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EDITORIAL COMMENT

Drug-Eluting Balloons or Stents for Bare-Metal Stent Restenosis*

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Drug-eluting stents (DES) represent the gold standard device for percutaneous coronary intervention (1). Nevertheless, bare-metal stents (BMS) are still used in patients at high bleeding risk or if immediate surgery is pending, to allow shorter dual-antiplatelet therapy duration in comparison with DES. Furthermore, economic restraints and limited availability of DES in some regions justify continued use of BMS. Consequently, we will continue to encounter BMS in-stent restenosis (ISR), which may affect up to 30% of patients treated with these devices (2).

The optimal treatment of ISR, irrespective of whether it affects BMS or DES, remains a matter of debate. Current guidelines consider treatment with drug-eluting balloons (DEB) or DES to be equally efficacious, without differentiating between BMS and DES restenosis (1). However, neointimal composition is different for BMS and DES ISR, which may affect the efficacy and safety of the interventional approach used for its treatment (3).

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In this issue of *JACC: Cardiovascular Interventions*, Alfonso et al. (4) describe long-term clinical outcomes of patients with BMS ISR who were randomized to treatment with either a new-generation DES or a SeQuent Please DEB in the setting of the RIBS (Restenosis Intra-Stent of Bare-Metal Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent) V trial. This group of investigators has uniquely contributed to defining the optimal treatment strategy in patients with ISR. The RIBS V trial demonstrated superior angiographic performance of DES over DEB at 6 to 9 months (5). The present study shows that at 3-year follow-up, there was also a significantly lower rate of target lesion revascularization in the DES arm (2% vs. 8%; $p = 0.04$). It is notable that the need for target lesion revascularization beyond 1 year was similar in both groups (1% vs. 2.1%; $p = 0.54$), meaning that the overall rate was driven mainly by events within the first year after intervention.

The present data add valuable information to the existing evidence on the relative merits of DEB and DES for treatment of both BMS and DES ISR. **Table 1** summarizes the main follow-up angiographic measures of existing randomized trials comparing DEB with DES in patients with ISR. It is evident that both are effective in reducing the degree of ISR, irrespective of whether it is BMS or DES related. However, the relative efficacy of DES compared with DEB depends on the type of DES used. Although there is no difference in angiographic efficacy between first-generation DES and DEB in this setting, second-generation DES appear to provide superior angiographic results over DEB (**Figure 1**). However, recent data show that in patients with DES ISR, DEB provide not only comparable angiographic results to those achieved by first-generation DES but also improved long-term clinical outcomes (6). The findings of Alfonso et al. (4) confirm the favorable long-term clinical results obtained by DEB in patients with ISR. In addition, they show that the short-term efficacy superiority of second-generation DES over DEB with respect to angiographic outcomes is maintained at 3 years after treatment of ISR.

The results of a recent meta-analysis of ISR treatment (7) show that new-generation DES and DEB both have favorable efficacy and safety profiles. DES have the advantage of superior prevention of recurrent restenosis, whereas DEB have the advantage of avoiding a new stent layer, enabling better side branch access, if needed, and potentially shorter

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TABLE 1 Follow-Up Angiographic Outcomes With Drug-Eluting Stents Versus Drug-Eluting Balloons for In-Stent Restenosis

Study (Ref.#)	Comparison	Location of ISR	Time of Follow-Up Angiography (months)	MLD (mm)	Diameter Stenosis (%)
RIBS V (5)	DEB vs. DES (new generation)	BMS	6–9	DEB: 2.01 ± 0.6 DES: 2.36 ± 0.6 p < 0.001	DEB: 25 ± 20 DES: 13 ± 17 p < 0.001
PEPCAD II (11)	DEB vs. DES (first generation)	BMS	6	DEB: 2.03 ± 0.56 DES: 1.96 ± 0.82 p = 0.60	DEB: 29 ± 18 DES: 34 ± 24 p = 0.23
RIBS IV (12)	DEB vs. DES (new generation)	DES	6–9	DEB: 1.80 ± 0.6 DES: 2.03 ± 0.7 p = 0.004	DEB: 30 ± 22 DES: 23 ± 22 p = 0.009
PEPCAD China (13)	DEB vs. DES (first generation)	DES	9	DEB: 1.80 ± 0.58 DES: 1.76 ± 0.71 p = 0.69	DEB: 29 ± 21 DES: 31 ± 25 p = 0.59
ISAR-DESIRE 3 (14)	BA vs. DEB vs. DES (first generation)	DES	6–8	DEB: 1.79 ± 0.74 DES: 1.82 ± 0.74 p = 0.71	DEB: 38 ± 22 DES: 37 ± 22 p = 0.80

BA = balloon angioplasty; BMS = bare-metal stent(s); DEB = drug-eluting balloon(s); DES = drug-eluting stent(s); ISAR-DESIRE = Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis; ISR = in-stent restenosis; MLD = minimal luminal diameter; PEPCAD = Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease; RIBS = Restenosis Intra-Stent of Bare-Metal Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent.

dual-antiplatelet therapy duration. Consideration of these relative merits should guide the choice between DES and DEB. In the event of BMS restenosis, treatment with a new-generation DES should be considered. However, prior ISR increases the risk for recurrence (8), and the presence of multiple stent layers is reason enough to give primary consideration to DEB therapy. This is a relatively simplistic approach in the selection of treatment options for ISR. The underlying mechanism of ISR might, however, be more complex. Stent underdeployment, strut fractures, and geographic miss are well-known triggers of ISR, with different morphologies requiring identification with intravascular imaging (3). Their differentiation may facilitate the decision between stent- and balloon-based treatment options for ISR. Furthermore, intravascular imaging with optical coherence tomography helps characterize the tissue responsible for ISR. Whether assessment of the presence and extent of neoatherosclerosis may guide the treatment of ISR remains an unanswered question for future dedicated investigation.

It is not known whether current DEB technology represents the optimum of what can be achieved with balloon-based approaches. Paclitaxel, the sole drug used to date for DEBs, is an inferior drug for the prevention of restenosis compared with limus-family drugs (sirolimus, everolimus, biolimus). The latter are being investigated as substitutes for paclitaxel in new DEB models. Furthermore, the results of a study investigating the role of debulking techniques, using scoring or cutting balloons in combination with DEBs, are pending (ISAR-DESIRE 4 [Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis]; NCT01632371).

Finally, drug-eluting bioresorbable vascular scaffolds may be a new option in the treatment of ISR, providing antiproliferative properties without the drawback of an additional permanent stent layer in ISR lesions (9). A small prospective study of 116 patients with ISR lesions treated with bioresorbable vascular scaffolds demonstrated reasonable midterm results (10).

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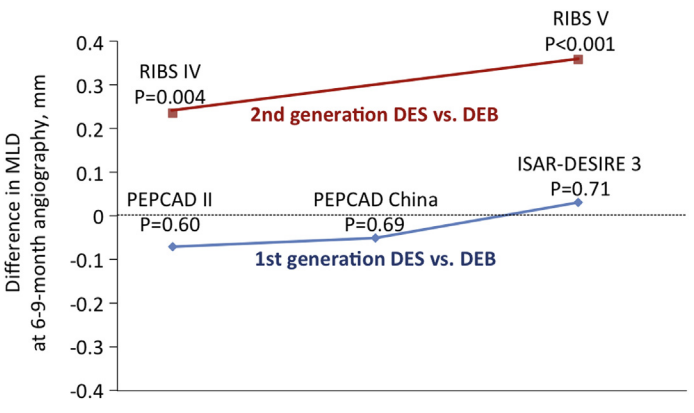
FIGURE 1 Difference in Minimal Luminal Diameter at Follow-Up Angiography Between Drug-Eluting Stents and Drug-Eluting Balloons in Randomized Trials of Treatment of In-Stent Restenosis



DEB = drug-eluting balloon; DES = drug-eluting stent(s); ISAR-DESIRE = Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis; MLD = minimal luminal diameter; PEPCAD = Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease; RIBS = Restenosis Intra-Stent of Bare-Metal Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent.

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