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In-stent restenosis: new approaches to an old problem

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Intracoronary stents have an unequivocal role in the realm of percutaneous coronary intervention. By preventing early complications and attenuating restenosis, they have been widely adopted by the cardiology community. Re-narrowing of dilated coronary arterial segments, however, has proven to be a consistent and resistant problem. This shift in practice means most restenotic lesions are occurring in a previously stented vessel. As the incidence of this iatrogenic disease continues to grow, it is time to re-evaluate the mechanisms and therapeutics in our armamentarium to treat this new phenomenon.

Limitations of stent technology

The introduction of intracoronary stents improved the safety and effectiveness of percutaneous interventions.[1] As a metal scaffold, they tent arterial wall dissections and reduce passive vessel recoil following balloon dilatation, resulting in larger post-procedural lumens.[2] Early procedural complications related to this technology, namely thrombosis and vessel closure, have been addressed through more effective anti-platelet regimens, optimizing stent expansion and more accurate sizing of target vessel.[2]

Over time, however, there is an enhanced proliferative response of the arterial wall to injury; this is known as neointimal hyperplasia. Initially, inflammatory cells appear at the stent struts. This is followed by the migration and proliferation of activated smooth muscle cells from the media to the intimal layer, a process similar to that following balloon injury. This leads to increases in extracellular matrix (ECM) volume with collagen synthesis and deposition, and an inflammatory response.[2-4] Thus, the initial gain in lumen size is, to varying degrees, lost due to the encroachment of tissue over the months following the procedure. While stents are effective in attenuating recoil from balloon inflation, the subsequent tissue in-growth is more aggressive when the "late loss" overwhelms the "early gain" post-dilatation, restenosis results.

In the literature, rates of in-stent restenosis vary from 7%[5] to 40%[6] This is in part, dependent on the outcome measure employed (angiographic vs. functional vs. events), population studied, and whether measured from randomized trials or cohorts studies.

Classification of ISR

Stents alter the geometry and characteristics of coronary vessels such that grading systems predicting the risk of restenosis in native vessels no longer apply. For example, markers for native vessel complications including restenosis (eg, irregular lesion contour and calcification), are no longer predictive when stenosis develops in a successfully deployed stented segment.

In an attempt to prognosticate in-stent stenotic lesions, Mehran and colleagues followed 245 consecutive patients undergoing catheter-based procedures for varying amounts of in-stent restenosis.[6] Patterns of disease were categorized according to their angiographic appearance, by the degree of tissue proliferation, and from focal (types 1A-1D) to diffuse (> 10 mm, types II-IV) (Figure 1). More diffuse patterns were found among patients with diabetes mellitus and a history

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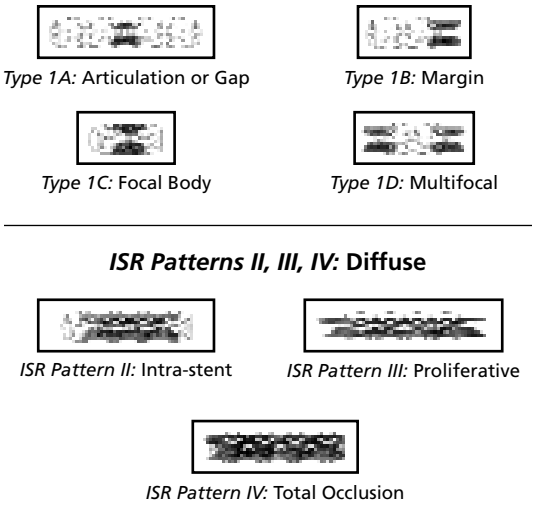
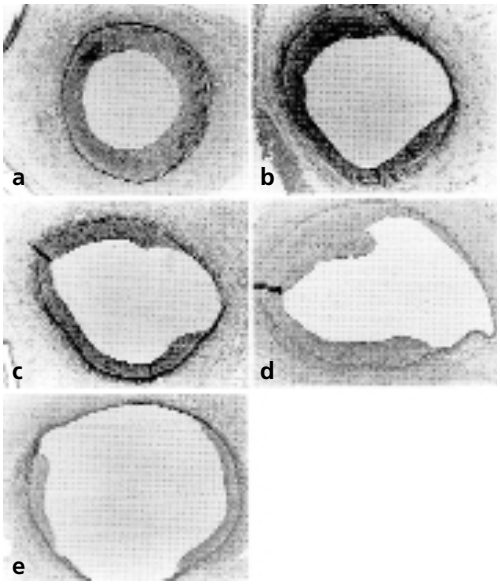
Figure 1: Classification of in-stent restenosis[6]



of previous in-stent restenosis (ISR). Choice of device used to treat ISR was left to the discretion of the operator, and all interventions were IVUS (intravascular ultrasound)-guided. While post-procedural results were similar across all groups, one-year event rates, (specifically, target lesion revascularization [TLR] rates), were strongly related to presenting pattern of disease, and independently related to a history of in-stent restenosis and diabetes (Table 1). This study demonstrated that, compared to re-narrowing following balloon angioplasty, certain patterns of in-stent restenosis reflecting the burden of disease can be particularly aggressive in nature and extremely difficult to treat.

Because of the volume of clinical data regarding PCI outcomes, other factors have long been established as predictors of in-stent restenosis. These include small reference vessel size (less than 2.75 mm in diameter), ostial disease, vein graft lesions and unstable symptoms.[2,3]

Figure 2: Increasing doses of endovascular radiation blunts intimal growth after balloon injury in a porcine model[15]



Treatment options

Treatment trials for ISR have reflected the observations of Mehran and colleagues: focal lesions seem to respond to most interventional techniques, while diffuse restenosis is much more aggressive and likely to recur.

In centres with extensive experience, most catheter-based techniques to treat ISR have been disappointing. Repeat balloon angioplasty, with or without IVUS assistance, has been used to dilate stenotic lesions with limited success. Despite good post-procedural results, studies suggest that the luminal gain after a second balloon inflation is in large part due to over-expansion of the original stent

Table 1: 6-month outcomes after intervention according to classification for in-stent restenosis[6]

	Patterns of ISR			
	Focal	**Intrastent**	**Proliferative**	**Total Occlusion**
Death	2.5	2.6	3.3	0.0
Myocardial infarction	1.2	2.6	0.0	0.0
TLR*	19.1	34.5	50.0	83.4
PTCA*	14.8	26.3	36.3	66.7
CABG*	4.3	8.2	13.7	16.7

Values are expressed as percentages. CABG indicates coronary artery bypass surgery.
*p<0.0001 by ANOVA.

with a lesser impact on the hyperplastic intima, resulting in a failure to achieve original post-procedure lumen size.[7,8] In the literature, clinical and angiographic *recurrent* restenosis rates vary between 20 to 83%, and 5 to 54% respectively.[6,8]

Recognizing the proliferative nature of in-stent restenotic lesions, an attractive approach has been to debulk lesions before proceeding to repeat balloon dilatation. Few studies of directional atherectomy and rotational ablation of intimal tissue have been undertaken among in-stent lesions. In a cohort followed by Sharma and colleagues, although adequate early lumen gain was demonstrated, repeat target vessel revascularization rates were 28%.[9] The factors associated with re-narrowing were similar to those described above. Other studies have corroborated these results.[10] Excimer laser therapy, a second method of ablating excess tissue, has produced similar, dissatisfying results. An angiographic follow-up study of 98 patients undergoing laser treatment ablation and adjunctive angioplasty found a TVR rate of 21%.[11] In a similar cohort, Koster and colleagues report a 6-month clinical event rate of 50%.[12]

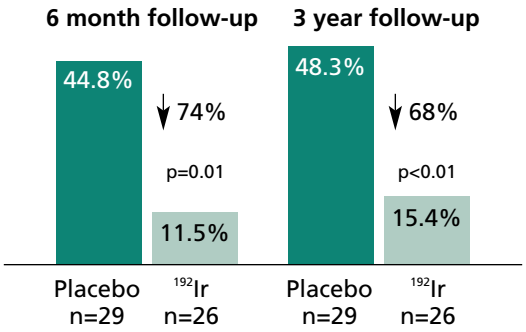
Intravascular ultrasound examinations following debulking procedures have shown that the components of lumen gain are divided between tissue removal, tissue extrusion through the stent, and further stent expansion.[10,11] These studies demonstrate that the tissue response to injury is not unique to a specific type of intervention, and effective therapy may need to focus on attenuating this important mechanism.

Radiation therapy

Recently, ionizing radiation has shown promise as a novel method of dealing with stented, restenotic coronary disease. Its ability to kill rapidly dividing cells and subsequent fibrosis may prevent the proliferation and migration of responsible smooth muscle cells. Intracoronary radiation is a potent inhibitor of vessel in-growth in the porcine balloon injury model, and in early phase, human trials (Figure 2).[13-15]

Two catheter-based forms have been studied most extensively: beta and gamma emitters. Gamma radiation, in the form of ^{192}Ir, has the most clinical experience and has demonstrated the most potent inhibitory effect.[3,14] Despite a relatively steep dose drop off (40% found at 2.5 mm from reference seed), it is deeply penetrating and cannot be shielded by conventional lead aprons. When delivered manually via impregnated seeds forming a ribbon, treatment times are approximately 30 minutes. Higher doses, and thus lower treatment times, can be achieved with the use of a dose-rate afterloader, equipment that requires special shielding, the cooperation of personnel trained in radiation (nuclear physician or radiation oncologist), and even a temporary withdrawal of personnel from the cath lab room during the exposure time.[3] With these precautions, a recent report measured the radiation dose absorbed among personnel following typical gamma catheter-based therapy to be <1% of the annual limit for personnel working fluoroscopic equipment.[16]

Figure 3: Differences in target lesion revascularization rates are preserved at 6 months and 3 years following ^{192}Ir[18]



Gamma sources

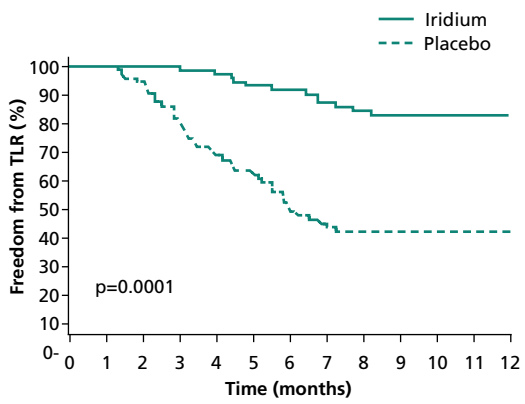
Two trials have tested the effectiveness of gamma ^{192}Ir to treat restenosis. Tierstein and colleagues randomized 55 patients presenting with coronary restenosis for stent placement, to adjunctive catheter-mounted ^{192}Ir or placebo.[17] The majority of patients had in-stent restenosis at baseline and the mean lesion length was approximately 12 mm in each group. The primary endpoint of angiographic restenosis, described as late lumen loss, was significantly lower in the treatment group at 6 month follow-up. This finding was mirrored in the rates of TLR, and maintained at 3 years follow-up.[18] (Figure 3).

More recently, Waksman and colleagues conducted the largest trial of radiation treatment in patients with in-stent restenosis.[19] They tested the ability of gamma ^{192}Ir to decrease clinical events in 130 patients presenting with primarily diffuse in-stent disease, in a double-blind, placebo-controlled fashion. All patients underwent optimal percutaneous coronary intervention (PCI) with similar immediate post-procedural results. At six-month follow up, the relative rates of death/MI/TLR between treatment and placebo groups was 29% and 67%, respectively ($p<0.001$). Angiographic and IVUS studies confirmed low rates of restenosis. At 12 months, the effect was preserved, translating into a relative risk reduction of 48%, and in this high-risk population, the average number of patients needed to treat was 3 (Figure 4). As with the former study, there were no arterial aneurysms, nor increased complications in the treated arm.

Beta sources

Beta emitting sources, primarily in the form of 90Sr/Y, have been studied less extensively.[14,20] In contrast to

Figure 4: Kaplan Meier estimates of freedom to target lesion revascularization[19]



gamma sources, they have limited tissue penetration and can be delivered via catheter by the operator over 4 minutes, resulting in 1/10,000 the absorbed total body dose relative to gamma sources. The total patient dose would represent .001% of the exposure from average fluoroscopy time following PCI.

Cohort studies have assessed the safety and efficacy of beta radiation after balloon angioplasty.[20-22] All have found consistently low rates of angiographic late lumen loss and binary restenosis. Raizner and colleagues recently compared catheter-delivered Beta 32P sources to placebo for a spectrum of lesion types in a randomized-controlled fashion.[23] They found significantly lower rates of angiographic restenosis and target vessel revascularization at 6 months for the treatment group over a range of dose deliveries. However, there was a trend towards higher rates of myocardial infarction in the radiation arm at 12 months.

Taken together, both gamma and beta-emitting sources both seem to demonstrate an extremely potent inhibitory effect on restenosis. Catheter-based radiation delivery currently represents the most promising therapy for diffuse in-stent restenosis.

Radioactive stents

Radioactive stents are generated through nuclear reactors to emit various isotopes and deliver higher total doses of radiation by emitting lower doses over a greater length of time.[22,24] Gold-emitting devices (198Au) have lead to an *increased* neointimal response in the animal model.[24] Remo and colleagues have demonstrated "edge effects" of disproportionate dosing 32P-emitting stent, resulting in restenosis.[22] Termed the "candy wrapper," it occurs as a consequence of low dose delivery at the borders of the stent.

Limitations of radiotherapy

The enthusiasm for radiation therapy to prevent ISR is tempered by some potential limitations. The challenge of delivering the isotopes at a reasonable exposure risk to personnel requires some changes in cath lab equipment and procedure. The time over which restenosis and clinical events occurs appears to be longer in the treatment groups. Some authors have speculated that this may, in fact, represent the ability of radiation to delay, but not abolish the process of restenosis.[25]

Late thrombosis is a significant complication common to catheter-based techniques, particularly when radiation is combined with stenting. A trend towards increased late occlusion is consistent among recent treatment trials, with an incidence ranging from 6.6% to 10% up to 15 months after radiation therapy.[23,26] The largest experience with radiation therapy recently reported an incidence of late thrombosis of 9.1% from all clinical studies of all source-emitters.[27] Nearly half presented with acute myocardial infarction. These events may be the detrimental consequence of radiation-inhibited tissue healing, thus compromising re-endothelialization of the stent surface and healing of dissections. Longer antiplatelet regimens may be required.[25]

Finally, the longer-term effects of treatment are unknown. While the relation between ionizing radiation and increased coronary disease is poorly substantiated, higher doses of radioactive stents induce neointimial proliferation in animal models.[28,29] The deleterious effects on vessel wall integrity may potentially interfere with further revascularization, either PCI or arterial bypass.

Future research

Taken together, these data suggest that future efforts may need to focus on balancing the important arterial functions of maintaining integrity and endothelialization, with the deleterious effects of the hyperplastic response leading to restenosis. This would involve examining the role of radiation-emitting stents, as well as improving adjunctive medical therapy following catheter-based isotope delivery. Stents that elute drugs, such as glycoprotein IIb/IIIa inhibitors may prove effective.[3] Matrix metalloproteinases (MMPs) have been shown to play a pivotal role in smooth muscle activation, migration, and extracellular matrix synthesis in the restenosis model.[30,31] Animal and human studies of MMP inhibitors have demonstrated a blunting of ECM in coronary artery segments[32,33] Finally, gene therapy holds promise for treating both native and restenotic

lesions through either decreasing intimal hyperplasia or increasing collateral formation.[34,35]

Summary

In current practice, in-stent restenosis presents in a substantial number of patients undergoing PCI. Its development is unique and different from that of balloon injury to the vessel wall and stems from a reaction to the stent itself and the interplay of recoil and hyperplasia known as remodeling. The prognosis of such lesions is variable and dependent on clinical characteristics and the extent of tissue proliferation in the stented segment.

The treatment of high-grade ISR with conventional percutaneous modalities has been largely dissatisfying. Radiation therapy has proven to be potent and highly effective and holds the most promise for addressing difficult in-stent restenotic lesions. The practicality and safety of this procedure demands further, long-term study before it can be adopted in a widespread manner. Directions for further research should target primarily the attenuation of the vessel wall response to injury.

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Abstracts of Interest

Cost-effectiveness of vascular brachytherapy for treatment of in-stent restenosis: Influence of angiographic restenosis pattern

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Recent studies have demonstrated that vascular brachytherapy (VBT) is an effective adjunct to standard percutaneous coronary intervention (PCI) for pts with in-stent restenosis (ISR). However, the cost-effectiveness (C/E) of this technology is unknown.

Methods: We developed a computer-based Markov model to project 2-year medical care costs and outcomes for pts with ISR treated with repeat PCI, with or without VBT. Recurrence rates after treatment were derived from the published literature and assumed to vary with the pattern of restenosis. Cost estimates for repeat revascularization (RepRev) procedures were derived from pooled economic data from 5 U.S. multicenter trials involving 3128 pts. We estimated that VBT would cost $3000 per treatment (including procedural time and MD fees) and would reduce the rate of recurrent restenosis by 60%.

Results: Under our baseline assumptions, adjunctive VBT for pts with focal ISR improved outcomes but increased 2-yr costs by $1260, with an incremental C/E ratio of $8034 per RepRev avoided. The C/E ratio remained <$12,000 per RepRev avoided (similar to the C/E of stenting in Benestent II) as long as VBT cost <$3620 per treatment or the restenosis risk reduction were >50%. For pts with diffuse intrastent restenosis (confined to the stent body), the C/E ratio for VBT was highly favorable at $843 RepRev avoided and remained acceptable unless VBT cost >$5600 per pt or the restenosis risk reduction were <32%. For pts with either a diffuse proliferative pattern or total stent occlusion, VBT was projected to both improve outcomes and reduce overall 2-yr costs.

2-year economic outcomes of VBT

Restenosis Pattern	RepRev Rate without VBT	Incremental cost of VBT	C/E ratio ($/RepRev avoided)	C/E Threshold**
Focal	19.0%	$1260	$8034	$3620/50%
Diffuse intrastent	26.1%	$200	$840	$5650/32%
Diffuse proliferative	31.8%	-$647	Dominant*	$7270/25%
Total occlusion	44.8%	-$2181	Dominant*	$10,300/18%

*Dominant = Improves outcomes and reduces costs

**Maximum treatment cost or minimum effectiveness level to achieve CE ratio = $12,000/RepRev avoided.

Conclusions: Despite its substantial cost, VBT appears to be highly cost-effective (if not cost-saving) for most pts with diffuse ISR. For pts with focal ISR, VBT is projected to increase overall costs, and thus its economic value will depend on society's willingness to pay for reductions in restenosis.

Three-dimensional intravascular ultrasound assessment of non-injured edges of ß-irradiated coronary segments

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Objective: The aim of this study was to assess the "edge effect" in non-injured margins adjacent to the irradiated segments after intracoronary catheter-based beta-irradiation.

Methods: Fifty-three vessels were assessed by means of three-dimensional intravascular ultrasound at post-procedure and 6-8 months follow-up. Fourteen vessels (placebo group) did not receive radiation (sham source), whereas 39 were actually irradiated. In the irradiated group, 48 edges (5-mm in length) were identified as non-injured, whereas 18 non-injured edges were selected in the placebo group. We compared the volumetric IVUS measurements of the non-injured edges of the irradiated vessels with the fully irradiated non-stented segments (IRS, n=27) (26-mm segments receiving the prescribed full dose) and the non-injured edges of the placebo patients.

Results: We observed a similar increase in plaque volume in all segments; non-injured edges of the irradiated group (19.6%), non-injured edges of the placebo group (21.5%) and IRS (21.0%). Total vessel volume increased in IRS significantly between 3 groups (+9.4% of IRS; -1.0% at non-injured edges of the irradiated vessels; +3.8% at non-injured edge of the placebo, p=0.021). Percent changes in lumen volume were different (+1.7% vs. -10.0% vs. -2.5%, respectively, p=0.049) among 3 groups. Lumen volume tended to decrease in non-injured edges of irradiated patients compared with IRS (p=0.053). Increase in plaque volume tended to be greater in the proximal edges compared to the distal edges (+27.0% vs +9.2%, p=0.08). No edge segment was subject to repeat revascularization.

Conclusions: Plaque growth and lumen loss were observed in the non-injured margins of radiation source train in both irradiated and placebo patients at follow-up. Thus, low-dose radiation may not play an important role in this phenomenon, whereas non-measurable device injury may be considered as a plausible alternative explanation.

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