EDITORIAL COMMENT

In-Stent Restenosis: Should an Old Device Treat a New Problem?*

Joseph P. Carrozza, Jr., MD, FACC
Boston, Massachusetts

Thirty-five years after Charles Dotter first proposed the concept of an endovascular prosthesis, stenting has now emerged as the dominant technology for percutaneous coronary revascularization (1). In many laboratories, more than half of all patients undergoing catheter-based intervention receive at least one stent, and in some the use of stents approaches 80%. Although originally approved as treatment for abrupt vessel closure after conventional balloon angioplasty, in 1994 the landmark Stent Restenosis Study (STRESS) and Benestent trials demonstrated for the first time that an adjunctive therapy (i.e., elective stenting) could significantly improve acute outcome and reduce restenosis compared with balloon angioplasty alone (2,3).

Tempering this initial enthusiasm for stenting was the need for Draconian pharmacotherapy to prevent stent thrombosis. Colombo et al. (4) and other European investigators elegantly showed that the routine use of high-pressure postdilation and the substitution of the ADP-receptor antagonist, ticlopidine, for warfarin resulted in a reduction in the incidence of stent thrombosis, hemorrhagic complications and length of hospitalization. Concomitantly, the availability of new second and third generation sheathless stents in a variety of lengths and sizes greatly facilitated application of stenting to lesions subsets previously deemed “unstentable.” Given the excellent results achieved predictably with stenting and the suboptimal outcome with balloon angioplasty alone in many problematic lesions subsets, the use of stents in these “non-STRESS/Benestent” subsets is now routine practice. This exponential growth in the use of coronary stents has not been without its critics, as some charged that this trend was not driven by data, but by preoccupation with luminal appearance rather than clinical outcome (5). However, in the past five years a plethora of randomized trials and prospective registries have documented the benefits of stenting for a broad range of lesions, including saphenous vein graft lesions, prior restenosis, chronic total occlusions and acute myocardial infarction. Thus, the availability of better stents, abundance of evidence supporting their benefit and the freedom from prolonged anticoagulation has fanned the embers of “stentmania.”

While the early trials demonstrated that stenting was associated with significantly lower rates of angiographic and clinical restenosis, it was evident that stenting did not “cure” restenosis. As first proposed by Kuntz et al. (6), and subsequently verified in randomized trials, the salutary effects of stents are due entirely to their ability to provide predictably larger lumens, rather than an independent device effect. In fact, stenting is associated with greater late lumen loss (the difference between posttreatment and follow-up lumen diameter) than balloon angioplasty or directional atherectomy. Late lumen loss after stenting is due almost entirely to smooth muscle cell proliferation rather than vascular remodeling, which is a significant contributor to restenosis after balloon angioplasty or atherectomy (7). This proliferative response is ubiquitous after arterial injury and serves a beneficial effect by rendering the stent nonthrombogenic. However, since this response follows a near Gaussian distribution, some patients develop proliferation of sufficient magnitude to cause flow-limiting restenosis within the first year after stent implantation. Furthermore, with improvements in stent technology, interventional cardiologists are now “pushing the envelope” by stenting longer lesions, smaller vessels and bifurcation stenoses, all of which are associated with significantly higher rates of angiographic and clinical restenosis than the focal, de novo lesions in large vessels treated in the STRESS and Benestent trials. For example, stenting long lesions in small vessels in diabetic patients may be associated with recurrence rates that exceed 50%.

Based on conservative assumptions, it is estimated that approximately 25,000 to 50,000 patients a year in the U.S. will require treatment for in-stent restenosis. Thus, the management of this problem is highly relevant to contemporary practice. It is important to remember that patients with in-stent restenosis who are asymptomatic, without provokable ischemia have excellent long-term prognosis and may be managed medically (8). However, when in-stent restenosis results in myocardial ischemia, luminal reenlargement can be achieved in almost all patients by a variety of catheter-based techniques. The initial experience for treatment of in-stent restenosis involved balloon dilation within the stent. In the first large series of percutaneous treatment of in-stent restenosis, Baim et al. (9) demonstrated that balloon dilation was associated with acute success in all patients, without need for additional anticoagulation. The excellent acute angiographic appearance achieved usually with only one balloon inflation suggested that in-stent restenosis could be effectively treated in a cost-effective and straightforward manner using a “low-tech” solution, balloon

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From the Cardiovascular Division, Beth Israel-Deaconess Medical Center, Boston, Massachusetts.
angioplasty. However, the optimism generated by this approach was dampened by a relatively high rate of recurrent restenosis (~50%) in this series (limited by angiographic follow-up of only 50%).

In the this issue of the Journal, Bossi et al. (10) report a target vessel revascularization rate of only 21.4% after balloon dilation of in-stent restenosis in 234 patients. This encouraging outcome is in accord with earlier, smaller series reporting clinical recurrence rates of 11% to 35% (11–13). Since repeat dilation is the least technically demanding and cheapest way to treat in-stent restenosis, it is tempting to view these studies as justification for balloon-based strategies. However, seminal observations by Kimura et al. (14) relating morphology of in-stent restenosis to subsequent risk of recurrent restenosis after balloon angioplasty have enlightened us to the fact that not all in-stent restenosis responds favorably to repeat dilation. Their report of an angiographic restenosis rate of 75% for stents with a diffuse pattern of restenosis (compared with only 8% for focal in-stent restenosis) was sobering. These findings are corroborated by contemporary series by Eltchaninoff et al. (13) and Bauters et al. (11), both of whom reported significantly higher rates of angiographic restenosis for balloon dilation of diffuse, compared with focal, in-stent restenosis. More importantly, patients with diffuse in-stent morphology are significantly more likely to require repeat revascularization procedures after balloon angioplasty. Target vessel revascularization rates of 25% to 63% have been reported after balloon dilation of diffuse in-stent restenosis (11–13,15). In this study, repeat revascularization was required in 26.7% and 31.1% of patients with diffuse (≥10 mm) and proliferative (≥10 mm and extending beyond the stent margins) patterns of in-stent restenosis, respectively. In contrast, repeat revascularization was required in only 12.5% of patients with focal in-stent restenosis. Furthermore, patients with diffuse in-stent restenosis treated by atherectomy were excluded from their analysis. If atherectomy were chosen based on operator perception that those lesions would respond poorly to balloon dilation, their exclusion may represent a selection bias toward better outcome in this series. The study also confirmed that early (<90 days) presentation of restenosis, nonfocal morphology and smaller posttreatment lumen diameter are all independently associated with the need for subsequent revascularization. These important observations should underscore the fact that patients with early onset or diffuse in-stent restenosis represent a high-risk subset and may require adjunctive treatment beyond balloon dilation. In addition, the “bigger is better” paradigm linking acute angiographic and late clinical outcome also applies to treatment of in-stent restenosis as well.

Why is balloon angioplasty of diffuse in-stent restenosis plagued by such high recurrence rates? The mechanism of luminal enlargement after balloon expansion includes a combination of stent expansion (56% of area gain) and a decrease in hyperplastic material resulting from both plaque compression and extrusion through the struts (44% of area gain) (16). Despite high-pressure dilation, the residual stenosis is relatively high (~18%), and the cross-section area within the stent is almost always less than that obtained when the stent was originally deployed. Furthermore, using intravascular ultrasound, Shiran and colleagues (17) have elegantly demonstrated that immediate recoil of hyperplastic material compressed and extruded through the stent struts further erodes approximately 20% of the initial gain achieved with balloon dilation. This early reduction in lumen cross-sectional area is most pronounced after treatment of diffuse in-stent restenosis, probably due to the higher total plaque volume.

These observations became the impetus for investigation of other strategies employing “debulking” techniques, in which a portion of the plaque within the stent is removed or ablated before balloon dilation. Several investigators have reported repeat revascularization rates from 20% to 38% after rotational atherectomy for diffuse in-stent restenosis (15,18,19). In a retrospective analysis, Dauerman and colleagues reported a reduction in subsequent target vessel revascularization from 46% to 28% in patients with diffuse in-stent restenosis treated with rotational or directional atherectomy compared with balloon angioplasty alone. Independent predictors of target vessel revascularization included diabetes mellitus, lesion length and smaller post-treatment lumen diameter. Similar results have also been reported after the use of directional atherectomy or excimer laser angioplasty (16,20,21). In the randomized Rotablator Versus Balloon for Stent Restenosis trial, 150 patients with in-stent restenosis were randomized to treatment with balloon angioplasty or rotational atherectomy. Patients in the rotational atherectomy cohort had significantly greater lumen area gain and a 53% reduction in clinical restenosis (20% vs. 43%) (19). The benefits of rotational atherectomy in the treatment of diffuse in-stent restenosis are best explained by the observations that tissue removal is the predominant mechanism of luminal enlargement, with a smaller contribution of compression and extrusion of plaque and additional stent expansions (18,19).

Despite these promising results observed with debulking of in-stent restenosis, many patients with diffuse in-stent restenoses will require additional interventions to treat this aggressive proliferative response, which some have termed “malignant restenosis.” Since in-stent restenosis is due almost entirely to a proliferative process, therapies that can inhibit smooth muscle cell division offer the best hope for the prevention and treatment of in-stent restenosis. The observations that ionizing radiation is effective in the treatment of other benign proliferative disorders (e.g., ocular pterygium and keloid formation) provided the theoretical basis for the investigation of brachytherapy as a treatment for restenosis. In the Scripps trial, patients at high risk for restenosis (the majority of whom had in-stent restenosis) were randomized to gamma irradiation with 192I or placebo (21). Patients in the radiation cohort had a marked reduction in angiographic restenosis (17% vs. 54%) and target lesion revascularization (12% vs. 45%). These dramatic benefits of gamma irradiation were confirmed in the larger multicenter Gamma 1 trial where in-stent angiographic
restenosis was reduced from 52% to 22% in lesions treated with gamma irradiation (22). In the Washington Radiation For In-Stent Restenosis Trial (WRIST), in which patients with in-stent restenoses in either native coronary arteries or saphenous vein grafts were randomized to intracoronary gamma irradiation or placebo, a significant reduction in angiographic restenosis (19% vs. 58%) and subsequent target lesion revascularization (26% vs. 67%) was observed in the active treatment cohort (23). The long-term outcome of patients with in-stent restenosis treated with beta irradiation is being evaluated in the randomized Stents and Radiation Therapy trial in which patients are randomized to beta irradiation with a 90Strontium/Yttrium source (Beta-Cath System, Novoste Corp, Norcross, Georgia) or placebo. While the preliminary findings from this study suggest that intravascular radiation therapy reduces angiographic restenosis by 47% and target vessel revascularization by 34% (24). Issues such as dosimetry, radiation source, importance of source “centering,” “geographic mismatch” and long-term safety must be thoroughly addressed before widespread adoption of this promising therapy can be recommended.

While there are many unresolved issues regarding the treatment of in-stent restenosis, several principles have emerged over the past few years. First, interventional cardiologists should heed the old adage that “an ounce of prevention is worth a pound of cure” and strive to optimize stent expansion at the time of deployment, rather than looking for the fastest and cheapest way to complete the case. This may involve debulking calcified or bulky plaques before stent placement, post-dilating the stent with larger balloons or use of on-line quantitative angiography, intravascular ultrasound or physiologic assessment to confirm optimal stenting. Second, the “oculo-stenotic reflex” of repeat intervention is best avoided when patients with in-stent restenosis are asymptomatic and lack provocable ischemia, since it carries a favorable prognosis and may regress over time. As illustrated in this study, ischemia due to focal in-stent restenosis can be safely and reliably treated with balloon dilation with low likelihood of clinical recurrence. At the present time, for the more problematic subset of patients with diffuse in-stent restenosis, debulking before redilation allows the operator to obtain better acute results, which offers the best chance of long-term patency. In the future, adjunctive brachytherapy may reduce the exuberant cellular proliferation that still plagues this breakthrough technology.

**Reprint requests and correspondence:** Dr. Joseph P. Carrozza, Jr., Cardiovascular Division, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215. E-mail: jcarrozza@caregroup.harvard.edu.

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