

## EDITORIAL COMMENT

# Sirolimus-Eluting Stents: Does a Great Stent Still Need a Good Interventionalist?\*

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The history of interventional cardiology has been an exemplar of the old saying: "Two steps forward and one step back." Without a doubt, percutaneous coronary angioplasty offered an important therapeutic option intermediate to the extremes of medical management and bypass surgery. However, although balloon angioplasty has been acutely successful in more than 90% of patients, many patients experienced the new iatrogenic disease of restenosis. Restenosis is a complex pathophysiologic process recapitulating many elements of wound healing such as inflammation, thrombosis, cellular proliferation, and ground matrix deposition (1). Ultimately, elastic recoil, vessel contraction, and smooth muscle cell proliferation culminate in flow-limiting luminal narrowing in 20% to 50% of dilated vessels (2). The use of endovascular prostheses (i.e., stents) essentially eliminated vascular recoil and remodeling, resulting in significant reductions in restenosis in almost every lesion and patient subset. But the price of stenting is an exaggerated proliferative response commensurate with acute gain. The problem of in-stent restenosis (ISR) became the "one step back" of stenting.

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Concurrent with the emergence of stenting as the predominant catheter-based revascularization technique was the demand for outcomes derived from evidence-based medicine. Thus, the large randomized trial became a prerequisite for acceptance of most conclusions related to stenting. Catheter-based therapeutics, especially stenting, became one of the most closely studied treatments in medicine. One consistent paradigm repeatedly validated in the literature of interventional cardiology was the "bigger is better theory" which linked acute angiographic outcome with freedom from restenosis (3). This simple concept, as well as the empiric findings from intravascular ultrasound studies of optimal stenting, clearly established the importance of the operator in maximizing outcome with this breakthrough technology.

Despite the emergence of better and more deliverable

stents and routine high-pressure dilation, the problem of ISR has remained. Stent placement in diabetic patients, long lesions, small vessels, bifurcation stenoses, and in the presence of end-stage renal disease is associated with a restenosis rate that may exceed 50% (4). In the U.S. alone, approximately 200,000 repeat revascularizations were performed in 2001 at an annual societal cost of \$1.5 billion. Systemic pharmacotherapy has had little impact on restenosis, limited by the inability to deliver therapeutic levels to the vascular wall without incurring systemic toxicity. While intravascular brachytherapy has emerged as a powerful tool for reducing recurrent restenosis in patients who suffered ISR, it required an additional procedure and mandated prolonged dual antiplatelet therapy to prevent the risk of late stent thrombosis. Clearly, a "preemptive strike" was needed. In 2001, Sousa et al. (5) reported that stents which elute the immunosuppressive macrocyclic lactone rapamycin reduced in-stent neointimal volume by 95%, resulting in freedom from restenosis in all treated patients. Although this "First-in-Man" registry consisted of only 45 patients, it engendered great enthusiasm that the concept of "targeted drug delivery" might safely lead to the elimination of the scourge of restenosis.

The larger Randomized Study with the Sirolimus-Coated Bx-VELOCITY Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) raised expectations to the highest levels for the concept of drug-eluting stents by demonstrating a reduction in angiographic restenosis and target lesion revascularization from 27% to 0% (6). All of the expected terms were used to describe this breakthrough technology: "magic bullet," "home-run," and "landmark discovery." Aside from being safe and highly efficacious, drug-eluting stent placement would require no additional training and could be performed by any interventional cardiologist qualified to place a bare metal coronary stent. Presumably, drug-eluting stenting might even be easier for the interventionalist because the profound suppression of late loss might negate the need for optimal stenting. The U.S. pivotal Study of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) randomized almost 1,100 patients to treatment with either the sirolimus-eluting Cypher stent (Cordis Corp., Miami Lakes, Florida) or bare metal Bx-VELOCITY stent (Cordis Corp.) (7). Patients in SIRIUS had a higher frequency of diabetes mellitus, longer lesions, and greater lesion complexity than patients in the earlier RAVEL. As in RAVEL, in-stent late loss was negligible, leading to a 91% reduction in ISR from 35% to 3.2%. However, tempering the enthusiasm for this new technology was a somewhat disappointing finding of an 8.9% restenosis rate when the core angiographic laboratory measured not only the area within the stent but also the segment of the vessel encompassing the stent and 5 mm proximal or distal to its edges. Specifically, these additional in-segment restenoses were driven primarily by an incomplete suppres-

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sion of proliferation at the proximal edge of the stent, especially in smaller vessels.

A number of mechanisms were proposed to explain this phenomenon, including inadequate diffusion of sirolimus beyond the stent edge, inadvertent injury to the proximal edge from aggressive predilation, inadequate stent-to-lesion ratios, and overexpansion of the ends of the stent delivery balloon during high-pressure deployment. Clearly, the latter three mechanisms are operator- and technique-dependent. This raised an interesting question: are optimal outcomes with drug-eluting stents achieved by a device only, or does a great stent still need a good interventionalist? Specifically, can changes in operator technique result in restenosis rates even lower than those observed in SIRIUS? This hypothesis was tested in two additional randomized trials, namely E-SIRIUS and C-SIRIUS. In the European E-SIRIUS, 352 patients were randomized to either sirolimus-eluting stent (SES) or bare metal stent (BMS) (8). Although patients treated in E-SIRIUS had longer lesions and smaller vessels, binary in-segment restenosis was reduced by 33% in the drug-eluting stent cohort compared with patients receiving drug-eluting stents in SIRIUS. Unlike SIRIUS where late loss at the proximal edge was reduced by only 48% with the SES, in E-SIRIUS there was little difference in the relative reduction in in-stent and in-segment late loss (~75% to 80%). These findings are best explained by important differences in technique. Operators in E-SIRIUS deployed longer stents per lesion length, avoided gaps between overlapped stents, and employed direct stenting (i.e., without predilation in 26% of lesions). Effectively, the operators were careful to avoid leaving injured but unstented segments of the artery.

If this theory were true, it would place demands on the operator similar to other interventional techniques. Alternatively, the findings in E-SIRIUS might be explained by chance alone. It is sobering to believe that after publication of three multicenter, randomized trials comparing the same treatments, questions remain about optimal usage. Interestingly, neither SIRIUS nor E-SIRIUS corroborated the findings of its predecessor studies. In this issue of the *Journal*, Schampaert et al. (9) present data from the Canadian randomized trial, C-SIRIUS, the fourth randomized trial comparing SES to BMS.

At first glance, the C-SIRIUS study appears quite similar to the E-SIRIUS study except for a smaller sample size. Factors that influence restenosis such as diabetes mellitus, vessel size, and lesion length were similar. However, binary in-lesion restenosis in the BMS cohort was 52.3%, the highest reported for the four trials, suggesting that this was perhaps the most challenging subset of patients and lesions of the four randomized trials. Nevertheless, the in-lesion restenosis rate for patients treated with the SES was only 2.3%, lower than that seen in SIRIUS or E-SIRIUS, an

absolute reduction of 50% compared to E-SIRIUS. It is not surprising that the outcomes in C-SIRIUS more closely resembled those of E-SIRIUS than of SIRIUS. To an even greater extent than in E-SIRIUS, the operators placed stents without predilation, used longer stents resulting in higher stent to lesion ratios, and post-dilated many stents. Late loss in C-SIRIUS was actually lower at the edges than within the stent. Thus, the problem of suboptimal suppression of proliferation at the proximal edge, which drove the restenosis rate to 8.9% in SIRIUS, has been largely eliminated.

As with RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS provides valuable information regarding this wonderful new technology of drug-eluting stents. Moreover, C-SIRIUS validates the hypothesis offered in E-SIRIUS, namely that *optimal outcomes with a potent therapy such as drug-eluting stents are still operator-dependent*. A great stent still needs a good interventionalist, or at least one who takes advantage of the important findings in these four trials. Only in this way can we take the two steps forward without the one step back.

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