JACC: CARDIOVASCULAR INTERVENTIONS VOL. 11, NO. 10, 2018
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PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Drug-Eluting Balloon Therapy for In-Stent Restenosis of Drug-Eluting Stents

Choose and Prepare the Appropriate Lesion*

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Drug-eluting stents (DES) were developed to eradicate the problem of in-stent restenosis (ISR) that plagued bare-metal stents. However, ISR remains a sizable problem in patients receiving DES, especially in complicated anatomy (small-caliber vessel, calcification, diffuse disease) and certain clinical substrates (diabetes, renal disease) (1). Although neointimal hyperplasia remains the predominant pathological mechanism for ISR, DES recipients are more likely to have neoatherosclerosis. Features of the latter can be readily evaluated by optical coherence tomography (OCT). Characteristics of unstable plaque with thin-cap fibroatheroma, neointimal disruption, lipid pools, macrophage accumulation, plaque rupture, and nonocclusive intracoronary thrombus have been reproducibly demonstrated and expand the spectrum of DES ISR to also include presentations with acute coronary syndrome (2). Intravascular imaging is key to identifying the etiology of ISR. Although both intravascular ultrasound (IVUS) and OCT can elucidate the anatomic (geographic miss, stent gap, or uncovered segment with balloon barotrauma) or mechanical (stent underexpansion, nonuniform strut distribution, or stent fracture) factors leading to DES ISR, IVUS gives a better visualization of residual plaque behind the stent struts and more accurate vessel sizing, as the external elastic lamina is well delineated. There may also be biologic factors leading to ISR; these were more pronounced for earlier generation DES (drug resistance and hypersensitivity reactions to DES polymer) and are considered less important with zotarolimus- or everolimus-eluting stents.

With this background, evaluating therapy options for DES ISR is particularly challenging given that this patient subset arises after defeating our most potent weapon against neointimal hyperplasia. Although repeat DES implantation has repeatedly been shown to be the superior treatment of DES ISR (3), drug-eluting balloons (DEBs) remain a topic of interest because of the potential to avoid multiple layers of metal in a patient or lesion especially prone to ISR. ISAR DESIRE 3 (Efficacy Study of Paclitaxel-eluting Balloon, -Stent vs. Plain Angioplasty for Drug-eluting Stent Restenosis) investigators showed comparable repeat revascularization rates for paclitaxel-eluting balloons and paclitaxel-eluting stents (4). However, compared with everolimus-eluting stents, drug-coated balloons fall short, with higher repeat revascularization at 1 year (5).

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In this issue of *JACC: Cardiovascular Interventions*, Rhee et al. (6) present their findings on DEB treatment in 256 consecutive patients with DES ISR from a prospective registry focusing on lesion preparation and optimization of DEB use. They found an overall target lesion failure rate of 20.3% after 2 years. If the lesions were fully optimized (residual stenosis <20%, balloon-to-stent ratio >0.91, and DEB inflation time >60 s), the target lesion failure rate was quite low, at 8.3%, compared with 19.2% and 66.7% for partially optimized and nonoptimized groups, respectively. However, only a very small minority of lesions were treated to full optimization, whereas the bulk of lesions fell in the partially optimized category (up to 2 optimization features not met). Thus, this study suggests that with current DEB technology, a more

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.03.014

stringent focus on aggressive pre-dilation may produce higher acute lumen gain while allowing the DEB to decrease late loss. Additionally, 1:1 balloon-to-artery sizing and longer inflation times to maximize contact of paclitaxel with intima may bridge the DEB-DES gap. Using relatively larger diameter DEBs and for longer inflation times did not lead to greater levels of myonecrosis as assessed by biomarker release. This is an important takeaway because this is the first prospective study to look at DEB size and optimal inflation as significant factors for clinical outcomes. Thus, a study with predetermined stringent cutoffs for DEB use may provide a validation of these results. Outcomes of the fully optimized group are comparable or even somewhat better than those of the everolimus-eluting stent group in the RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent) study (5).

One critical step missing in this study is a description of lesion characteristics via IVUS or OCT at baseline and after lesion preparation. Further investigation with intravascular imaging could potentially classify patients into the following groups: 1) focal neointimal hyperplasia in an otherwise well-expanded and apposed stent; 2) stent malapposition or underexpansion in a vessel without severe calcification; 3) diffuse neointimal hyperplasia; 4) stent fracture, stent gap, or stent edge restenosis; 5) stent underexpansion because of 360° calcification or nodule; and 6) neoatherosclerosis with unstable plaque features.

At least in theory, groups 1 and 2 would be well suited to DEB therapy. Group 3 may be better suited for DES therapy, but if vessel diameter is small and lesion preparation yields an optimal result, DEB placement may be an acceptable option also. A majority of operators would treat patients in group 4 with another DES, while those in group 5 will likely require extensive preparation with cutting or scoring balloons, laser ablation, or atherectomy prior to another DES implantation. An optimal acute gain result with a scoring or cutting balloon may even allow DEB use, as there were no adverse outcomes with this strategy in the ISAR DESIRE 4 study, and the angiographic follow-up outcomes were better (7). Group 6 would also likely fall in the DES treatment bucket unless optimization parameters are excellent. Post-optimization IVUS or OCT will also provide information regarding extensive dissection or intramural hematoma formation, which may further stratify choice between DES and DEBs in all groups, taking into account the clinical situation, vessel size, and amount of pre-existing metal.

Thus, this paper provides grounds for further investigation into which DES ISR lesions are suitable for DEB therapy and how to best optimize the DEB procedure. A prospective study that incorporates the ideas of this group with intravascular imaging evidence to choose between DEB and DES is required to bridge the knowledge gap on this issue. Further device development with DEBs using "limus" analogues also has the potential to improve the outcomes achieved by paclitaxel-coated balloons, as shown by the promising results of the SABRE (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis) study (8). Increasing evidence of at least somewhat successful use of DEBs in Europe and Asia prompts the question of when these might enter the U.S. market. There is a sizable population with multiple coronary stent layers for whom avoiding the next layer of metal may prevent or delay coronary artery bypass grafting, even at the cost of a 20% chance of repeat intervention within 2 years.

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KEY WORDS drug-coated balloon, in-stent restenosis, repeat revascularization