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EDITORIAL COMMENT

New Roads, New Ruts

Lessons From Drug-Eluting Stent Restenosis*

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The Achilles' heel of coronary stenting has long been the occurrence of arterial renarrowing or restenosis in the months after intervention (1). The advent of drug-eluting stent (DES) therapy appeared initially to herald the eradication of in-stent restenosis and the culmination of innovation in interventional cardiology. However, although this technology has undoubtedly facilitated the expansion of percutaneous intervention into domains formerly limited by either unsatisfactorily high incidence or inacceptable consequences of restenosis, the passage of time has shown us that reports of the demise of coronary restenosis were perhaps greatly exaggerated. Indeed, partly a victim of its own success, the number of patients developing restenosis after DES may be as high as 200,000 per annum in the U.S. alone (2).

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From a pathophysiological standpoint, stent implantation during percutaneous intervention largely negates the impact of mechanical factors that contribute to restenosis: namely, prolapse of disrupted plaque, elastic vessel recoil, and constrictive arterial remodeling. Indeed restenosis within bare-metal stents (BMS) is caused almost exclusively by neointimal hyperplasia, an iatrogenic process characterized by vascular smooth muscle hyperplasia and extracellular matrix deposition (3,4). Whereas DES therapy successfully inhibits neointimal hyperplasia across the spectrum of coronary disease lesions and presentations, it does so at the expense of a systematic delay in healing of the stented arterial segment (5). One consequence is that the time course of restenosis after DES is temporally right-shifted. Indeed, numerous imaging studies have documented unequivocal evidence of late erosion of antirestenotic efficacy ("late luminal creep") beyond the 6- to 8-month window during which BMS restenosis tended to have reached its peak (6,7). Although the clinical impact of this late catch-up appears low, there are important implications in the choice of time point assessment in trials evaluating antirestenotic efficacy and also for future stent design (with polymer-free platforms perhaps immune from this phenomenon). Finally, when it occurs, DES restenosis may be morphologically somewhat distinct from restenosis after bare-metal stenting, with a relatively cell-depleted neointima composed predominantly of extracellular matrix, and perhaps an excess of de novo in-stent atherosclerosis (1,8,9).

In this issue of *JACC: Cardiovascular Interventions,* Latib et al. (10) report on 392 patients presenting with DES restenosis who were managed with repeat percutaneous intervention. In the past, the Milan group has contributed significantly to our understanding of coronary restenosis, and although the present report is subject to the typical limitations imposed by an observational registry design, it represents a relevant addition to literature concerning the ever-increasing number of patients with DES restenosis. In many respects, their article is an extension of the important paper of Cosgrave et al. (11) from the same group, with the advantage of an additional 3 years of patient enrollment and an extension of follow-up from a median of 13 months out to 3 years. So what are the lessons that we can distill from the investigators' observations and indeed from experiences in general with DES restenosis over the last decade?

Lesson #1: In DES Treatment Failure, the Pattern of Restenosis Is More Often Focal

Many studies have described a ratio of focal/nonfocal restenosis after DES implantation of approximately two-thirds/one-third (12–14). This is precisely the breakdown observed in the present report (Fig. 1). In contrast, in BMS restenosis, the ratio is of the order of 40%/60% (15). This difference can be accounted for in at least 2 ways. First, the high-efficacy inhibition of neointimal formation by DES means that technical factors (e.g., mal-expansion or stent fracture), which are associated with more focal-pattern restenosis, play a *relatively* greater causative role. Second, mal-apposition may arguably have proportionately greater impact on restenosis after DES, as it may also hinder effective drug transfer to local tissue. In a similar vein, although largely unstudied, it is conceivable that the absolute incidence of stent fracture may be higher after DES than after bare-metal stenting, consequent, hypothetically, on enhanced local instability and altered arterial shear forces secondary to low volume neointimal overgrowth. It is anticipated that newer, more sophisticated intracoronary imaging modalities may shed further light on these mechanisms and facilitate more thorough classification of DES restenosis (16).

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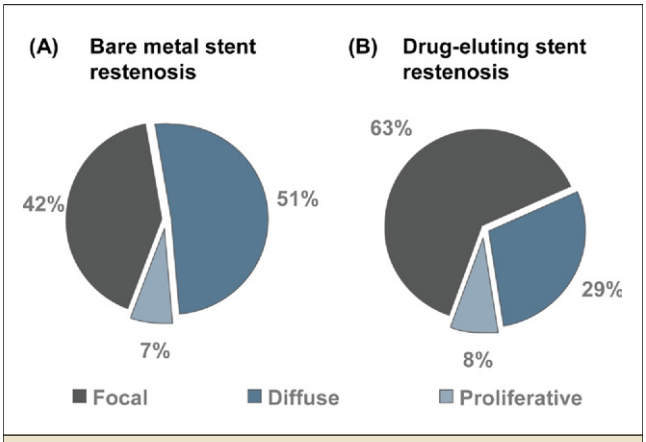

Figure 1. Distribution of Morphological Patterns of Restenosis After Bare-Metal and Drug-Eluting Stents

(A) Bare-metal stent(s); data from Mehran et al. (15). **(B)** Drug-eluting stent(s); pooled data from Latib et al. (10) and Mehilli et al. (24).

Lesson #2: In DES Restenosis, the Pattern Continues to Predict the Outcome

In BMS restenosis, the angiographic patterns of neointimal overgrowth were shown to be an important prognostic indicator (15). The current report re-emphasizes that in DES restenosis this tenet also holds true. Latib et al. (10) use a modified Mehran classification to divide restenosis into 3 groups: focal, diffuse, and occlusive. Although the rate of surveillance angiography is low, the rate of a second restenosis increased progressively across the groups: from 29% (focal restenosis) to 46% (diffuse restenosis) to 66% (occlusive restenosis). It should be acknowledged that this trend did not hold true for clinical restenosis. Although the rate of target lesion revascularization increased from 16.5% for focal to 28% for diffuse, it dropped to 22% for patients with occlusive restenosis. This discordance indicates that chronic vessel occlusion in the setting of a second restenosis is often accepted as a sign that a revascularization strategy has failed, and in the present dataset, a significant number of patients proceeded to a trial of medical therapy, at least initially. Finally, the difficulty in correlating pattern of restenosis with hard clinical events should be recognized; after all, pattern classification is often accompanied by repeat intervention in the same sitting, and as such, the natural history of the index restenotic lesion is altered.

Lesson #3: Diabetes Mellitus–Associated Relative Restenosis Risk Is Greatly Attenuated With DES

Although the presence of diabetes mellitus conferred a clear increased risk of BMS restenosis, the introduction of DES seems to be associated with a leveling of the playing field in this respect. Indeed a number of large analyses from groups in Seoul, Korea; Washington, DC; and our center in Munich, Germany have shown similar rates of restenosis in patients with and without diabetes (17–19). The current report contains a signal that the same also holds true for the treatment of DES restenosis (most often managed with repeat DES implantation). The rate of recurrent restenosis was comparable in diabetics versus nondiabetics (35.2% vs. 38.4%; $p = 0.65$). Looking at the bigger picture, it seems that the high efficacy of DES devices has greatly attenuated the excess risk of restenosis in patients with diabetes.

Lesson #4: Event Rates After Treatment for DES Restenosis Remain High

The overall rate of major adverse events at 3 years in the present report (10) was not inconsiderable at 32.8%. This is not out of step with findings from other reports (12–14) and serves as a valuable reminder that in this disease subset, there remains some distance to be traveled before either patient or physician can be satisfied with treatment outcomes. Furthermore, the overall rate of target lesion revascularization at 3 years approaches 20%. Indeed, it might be observed that DES restenosis is a more recalcitrant disease process, with rather higher rates of target lesion revascularization seen than after treatment of BMS restenosis (20).

Lesson #5: The Optimal Management of DES Restenosis Remains Unclear

Comparative treatment efficacy analysis in registry reporting always entails considerable hazard due to the effects of residual unmeasured confounding (21). In this respect, although the investigators were careful to avoid direct comparisons between outcomes of restenosis treated with balloon angioplasty versus repeat DES therapy, their assertion that "the treatment of DES restenosis with repeat DES implantation appears to be associated with a reduction in recurrent restenosis (without) impact on the risk of late stent thrombosis" is perhaps the most tenuous of their findings. Certainly, the rate of definite stent thrombosis (2 incident cases [0.5%]) is indeed low, and this is certainly an encouraging safety signal. However, a registry report helps little in defining the most effective management strategy for patients with DES restenosis, and more randomized controlled trial data are urgently required.

So what are the options available for treatment of DES restenosis? First, as the predominant pattern of restenosis within DES is focal, repeat catheter intervention is likely to remain the mainstay of initial management. In this respect, we believe that the principal options are: 1) plain balloon angioplasty; 2) drug-eluting stenting; and 3) drug-coated balloon dilation. It might also be commented that oral therapy has not been investigated for DES restenosis.

Indeed the terrific success of DES led directly to the extinction of this therapeutic newborn despite encouraging clinical evidence (22,23). In addition, some colleagues might add brachytherapy as a further treatment option. Without entering into details about the strength of evidence in its favor, the lack of enthusiasm for embracing this therapy is not a sign of a bright future.

In respect of the 3 principal treatment options, certain lessons learned from BMS restenosis likely hold true: by virtue of a combination of high acute gain and low late loss, repeat DES implantation may remain superior to the other modalities listed. Furthermore, our experiences from the ISAR-DESIRE-2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis-2) study lead us to believe that a strategy of implanting a DES eluting the same class of drug as the failed initial DES or a switch to DES eluting another drug type are similarly efficacious (24). However, in light of encouraging data in BMS restenosis (25), the role of drug-coated balloon therapy in this therapeutic niche deserves further investigation. The hypothesized advantage is intuitive. The presence of an existing stent backbone from the index intervention continues to oppose arterial recoil and remodeling, whereas the brief local application of active drug at the time of angioplasty may deliver durable inhibition of neointimal regrowth. Along similar lines, the fact that multiple layers of stent do not offer any advantage in restenosis prevention highlights further the pressing need for an effective completely resorbable DES. Finally, against this background, we hope that data from the ongoing ISAR-DESIRE-3 trial—in which patients with limus-agent DES restenosis are randomized to plain balloon angioplasty, paclitaxel-eluting stent, or paclitaxel-coated balloon—will shed some further light on the management of patients with this challenging clinical condition.

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