Coronary in-stent restenosis — predictors, treatment and prevention

R. Hoffmann¹ and G. S. Mintz²

¹Medical Clinic I, University Clinic RWTH Aachen, Department of Internal Medicine, Division of Cardiology, Aachen, Germany; ²Washington Hospital Center, Washington, D.C., U.S.A.

Introduction

Stent implantation in human coronary arteries, initiated in 1986 by Sigwart et al. is intended to reduce coronary restenosis¹. High pressure balloon inflations and anti-thrombotic pharmacological regimens have almost abolished subacute thrombosis and the associated anticoagulation-related bleeding. This has resulted in acceptance of coronary stents as primary catheter-based therapy. It is not an exaggeration to claim that interventional therapy has been revolutionized in a wave of ‘stent mania’ with the number of lesions treated with stents exceeding 50% of all interventional procedures. Although stents have been demonstrated to reduce restenosis compared to balloon angioplasty, in-stent restenosis occurs in about 10–60% of cases²–⁵. As a result, in-stent restenosis has developed into a significant clinical problem. It has been estimated that up to 250 000 patients developed in-stent restenosis in 1999 alone.

Mechanism of in-stent restenosis

The mechanism of restenosis after balloon angioplasty is a combination of recoil, arterial vessel remodelling, and neointimal hyperplasia⁶,⁷. In contrast, stents inhibit both recoil and the vascular remodelling process. Late lumen loss in stented segments is the result of intimal hyperplasia⁸,⁹. Animal data and information from some human post-mortem samples have given insight into the cellular basis of in-stent restenosis. There is an inflammatory reaction centred at the stent struts, the severity of which is related to the trauma to the vessel wall induced by the stent struts¹⁰. Stimuli for the restenosis process are disruption of the endothelial barrier layer as well as mechanical stretch and disruption of media and adventitia. This mechanical injury of the vessel wall stimulates migration of smooth muscle cells (from the media) and myofibroblasts (from the adventitia) to the intima where they proliferate¹¹. The disrupted vessel layers may facilitate contact with circulating blood factors, further stimulating intimal hyperplasia.

Early thrombus formation was found to be insignificant in a porcine proliferative restenosis model and to account only for a small portion of subsequent neointimal formation¹². Instead, analysis of directional atherectomy specimens of early in-stent restenosis tissue showed predominantly smooth muscle cells. After weeks and months the lesion cellularity decreases as a function of time, and extra-cellular matrix (proteoglycans and collagen) is the predominant component of restenotic lesions.

Smooth muscle cell proliferation was shown to correlate with the degree of vessel injury during oversized stent placement¹³. Previous pathological studies of human coronary arteries and of a rabbit restenosis model found a more prolonged inflammatory reaction, more cellular proliferation, and greater lumen loss after stent implantation compared to balloon angioplasty²,³,¹³. This may be explained by the different nature and time-course of the two injuries: stent struts produce local deep trauma and a chronic stretch of the vessel wall; whereas balloon injury, which may also be deep, tends to be transient and focal, with dissections rather than circumferential stretch. However, the mechanical factors resulting in increased neointimal tissue formation after stent placement are not fully understood. For example, it is not known which vessel wall component is especially sensitive to mechanical trauma or whether it is pressure or shear stretch which results in tissue proliferation.

Tissue accumulation within the stent peaks at about 6 months. Afterwards the neointimal tissue becomes thinner. This results in an increase in minimal lumen diameters between 6 months and 3 years, as demonstrated in a serial angiographic follow-up study¹⁴. Fibrotic maturation of the intimal hyperplasia has been suggested as the mechanism for the observed late improvement in lumen dimensions.
Factors predisposing to in-stent restenosis (Fig. 1)

Restenosis rates up to 60% have been reported after placement of stents \[2 - 5,15\]. In designing strategies to reduce restenosis it is important to know what predisposes to in-stent restenosis. Currently, factors predictive of in-stent restenosis can be divided into patient-related, procedure-related and lesion-related factors.

Patient-related factors for in-stent restenosis are diabetes and a history of restenosis \[16 - 18\]. A description has been made of the likelihood of developing restenosis following an interrelationship among multiple lesions within the same patient \[19\]. There are important but so far unidentified patient-related factors which have an impact on the likelihood of in-stent restenosis. Genetic factors, such as the PT\(\beta\) polymorphism of glycoprotein III\(\alpha\) \[20\], the insertion/deletion polymorphism and the plasma activity of angiotensin I-converting enzyme \[21\] have been reported to be important patient-related risk factors of in-stent restenosis.

Procedure-related factors include the number of stents being used \[22\], the total stent length, and stent overlap. An important predictor of subsequent restenosis is the post procedural minimal lumen diameter and the minimal lumen cross-sectional area determined by intravascular ultrasound. In the CRUISE (Can Routine Ultrasound Influence Stent Expansion) trial, a randomized trial with 499 lesions subject to either angiographic or intravascular ultrasound guided stent expansion, the final lumen cross-sectional area within the stent was found to be the only multivariate predictor of subsequent target lesion revascularization \[23\]. A large balloon/artery ratio and very high balloon deployment pressures may result in greater acute trauma to the vessel wall as well as more chronic stretch of media and adventitia \[7,24,25\]. This has been considered to result in an increased late loss or even higher restenosis rate. However, a randomized study comparing low-pressure (8–13 atm) with high-pressure (15–20 atm) implantation techniques in 934 patients did not show a difference in clinical event rates at the 1 year follow-up \[26\]. Adjunctive directional atherectomy prior to stent placement to remove plaque seems to lower the rate of restenosis \[27,28\].

The design of the stent structure may have a significant impact on the amount of neointimal hyperplasia \[29\]. Corrugated ring stents have been shown in an animal model to achieve the same initial lumen diameter as slotted tubular stents, but to impose a 42% \((P<0.0001)\) lower arterial injury score; this resulted in 38% less neointimal hyperplasia. These results were confirmed in a finite element analysis showing that high inflation pressures, wider stent-strut openings, and more compliant balloon materials cause more vascular injury during stent implantation \[30\]. However, with the exception of Gianturco-Roubin II (GR-II) data, clinical trials performed to date comparing stents did not demonstrate a significant difference between different designs.

Lesion-related characteristics which impact on the rate of restenosis include small vessel size \[31\], long lesion length \[32\], and severity of pre-treatment as well as post-treatment lesion stenosis \[32\]. Chronic total occlusion \[33\], ostial lesion location, lesion calcification and saphenous vein graft lesion location have been discussed as other lesion-related parameters. The tremendous impact of
vessel size on the rate of restenosis was demonstrated by Elezi et al. in an analysis of 2602 patients. The restenosis rate of vessels <2.8 mm in diameter was 38.6% as compared to 28.4% for vessels 2.8–3.2 mm and 20.4% for vessels >3.2 mm. Data indicating similar late loss for different sized vessels support the impression that vessel size, which directly determines the final stent dimension, is probably the most important lesion-related factor, together with the lesion length. Using the ACC/AHA system to grade lesion complexity, more complex lesions have a larger late lumen loss as well as a higher restenosis rate.

In addition to these angiographic parameters, intravascular ultrasound analysis showed the plaque burden before stent placement to be an important independent predictor for in-stent restenosis. There is a correlation ($r=0.50$, $P<0.01$) between the residual plaque burden after coronary stent placement and the amount of in-stent neointimal proliferation. This finding is of significant importance as it supports the concept that plaque removal before stent placement may reduce subsequent restenosis rates.

### Treatment of in-stent restenosis

While the rate of restenosis in stented lesions is in the range of 14–60%, there is a need for repeat revascularization procedures in 60–80% of restenotic lesions. So far, recommendations for the treatment of in-stent restenosis are mainly based on small non-randomized patient series. The comparison of different treatment modalities from retrospective studies is difficult due to (1) varying definition of recurrence, (2) the analysis of uncontrolled registries, and (3) the inclusion of various severities and lengths of in-stent restenosis lesions.

Medical therapy can be considered for asymptomatic restenosis not producing myocardial ischaemia, in cases of angiographically proven borderline restenosis with well-collateralized distal territories, and in patients with minimal angina or without proven myocardial ischaemia, especially if detected 4 to 6 months after stent implantation. This approach is encouraged by the fact that there is rarely any progression in lesion severity more than 6 months after stent implantation.

Furthermore, there is late angiographic improvement of minimal lumen dimensions between 6 months to 3 years, while repeat interventional procedures might reinitiate the process of intimal hyperplasia and lumen loss.

In cases of significant in-stent restenosis, the optimal interventional strategy should fulfil several criteria: (1) safety, (2) not disrupt the stent structure, (3) ease of use (4) result in large lumen dimensions, and (5) have a low rate of recurrence. None of the currently available interventional procedures fulfills all of these criteria.

Balloon angioplasty is the most widely used interventional therapy for treatment of in-stent restenosis. The restenotic lesion can normally be recrossed and dilated easily. Furthermore, it is a very safe procedure probably entailing less risk than dilatation of unprotected coronary vessels. Additional stent expansion and a decrease in neointimal tissue contribute to the enlargement in minimal lumen area. However, balloon angioplasty of in-stent restenosis typically fails to achieve minimal lumen dimensions similar to the result immediately after stent placement. Even using high, maximal balloon pressure and a large balloon-to-artery ratio, the residual diameter stenosis is high; this is primarily due to neointimal tissue remaining within the stent. In addition, intravascular ultrasound studies demonstrated significant tissue retraction shortly after treatment of in-stent restenosis. Suboptimal immediate results, in combination with early lumen loss, may contribute to a high recurrence of restenosis.

Recurrence restenosis rates after balloon angioplasty for stent treatment have been reported to be 22%, with target vessel revascularization rates of 11–17% in cases of focal in-stent restenosis. Higher restenosis rates have been reported for recurrent in-stent restenosis lesions; and recurrence rates of up to 80% have been reported in cases of diffuse in-stent restenosis. The prognostic impact of the pattern of restenosis on the need for recurrent target lesion revascularization has been studied systematically in a recent publication by Mehran et al. Four patterns of in-stent restenosis were defined: I focal (≤10 mm in length), II in-stent restenosis >10 mm within the stent, III in-stent restenosis >10 mm extending outside the stent and IV totally occluded in-stent restenosis. Target lesion revascularization increased with increasing in-stent restenosis class; it was 19%, 35%, 50% and 83% in class I to IV, respectively ($P<0.001$). In addition to the pattern of restenosis the percent stenosis before PTCA of the in-stent restenosis lesion proved to be predictive for recurrent in-stent restenosis.

Interest has focused on ablative techniques as an alternative to balloon angioplasty. In general, these techniques achieve a larger lumen following treatment of in-stent restenosis. Considering the ‘bigger is better’ hypothesis, it seemed logical to expect improved follow-up results. Strauss et al. demonstrated that directional atherectomy was technically feasible, safe, and achieved angiographic results similar to those immediately after stent placement (minimum lumen diameter of 2.31 ± 0.38 mm vs 2.44 ± 0.35 mm). In another study of 45 patients undergoing directional atherectomy for treatment of in-stent restenosis, the 12-month target lesion revascularization rate was 28.3%. In this study, no complications occurred after directional atherectomy. However, there have been concerns about the safety of directional coronary atherectomy due to reports of stent struts or wires being cut with subsequent disruption of the stent.

In a matched analysis of 107 lesions, laser angioplasty resulted in a 29% larger lumen area gain, a 63% greater decrease in intimal hyperplasia, a larger final lumen area, and a tendency for less frequent target vessel revascularization compared with balloon angioplasty. The LARS Surveillance Study of 440 patients demonstrated a procedural success rate of 91% using excimer
Laser angioplasty followed by balloon angioplasty with a low complication rate. The diameter stenosis could be reduced to 41 ± 17% after laser angioplasty and to 7 ± 13% after adjunct balloon angioplasty. In spite of the demonstrated feasibility, most long-term data demonstrate a high recurrence of restenosis, results not supportive of laser treatment for in-stent restenosis.

Several reports have demonstrated the feasibility, safety and effectiveness of rotational atherectomy for treatment of in-stent restenosis. Rotational atherectomy improves lumen dimensions by plaque removal; subsequent adjunct angioplasty adds to the lumen gain by further stent expansion and tissue extrusion (Fig. 3). Recurrence of restenosis amounting to 28–56% have also been reported after rotational

**Table 1 Recurrent restenosis rates after mechanical treatment of in-stent restenosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment device</th>
<th>Number of patients</th>
<th>Follow-up period (months)</th>
<th>TVR</th>
<th>Recurrent restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reimers[43]</td>
<td>Balloon angioplasty</td>
<td>124</td>
<td>27</td>
<td>11%</td>
<td>—</td>
</tr>
<tr>
<td>Bauters[44]</td>
<td>Balloon angioplasty</td>
<td>103</td>
<td>6</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>Elchimoff[45]</td>
<td>Balloon angioplasty</td>
<td>52</td>
<td>6</td>
<td>35%</td>
<td>54%</td>
</tr>
<tr>
<td>Scharma[46]</td>
<td>Rotational atherectomy</td>
<td>100</td>
<td>13</td>
<td>26%</td>
<td>28%</td>
</tr>
<tr>
<td>Vom Dahl[47]</td>
<td>Rotational atherectomy</td>
<td>100</td>
<td>5</td>
<td>35%</td>
<td>49%</td>
</tr>
<tr>
<td>Vom Dahl[48]</td>
<td>Rotational atherectomy</td>
<td>152</td>
<td>6</td>
<td>48%</td>
<td>65%</td>
</tr>
<tr>
<td>Radtke[49]</td>
<td>Rotational atherectomy</td>
<td>45</td>
<td>6</td>
<td>38%</td>
<td>45%</td>
</tr>
<tr>
<td>Mehran[50]</td>
<td>Laser angioplasty</td>
<td>47</td>
<td>6</td>
<td>21%</td>
<td>—</td>
</tr>
<tr>
<td>Köster[51]</td>
<td>Laser angioplasty</td>
<td>73</td>
<td>6</td>
<td>33%</td>
<td>52%</td>
</tr>
<tr>
<td>Mahdi[52]</td>
<td>Directional atherectomy</td>
<td>45</td>
<td>12</td>
<td>28%*</td>
<td>—</td>
</tr>
</tbody>
</table>

TVR = target vessel revascularization.
*Combined ischaemic event end-point of MI, repeat target artery revascularization, CABG and death.
atherectomy\(^{52-55}\). A small burr-to-artery ratio, the amount of acute neointimal recoil, pre-intervention diameter stenosis, and diffuse type in-stent restenosis were associated with recurrent restenosis\(^{55}\).

Meanwhile, a retrospective study on follow-up after ablative therapy for in-stent restenosis has dampened optimism that ablative therapy may result in a significant reduction of recurrent restenosis. A report on 821 in-stent restenotic lesions found similar recurrence rates after ablative therapy using laser angioplasty or rotational atherectomy, additional stent placement, or balloon angioplasty\(^{56}\). The results of the first two randomized trials, comparing rotational atherectomy vs balloon angioplasty, demonstrated conflicting data (Fig. 4). The Randomized trial of Rotational Atherectomy v. Balloon Angioplasty for in-stent Restenosis (ROSTER), a monocentre study of 150 patients, demonstrated a clinical restenosis rate of 20% after rotational atherectomy as compared to 43% after balloon angioplasty \(P=0.01\)\(^{57}\). However, the Angioplasty vs Rotational atherectomy for Treatment of In-Stent restenosis (ARTIST) trial, a multicentre study of 300 patients, showed a worse outcome after rotational atherectomy, with a restenosis rate of 64.8% vs 51.2% after PTCA \(P=0.04\) and a need for recurrent target vessel revascularization of 47.8% after rotational atherectomy vs 36.2% \(P=0.06\) after balloon angioplasty\(^{58}\). Thus, the effectiveness of rotational atherectomy for treatment of stent restenosis has also been questioned recently. It is only directional atherectomy, as a mechanical device to remove intimal hyperplasia, which still holds some promise to reduce recurrent restenosis. The capacity of directional atherectomy to remove a greater amount of intimal hyperplasia may also result in a better long-term result.

Additional stent implantation has been advocated, particularly in the presence of focal in-stent restenosis involving the edge of a stent or tissue prolapse through

---

**Figure 3** Cross-sectional images obtained by intravascular ultrasound of a restenotic stent. The left panel (A) shows the restenotic stent prior to treatment. The middle and the right panel demonstrate the effect of rotational atherectomy (B) plus subsequent balloon angioplasty (C).

**Figure 4** Results of the ARTIST trial (data from: vom Dahl, Am J Cardiol 1999; 84(Suppl 6A): TCT237) and the ROSTER trial (data from: Sharma, Eur Heart J 1999; 20: 281A). Target vessel revascularization rates 6 month after rotational atherectomy (ROTA) vs balloon angioplasty (PTCA) for in-stent restenosis in both trials.
the articulation of a Palmaz-Schatz stent or a gap between two adjacent stents. However, except for these selected situations, there is a lack of utility of stenting a restenotic stent.

Prevention

Recently evaluated methods for the prevention of in-stent restenosis and its recurrence include improved implantation techniques, improved stent design, stent coatings with drugs or non-pharmaceutical agents, and radioactive stents, intraluminal radiotherapy, and gene therapy. Thus, besides approaches which aim at improving the interventional procedure and the acute interventional result, new approaches focus on inhibition of induced tissue proliferation. Some of the techniques consider the current knowledge on factors predisposing the development of in-stent restenosis.

It has been suggested that aggressive implantation techniques resulting in a minimal stent cross-sectional area of 90% of the reference areas result in low restenosis rates. This approach usually utilizes intravascular ultrasound guidance to optimize stent dimensions. While ultrasound guidance allows more accurate determination of the true vessel size for more optimal balloon selection, there is as yet no convincing proof that this approach translates into reduced restenosis rates compared to aggressive stent placement without intravascular ultrasound guidance. In the CRUISE trial, 499 lesions were subject to either intravascular ultrasound or angiographic guidance of stent implantation. The minimal stent area post intervention was significantly larger in the ultrasound guided lesions. Target vessel revascularization rate at 9 months was reported to be 8.9% for the ultrasound guided group and 14.8% for the angiographically guided group. Two other multicentre trials, the Angiography Versus Intravascular ultrasound-Directed stent placement (AVID) trial and the OPTimization with ICUS to reduce stent restenosis (OPTICUS) study showed conflicting results. In AVID, there was a strong trend toward improved outcome in the entire cohort of the ultrasound-guided group; this trend became statistically significant once ‘protocol-violation’ lesions were excluded. The OPTICUS study was negative perhaps because the results in the angiography arm were surprisingly good.

Less aggressive stent implantation techniques with less vessel trauma and less subsequent intimal hyperplasia are also conceivable as the optimal stent implantation pressure and balloon-to-artery ratio resulting in a large acute lumen gain with minimal subsequent intimal hyperplasia still has to be defined.

Another mechanical approach is the application of directional atherectomy prior to stent placement. Low restenosis rates of 6-8% and 11% have been reported after directional atherectomy followed by coronary stenting. The theoretical basis of this approach is that the plaque burden prior to stent placement is a strong predictor of subsequent restenosis. The concept of directional atherectomy prior to stent placement for reduction of angiographic restenosis is currently evaluated in the AMIGO (Atherectomy before Multi-link Improves Lumen Gain Outcome) trial, which is a large randomized trial on 750 lesions.

‘Focal or spot stenting’ has been advocated in the treatment of long lesions. Stents are implanted only at those spots within the long lesion that absolutely require a stent.

Improved stent design has also been studied. In animal models, stent design has been found to have a major impact on vessel trauma and subsequent intimal hyperplasia. Several stent design-related factors may determine the rate of restenosis. Stent design probably influences the final diameter stenosis with the final diameter stenosis being a major determinant of restenosis. Stent designs without articulation points result in less acute plaque prolapse through the stent structure and thus a larger final lumen diameter. Strut design influences intimal trauma, i.e. do corrugated ring stents result in less subsequent intimal hyperplasia than tubular-slotted stents? The optimal metal coverage by the stent is still in question. A high metal coverage was considered detrimental due to a fear of a marked reaction to the foreign material. Subsequently, it became clear that a high metal surface coverage is an important consideration to prevent acute tissue protrusion especially in lesions with large plaque burden and allows a more evenly distributed stress of the stent struts on the vessel wall. Thus, a higher metal coverage prevents the existence of strut-intersections with a very high mechanical impact on the vessel wall. Recently coronary stent grafts consisting of two coaxially aligned stainless steel stents which encompass a microporous PTFE (polytetrafluoroethylene)-membrane have become available. In theory, stent-grafts prevent in-stent restenosis by providing a barrier to the migration of inflammatory cells from the lumen to the vessel wall and for smooth muscle cells to the lumen. Studies have shown that proliferation is only minimal in the body of PTFE stent-grafts and increases at the stent edge. Gold-plated stents improve the thrombogenic and electrostatic characteristics of the stent and, thus, may reduce restenosis. However, a randomized trial comparing the gold-plated steel stent with conventional steel stents demonstrated an even exaggerated hyperplastic response of the vessel wall.

Drug therapy to prevent restenosis after balloon angioplasty by reducing intimal hyperplasia has been evaluated without success. However, intimal hyperplasia was assumed to be the mechanism of restenosis after balloon angioplasty while in fact it is not. Because restenosis after stent placement is entirely the result of intimal hyperplasia, both local and systemic delivery of antiproliferative drugs may reduce in-stent restenosis. The stent itself may become the vehicle for prolonged local drug delivery. The metal stent can be coated with a matrix allowing controlled drug release, or the pharmacological agent can be incorporated into a polymer–metal composite stent. Incorporating the drug into a...
polymer coating has the advantage that the binding process has no effect on the biological activity of the drug. Polymer coatings were studied several years ago in an attempt to reduce the foreign-body-reaction of the vessel to the stent. Although the objective was to produce a non-reactive stent, initially tested polymer compounds were associated with an increased inflammatory reaction resulting in even more intimal hyperplasia [65]. Meanwhile, a synthetic polymer containing phosphorylcholine mimicking the phospholipid of the cell membrane was developed; phosphorylcholine does not induce an excessive inflammatory response. Although phosphorylcholine seems to decrease protein deposition and platelet adhesion, a reduction of in-stent restenosis has not been demonstrated.

Subsequently, attention has shifted towards the use of the polymer coating as vehicle for local drug delivery. Local drug therapy using the endovascular stent as carrier for drug delivery has several advantages. Pharmacological agents which failed to prevent restenosis when given systemically may be effective if administered locally at higher concentration; and the incidence of systemic side effects is likely to be lower. The correct balance between the rate of elution and the degree of drug retention is of importance. Embedding an antiproliferative agent like methotrexate into a biocompatible polymeric coating may result in a hybrid stent design consisting of the metallic frame to prevent the recoil and vessel remodelling and a coating to inhibit tissue proliferation. However, despite a wealth of potential drugs, it remains unclear which agent can be delivered locally in sufficient concentrations over an adequate period to achieve a favourable antiproliferative effect [66,67].

In a porcine coronary in-stent restenosis model, continuous systemic administration of angiopeptin has been found to reduce the neointimal hyperplasia growth by almost 60% compared to a control group [68]. Recently, a significant reduction of intimal hyperplasia was demonstrated after the oral administration of a selective ETA receptor antagonist [69]. Stimulation of the ETA receptor results in increased vascular smooth muscle cell proliferation; it may be involved in both the pathogenesis of atherosclerosis and play an important role in the proliferation of neointimal hyperplasia after stent placement.

Several approaches using gene therapy are under evaluation to prevent or reduce intimal hyperplasia. Adenoviruses have been used as vectors for gene delivery to areas of vascular injury [70,71]. Gene therapy for inhibition of neointimal hyperplasia may involve the direct transfer of a gene into the proliferating cell. The delivered genes can encode for proteins that are either directly or indirectly cytotoxic or cell cycle-inhibitory. A possible approach involves the delivery of a gene product capable of metabolizing a relatively innocuous product into a more potent inhibitor of cell proliferation [71]. The transferred gene may also encode an angiogenic protein like VEGF to accelerate reendothelialization. The mode of gene delivery may be endoluminal administration of DNA containing solutions or direct contact to the arterial wall using a DNA-eluting polymer-coated stent [70].

The inhibition of several of the mediators of the cell cycle with antisense oligonucleotides has been pursued [72]. Antisense oligonucleotides are pieces of DNA which interact due to their complementary characteristics with specific messenger RNAs, thereby inhibiting the action of this messenger RNA. A significant reduction of smooth muscle cell proliferation was demonstrated in several different animal studies. Incorporation of antisense oligonucleotides into an appropriate polymeric matrix is an attractive possible mode of delivery.

Figure 5 Late lumen loss determined by coronary angiography and volume of tissue growth measured by intravascular ultrasound at 6 months follow-up for lesions treated with stenting plus Iridium-192 and those treated with stents alone (placebo). The group of lesions treated with catheter-based brachytherapy had a significantly lower late lumen loss and tissue growth as compared to the placebo group (data from: Teirstein, N Engl J Med 1997; 336: 1697–703).
Another approach that has been suggested is the administration of matrix metalloproteinases inhibitors\[73]. Matrix-degrading metalloproteinases are necessary to degrade the extracellular matrix, thereby allowing smooth muscle cell migration and proliferation. Inhibitors of metalloproteinases have been shown to inhibit smooth muscle migration and proliferation. However, this technique has not been shown to prevent in-stent restenosis\[74].

Radiation therapy has evoked significant interest and enthusiasm. Both intraluminal irradiation with a \(\beta\)- or \(\gamma\)-emitter placed within the coronary vessel using afterloading techniques or the use of a radioactive stent are being evaluated\[75-80]. Radiation therapy has been applied to prevent the development of first in-stent restenosis as well as to inhibit recurrent in-stent restenosis. Studies involving intracoronary as well as peripheral intravasal \(\beta\)- or \(\gamma\)-irradiation with a dosage of 10 to 18 Gy have shown in restenosis models to result in a reduction of smooth muscle cell number and neointimal thickness. Waksman et al.\[75\] described a significant reduction of neointimal formation in pig coronary arteries treated with \(\gamma\)-irradiation (\(^{192}\)Ir) or \(\beta\)-irradiation (\(^{90}\)Sr/Y) prior to stent placement. Hehrlein\[77\] were the first to use the stent to deliver radiation in an animal restenosis model. Radioactive sources bound to the stent have been shown to deliver effective doses to all depths of the vessel wall. In porcine animal models, stents covered with the low-dose \(\beta\)-emitting \(^{32}\)P have been demonstrated to result in significantly reduced neointimal areas compared with controls\[75,76\].

There is still controversy as to the use of gamma or beta energy in clinical practice. While there are convincing data to support the clinical utility of \(\gamma\)-radiation for the prevention of stent restenosis, there are conflicting results as to the use of \(\beta\)-radiation with a lack of data indicating a clear benefit in clinical outcome. The fact that beta energy can be easily shielded and does not penetrate far is an advantage with respect to radiation safety. At the same time it is a potential disadvantage with respect to efficacy. Current understanding requires adequate radiation energy at the adventitial target. Due to the rapid decline in beta radiation energy it is probably impossible to deliver adequate energy to the adventitial layers of large vessels without inadequately high radiation levels at the intimal layer. In addition, beta energy is partially shielded by the metallic stent requiring dose adjustment in case intraluminal radiation is applied after stent delivery\[79\]. The main disadvantage of \(\gamma\)-irradiation is the difficulty of shielding resulting in higher radiation exposure for the patient and potentially for the health care personnel.

Teirstein et al.\[80\] were the first to apply \(^{192}\)Ir, a gamma emitter, in a randomized comparative study in patients with restenosis. In the SCRIPPS trial 26 patients were assigned to coronary stenting followed by \(^{192}\)Ir irradiation and 29 to coronary stenting followed by placebo. There was a 65% reduction of intimal hyperplasia (Fig. 5), resulting in a restenosis rate of 16.7% for patients treated with \(^{192}\)Ir vs 53.6% for placebo patients (\(P=0.009\))\[80\]. These favourable results persisted even after a 2-year follow-up with the combined death, myocardial infarction and target lesion revascularization rate being 23.1% in the gamma radiation patients vs 51.7% in the placebo group (\(P=0.03\))\[81\]. Initial clinical experience with \(\beta\)-particle emitting stents to test the safety of 0.5 to 1.5 \(\mu\)Ci \(^{32}\)P was obtained in the Isostent for Restenosis Intervention Study (IRIS). This study proved feasibility. However, the applied radiation dosage was probably too low and restenosis rates were not reduced\[82\].

Recent reports of late stent thrombosis rates between 6 and 9% after endoluminal radiation have provided a note of caution\[83\]. Further concerns have been a delayed development of restenosis, late fibrosis induced by radiation therapy and a potential for accentuated proliferation at the margin of the therapeutic range, the edge or ‘candy-wraper effect’.

Considering the difficulties in the treatment of stent restenosis, avoidance of stent placement in lesions likely to be associated with a high rate of restenosis or even diffuse in-stent restenosis seems to be wise. Some authors have recommended a strategy of aggressive, optimal balloon angioplasty and provisional stenting in case of an insufficient result after balloon angioplasty. This strategy, which has been combined with intravascular ultrasound guidance in a few reports, has resulted in restenosis rates similar to primary stenting but avoids the dilemmas provided by the occurrence of stent restenosis\[84\].

**Conclusion**

In-stent restenosis is a major challenge for the interventionalist. None of the available interventional modalities provides optimal acute results, and long-term results are even poorer. This is especially true for diffuse in-stent restenosis lesions which have high recurrence rates. Thus, mechanical treatment modalities for evolved in-stent restenosis can only be one step in a comprehensive strategy for prevention and treatment. Brachytherapy as an adjunct seems to be especially promising, but late thrombosis, delayed restenosis and the potential for very late fibrosis are matters of concern. As attention has turned towards the prevention of in-stent restenosis new techniques such as drug delivering stents and gene therapy to inhibit the biological reaction of the vessel wall are likely to obtain greater importance.

**References**


