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EDITORIAL COMMENT

Drug-Eluting Balloons

Effective and Durable Treatment for In-Stent Restenosis*

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The introduction of percutaneous transluminal coronary angioplasty (PTCA) by Andreas Gruentzig was a game changer for coronary revascularization (1). However, PTCA is associated with significant rates of acute closure and restenosis resulting from vascular recoil, neointimal hyperplasia, and negative remodeling. Bare-metal stents (BMS) effectively treat acute closure and limit restenosis by preventing vascular recoil and negative remodeling (2). With widespread adoption of BMS emerged in-stent restenosis (ISR), a lesion resulting from aggressive smooth muscle cell proliferation and extracellular matrix production that has been significantly reduced by drug-eluting stents (DES). Nevertheless, both BMS and DES are deployed for patient and lesion specific reasons and hence ISR is not uncommonly encountered in clinical practice. Furthermore, ISR may present as unstable angina (16% to 66%) or myocardial infarction (1% to 20%) and therefore continues to be a significant limitation of contemporary percutaneous coronary intervention (3–5).

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A number of strategies including conventional PTCA, scoring or cutting balloons, rotational atherectomy and excimer laser have proved ineffective for the treatment of BMS restenosis (6). Brachytherapy was more effective but was associated with increased risk for late stent thrombosis and residual stent edge restenosis (7,8). DES have emerged as the standard of care for treatment of BMS restenosis, although recurrent restenosis persists and the 2-stent sandwich is not conceptually appealing. The approach to DES restenosis arguably poses a greater challenge as the DES card has already been used. Intravascular imaging with ultrasound or optical coherence tomography (OCT) can evaluate whether the mechanism of DES restenosis is primarily stent under-expansion or intense neointimal hyperplasia. The treatment is then tailored to tackle the underlying mechanism of restenosis with aggressive balloon dilatation for under-expanded stents and repeat DES (usually with a different antiproliferative agent) for intense neointimal hyperplasia in otherwise well-expanded stents (9). Despite these interventional strategies, the risk of repeat revascularization for patients with DES restenosis remains high (22% to 40%) (9,10).

The concept of restoring luminal patency and delivering effective antiproliferative agents to treat ISR without deployment of a redundant second stent layer is highly attractive and has inspired the development of the drug-eluting balloon (DEB) technology. A major hurdle that was overcome to achieve an effective DEB was the application of a matrix coating on the balloon that uniformly releases the antiproliferative drug during a single balloon expansion. Early animal studies of DEB demonstrated that paclitaxel had better adsorption and tissue retention levels than sirolimus (11,12). The unique lipophilic characteristic of paclitaxel augments its rapid adsorption at the site of delivery and prolongs drug retention after even short balloon expansion times, making paclitaxel the antiproliferative drug of choice for DEB (13).

The clinical rationale for use of DEB for treatment of ISR stems from both its efficacy and safety features. From an efficacy standpoint, the predominantly firm fibrous nature of the neointimal hyperplastic tissue makes acute vessel wall recoil and abrupt vessel closure after PTCA less likely than after PTCA of native lesions, obviating the need for stent placement. From a safety standpoint, the shorter duration of drug release and lack of a second durable polymer/stent platform with DEB favors earlier vascular healing, reduced hypersensitivity, and lower likelihood of stent thrombosis. In addition, the shorter duration of dual antiplatelet therapy following DEB (3 months) would result in lower bleeding risk and medical cost (14,15).

The initial clinical trials of DEB were for the treatment of native peripheral arterial disease where, compared to conventional PTCA, DEB showed significantly lower rates of mean late lumen loss and target lesion revascularization (16,17). Similarly, for treatment of coronary ISR, studies comparing paclitaxel-coated DEB with PTCA have demonstrated superiority of DEB in terms of angiographic and clinical outcomes (18–20). DEB were also shown to be noninferior to first-generation, paclitaxel-eluting stents for treatment of DES restenosis (21,22). A recent meta-analysis comparing DEB with either PTCA or a first-generation DES for treatment of ISR found that, compared to PTCA or DES, DEB significantly reduced the need for target lesion revascularization and major adverse cardiac events at 1- to 5-year follow-up (23). Currently, 2 ongoing trials (DARE [Drug Eluting bAlloon for In-stent REstenosis.

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Multi-center, Randomized Trial to Study the Effect of the SeQuent Please Drug-eluting Balloon Versus the Xience Prime Drug-eluting Stent for the Treatment of In-stent Restenosis] [NCT01127958] and RIBS IV [Restenosis Intra-stent of Drug-eluting Stents: Paclitaxel-eluting Balloon vs Everolimus-eluting Stent, A Prospective, Multicenter and Randomized Clinical Trial] [NCT01239940] are evaluating the comparative efficacy of paclitaxel-coated DEB and everolimus-eluting stents for treatment of both BMS and DES restenoses.

In this issue of *JACC: Cardiovascular Interventions*, Agostoni et al. (24) present an interesting paper that sheds light on the mechanism behind the favorable outcomes of DEB in 25 patients with BMS or DES restenosis who presented with stable angina, unstable angina or silent ischemia. Lesions were pre-dilated with standard balloons using a 0.9:1 balloon to previous stent ratio at high pressure (12 to 18 atm) followed by DEB inflation at lower pressure (8 to 12 atm) with a balloon to previous stent ratio of 1.1:1. The investigators performed serial quantitative coronary angiography, fractional flow reserve (FFR), and OCT pre- and immediately post-DEB angioplasty and at 6-month follow-up. They report a device success rate of 92% with 2 of 25 patients requiring adjunctive stenting for edge dissection and residual stenosis. Angiographic and FFR follow-up was available in 23 patients and baseline and follow-up OCT data were available in 17 patients. Baseline minimal luminal diameter increased from 0.58 ± 0.38 mm pre-procedure to 1.83 ± 0.47 mm post-DEB and remained at 1.83 mm ± 0.62 at 6 month follow-up. Similarly, the OCT minimal luminal diameter increased from 1.13 (1.04 to 1.33) mm to 1.97 (1.69 to 2.21) mm and remained stable at 6 months at 2.02 (1.71 to 2.32) mm. Perhaps because of the aggressive pre-dilatation employed, the investigators achieved excellent post-DEB minimal stent area as well, increasing from 5.42 (4.43 to 7.22) mm^2 to 8.00 (6.46 to 9.56) mm^2 after the procedure. Importantly, post-procedure FFR assessment paralleled the anatomic findings with FFR distal to lesion increasing from 0.58 ± 0.17 to 0.92 ± 0.05 after DEB, and remained at 0.92 ± 0.07. Although this study did not have a control arm, the sustained luminal gains over 6 months with DEB are significantly greater than those observed in historical controls after conventional PTCA for ISR and likely result from inhibition of recurrent neointimal formation by paclitaxel. Notably, post-DEB diameter stenosis in this study (28 ± 16%) was greater than that observed from other studies when ISR was treated with DES (11 ± 7%) (25). The authors report that 4 of 23 patients demonstrated angiographic binary restenosis (only 2 of which had ischemic FFRs and underwent DES percutaneous coronary intervention). Post-DEB dissections were observed by OCT in all patients but, importantly, completely resolved at 6 months. Another reassuring safety signal of DEB is the finding that >97% of stent struts remained embedded at 6 month. The authors conclude that DEB result in circumferential luminal gain due to compression and dissection of the neointimal layer and dilatation of the old stent.

Several limitations of the current study should be noted. First of all, this is a small, single-center observational study. Although the authors state that unstable angina patients were included in this study, they acknowledge in the limitations section that they did not enroll acute coronary syndromes patients due to the rigorous nature of the study. Therefore, this paper does not investigate mechanisms of action of DEB in patients with ISR presenting with acute coronary syndromes. The other obvious limitation of the study is the absence of a control arm that could have clarified the pure mechanical effects of balloon expansion versus the combined effects of mechanical expansion and drug release. One potentially interesting mechanistic aspect that was not explored in the present investigation is the impact of DEB on wall shear stress (WSS), abnormalities of which have been associated with restenosis and atherosclerosis progression (26,27). Indeed, by aggressively inhibiting the early neointimal response, DEB may attenuate the stimulus for the development of heterogeneity in WSS that may be seen after conventional PTCA with areas of high WSS within the restenotic segment and low WSS distal to it. Also unlike DES, DEB do not straighten vessels and therefore avoid areas of low WSS at the edges of the previous stent. On the other hand, compared to conventional PTCA, the release of cytotoxic drugs from DEB has the potential of adversely affecting both epicardial and microvascular endothelial function which could lead to detrimental vascular effects. Taken together, the present paper contributes to our understanding of the favorable clinical effect of DEB for the treatment of ISR.

In the foreseeable future, DEB are likely to play a significant role in endovascular therapy for peripheral arterial disease and have appeal for treatment of certain subsets of native coronary disease such as diffuse small vessel and bifurcation lesions where stenting has limitations. As far as DEB use for treatment of ISR, the European guidelines recommend its use for BMS restenosis (Class IIb) but continue to recommend DES for DES restenosis (28). In the United States, DEB are not currently approved by the Food and Drug Administration and therefore are not recommended by the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for treatment of coronary ISR (29). However, with the accumulating evidence supporting their effectiveness for the treatment of ISR, DEB will likely become the mainstay of therapy for this challenging clinical conundrum.

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