In-Stent Restenosis

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The decrease in restenosis rates compared with conventional angioplasty, stable angiographic results with a subsequent decreased need for urgent or emergency coronary bypass graft surgery, and reliable treatment of acute or threatened closure resulting from conventional angioplasty have all made stents the treatment of choice for many patients undergoing percutaneous intervention. In-stent restenosis (ISR), however, has become a significant problem. Neointimal hyperplasia with vascular smooth muscle cells is even more exaggerated with stent placement than with conventional angioplasty. In addition, failure to deploy the stent optimally at the time of the initial placement may result in increased restenosis. Symptoms of ISR typically occur within 6 to 9 months following intervention, and range from asymptomatic angiographic narrowing, or even occlusion, to recurrent angina/ischemia or myocardial infarction. Evaluation is by repeat angiography. Treatment with balloon angioplasty is effective for focal in-stent restenotic lesions; for other lesions excimer laser, rotational atherectomy, and directional coronary atherectomy are associated with excellent initial outcome, but long-term outcome of these procedures is unclear. Brachytherapy with both gamma and beta sources has been found to result in improved outcome with less angiographic restenosis and decreased target vessel revascularization. Late thrombosis has been documented in up to 10% of patients treated with vascular gamma brachytherapy, and increased stenosis at the edges of the treated segment is also seen. Prolonged dual antiplatelet therapy and avoidance of a new stent has been shown to reduce late thrombosis in patients treated with vascular brachytherapy. [Rev Cardiovasc Med. *2001;2(3):115–119*]

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Stents are now used in approximately 80% to 90% of all interventional cardiology procedures.[1,2] This practice pattern is the result of several factors: 1. the documented decrease in restenosis rates compared with conventional angioplasty in multiple patient and angiographic subsets; 2. achievement of stable, predictable, initial angiographic results, even in complex lesions. This is associated with a subsequent decreased need for urgent or emergency coronary bypass graft surgery compared with conventional angioplasty; and

3. reliable treatment of acute or threatened closure resulting from conventional angioplasty. Despite these major advantages, stents have some disadvantages, including, among others, side-branch access and in-stent restenosis (ISR). The latter is the most significant problem.

Stents have some disadvantages, including side-branch access and in-stent restenosis.

A considerable body of knowledge has accumulated on the pathology and clinical manifestation of and treatment approaches to restenosis.[3,4] The restenosis process has several components:

1. Elastic recoil, which occurs within approximately 60 minutes after initial balloon dilation and results in loss of some of the initial gain;
2. Negative or constrictive remodeling, which occurs within the several months of balloon dilation—this phenomenon results in constriction of the segment treated such that the area encompassed by the external elastic membrane decreases and stenosis results;
3. Neointimal hyperplasia with vascular smooth muscle cells—this phenomenon also occurs within the first several months following treatment of the coronary stenosis;
4. Matrix formation—in animal models and the human setting, restenotic tissue contains substantial matrix which includes, among other substances, proteoglycans. This matrix accounts for a substantial amount of the volume of the restenotic lesion. In animal models, this matrix accounts for more than 50% of the volume of the restenotic lesion.

The relative amount that each of these components contributes to the restenotic process depends upon multiple factors, including, among others, the specific treatment device used, and specific clinical characteristics, for example diabetes, or prior treatment at the site. With stent implantation, the negative remodeling (constriction) that was an important feature of restenosis with conventional angioplasty is no longer operative. The restenosis that may occur with stent implantation is a function of neointimal hyperplasia, which is even more exaggerated with stent placement than with conventional angioplasty. The mechanism by which stents prevent restenosis is by achieving a larger initial lumen, which can accommodate the more aggressive neointimal hyperplasia as well as preventing negative remodeling. A component that may be operative for some patients with ISR is failure to deploy the stent optimally at the time of the initial placement, thereby not obtaining the optimal immediate postprocedural result.

The clinical manifestations of ISR are variable; some of this variability depends on the definition of ISR that is used. The manifestations range from asymptomatic angiographic narrowing, or even occlusion, to recurrent angina/ischemia or myocardial infarction. Recurrent angina is probably the most common. Symptoms of ISR typically occur within 6 to 9 months following the index intervention; the time course is quite similar to that seen after conventional angioplasty.

Repeat angiography is the gold standard for evaluation of restenosis after stent placement. Four different angiographic patterns have been described[3]:

1. Focal ISR of less than 10 mm in length, confined within the stent borders;
2. ISR over 10 mm in length but still confined to within the stent borders;
3. ISR over 10 mm in length and extending beyond the stent borders; and
4. Complete occlusion from ISR. These patterns appear to have prognostic importance. Target lesion revascularization rates increase from 19% for the focal pattern to 83% for the occlusive ISR pattern. (See Figures 1–4.)

Evaluation or the treatment for ISR has been problematic, in part because of the multiple patterns of ISR, which have often been considered together, and because of the widely variable approaches that have been used. An additional problem is the issue previously alluded to: that in some patients with ISR, the pathophysiology is predominantly underexpansion of the stent and not neointimal hyperplasia, whereas in other patients it is almost completely neointimal hyperplasia. What can be said is that treatment with balloon angioplasty is effective for focal ISR lesions and is usually associated

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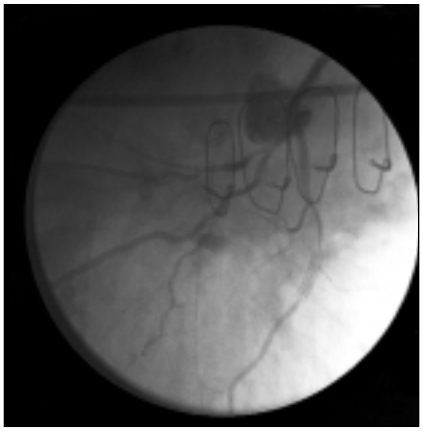

Figure 1. *Diffuse proliferation in-stent restenosis in the middle LAD, which extends beyond the stent margins. The recurrence rates in patients with this angiographic finding are very high.*

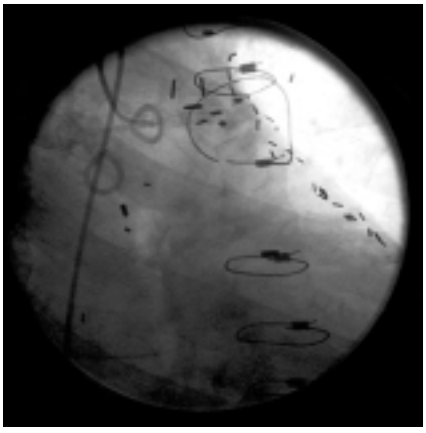

Figure 2. *Total occlusion of a stent previously placed at the ostium of a saphenous vein graft. Patients in this group have the highest recurrence rates.*

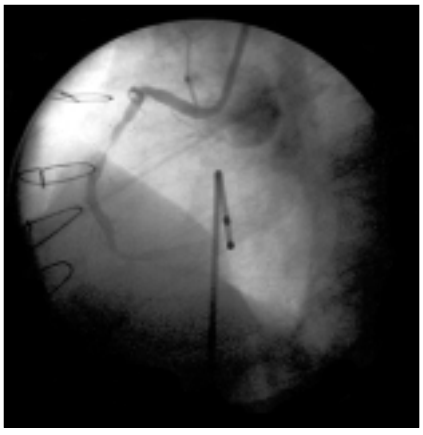

Figure 3. *Focal in-stent restenosis in the mid-right coronary artery. Lesions like this may respond well to conventional dilation.*

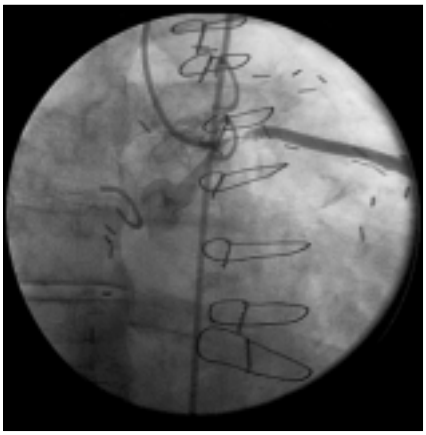

Figure 4. *Relatively focal in-stent restenosis at the ostium of a vein graft. Filling defects are present at the distal end of the stenosis, possibly representing thrombus.*

with excellent initial angiographic and longer-term results. The other lesion types are clearly more difficult to treat. Debulking has been studied using excimer laser, rotational atherectomy, and directional coronary atherectomy.[5-7] In general, these techniques are associated with excellent initial outcome. For example, in a multicenter surveillance study, excimer laser was studied in 440 patients with 527 restenotic or occluded stents.[7] Adjunctive angioplasty was used in 99% of the cases. Procedural success was achieved in 91% of cases, and in-hospital outcome was excellent, with Q-wave myocardial infarction rates at 0.5%, non-Q-wave myocardial infarction at 2.7%, coronary bypass surgery at 0.2%, and 1.6% mortality. Whether this approach will result in improved long-term outcome is unclear.

In a smaller study of patients treated with dilatation or laser for ISR, in 98 patients the target lesion revascularization was somewhat lower; the excimer laser–treated patients had 21% target lesion revascularization (TLR) versus 38% TLR with conventional dilatation, but this was not statistically significant.[6] Other data indicate that laser treatment does not improve the longer term outcomes at all. In a recent series of 96 patients treated with excimer laser and angioplasty for ISR the recurrent restenosis rate was 54%.[8]

Rotational atherectomy has also been evaluated.[4,5] In a small series[4] of 45 patients, rotational atherectomy resulted in an initial improvement in minimal lumen diameter by a combination of ablating neointimal hyperplasia and adjunctive dilatation of the stented segment, but recurrent restenosis at 6 months was seen in 45%. In a recent randomized trial[5] of 298 patients treated with rotational atherectomy or conventional angioplasty for ISR, both approaches resulted in restenosis rates greater than 50%. In fact, restenosis rates with rotational atherectomy were higher at 64.8%, as compared with conventional angioplasty at 51.2%. The majority of these patients had a diffuse pattern of ISR and so they were at particularly high risk for recurrence.

Stenting for ISR has also been studied in observational studies. Although it is also associated with high initial success rates and initial improved minimal lumen diameter, the long-term benefit remains unproved, particularly for those patients with diffuse ISR. In the control limbs of some of the vascular brachytherapy studies, stenting was used frequently. In this setting, where stents were deployed but no radiation was delivered, recurrent restenosis rates were very high and in some patients approached 60%.

New technologies have been developed and are being tested in these higher-risk patient groups. Some of these technologies have been subjected to well-controlled randomized clinical trials; others are being evaluated just in registry

series. The most advanced technology evaluated is brachytherapy.[9-14] Clinical trials have enrolled more than 4000 patients. Some of these studies now include follow-up to 3 years, so that longer-term clinical and angiographic data is available. A number of sources for brachytherapy have been tested, as well as a number of different delivery systems. Both gamma and beta sources have been found to result in improved outcome, with less angiographic restenosis and decreased target vessel revascularization as well as improved composite clinical end points. Gamma and beta sources both have advantages as well as disadvantages, and both are in the final stages of commercialization after FDA approval. There have been no trials comparing the two sources head to head.

Gamma Radiation

Iridium 192 is the gamma emitter used in all the previous and ongoing clinical trails. Two single-center studies preceded the pivotal GAMMA-1 trial, which was a multicenter trial of 252 patients with ISR. This pivotal trial documented a decrease in angiographic restenosis from 52% in the placebo control to 21.6% in the treated patients. This was accompanied by a corresponding significant decrease in target lesion revascularization. This pivotal study documented a dose response curve, which identified that over 14 Gy resulted in improved outcome compared with 10 Gy to 12 Gy. Some groups of patients and lesions, which showed particular benefit with gamma radiation, included patients with diabetes and those with long lesions. Patients with these conditions are at highest risk for recurrent restenosis when treated with conventional therapy.

These three trials formed the basis of FDA approval for this technology. There are other ongoing investigations. Some of these trials are aimed at evaluating other gamma systems from different manufacturers. Others are aimed at identifying the optimal dose for treatment of ISR or the most effective treatment of longer lesions or vein grafts.

Two important findings have surfaced, neither of which was expected. Both of these have important implications, and both are seen with gamma as well as beta systems. Late subacute closure, or late thrombosis, has now been documented to occur in up to 10% of patients treated with vascular brachytherapy.[13,14] It has been seen irrespective of the type of radiation source, that is, gamma or beta. The mean time to late total occlusion in one of the larger series was 5.4 ± 3.2 months. When it occurs, late total occlusion presents as acute infarction in approximately 45% of patients and unstable angina in approximately 50%; only a small minority of patients are asymptomatic.

The mechanism of late total occlusion has been postulated to be related to delayed or impaired re-endothelialization after vascular brachytherapy. Two factors have been identified as important associations with late total occlusion: 1. placement of a new stent at the time of vascular brachytherapy; and 2. lack of prolonged antiplatelet treatment. When new stent implantation is avoided at the time of brachytherapy and prolonged antiplatelet therapy with aspirin and a thienopyridine is administered, the risk of late total occlusion appears similar to that seen in patients not receiving vascular brachytherapy. The exact duration of dual antiplatelet therapy required is unclear but is probably at least 6 months and may be longer if a new stent is placed.

The second problem, which was also unexpected, was documentation of increased stenosis at the edges of the treated segment—sometimes known as the edge effect or candy wrapper effect. This was seen particularly with the radioactive stents but has also been documented with both gamma and beta catheter systems. In patients with this problem, although the treated segment may remain free of significant restenosis, the edges may develop significant or even severe stenoses so that treatment is subsequently required. There are several putative mechanisms for this phenomenon: enhanced neointimal hyperplasia from low-dose radiation; uncovered diseased segments subjected to balloon trauma that are not covered by the radioactive source; or geographic miss, where the treated segment is only partially irradiated. This problem has focused attention on meticulous placement of the radioactive source to cover the entire treated segment.

Beta Radiation

Several beta emitters have been tested both in registry series and in large multicenter, placebo-controlled randomized trials.[13] Interestingly, beta sources have also been tested for treatment of de novo lesions as well as ISR. The pivotal ISR trial, in which the FDA approved this technology, was the START trial, which used the Beta Cath™ system and evaluated safety and efficacy in 485 patients from 55 centers. Patients received doses of 16 or 20 Gy, depending on the vessel size. At 8 months there were reductions in angiographic restenosis (29% versus 45%; P = .001) and target lesion revascularization (16% versus 22%; P = .008). In this study, new stents were placed infrequently (~20%), and dual antiplatelet therapy was

prolonged and included at least 3 months of therapy. This resulted in marked reduction in late thrombosis compared with other beta or gamma studies previously reported. This further emphasizes the importance of avoidance of new stents and use of prolonged dual antiplatelet therapy. Only one beta source system is currently approved, but others are expected.

New Approaches

Other approaches are being tested for ISR. One of these involves a miniaturized x-ray tube for the delivery of soft x-rays to the treated segment.[15] This would have the potential of avoiding some of the administrative delivery issues related to vascular brachytherapy, such as the mandatory involvement of a radiation oncologist and physicist. Still other approaches include sonotherapy, light activation, and local arterial wall alcohol injection. A most promising technology includes drug-coated stents. Both sirolimus and Taxol are being studied in human trials. So far, these trials have included only de novo arterial lesions. The results, however, look very promising. Undoubtedly, these drug-coated stents will be evaluated in patients with ISR.

Conclusion

ISR remains a significant problem. It can result in the need for repeated percutaneous interventions and, in some patients, eventual coronary bypass graft surgery. In other patients, the potential for ISR is disquieting enough that the patient or physician opts for initial coronary bypass graft surgery, for example in patients with proximal or ostial left anterior descending (LAD) stenoses. Fortunately there is a new approved technology, vascular brachytherapy, which has been documented to be safe and effective for treatment for ISR. Continued technological development with alternative approaches should further improve the interventional approach for the treatment of patients with coronary artery disease. ■

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Main Points

- Stents prevent restenosis by achieving a larger initial lumen which can accommodate the more aggressive neointimal hyperplasia as well as preventing negative remodeling.
- Neointimal hyperplasia is more exaggerated with stent placement than with conventional angioplasty.
- Clinical manifestations are variable and range from asymptomatic angiographic narrowing, or even occlusion, to recurrent angina/ischemia or myocardial infarction; prognosis differs according to angiographic findings of diffuse or focal restenosis or total occlusion.
- Treatment with balloon angioplasty is effective for focal in-stent restenotic lesions; excimer laser, rotational atherectomy, and directional coronary artherectomy provide excellent initial outcome for diffuse or occluded lesions, but long-term outcome is unclear.
- Brachytherapy with both gamma and beta sources has been found to result in improved outcome with less angiographic restenosis and decreased target vessel revascularization.