR treatment, regardless of the treatment devices. The performance of new-generation DEB should also be investigated, considering the results of the recently published SABRE (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis) trial (8), which reported the promising therapeutic effect of the sirolimus-eluting balloon for ISR. Despite the excellent performance of new-generation DES, there is a niche for DEBs, particularly for ISR lesions already covered with 1 or more metal layers. Most of all, we should remember again that a DEB is basically a balloon that requires careful lesion selection and meticulous procedural optimization to achieve better outcomes comparable with those attained using new-generation DES.

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