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EDITORIAL COMMENT

Drug-Eluting Stent Restenosis

A Need for New Technology?*

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In this 35th year of percutaneous coronary intervention, restenosis after stent implantation remains a significant limitation, resulting in increased costs and morbidity, reduced quality of life, and in some patients, a need for surgical coronary revascularization. Drug-eluting stents (DES) proved superior to bare-metal stents (BMS) in preventing restenosis, but as increasingly complex lesions were treated, drug-eluting stent–in-stent restenosis (DES-ISR) exceeded the single digit rates initially reported for simple lesions (1,2). Some seek solace in the observation that DES-ISR is more frequently focal, due perhaps to the potent anti-proliferative drug effects as well as mechanical factors, such as focal stent under-expansion, stent fracture, loss of longitudinal integrity, and/or incomplete stent apposition (3–5). Although bare-metal stent–in-stent restenosis (BMS-ISR) lesions have been shown to respond favorably to balloon dilation, especially when focal, and significantly better after DES implantation in a randomized trial (6),

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there is increasing evidence that even focal DES-ISR is a more resistant lesion that is associated with high subsequent major adverse cardiac events after percutaneous retreatment (7–9). Optimal therapy of DES-ISR is essential to avoid a third symptomatic or ischemic presentation that might signal a need for surgery, especially in the presence of left main or left anterior descending coronary artery lesions. Observational studies have shown that the extent of the DES-ISR lesion determines the outcome of percutaneous therapy. Restenosis occurred in 29% of focal (≤10 mm) lesions, 46% of diffuse (>10 mm) lesions, and 66% of total occlusions among 481 consecutive de novo DES-ISR lesions during a median follow-up of 3 years (2). Major adverse cardiac events were reported in one-third of patients with DES-ISR, irrespective of lesion type (2). Observational studies have provided evidence that DES are more effective than simple balloon angioplasty for treatment of diffuse as well as focal DES-ISR lesions, but this comparison has not been evaluated in prospective randomized trials (1,2). In this issue of *JACC: Cardiovascular Interventions*, Alfonso et al. (10) in a prospective observational trial attempt to assess the value of treating a DES-ISR lesion with a different DES, compared with alternative strategies (balloon dilation, BMS, or the same DES). This report is the third in a series of studies by this group analyzing treatment strategies for stent restenosis. It has the advantage of being performed by experienced investigators in a network of participating centers.

The RIBS-III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) was a prospective, observational study that analyzed outcomes of 363 patients with DES-ISR treated in 12 Spanish university hospitals. The recommended strategy of implanting a different DES was carried out in 274 patients (75%), and the remaining 89 patients (25%) were treated at the discretion of the operator with balloon angioplasty (n = 29, 33%), BMS (n = 9, 10%), or the same DES that was initially implanted (n = 51, 57%). Follow-up angiography was performed in 275 of 355 (77%) eligible patients at a median of 278 days. The main angiographic endpoint was in-segment minimal lumen diameter (MLD) at 9-month follow-up as assessed by quantitative coronary angiography in a core laboratory. The main clinical outcome was a composite of cardiac death, myocardial infarction, and target lesion revascularization at 1 year. Angiographic evaluation at 9 months revealed a larger MLD in patients receiving a different DES, compared with 89 patients treated with alternative strategies (1.86 vs. 1.40 mm, p = 0.003), and recurrent restenosis was less (22% vs. 40%, p = 0.008). The combined primary clinical endpoint occurred less frequently in the different DES group (23% vs. 35%, p = 0.039), because of less target lesion revascularization. The rate of definite/probable stent thrombosis was low and similar in both groups (0.7% vs. 1.1%). Propensity score analysis was used in an attempt to correct for baseline differences. What does this study tell us? Simply stated, in an observational study patients with DES-ISR lesions fared better with a different DES than a group of patients treated with either balloon dilation, BMS, or the same DES. As always, comparisons of treatment effectiveness in an observational study are risky, due to potential unknown and unmeasured confounders. For a number of reasons, the findings reported should be no surprise.

Although the reference vessel diameter in the 2 groups of patients was similar (2.41 mm vs. 2.46 mm, p = 0.45), the MLD achieved after treatment of the DES-ISR lesions was significantly smaller in the "other strategy" group (2.08 mm vs. 2.26 mm, p = 0.007). This parallels the findings in the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) randomized comparison of balloon angioplasty versus

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DES for BMS-ISR where the MLD achieved acutely with balloon angioplasty was significantly smaller than with implantation of 2 different DES (2.07 mm vs. 2.52 mm and 2.56 mm, $p < 0.001$) (6). Although this might represent a form of elastic recoil or tissue prolapse, an additional component of stent under-expansion cannot be excluded, because intravascular imaging was used in <40% of patients in the RIBS-III study. The authors reported significantly better acute and 9-month angiographic results when imaging was used, suggesting under-expansion might have existed in unimaged patients.

The late lumen loss reported in the "other strategy" group was significantly greater than in the group of patients treated with a different DES (0.63 vs. 0.42 mm, $p = 0.02$). The magnitude of the late loss in the "other strategy" was similar to that reported after balloon angioplasty of BMS-ISR in the RIBS-II study of 0.69 mm (11) and that reported after balloon angioplasty of sirolimus-eluting stent (SES)-ISR by Habara et al. (12) of 0.72 mm. The late loss of 0.42 mm reported for the "switch" group is similar to that reported by Mehilli et al. (13) in the ISAR-DESIRE 2 study when SES-ISR lesions were treated with either SES or paclitaxel-eluting stent (0.38 and 0.40 mm, respectively).

The 9-month angiographic follow-up interval that was chosen would be expected to capture most restenoses after balloon angioplasty or BMS implantation, but persistence of in-stent lumen loss beyond this time frame after DES implantation is known to occur and would not be detected. The authors make note of a "low but persistent event rate beyond the first year."

The 4 types of DES implanted in this study have differing antirestenotic effects, with everolimus- and sirolimus-eluting stents displaying increased potency in most (1) but not all studies (13). The choice of DES was operator-determined. The authors report in this study that patients receiving limus-DES or second-generation DES had less restenosis. However, the distribution of limus–DES and second-generation DES between the 2 treatment groups was not provided.

Pharmacotherapy was not the same for the 2 groups of patients. Dual antiplatelet therapy for 1 year was given to patients with repeat DES implantation, but the 43% of "alternative strategy" patients treated with balloon angioplasty or BMS received dual antiplatelet therapy for 1 month.

This report is 1 of several observational studies indicating that implantation of a DES to treat DES-ISR was safe and associated with better long-term outcomes, primarily reduced recurrences, when compared with alternative strategies, which included balloon angioplasty (1,14,15). However, a randomized controlled trial comparing these treatments has not been performed. The authors report that this study is the sixth observational trial in which a switch in DES strategy has been analyzed. Most report similar outcomes, whether DES were changed or the same. In the only randomized controlled trial, Mehilli et al. (13) reported outcomes of 450 patients with SES-ISR randomized to receive paclitaxel-eluting stent or SES. There were no differences in late lumen loss, restenosis, target lesion revascularization, safety outcomes, or stent thrombosis. Should one infer that the absence of the usual SES superiority in a patient with SES failure indicates drug resistance? Perhaps, but more data are needed to determine whether a different, the same, or simply the most potent DES is the best current treatment for DES-ISR.

Randomized trials comparing the efficacy of potent second-generation DES, the promising new and largely untested drug-eluting balloons, bioresorbable drug-eluting scaffolds, and conventional balloon angioplasty will be required to establish optimal therapy for this resistant new "disease," DES-ISR. A breakthrough technology is sorely needed to treat this malady or prevent its occurrence.

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