EDITORIAL COMMENT
Treatment of Stent Restenosis
Moving Beyond Momentum*
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The journey taken for treatment of in-stent restenosis (ISR) began similarly to and then diverged markedly from the path traveled for de novo lesions. Similar to de novo lesions, balloon angioplasty initially demonstrated safety and moderate success rates for treatment of ISR (1). With more challenging lesions (i.e., diffuse ISR), though, balloon angioplasty proved to be far from adequate (Fig. 1) (2,3). For both ISR and de novo lesions, a geometric model of treatment success was embraced (4): Optimization of final lumen diameter became the goal. Registry studies suggested a potential geometric benefit for debulking before angioplasty for both de novo and ISR lesions (5,6). Thus, interventional cardiologists embraced a variety of atherectomy techniques (7,8) to optimize final lumen diameter during ISR treatment. Although these options appeared to improve lumen diameters and recurrence rates in registry studies of ISR, they failed to establish superiority in the setting of multiple operators participating in randomized clinical trials (9–11).

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Stent restenosis therapy headed down its own road following pivotal brachytherapy trials that demonstrated benefit among patients with ISR but not with de novo lesions (12–15). Treatment of de novo lesions focused on optimization of final lumen diameter with stents. On the other hand, attempts to treat restenotic lesions with further implantation of bare metal stents did not show improved outcomes compared with balloon angioplasty (11). Thus, five years ago, treatment of de novo lesions (bare-metal stents to optimize lumen diameter) and restenotic lesions (brachytherapy to reduce late loss) followed divergent paths in interventional cardiology.

DRUG-ELUTING STENTS (DES)
FOR TREATMENT OF ISR

Brachytherapy has practical limitations, efficacy concerns, and safety issues (12). Thus, the opportunity for both de novo and restenotic lesions to converge again with the simpler DES-based inhibition of late loss was embraced after approval of DES for de novo lesions (16). Rapid adoption of DES for such high-risk groups represented momentum and encouraging registry findings (17), but randomized superiority of DES to other therapies in enriched higher-risk populations had yet to be established. In this issue of the Journal, the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stent Implantation (RIBS-II) trial moves us beyond momentum by confirming superiority for sirolimus DES compared with balloon angioplasty for the treatment of patients with ISR (Fig. 1) (18). Although the study sample is strikingly small (n = 150) compared with the phase III clinical trials of DES (n >1,000), the enriched population of high-risk patients allows for meaningful comparisons of clinical end points.

This study amplifies the findings of the randomized Intracoronary Stenting With Antithrombotic Regimen–Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial (19). In both studies, DES is associated with a greater than 50% reduction in recurrent restenosis compared with balloon angioplasty. In the RIBS-II trial, we see the true convergence of de novo and ISR therapies via mechanistic insights from the intravascular ultrasound substudy. Namely, the mechanism of benefit of DES for ISR is the same as DES for de novo lesions: Stents improve acute gain compared with angioplasty (a geometric benefit [4]), and the drug/polymer combination minimizes late loss (16).

Although both the ISAR-DESIRE and RIBS-II studies compared DES to a less effective therapy (balloon angioplasty) for ISR, DES for ISR is still superior when compared to the gold standard of brachytherapy (20). Thus, there is no convincing argument to sway operators to the divergent path of brachytherapy. Finally, the benefits of DES for ISR extend to even lower-risk ISR subgroups (i.e., focal lesions) that might have favored angioplasty alone (3).

Practical questions arise from the RIBS-II and ISAR-DESIRE studies:

- The randomized population for both studies had ISR of bare metal stents. Currently, the vast majority of ISR will be related to DES failure in increasingly complex lesion types (21). Will DES failures be more resistant than bare metal stents to reimplantation with DES?
- The benefit of brachytherapy as compared to balloon angioplasty is diluted over five-year follow-up (12). Given that both DES and brachytherapy similarly share inhibition of late loss as the mechanism of benefit, are six-month (ISAR-DESIRE) and one-year (RIBS-II) end points conclusive?
- The RIBS-II protocol required >12 atm inflation for repeat stenting, although the average deployment pressure was 15.8 ± 2.9 atm. Caution may be warranted in extending these excellent outcomes to a strategy of lower pressure deployment; concern about stent underexpansion is warranted when dealing with multiple layers of stent and polymer (22).
If DES failure occurs in a sirolimus-eluting stent, is this a marker for a specific drug resistance favoring reimplantation with a non-sirolimus-eluting stent?

Finally, what role does adjunctive pharmacology have with respect to restenosis outcomes? The similar and marked systemic inflammatory response after both bare-metal and drug-eluting stenting (23) suggests that the benefit of DES for ISR is entirely local; therefore, systemic pharmacotherapy is unlikely to have a major role in further improving restenosis rates.

MOVING BEYOND MOMENTUM

Landmark trials in lower-risk lesions defined the beginning of a new DES era (16). A leap of faith occurred as we embraced a nearly universal application of drug-eluting stenting (17) based on the simplicity of the technique and its marked potential to improve patient outcomes. Like other randomized DES trials involving higher risk patients (24), the RIBS-II study moves us firmly beyond the beginning of the drug eluting stent era. We are now beyond momentum alone as a justification for higher-risk applications of drug-eluting stenting. As we look now toward the challenges of our DES middle age, we need not necessarily discard our youthful exuberance (“no more restenosis, no more surgeons”). Rather, we have defined a successful model for evaluating this single convergent standard of care—DES to simply optimize acute gain and minimize late loss. As with treatment of stent restenosis, momentum must be justified by well designed randomized studies in high-risk populations (i.e., diabetics with multivessel disease, bifurcation lesions, and prevention of infarction) in order to confirm our continuing, if no longer youthful, exuberance.

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