

# Restenosis

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# Restenosis—narrowing in on the cause and cure

**Craig R. Narins, MD; Eric J. Topol, MD**

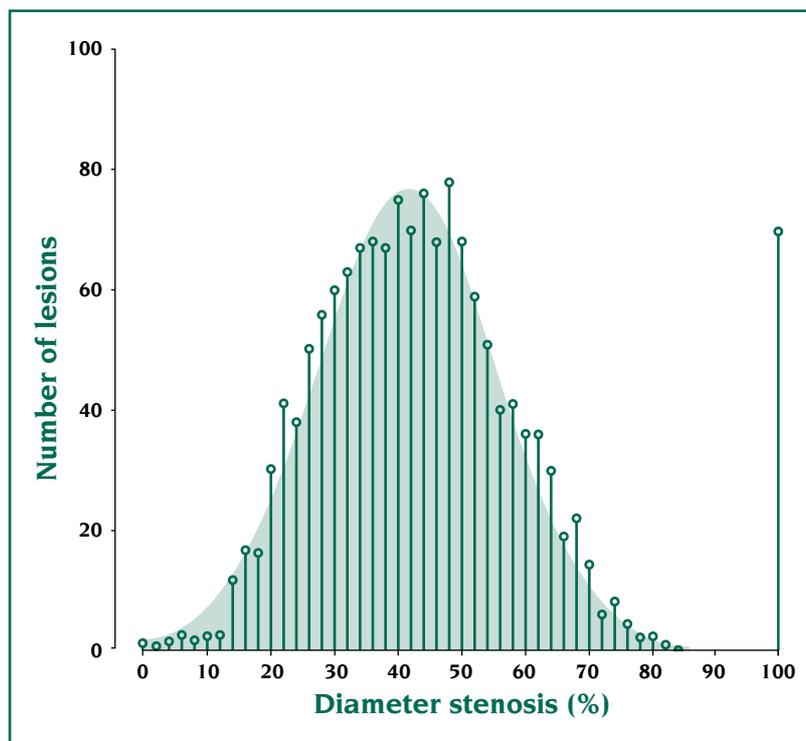
*Department of Cardiology and Joseph J. Jacobs Center for Vascular Biology - The Cleveland Clinic Foundation - Cleveland, Ohio - USA*

*Despite recent pharmacologic and mechanical innovations that have improved acute procedural outcomes, restenosis remains a major limitation of all percutaneous revascularization techniques. Early models of restenosis implicated excessive proliferation and secretion by smooth muscle cells as the primary process responsible for luminal renarrowing after angioplasty. However, the failure of a multitude of pharmacologic agents aimed at inhibiting neointimal hyperplasia to limit restenosis in clinical trials coupled with recent experimental observations has served to highlight the importance of other mechanisms involved in stenosis recurrence. Intracoronary stents, which essentially eliminate immediate elastic recoil and late vascular remodeling following angioplasty, have demonstrated the ability to reduce both angiographic and clinical parameters of restenosis in selected patients. Likewise, potent antiplatelet therapy with the chimeric platelet glycoprotein IIb/IIIa receptor Fab has recently been shown to improve late clinical outcome following angioplasty in two large randomized trials. Several emerging therapeutic approaches targeting restenosis, including locally delivered radiation, gene-based therapy, and a variety of novel pharmacologic agents, have shown promise in preclinical and preliminary clinical studies.*

**T**wenty years after the first application of percutaneous coronary revascularization, restenosis—the process of late arterial renarrowing at the site of an initially successful intervention—remains a major limitation of the procedure and continues to pose a vexing problem for clinicians and basic scientists alike. Initially construed as an “all or none” phenomenon, restenosis is now understood to represent one end of the spectrum of the complex and incompletely understood normal reparative response to vascular injury. In an attempt to develop effective prophylactic therapies, tremendous effort has been devoted toward understanding the basic pathogenesis of restenosis. Early experiments implicated overexuberant proliferation and secretion by vascular smooth muscle cells (termed neointimal hyperplasia) as the fundamental process responsible for restenosis. However, despite encouraging results from animal trials with agents administered to inhibit neointimal hyperplasia, a multitude of early human pharmacologic trials yielded, almost universally, disappointing results. These negative studies have served to highlight the multifactorial nature of the vascular healing process, and have spawned continuing basic research that has brought about recent expansion and fundamental revisions in the restenosis paradigm (eg, the importance of changes in vessel geometry). This review will focus on evolving concepts regarding the biology of restenosis, summarize previous pharmacologic and catheter-based prevention trials, and discuss several novel therapeutic strategies targeting restenosis.

## DEFINITIONS OF RESTENOSIS

Despite the tremendous amount of attention that restenosis has received in the past decade and a half, uncertainty still exists regarding the most appropriate means of defining the process. A variety of definitions have been used, based on either the presence and degree of recurrent narrowing on follow-up angiography (angiographic restenosis) or the occurrence of adverse



**Figure 1.** The distribution of stenosis severity on late follow-up angiography in a series of 1445 patients who underwent successful coronary angioplasty. The curve approximates a Gaussian (normal) distribution. Adapted from the Journal of the American College of Cardiology, 1997;19(No. 5):939-945, with permission from the American College of Cardiology.

clinical events, typically death, nonfatal myocardial infarction, or need for repeat revascularization during follow-up (clinical restenosis).

### Angiographic definitions

Early investigators recognized the inherent difficulty and somewhat empirical nature of devising an appropriate binary definition of restenosis. The initial registry report by the National Heart, Lung, and Blood Institute (NHLBI) in 1984<sup>1</sup> used four separate definitions of restenosis based on the follow-up angiogram:

(i) increase of  $\geq 30\%$  from the postangioplasty result; (ii)  $\geq 70\%$  stenosis at follow-up; (iii) stenosis severity  $\leq 10\%$  below the predilated lesion severity; and (iv) loss of  $\geq 50\%$  of the gain achieved by angioplasty. On the basis of the variability of serial measurements of normal coronary artery segments obtained by the quantitative angiography equipment at their institution, Reiber et al<sup>2</sup> proposed that a  $>0.72$ -mm absolute decrease in luminal diameter at the lesion site between immediate postprocedure and late follow-up angiography be used to define restenosis. Investigators at Emory,<sup>3</sup> reflective of the variable tendency for coronary flow impairment to occur once a stenosis has exceeded 50%

of the luminal diameter, used the presence of a  $>50\%$  stenosis at late angiography to signify restenosis, and this definition has become the most frequently used binary criterion for restenosis in recent multicenter trials. Work in the early 1990s, led by Kuntz, Baim and the investigators at the Thoraxcenter,<sup>4</sup> resulted in fundamental changes in the way that restenosis is viewed by suggesting that luminal renarrowing at the site of prior coronary intervention is not an “all or none” phenomenon, as implied by the binary definitions of restenosis, but rather a process that occurs at all lesion sites to variable degrees. This concept was supported by serial angiographic studies in populations of postangioplasty patients. Rensing et al,<sup>5</sup> for example, performed quantitative coronary angiography on 1445 patients who underwent successful coronary angioplasty. Frequency plots of minimal lumen diameter, percent diameter stenosis, and “late loss” (defined as the immediate postprocedural luminal diameter minus the luminal diameter at follow-up angiography)

on 6-month follow-up angiography approximated a Gaussian (normal) distribution (Figure 1).

Precise mathematical modeling in large populations has indicated that these apparently bell-shaped curves may in fact depart from the Gaussian ideal, as distinct subpopulations of lesions appear to exist which are either more or less prone to late renarrowing.<sup>6</sup> However, frequency distribution analysis has confirmed the general concept that late renarrowing after angioplasty occurs in virtually all lesions to variable degrees.

### Clinical definitions

While quantitative angiography has confirmed that restenosis is a continuous rather than a binary phenomenon, fundamental limitations are inherent in the use of angiographic end points to define restenosis. From a practical standpoint, while angiography remains the clinical “gold standard” for the detection of coronary artery disease, the ability of this technique to precisely quantify stenosis severity is subject to a multitude of technical and operator-dependent shortcomings.<sup>7</sup> From a more philosophical perspective, any medical intervention, as a rule, should be undertaken only in an attempt to satisfy at least one



of the following three objectives: to improve patient longevity; to prevent future adverse events; and/or to provide symptomatic relief. The true test of a therapy designed to reduce restenosis, therefore, lies in its ability to reduce death, myocardial infarction, and recurrent angina requiring target vessel revascularization, which constitute the three clinical end points in therapeutic trials for restenosis. The minimal luminal diameter at 6-month follow-up angiography only serves as a surrogate for these clinical end points, and an imperfect one at that. Several recent therapeutic trials demonstrated the potential for discordance between clinical and angiographic end points. It has been proposed that the ideal clinical trial to determine the efficacy of a therapy designed to prevent restenosis would use clinical outcome as the primary end point, while employing follow-up angiography in a subset of enrolled patients to gain mechanistic insights into the treatment under study.<sup>7</sup>

### INCIDENCE OF RESTENOSIS

In the initial NHLBI registry report in 1984,<sup>1</sup> the restenosis rate following successful balloon angioplasty in 557 patients with angiographic follow-up, defined as the occurrence of either a >30% absolute increase in stenosis severity from the postprocedure angiogram or a >50% loss of the gain achieved by the intervention, was 33.6%. The incidence of angiographic restenosis following conventional angioplasty does not appear to have changed substantially in subsequent years. The restenosis rates reported for the placebo arms in 28 large (n>100) prospective trials of adjunctive pharmacologic therapy following balloon angioplasty published between 1985 and 1993 varied from 19% to 63%, with the majority falling in the 30% to 50% range.<sup>8</sup> The variability of the reported incidence of restenosis among the various trials is likely a reflection of differing definitions of restenosis, methods of angiographic interpretation, patient populations, and rates of angiographic follow-up (which varied considerably, from 37% to 100%, in these 28 trials).

The incidence of clinical restenosis, typically defined as either recurrent angina requiring repeat revascularization or major cardiovascular events (death or nonfatal myocardial infarction) within 6 months of the intervention, tends to be slightly lower than that of angiographic restenosis. For example, in the 459 patients who underwent balloon angioplasty in two recently published prospective trials, the combined angiographic restenosis rate was 36.7%, while the incidence of clinical restenosis was 27.5%.<sup>9,10</sup> This discrepancy

between clinical and angiographic restenosis rates can be attributed to: (i) physiologic data indicating that some lesions with an intermediate degree of angiographic severity (50% to 70% diameter stenosis) do not impair coronary flow reserve and therefore will not result in ischemia<sup>11</sup>; (ii) the impact of physician and patient preference in determining which patients with recurrent angina will undergo repeat revascularization; (iii) the potential absence of symptoms in patients with angiographic restenosis due to physical inactivity; and (iv) restenotic lesions which result in silent ischemia.<sup>12</sup>

### PATHOGENESIS OF RESTENOSIS

Early models of restenosis, based primarily on human necropsy studies and experimentally induced vascular injury in various animal models, implicated neointimal formation as the primary process responsible for luminal renarrowing after angioplasty.<sup>13,14</sup> However, the failure of a multitude of pharmacologic agents aimed at inhibiting neointimal hyperplasia to limit restenosis in clinical trials, coupled with new basic research and clinical tools such as intravascular ultrasound, continues to underline the complexity and multifactorial etiology of restenosis.

#### Elastic recoil

Immediate recoil at the site of angioplasty is a direct result of the elastic properties of the vessel wall.<sup>15</sup> Estimates of the magnitude of the loss in luminal area that occurs within seconds to minutes following balloon deflation have ranged from 17% to 50% based on various measurement strategies. Rensing et al<sup>16</sup> used quantitative angiography following angioplasty at 151 lesion sites to measure the difference between the mean cross-sectional area of the fully inflated balloon ( $5.3 \pm 1.6 \text{ mm}^2$ ) and the mean cross-sectional area immediately following balloon deflation ( $2.8 \pm 1.4 \text{ mm}^2$ ), which represented an area loss of 46%. Nobuyoshi et al<sup>17</sup> found that of 229 patients who underwent routine angiography the day following successful balloon angioplasty, 14.6% already demonstrated "restenosis" when defined as a  $\geq 50\%$  loss of gain. Variables associated with a propensity for recoil include lesion eccentricity, which results in preferential stretching of the relatively nondiseased region, and oversizing of balloon diameter relative to vessel diameter.<sup>16,18</sup>

Several authors have documented a relationship between the degree of early elastic recoil and subsequent late angiographic restenosis.<sup>19,20</sup> Larger degrees of early vessel recoil, however, are not associated with more late loss in vessel diameter.

Rather, early recoil appears to simply place an angioplasty site at an initial “disadvantage” whereby a smaller absolute amount of subsequent narrowing is required to meet the critical binary thresholds (eg,  $\geq 50\%$  stenosis) that are used to define restenosis.<sup>19</sup>

New mechanical devices which rely on plaque ablation or removal rather than vessel expansion have the potential to reduce the degree of vascular recoil. Directional coronary atherectomy is associated with less recoil than balloon angioplasty, although the impact of this device on late restenosis remains controversial.<sup>21</sup> One report failed to detect a difference in immediate recoil between excimer laser angioplasty and balloon angioplasty, although adjunctive balloon dilation was routinely used in the laser group.<sup>22</sup> Coronary stenting has been shown to essentially eliminate the potential for acute recoil compared to balloon angioplasty.<sup>23</sup>

### Mural thrombus

Both platelets and soluble coagulation factors are fundamental participants in the restenosis process. These elements contribute to late vessel renarrowing primarily by functioning as intermediaries that are capable of promoting smooth muscle cell migration and proliferation. Local thrombus also may serve as a “bioabsorbable matrix” upon which vascular smooth muscle cell migration and proliferation can occur.<sup>24</sup>

Immediately following angioplasty-induced injury to the vascular wall, circulating platelets adhere to exposed subintimal elements such as collagen, von Willebrand factor, fibronectin, and laminin via a number of glycoprotein membrane receptors that specifically bind to one or more of these elements. Platelet adhesion in turn promotes: (i) the release of contents of platelet granules (including thromboxane A<sub>2</sub>, adenosine diphosphate, and serotonin) which promote further platelet adhesion and aggregation; and (ii) the release of cytokines and growth factors including platelet-derived growth factor (PDGF), transforming growth factor  $\beta$  (TGF- $\beta$ ), and basic fibroblast growth factor (bFGF), which, in experimental settings, can result in smooth muscle cell proliferation and, ultimately, neointima formation.<sup>25,26</sup>

The glycoprotein (GP) IIb/IIIa receptor on the platelet membrane serves as the final common pathway for platelet aggregation. Platelet activation results in a conformational change in the GP IIb/IIIa receptor that allows the receptor to bind fibrinogen. By binding simultaneously to receptors on multiple platelets, a fibrinogen molecule can serve to cross-link these

platelets.<sup>27</sup> Whereas aspirin and other agents that nonspecifically interfere with a variety of intermediary steps only partially impair platelet aggregation, pharmacologic blockade of the GP IIb/IIIa receptor can essentially eliminate the ability of platelets to aggregate and thus achieve a state of “passivation” at the site of arterial wall injury.<sup>28</sup>

Although the role of circulating coagulation factors in restenosis is less well characterized than that of platelets, an association between several of these soluble proteins and neointimal hyperplasia appears to exist. Several investigators have demonstrated a stimulatory effect of various coagulation factors, including factors Xa and thrombin, on smooth muscle cell proliferation in vitro.<sup>29,30</sup> Thrombin acts as a strong direct smooth muscle cell mitogen, and can stimulate smooth muscle cells to release a variety of potent growth factors (including PDGF, FGF, and TGF- $\beta$ ). In experimental models, the direct inhibition of thrombin and factor Xa has resulted in reduced neointima formation.<sup>31</sup>

### Smooth muscle cells

Arterial injury directly and indirectly results in several events, which in experimental models promote smooth muscle cell proliferation and migration. These events include: (i) the mechanical stretching of the arterial wall; (ii) rupture of the internal elastic membrane; (iii) endothelial cell denudation; (iv) release of cytokines and growth factors from platelets, endothelial cells, smooth muscle cells, and inflammatory cells; and (v) exposure to plasma components including plasmin and angiotensin II.<sup>32</sup> These stimuli have the ability to promote proto-oncogene expression (eg, *c-myc*, *c-myb*, *c-fos*), which is believed to regulate the observed transformation of smooth muscle cells from a contractile to a secretory phenotype.<sup>33</sup> Increased expression of these genes can be detected within minutes of vessel injury. Proliferation and migration of smooth muscle cells from the adventitia and medial layers of the vessel wall to the intima is a universal phenomenon in animal models of restenosis. However, the bulk of neointimal tissue is composed not primarily of smooth muscle cells themselves, but of the fibrocollagenous extracellular matrix they secrete following activation. In human neointima, only 11% of neointimal tissue mass is composed of cellular elements.<sup>34</sup>

Despite the critical role that smooth muscle cell proliferation and migration play in the intensively studied animal models of restenosis, it remains controversial to what degree these processes are involved in restenosis following coronary angioplasty in man.



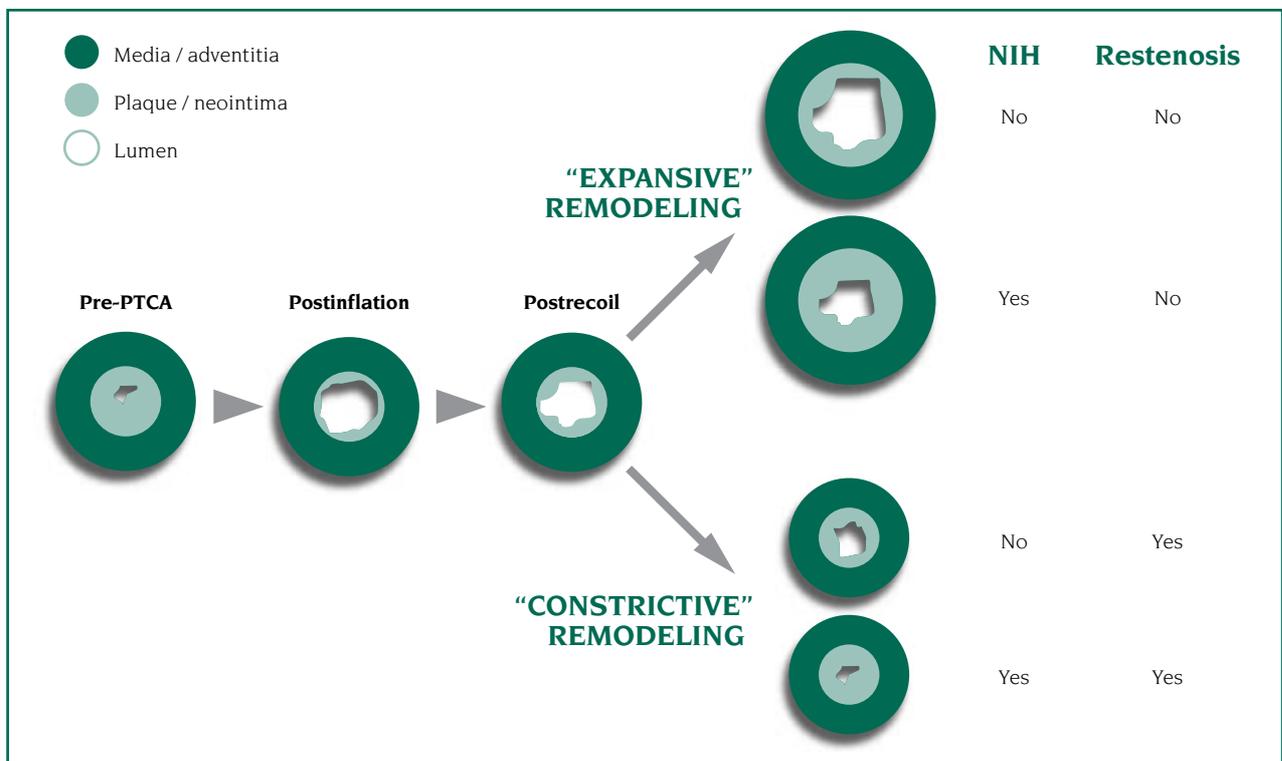
Smooth muscle cell migration and proliferation have never been convincingly demonstrated in human restenotic lesions.<sup>34</sup> O'Brien et al<sup>35</sup> found that 74% of tissue specimens recovered from human restenotic lesions had no evidence of proliferative cell nuclear antigen (PCNA) on immunocytologic staining. PCNA-labeling was detected anywhere from 1 to 390 days after the initial procedure without an obvious temporal peak. The frequency of PCNA positivity did not differ significantly between specimens obtained from restenotic versus de novo lesions. These findings suggest that cellular proliferation may be a relatively infrequent occurrence in human restenotic lesions, which may partially explain why antiproliferative agents have been unable to limit restenosis in a host of clinical trials.

### Remodeling

Early models of restenosis assumed that the cross-sectional area of the coronary artery remained relatively constant following angioplasty, and the presence or absence of luminal renarrowing was ultimately dependent on the volume of neointimal tissue that encroached upon the vessel lumen. Ten years ago, Glagov et al<sup>36</sup> demonstrated the potential for “compensatory dilation”

whereby a human coronary artery can expand to accommodate a de novo atherosclerotic plaque occupying 40% of its area before luminal diameter is compromised. Subsequent studies in animal models have shown that injured arteries can potentially compensate for neointimal tissue equivalent to nearly 60% of the vessel’s total cross-sectional area before the luminal area begins to decline.<sup>37</sup> Lafont et al,<sup>38</sup> in the rabbit atherosclerotic model, found that although neointimal hyperplasia did occur following experimental angioplasty, the development of restenosis correlated histologically with the presence of chronic arterial constriction, but not with the degree of neointimal growth.

The propensity for an artery to enlarge or constrict during the first few months following angioplasty, termed remodeling, has assumed a fundamental role in the current paradigm of restenosis. During the arterial healing process, the overall cross-sectional area of the vessel can decrease (“constrictive” remodeling) or enlarge (“expansive” remodeling). Expansive remodeling can potentially prevent luminal narrowing despite significant neointima formation, while, conversely, restrictive remodeling can result in restenosis despite a paucity of neointimal growth (*Figure 2*).<sup>39</sup>



**Figure 2.** The concept of remodeling. With “expansive” remodeling, restenosis can be avoided despite significant neointimal hyperplasia, whereas if “constrictive” remodeling occurs, restenosis may ensue despite the absence of neointima formation. NIH, neointimal hyperplasia; PTCA, percutaneous transluminal coronary angioplasty.

The importance of arterial remodeling in humans was suggested by a necropsy study in which 40% of restenotic lesions demonstrated no evidence of neointimal hyperplasia.<sup>40</sup> Mintz and colleagues<sup>41</sup> at the Washington Hospital Center used intravascular ultrasound to confirm the presence and importance of remodeling in human restenosis. A cohort of 209 patients was studied immediately after and 5.6±3.4 months following coronary angioplasty or atherectomy. Remodeling was found to be bidirectional with 22% of lesions showing an increase in the vessel area ("expansive" remodeling), and 78% demonstrating a decrease ("constrictive" remodeling). The lesions that showed an increase in vessel area, despite possessing on average more neointima formation, had a significantly lower binary restenosis rate (26% vs 62%) than did vessels with a decrease in overall size. Furthermore, it was determined that 73% of the average decrease in lumen area observed at 6 months was due to vessel constriction, whereas only 23% could be attributed to neointimal hyperplasia.

The mechanism of these late changes in vessel geometry is unclear, but remodeling appears to be an active, multifactorial process. Preliminary animal studies have demonstrated that arterial injury triggers the differentiation of adventitial fibroblasts into activated myofibroblasts by day 3 following injury.<sup>42</sup> The myofibroblasts have both synthetic capabilities (type I collagen) and the ability to translocate to the vessel intima.<sup>43</sup> These cells may contribute to fibrosis of the vessel wall and consequent constriction. There is evidence suggesting that soluble factors, including nitric oxide, also may play a role in the remodeling process.<sup>44</sup>

### **The vascular endothelium**

Endothelial cells serve to maintain vessel wall homeostasis both by their presence as a physical barrier, which protects the deeper layers from exposure to circulating cells and factors, and via their synthetic and secretory capabilities. Simple disruption of the endothelium, without concomitant injury to deeper structures, is sufficient to provoke substantial smooth muscle cell proliferation and neointima formation in animal models of restenosis. Products manufactured by endothelial cells that can inhibit smooth muscle cell proliferation include heparin and heparin sulfate, TGF- $\beta$ , and nitric oxide (endothelial-derived relaxing factor). Nitric oxide has also been shown to possess potent vasodilatory, antithrombotic, and anti-inflammatory properties.<sup>45</sup> Prostacyclin, which also possesses strong antithrombotic and vasodilatory effects, is also manufactured by the endothelium.

Damage to the endothelium, with consequent loss of these secretory products, would theoretically favor thrombus generation, vasoconstriction, and smooth muscle cell activation, which constitute the key contributors to restenosis. Experimental attempts to hasten endothelial regeneration following vessel injury by administration of vascular endothelial growth factor have met with variable success in animal models.<sup>46,47</sup> Exogenous administration of agents normally produced by functioning endothelial cells (eg, nitric oxide, prostacyclin) is another potential strategy to reduce restenosis. Human trials with these agents are in the preliminary stages.

### **Animals models and restenosis**

Animal models have provided much of the basis for the current conceptual model of restenosis and have implicated a multitude of potential targets for therapeutic intervention. Every pharmacologic agent (*Table I*) that has been subjected to a clinical restenosis trial has first shown efficacy in limiting restenosis in one or more animal models. Nearly all, however, have failed to duplicate their promising effects in humans, possibly for the following reasons<sup>34,48</sup>: (i) pharmacologic doses that are often required to prevent intimal hyperplasia in animals would produce systemic toxicity in humans; (ii) arterial injury in animals is induced in previously normal arterial segments, not upon an underlying atherosclerotic plaque; (iii) the time course of restenosis can differ considerably between animals and man, for example, the process is completed in 3 weeks in mice as opposed to several months in humans; and (iv) events that are prominent in most animal models of restenosis, for example, smooth muscle cell migration and proliferation, have not been clearly demonstrated in humans.

## **PHARMACOLOGIC TRIALS FOR RESTENOSIS**

### **Antiproliferative agents**

Given the prominent role of smooth muscle cell proliferation in animal models of restenosis, a variety of agents that interfere with potential mediators of cellular proliferation have been evaluated in clinical trials.

#### **Anti-inflammatory agents**

Both corticosteroids<sup>49-51</sup> and colchicine<sup>52,53</sup> have failed to improve angiographic or clinical outcome in several randomized trials. One small trial involving 80 patients demonstrated a significant reduction in angiographic restenosis in patients receiving ebselen, a nonsteroidal



anti-inflammatory agent with additional antioxidant properties.<sup>54</sup> No larger trials have been undertaken to confirm this potential benefit. Likewise, tranilast, an anti-inflammatory agent that has been used as a prophylactic agent to prevent keloid formation, was associated with improved rates of angiographic restenosis in two randomized trials following angioplasty and directional atherectomy.<sup>55,56</sup>

### Growth factor antagonists

Angiopeptin is a somatostatin analogue which, in experimental studies, has the ability to inhibit the proliferation of vascular smooth muscle cells induced by insulin-like growth factor (IGF-1) and PDGF. Administration of this agent to animals following balloon-induced vascular injury results in both

	PROBABLY BENEFICIAL*	POSSIBLY BENEFICIAL†	PROBABLY NOT BENEFICIAL‡	NOVEL APPROACHES
<b>Anticoagulants</b>			Warfarin	Tissue factor pathway inhibitor
			Heparin	Factor VIIa inhibitors
			Low-molecular-weight heparins	
			Hirudin/Hirulog	
<b>Antiplatelet agents</b>	GP IIb/IIIa receptor antibody	Prostacyclins	Aspirin	$\alpha_v\beta_3$ antagonists
			Dipyridamole	RGD peptides
			Thromboxane A <sub>2</sub> antagonists	
			Ticlopidine	
<b>Antiproliferative therapy</b>		Tranilast	Corticosteroids	Local radiation
		NSAIDs	Colchicine	Antisense therapy
		Trapidil	Ketanserin	Estrogens
		Angiopeptin		Vascular endothelial growth factor
<b>Lipid modulation</b>			HMG CoA reductase inhibitors	
			Fish oils	
<b>Vasodilators</b>		Calcium channel blockers	ACE inhibitors	Nitric oxide
<b>Mechanical approaches</b>	Coronary stents	Directional coronary atherectomy	Rotational atherectomy	
			Excimer laser angioplasty	

\*Probably beneficial: more than one positive large randomized clinical trial.  
†Possibly beneficial: positive preliminary trials or conflicting results from larger trials.  
‡Probably not beneficial: one or more negative large trial(s).  
GP, glycoprotein; HMG CoA, hydroxymethylglutaryl coenzyme A; NSAIDs, nonsteroidal anti-inflammatory drugs; RGD peptides, arginine glycine aspartic acid.

**Table 1.** Results of therapeutic trials for restenosis.

inhibition of neointima formation and a restoration of the vasodilator response to acetylcholine.<sup>57,58</sup> Three randomized trials, utilizing various doses of angiopeptin, have, however, yielded conflicting results.<sup>59-61</sup> Erikson et al,<sup>59</sup> in a randomized study which included 112 patients, discovered a significant reduction in angiographic restenosis (12% vs 40%,  $P=0.003$ ) and a trend toward reduced cardiovascular events at 12 months (25% vs 39%) in patients treated with angiopeptin. A subsequent large randomized trial of 1246 patients reported no clinical or angiographic benefits from angiopeptin.<sup>60</sup> Angiopeptin may have been suboptimally dosed in this large trial, however, as the drug was administered only twice a day despite its short (90-minute) half-life. Interestingly, the most recent trial ( $n=553$ ),<sup>61</sup> in which angiopeptin was administered via a continuous subcutaneous pump, reported no reduction in angiographic stenosis, but a marginally significant reduction in clinical events 1 year following angioplasty in patients who received the study drug (28.4% vs 36.4%,  $P=0.046$ ).

Serotonin (5-hydroxytryptamine) is among the preformed compounds released from platelet dense granules. In addition to its vasoactive properties, serotonin directly stimulates platelet aggregation, smooth muscle cell migration, proliferation, and synthesis of extracellular matrix components.<sup>62</sup> Following encouraging animal studies, the relationship between a selective serotonin S<sub>2</sub> antagonist and late outcome following angioplasty was examined in a prospective trial involving 658 patients.<sup>63</sup> Unfortunately, ketanserin failed to influence either clinical outcome or angiographic measures of restenosis relative to placebo.

### Vasodilators

#### Calcium channel blockers

Apart from their vasoactive properties, calcium channel blockers possess the ability in experimental situations to impair platelet aggregation and inhibit PDGF-mediated smooth muscle cell proliferation. In a meta-analysis including 919 patients enrolled in five randomized clinical trials examining the role of various calcium antagonists following angioplasty, Hillegass et al<sup>64</sup> reported a 30% decrease in the relative risk of restenosis in treated patients. This encouraging finding warrants further investigation in the form of a large randomized trial.

#### Angiotensin-converting enzyme inhibitors (ACEIs)

In vitro and animal studies have defined the involvement of the renin-angiotensin-aldosterone axis in the regulation of the vascular response to injury. Angiotensin II has been shown to induce *c-myc* proto-

oncogene expression in cultured vascular smooth muscle cells and promote smooth muscle cell proliferation in vivo.<sup>65</sup> Furthermore, administration of ACEIs to animals following arterial injury is associated with dose-dependent reductions in neointimal hyperplasia.<sup>66</sup> Despite the sound rationale for ACE inhibition gleaned from these experimental studies, large clinical trials failed to detect any angiographic or clinical benefit from treatment with various doses of the ACE inhibitors cilazapril or fosinopril.<sup>67,68</sup>

### Lipid-lowering therapy

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibition, despite favorable in vitro effects on platelet aggregability and efficacy in reducing neointimal hyperplasia in animal models, has failed to influence restenosis in two randomized trials. In the Lovastatin Restenosis Trial, no improvement in clinical or angiographic outcome was seen in the treatment group despite a 36% reduction in low-density lipoproteins (LDL).<sup>69</sup> Similarly, the combination of lovastatin and probucol proved ineffective in preventing restenosis in a subsequent trial.<sup>70</sup> In a separate small clinical trial, probucol monotherapy was associated with a reduction in angiographic restenosis, possibly as a result of this agent's antioxidant rather than its lipid-lowering properties.<sup>71</sup> Despite encouraging preliminary clinical experiences, omega-3 fatty acids have failed to reduce restenosis rates in several recent rigorous randomized trials.<sup>72,73</sup>

### Anticoagulants

Based on their primary role in thrombosis and the experimental association between serum proteins involved in the coagulation cascade, especially thrombin, and vascular smooth muscle cell proliferation, several large clinical trials have sought to determine whether treatment with various anticoagulants can affect restenosis. Warfarin, which interferes with hepatic production of the vitamin K-dependent factors II (prothrombin), VII, IX, and X, failed to influence restenosis rates in two prospective studies.<sup>74,75</sup> Heparin, apart from its ability to potentiate antithrombin III-mediated inactivation of factors X<sub>a</sub> and thrombin, has been shown to directly inhibit smooth muscle cell proliferation in vitro. However, neither heparin nor the low-molecular-weight heparins have been successful in preventing restenosis in several large randomized clinical trials.<sup>73,76,77</sup>

Hirudin, a peptide originally isolated from the salivary glands of the leech, is a potent anticoagulant that directly and irreversibly binds to thrombin at multiple



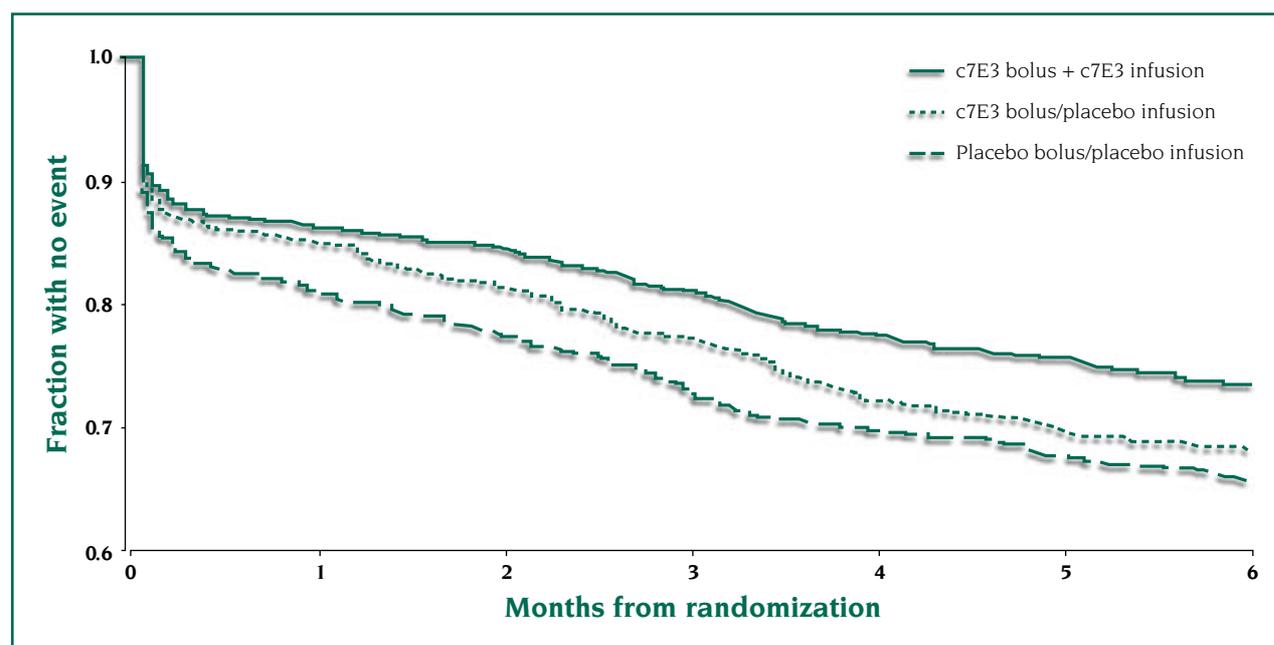
sites, circumventing the requirement for antithrombin III. Furthermore, unlike heparin, hirudin is able to inhibit thrombin molecules which are already bound to a clot, thereby reducing the propensity for further thrombus formation. Despite these theoretical advantages and a background of positive animal studies, hirudin and its analogue bivalirudin (Hirulog) failed to provide long-term benefit following angioplasty in two large randomized trials.<sup>78,79</sup> In the HELVETICA study,<sup>78</sup> 1141 patients undergoing balloon angioplasty were randomized to one of two dosage regimens of hirudin or heparin. Despite a significant reduction in early cardiac events in the hirudin group (relative risk =0.61, 95% confidence interval: 0.41-0.90), neither the 7-month event-free survival rate nor the incidence of angiographic restenosis was improved by hirudin. Likewise, in a randomized trial of 4098 patients who underwent angioplasty in the setting of unstable or postinfarction angina, no difference was encountered in the clinical event rate at 6 months among patients who received bivalirudin (Hirulog) or heparin at the time of the procedure.<sup>79</sup>

### Antiplatelet therapy

Platelets, through both the release of growth factors, cytokines, and vasoactive substances, and their central role in thrombus generation, appear to play an integral part in restenosis. In the late 1980s and early 1990s,

a number of agents that interfere with various aspects of platelet function and aggregation, including aspirin, dipyridamole, thromboxane A<sub>2</sub> antagonists, and ticlopidine, all failed to improve measures of angiographic or clinical restenosis in randomized trials. However, these individual agents, which impair only isolated aspects of platelet metabolism, tend to have relatively weak overall effects on platelet aggregation and adhesion at systemically tolerable doses, which may limit their efficacy.<sup>25</sup>

In 1983, Collier et al<sup>80</sup> demonstrated that blockade of the platelet GP IIb/IIIa receptor with a purified murine monoclonal antibody could completely inhibit the binding of fibrinogen to these receptors and profoundly impair platelet aggregation in vitro. Subsequent in vivo studies documented the ability of GP IIb/IIIa receptor blockade to achieve a state of prolonged arterial wall passivation (the near complete inhibition of platelet/thrombus formation), a condition that cannot be achieved with therapeutic doses of aspirin or other nonspecific antiplatelet agents.<sup>28</sup> To decrease the potential immunogenicity of the original murine monoclonal antibody to the GP IIb/IIIa receptor, a chimeric monoclonal Fab (originally termed 7E3, now called abciximab) was engineered, which consists of immunoglobulin variable regions derived from the original murine antibody linked to constant regions from human IgG.<sup>81</sup>



**Figure 3.** Clinical outcome in the EPIC study. Patients randomized to receive 7E3 demonstrated a significant reduction in combined ischemic end points (death, myocardial infarction, recurrent ischemia requiring repeat revascularization) both periprocedurally and at 6 months.<sup>97</sup>

The EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications) trial was a multicenter study designed to assess the efficacy of 7E3 in preventing both acute and delayed ischemic complications following high-risk coronary angioplasty.<sup>82</sup> Patients (n=2099) with recent or evolving myocardial infarction, unstable angina, or high-risk angiographic features were randomized to receive: (i) a bolus of 7E3 (0.25 mg/kg) followed by a 10- $\mu$ g/min infusion over 12 hours; (ii) a 7E3 bolus followed by a placebo infusion; or (iii) a placebo bolus and infusion. All patients received aspirin 325 mg at least 2 hours before angioplasty or atherectomy and daily thereafter, and heparin with a goal activated clotting time of 300 to 350 seconds. Compared with placebo, the 7E3 bolus and infusion group experienced a 35% relative reduction in the 30-day combined ischemic end point (12.8% vs 8.3%,  $P=0.008$ ).<sup>82</sup> The clinical benefit was maintained at 6 months with a 23% reduction in major ischemic events or repeat revascularization in the 7E3 bolus plus infusion group (35.1% vs 27.0%,  $P=0.001$ ) (Figure 3).<sup>83</sup> This difference was primarily the result of a 26% relative decrease in repeat target vessel revascularization in the bolus plus infusion group. The improved outcome of GP IIb/IIIa receptor blockade came at the cost of increased major bleeding complications in patients who received 7E3 rather than placebo (14% vs 7%). Furthermore, no routine angiographic follow-up was performed in EPIC to correlate the observed improvement in clinical measures of restenosis with a decrease in angiographic restenosis.

Following the encouraging results of the EPIC trial, the EPILOG (Evaluation in Percutaneous transluminal coronary angioplasty [PTCA] to Improve Long-term Outcome with c7E3 GP IIb/IIIa receptor blockade) study<sup>84</sup> was undertaken to address the following issues: (i) to determine if the increase in bleeding complications associated with abciximab could be reduced by alternative heparin dosing strategies, without compromising efficacy; (ii) to determine if the benefits of abciximab therapy evident in the high-risk population studied in EPIC apply to all patients undergoing angioplasty; and (iii) to determine the effects of abciximab on angiographic restenosis in an attempt to better define its mechanism of clinical benefit. In EPILOG, both high- and low-risk patients undergoing coronary angioplasty were randomized to one of three treatment arms: (i) abciximab bolus and 12-hour infusion with standard dose heparin (100 units/kg bolus) at the time of angioplasty; (ii) abciximab bolus/infusion with low-dose heparin (70 units/kg); or (iii) placebo plus standard heparin. The study

sought to randomize approximately 4800 patients, however enrollment was stopped by the Data and Safety Monitoring Committee after the entry of 2792 patients.<sup>84</sup> Compared with placebo, patients who received abciximab and low-dose heparin experienced a reduction in the composite 6-month end point of death, myocardial infarction, or repeat revascularization (25.8% vs 22.8%,  $P=0.034$ ) and a nonsignificant trend toward reduced major bleeding complications (3.1% vs 1.8%). The improvement in 6-month clinical outcome was primarily the result of reductions in myocardial infarction (9.9% vs 5.0%,  $P<0.001$ ) and need for urgent revascularization (6.7% vs 3.1%,  $P<0.001$ ) in the abciximab group. On subgroup analysis, low-risk patients enrolled in EPILOG derived a similar degree of benefit from abciximab at 30-day follow-up as patients with high-risk clinical and angiographic features.<sup>85</sup>

## MECHANICAL APPROACHES TO PREVENTING RESTENOSIS

A variety of novel devices have been conceived in an attempt to both enhance the immediate procedural success of percutaneous revascularization and reduce restenosis. The potential utility of the so-called new devices in curtailing late vessel narrowing rests conceptually with their potential to influence the mechanical aspects of restenosis, namely immediate vessel recoil and late remodeling. While balloon angioplasty relies on plaque compression and rupture with associated intimal dissection and stretching of the vessel wall to achieve luminal gain, several newer devices have been devised which produce luminal enlargement primarily on the basis of plaque removal or ablation, thereby reducing the propensity for vessel recoil.<sup>21</sup>

### Rotational atherectomy and laser angioplasty

The clinical efficacy of two ablative devices, excimer laser coronary angioplasty and rotational atherectomy, was examined relative to that of balloon angioplasty in the randomized ERBAC study<sup>86</sup> of 620 patients with high-risk angiographic lesion morphology. Despite significantly improved procedural success in patients randomized to rotational atherectomy relative to the other treatment strategies, neither of the new devices resulted in a reduction in the 6-month angiographic restenosis rate. Repeat target lesion revascularization was actually more frequent in patients who underwent laser angioplasty and rotational atherectomy relative to those treated with balloon angioplasty.



### Directional coronary atherectomy

Directional coronary atherectomy (DCA) employs a mechanical cutting device by which atherosclerotic plaque can be resected and removed. CAVEAT-I (Coronary Angioplasty Versus Excisional Atherectomy Trial) was a multicenter study that randomized 1012 patients with de novo coronary stenoses that were suitable for either conventional balloon angioplasty or DCA.<sup>87</sup> In this study, atherectomy was associated with an improved procedural success rate relative to angioplasty ( $\leq 50\%$  residual stenosis in 89% vs 80%) and resulted in a significantly greater acute increase in luminal diameter (1.05 vs 0.86 mm). The angiographic benefits seen in the atherectomy group, however, came at the cost of a significant increase in early procedural complications, predominantly abrupt vessel closure and non-Q-wave myocardial infarction. At 6-month follow-up, there was a trend toward decreased angiographic restenosis in the atherectomy group (50% vs 57%,  $P=0.06$ ). However, as a result of the increased incidence of periprocedural myocardial infarction, atherectomy patients had a significantly increased likelihood of death or myocardial infarction at 6 months (9.2% vs 5.0%,  $P=0.007$ ). One-year clinical follow-up revealed a surprising statistically significant excess mortality in the atherectomy group (2.2% vs 0.6%,  $P=0.035$ ).<sup>88</sup> The results of CAVEAT are concordant with those of the Canadian Coronary Atherectomy Trial (CCAT) in which 274 patients with disease involving the proximal left anterior descending coronary artery were randomized to treatment with DCA or balloon angioplasty.<sup>89</sup> Again, despite greater procedural success and significantly greater acute luminal gain, no improvement in clinical or angiographic restenosis was evident at 6-month follow-up in the group that underwent atherectomy.

Multivariate analysis by the CAVEAT investigators demonstrated that the most important determinant of luminal diameter at 6-month angiography was not whether the patient had undergone atherectomy or balloon angioplasty, but the final minimal luminal diameter immediately following the procedure. While this finding provided support for one of the seminal concepts in interventional cardiology—that it is the final luminal diameter (rather than the device used to achieve it) that determines late angiographic outcome<sup>90</sup>—it also raised a flag of caution regarding the dogma that “bigger is better” in that a slight improvement in late lumen diameter is meaningless if it is gained at the expense of increased adverse clinical outcomes.

Despite the sobering findings of CAVEAT-I and CCAT, a commonly voiced criticism by enthusiasts of DCA

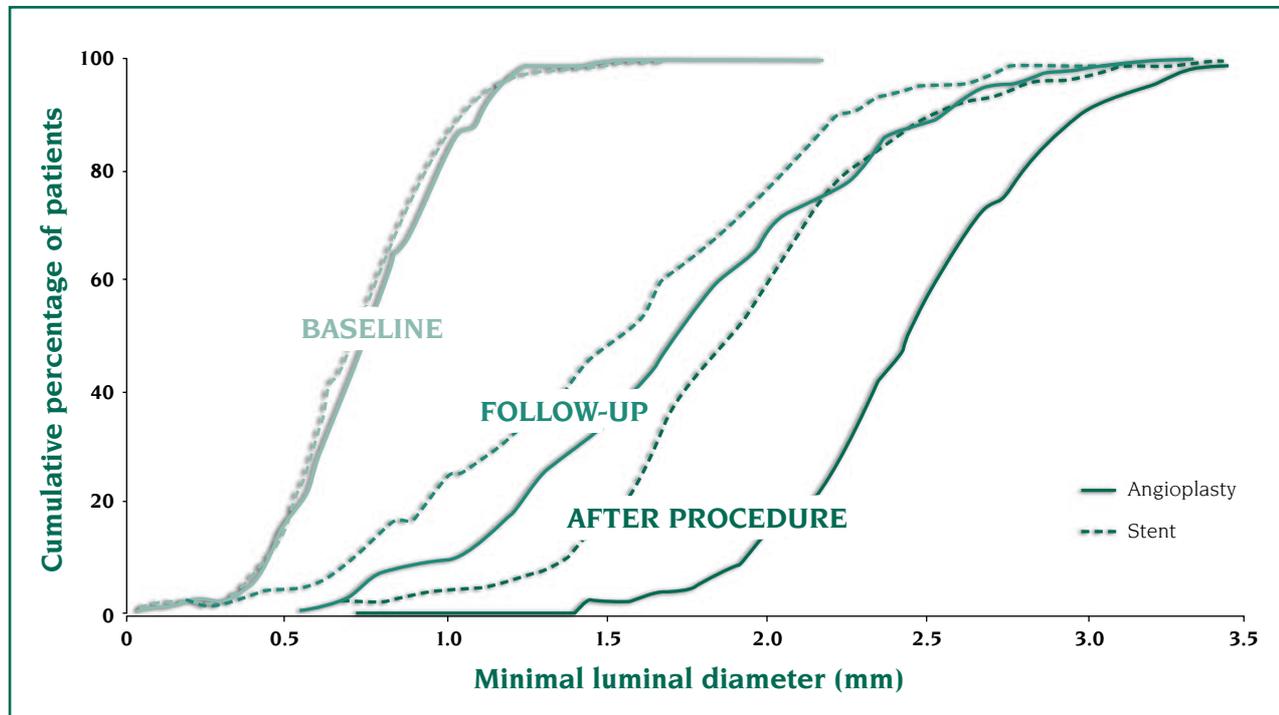
was that atherectomy may not have been used to its fullest potential in these trials. By performing “optimal atherectomy”—whereby the goal of DCA is to obtain the largest possible postintervention lumen short of causing vessel perforation (eg, residual stenosis  $<10\%$  to  $20\%$ )—it was argued that DCA may provide long-term benefits relative to balloon angioplasty by which final residual stenoses  $<30\%$  are often unachievable.

The results of the recently reported Balloon versus Optimal Atherectomy Trial (BOAT) provide support for this more aggressive approach to DCA.<sup>91</sup> In this large multicenter trial, optimal atherectomy resulted in a significantly reduced postprocedural residual stenosis relative to balloon angioplasty (14% vs 28%), which translated into improved minimal luminal diameter follow-up (1.86 vs 1.69 mm) and dichotomous restenosis rate (32% vs 40%,  $P=0.017$ ) at 6 months. However, there was no reduction of target vessel revascularization (17.1% vs 19.7%,  $P=0.33$ ). One-year mortality rates were low and did not differ significantly among patients treated with atherectomy or balloon angioplasty (0.6% vs 1.6%, respectively).<sup>91</sup>

While the preliminary results regarding optimal atherectomy are promising, several theoretical and practical issues regarding DCA remain. First, the improved angiographic results of aggressive atherectomy still come at the expense of an increased frequency of periprocedural elevations in myocardial enzymes and no reduction in the need for repeat procedures. Despite the lack of excess late mortality in BOAT, other recent reports have demonstrated a striking association between postprocedural myocardial enzyme elevations and adverse late outcomes.<sup>92</sup> Second, while atherectomy in BOAT was performed by highly experienced operators, DCA remains a more technically demanding procedure than balloon angioplasty or coronary stent placement with a steeper “learning curve.” Third, trials comparing DCA to angioplasty (or any comparative trials between devices) cannot be blinded, and thus have the potential for introduction of unintentional operator bias by proponents of a particular device. Finally, randomized comparisons between DCA and coronary stenting have yet to be performed.

### Coronary stents

Intracoronary stents were first approved in the United States as devices to treat actual or threatened abrupt closure during balloon angioplasty procedures. Based on experimental evidence that stents could virtually



**Figure 4.** Angiographic results from the STRESS trial. Coronary stent placement resulted in improved immediate luminal diameter relative to balloon angioplasty. Despite greater “late loss” in the stent group, stent placement was still associated with larger luminal diameter on follow-up angiography at 6 months.<sup>9</sup>

eliminate early vessel recoil and impact favorably on late remodeling, two randomized multicenter trials were undertaken to compare the rates of clinical and angiographic restenosis between patients undergoing coronary stent placement and balloon angioplasty.

The Stent REstenosis Study (STRESS)<sup>9</sup> randomized 410 patients with discrete de novo lesions in large ( $\geq 3$  mm) vessels to undergo elective Palmaz-Schatz stent implantation or standard balloon angioplasty. Stent implantation was associated with an improved procedural success rate and larger postprocedural luminal diameter. At 6-month angiography, stent patients had a significantly larger luminal diameter ( $1.74 \pm 0.60$  vs  $1.56 \pm 0.65$  mm,  $P=0.007$ ) which translated into a lower binary restenosis rate (31.6% vs 42.1%,  $P=0.046$ ) (Figure 4). The incidence of combined ischemic events at 6 months did not differ significantly between treatment assignments. However, revascularization of the original target lesion because of recurrent ischemia was less frequent in the stent group (10.2% vs 15.4%,  $P=0.06$ ). Similar findings were reported in the Belgium Netherlands Stent Study Group trial (BENESTENT)<sup>10</sup> in which 520 patients with stable angina and noncomplex lesion morphology were randomized to receive a Palmaz-Schatz stent or

balloon angioplasty. Immediate and 6-month luminal diameters were improved by stent implantation, as was the rate of angiographic restenosis (22% vs 32%,  $P=0.02$ ). The combined clinical end point of death, myocardial infarction, stroke, and need for repeat revascularization at 6 months was significantly reduced in the stent group, primarily as a result of less frequent need for repeat angioplasty. Major bleeding complications were more common in the group undergoing stent implantation (13.5% vs 3.1%,  $P<0.001$ ) as a consequence of the aggressive medical anticoagulation regimen used at the time that the study was undertaken. The initial clinical benefits of stent implantation were maintained at 1-year follow-up in both the STRESS and BENESTENT populations.<sup>93,94</sup>

Since the publication of STRESS and BENESTENT, the strategy of ensuring optimal stent deployment via high-pressure balloon inflation within the stent has reduced the incidence of subacute stent thrombosis, permitting the use of far less aggressive antithrombotic regimens following the procedure.<sup>95</sup> Using this approach in conjunction with heparin-coated stents, the BENESTENT-II investigators recently reported a 17.1% incidence of combined ischemic events at 6 months (versus 23.2% in the angioplasty arm) in a



trial involving 827 patients.<sup>96</sup> The reduced potential for bleeding complications, coupled with the superior immediate angiographic appearance afforded by stents and the reduced incidence of restenosis observed in STRESS and BENESTENT, has produced a situation where clinical enthusiasm for stent implantation for wide-ranging indications has currently outstripped the supporting scientific evidence.<sup>97</sup> Several words of caution are in order:

1. The results of STRESS and BENESTENT must be viewed in the light of their relatively narrow inclusion criteria. While preliminary reports are favorable, the particular benefit of stent implantation in patients without de novo, focal lesions in native coronaries (eg, long lesions requiring multiple stents, chronic total occlusions, angiographic thrombus, and saphenous vein graft disease) require further confirmation.
2. While intermediate-term follow-up data now exist to support the continued safety and efficacy of stents up to 3 to 6 years following implantation,<sup>98,99</sup> the long-term safety profile of these permanent endovascular prostheses remains uncertain.
3. While stenting has proved capable of reducing restenosis rates in certain patient and lesion subsets, implantation of these devices has engendered a new and problematic entity: in-stent restenosis. When in-stent restenosis does occur (as it did in 32% and 22% of the patients enrolled in STRESS and BENESTENT, respectively), the prognosis is poor as repeat percutaneous treatment is associated with rates of recurrent restenosis reported to be as high as 57%.<sup>100</sup>

These potential limitations of primary stenting, coupled with evidence that the risk of restenosis is related to final luminal diameter rather than the particular device used to achieve it,<sup>90</sup> suggest that a rational strategic approach for coronary intervention might consist of aggressive balloon angioplasty aiming for a “stent-like” angiographic appearance, with stent implantation reserved for a suboptimal balloon result. Support for this strategy comes from three recent clinical trials (EPILOG, BOAT, and BENESTENT-II) in which an optimal balloon angioplasty approach was used in the control arm. Late target vessel revascularization following angioplasty was remarkably low (<20% in each trial, compared to postballoon revascularization rates in excess of 20% or even 30% in older studies<sup>83,87</sup>), and only 14% of patients assigned to angioplasty in each trial required unplanned stent placement for a suboptimal balloon result (*Table II*).

#### LOCAL DELIVERY

One proposed explanation for the failure of many pharmacologic agents that have prevented restenosis in animal models to produce similar benefits in clinical trials rests on the inability to achieve sufficient concentrations of drug at the site of injury. Insufficient local concentrations of systemically administered drugs may result from: (i) the necessity of dose limitation due to the potential for systemic toxicity; (ii) inadequate uptake by intended targets within the vessel wall; or (iii) inadequate timing or duration of therapy. Techniques of local delivery have the potential to overcome these limitations by providing large concentrations of drug to the target area while limiting the total body dose.

TARGET LESION REVASCULARIZATION (%)					
Study	No.	Intervention assessed	Experimental arm	Balloon (control) arm	Stent use in balloon arm (%)
BENESTENT-II <sup>96</sup>	827	Stent	9.2	13.8	14
EPILOG <sup>85</sup>	2792	Abciximab	16.4	18.1	14
BOAT <sup>91</sup>	989	Directional atherectomy	17.1	19.7	14
<b>TOTAL</b>	<b>4608</b>		<b>15.4</b>	<b>17.5</b>	<b>14</b>

**Table II.** Target lesion revascularization rates with “aggressive” balloon angioplasty in three recent trials.

Several methods of percutaneous intravascular drug delivery have been developed.<sup>48,101</sup> These can be roughly subdivided into catheter-based infusion techniques, methods of endovascular implantation (active agent coupled to a stent or drug-eluting polymer), and systemic administration of agents which can be activated locally.

A variety of modified balloon catheters have been designed to enable delivery of agents to the site of the target lesion at the time of the percutaneous revascularization procedure. These catheters employ designs that allow drug-containing effluent to either: (i) passively diffuse into the adjacent vessel wall (eg, the double balloon catheter, the transport catheter, the dispatch catheter); or (ii) enter the vessel wall under hydrostatic pressure by being forced through microscopic holes on the balloon's surface (eg, Wolinsky and microporous balloon catheters).

Methods of local implantation include: (i) hydrogel-coated balloon catheters, which, prior to use, are dipped in the drug of interest and then inflated at the lesion site, thereby depositing the drug at the site of injury; and (ii) permanent or biodegradable stents, which are either coated or impregnated with the pharmacologic agent of interest prior to deployment.<sup>96,102</sup>

While implanted devices can provide prolonged exposure to the therapeutic agent, stent biocompatibility has been an issue in experimental models.<sup>103</sup>

Other design issues relative to these experimental devices include the efficiency of transfer, prevention of drug washout, and appropriate timing and duration of delivery.

Virtually all agents that can be administered systemically are amenable to local delivery. Agents that have been demonstrated to impair intimal hyperplasia in animals, but have failed to prevent restenosis when administered systemically to humans because of necessary dose limitations, are obvious candidates for human trials. Effective local delivery techniques are also essential for potential clinical applications of both radiation and gene therapy, which are discussed in detail below.

### GENE THERAPY

Gene-based therapy for restenosis is grounded on the premise that by promoting or inhibiting the expression of certain critical genes that are involved in response to angioplasty-induced injury, the vascular healing process can be modified in such a manner to reduce the likelihood of restenosis. Potential target genes

include a variety of proto-oncogenes (eg, *c-myb*, *c-myc*), which are activated following arterial injury and are believed to mediate vascular smooth muscle cell migration, proliferation, and extracellular matrix production, genes coding for various growth factors or growth factor receptors, and genes involved in the production of other suspected local mediators of restenosis (eg, nitric oxide).

Several strategies have been proposed to alter gene expression as a means of preventing restenosis. One promising approach devised to inhibit the expression of a selected gene involves the use of antisense oligonucleotides.<sup>104</sup> Antisense agents are short (typically 20 to 30 base pairs) genetically engineered, single-stranded sequences of DNA that are complementary to a specific region of messenger RNA transcribed by the target gene. Once introduced into the host cell, the antisense sequence anneals to its mRNA complement, preventing synthesis of gene product and promoting rapid degradation of the mRNA. Antisense oligonucleotides designed to inhibit the translation of several proto-oncogenes, including *c-myc*, *c-myb*, and PCNA, have resulted in marked reduction in neointima formation in animal angioplasty models.<sup>105,106</sup>

Other potential means of inhibiting the expression of a single target gene include ribozymes (enzymatically linked RNA molecules capable of inactivating complementary mRNA produced by a target gene),<sup>107</sup> or the introduction of "suicide genes," such as the retinoblastoma gene, whose products can result in target cell death.<sup>108</sup>

Distinct from techniques which aspire to "turn off" selected genes, another potential therapeutic strategy involves the introduction of genetic material into the area of vascular injury in an attempt to augment production of desired cellular products.<sup>109</sup> Transfer of genes coding for nitric oxide synthase and vascular endothelial growth factor—compounds which are believed to play a role in the processes of remodeling and endothelial regeneration, respectively—has recently been accomplished in experimental models.<sup>110</sup>

Several potential vectors exist by which nucleic acid sequences can be delivered to target cells in the vessel wall.<sup>104,111</sup> Liposomes and viruses rendered replication-deficient currently appear to be the most promising delivery vehicles for human gene therapy. Liposomes are lipid shells in which the therapeutic DNA sequence is packaged. The liposome-DNA complex fuses to, and is taken up by, the cell membrane, thereby gaining access to the target cell. While these



complexes are relatively easy to manufacture, this method of DNA delivery is hampered by a low efficiency of transfer and only transient expression of the delivered genetic material. Retroviral vectors, in which the gene of interest is inserted into the viral genome, appear to be limited by the technically cumbersome production process, the inability of these viruses to transfect cells that are not actively replicating at the time of exposure, and the potential for oncogene activation. Adenoviral vectors, on the other hand, appear to offer the greatest potential for safe and efficient human gene transfer. These carriers, which are able to infect both replicating and nonreplicating cells, allow transferred gene sequences to reside in the host cell nucleus within plasmids. This avoids the potential activation of oncogenes, but also limits the life span of the transfected gene.

Several practical and theoretical issues exist relative to the application of gene therapy to restenosis. First, given the highly complex nature of the vascular healing process, which likely involves the activation of hundreds of genes in a time-dependent manner, it must be determined which genes need to be promoted or inhibited, and when and for how long relative to the angioplasty procedure gene manipulation should occur. Second, the vascular healing process, as it has evolved, is a fundamental process required to maintain homeostasis within an organism. Interference with key cell regulatory processes that govern the manner in which vascular tissue responds to injury may have unforeseen adverse consequences. Third, restenosis is a multifactorial process. Successfully inhibiting one component, such as smooth muscle cell activation, by proto-oncogene inhibition will not necessarily translate into clinical benefits. Fourth, the ability to efficiently transfer genes depends on techniques of local delivery with their inherent limitations. Finally, multiple safety issues remain with respect to the use of adenoviral vectors and antisense oligonucleotides, including the possibility of persistent infection, the development of antigenicity and inflammation, and transfection of distant organs.<sup>48</sup>

### LOCAL RADIATION THERAPY

Ionizing radiation has been used successfully as a treatment for a variety of benign proliferative processes including keloid scar formation and heterotopic ossification. Given the close association between smooth muscle cell proliferation and restenosis, locally delivered intravascular radiation has recently received interest as a potential adjunctive therapy

following angioplasty. Ionizing radiation results in nonspecific breaks in chromosomal DNA, thereby inhibiting proliferation of cells that are actively dividing at the time of exposure. Potential secondary effects with respect to vascular healing include inhibition of migration and extracellular matrix production by smooth muscle cells, and possible favorable effects on remodeling.<sup>112</sup>

In an attempt to limit the systemic toxicity of radiation therapy, local coronary delivery following successful angioplasty can be achieved by means of seed-implanted catheters or radioactive wires. Stents rendered radioactive by ion implantation or cyclotron activation have been designed and allow more prolonged radiation exposure.<sup>113</sup> Both  $\beta$ - and  $\gamma$ -emitting isotopes are currently under investigation in preliminary clinical trials, and each offers various theoretical and practical advantages and disadvantages.  $\beta$ -Emitters such as <sup>32</sup>P and <sup>90</sup>Y, by virtue of lower tissue penetration, allow decreased radiation exposure for adjacent normal tissues. However, because of the rapid dose fall-off with  $\beta$ -emitting sources, the importance of centering the isotope within the arterial lumen becomes paramount to ensure equal and adequate tissue delivery. As described by Teirstein,<sup>114</sup> at a point only 2 mm away from an <sup>90</sup>Y- $\beta$  source, the delivered dose of radiation falls to only 15% of its intensity at the source. Given the asymmetry inherent in arteries following balloon angioplasty, homogeneous delivery of radiation to deeper vessel wall components (such as medial and adventitial smooth muscle cells) presents a challenge. To this end, special centering catheters are being evaluated.<sup>115,116</sup>  $\beta$ -Emitting stents may obviate the problem of source centering, but concerns including a theoretical increased risk of stent thrombosis resulting from delayed reendothelialization need to be addressed. While  $\gamma$ -emitters (<sup>192</sup>Ir) have greater tissue penetration, which ensures more even distribution in large and asymmetric vessels, increased radiation exposure occurs both in nonaffected tissues and among catheterization laboratory personnel.

Animal experiments in many species have demonstrated inhibition of smooth muscle cell proliferation, neointimal hyperplasia, and angiographic restenosis with varying doses of both  $\beta$ - and  $\gamma$ -emitting isotopes.<sup>113</sup> Human studies are in the preliminary stages. Verin et al<sup>115</sup> reported no complications in a safety and dose-finding trial using an endoluminally centered <sup>90</sup>Y- $\beta$  source at a dose of 18 Gy in 15 patients following successful balloon angioplasty; however, 6 of the

15 patients developed angiographic restenosis at 6 months. Interim results from the SCRIPPS trial,<sup>114</sup> the first randomized study to evaluate the efficacy of catheter-based delivery of <sup>192</sup>Ir- $\gamma$  (estimated dose 8 to 30 Gy) following percutaneous revascularization, appear encouraging. Among the first 55 patients enrolled, the incidence of 6-month angiographic restenosis was significantly reduced in the radiation-treated group (15.4% vs 48.3%). Major clinical end points at 12 months were likewise decreased in the treatment group (15.4% vs 48.3%). Important issues that need to be resolved in future trials include dose optimization and assessment of the potential for late adverse cardiac (aneurysm formation, enhanced atherogenesis) and noncardiac (secondary malignancy) sequelae.

## NOVEL PHARMACOLOGIC APPROACHES

### Platelet-derived growth factor (PDGF) antagonists

PDGF is a regulatory peptide that is synthesized by a variety of cells in response to vascular trauma. PDGF binds to target cells via specific membrane receptors and promotes the expression of nuclear proto-oncogenes (including *c-myc* and *c-fos*) and entry into the cell cycle.<sup>117</sup> Administration of exogenous PDGF enhances neointima formation in animal models of arterial injury, and interference with PDGF activity via the administration of specific antibodies, antisense oligonucleotides, or pharmacologic agents has been shown to reduce experimentally induced neointima growth.<sup>118</sup>

Three preliminary clinical trials examining the efficacy of trapidil, an antiplatelet drug with specific PDGF antagonism given at the time of angioplasty, have all yielded promising results.<sup>119-121</sup> In the largest of these studies, 384 patients undergoing elective angioplasty were randomized to receive trapidil 100 mg tid or aspirin beginning 3 days prior to the procedure with therapy continuing for 6 months. At follow-up angiography, the binary restenosis rate was significantly lower in the trapidil group (24.2% vs 39.7%,  $P < 0.01$ ), which corresponded to a significantly lower incidence of recurrent angina in patients assigned to trapidil.<sup>121</sup> Although this study was limited by a poor rate of angiographic follow-up (66.7%) and lack of automated quantitative coronary angiography, it demonstrates the potential for the antagonism of PDGF (or other critical growth factors including bFGF or TGF- $\beta$ ) as a means of reducing restenosis.

### $\alpha_v\beta_3$ receptor antagonists

The recently described  $\alpha_v\beta_3$  receptor, for which the extracellular matrix protein vitronectin serves as the primary ligand, is present on the surface of platelets as well as other cellular elements in the blood vessel wall including endothelial cells, smooth muscle cells, and monocytes.<sup>25</sup> The precise function of the  $\alpha_v\beta_3$  integrin has not been elucidated, but this receptor appears to be involved in the adhesion and migration of smooth muscle and endothelial cells, processes which are key components of neointima formation. Because  $\alpha_v\beta_3$  and GP IIb/IIIa share a common subunit ( $\beta_3$ ), both receptors are blocked by the monoclonal Fab directed against GP IIb/IIIa (abciximab), which has raised interesting questions regarding the mechanism of clinical benefits seen with this agent. Ongoing animal experiments with agents that selectively block  $\alpha_v\beta_3$  have strongly implicated the importance this pathway (relative to GP IIb/IIIa blockade) in the modulation of smooth muscle cell migration and neointima formation.<sup>122,123</sup>

### Blockade of early components of coagulation

Tissue factor, a recently characterized membrane-bound glycoprotein that is expressed by vascular cells following injury, plays a primary role in initiating both the intrinsic and extrinsic coagulation cascades. Once exposed, tissue factor forms a complex with circulating factor VIIa. The tissue factor–VIIa complex, in turn, converts factors IX (intrinsic pathway) and X (extrinsic pathway) into their active forms, ultimately resulting in the generation of thrombin from prothrombin.<sup>124</sup> As previously discussed, agents that directly inhibit thrombin activity have the capacity to prevent neointimal hyperplasia in experimental models, but have failed to reduce restenosis in human trials, probably as a result of necessary dose limitations to prevent bleeding complications.<sup>78,79</sup> Inhibition of the coagulation cascade at an earlier stage could theoretically result in profound inhibition of thrombin generation while avoiding overly aggressive systemic anticoagulation.

Two agents with the ability to inhibit tissue factor–related initiation of coagulation have been examined in animal models of restenosis.<sup>125,126</sup> Active-site inactivated factor VIIa (DEGR-VIIa), an inactivated form of endogenous factor VIIa, competitively blocks the binding of native factor VIIa to tissue factor. Recombinant tissue factor pathway inhibitor (TFPI)



binds to circulating factor Xa and effectively inhibits factor Xa from interacting with the tissue factor–VIIa complex. In one study, infusion of either DEGR-VIIa or TFPI prior to and for 72 hours following vascular injury in the atherosclerotic rabbit restenosis model was associated with significant reductions in neointima growth and angiographic restenosis compared to administration of placebo, hirudin, or tick anticoagulant peptide (a direct factor Xa inhibitor).<sup>125</sup> Issues that need to be addressed prior to initiation of clinical trials with these agents include uncertainties regarding proper dosing, optimal methods to monitor the degree of anticoagulation, and the uncertain importance that tissue factor plays in human restenosis.<sup>127</sup>

### Estrogen derivatives

Several large observational studies have demonstrated a strong association between estrogen replacement therapy and both a primary and secondary reduction of cardiovascular events in postmenopausal women. Based on its physiologic effects and results from experimental and preliminary clinical studies, estrogens may likewise have the ability to impact favorably on restenosis.

Estrogens interact with several of the processes which appear integral to restenosis. Therapy with estrogen is associated with beneficial hemostatic effects, including decreased plasma fibrinogen and plasminogen activator inhibitor type 1 (PAI-1) level, and increased levels of tissue-type plasminogen activator (tPA).<sup>128</sup> Platelet and inflammatory cell deposition at sites of arterial injury are reduced with estrogen administration.<sup>129</sup> Exogenous estrogen administration is associated with decreased *c-myc* gene expression and reduced neointima formation following vascular injury in rat carotid arteries.<sup>130</sup> Estrogen may also influence remodeling following angioplasty through its ability to enhance both the release and coronary vasomotor effects of nitric oxide, and through potentiation of acetylcholine-mediated vasodilation of coronary arteries.<sup>131</sup>

No prospective evaluation of estrogen therapy following angioplasty has been undertaken. O'Keefe et al,<sup>132</sup> in a case-control study of 337 women who underwent elective balloon angioplasty, found that estrogen therapy was associated with improved 7-year survival and freedom from major cardiovascular events (88% vs 65%,  $P=0.001$ ), although the rates of angiographic restenosis were not studied. O'Brien et al<sup>133</sup> retrospectively determined the hormonal replacement

status of 204 women enrolled in CAVEAT and discovered that late loss in minimal luminal diameter was significantly reduced in estrogen users (0.13 vs 0.42 mm,  $P=0.01$ ). Interestingly, on multivariate analysis, the benefit of estrogen therapy was restricted to women who underwent directional atherectomy. Estrogen did not reduce late loss in patients randomized to balloon angioplasty. The authors theorized that estrogens may therefore exert their favorable effects predominantly by limiting neointima formation (which is prominent after directional coronary atherectomy) rather than by influencing remodeling.

Given the powerful epidemiologic association between estrogens and reduced cardiovascular events in patients with proven coronary disease, estrogen replacement therapy should be strongly considered in all postmenopausal women following angioplasty. Prospective studies are needed to determine whether estrogens provide any additional salutary benefits with respect to restenosis.

### Nitric oxide

Nitric oxide (NO) is believed to play a critical role in maintaining vascular homeostasis. NO influences multiple potential contributors to restenosis. In experimental settings, NO can inhibit platelet activation and thrombus formation, limit vascular smooth muscle cell proliferation, promote vasodilation, and influence leukocyte chemotaxis and adhesion.<sup>134,135</sup> Vascular injury disrupts endothelial cell function, and may be associated with reduced local concentrations of NO during the healing process.<sup>136</sup> Several animal studies have documented inhibition of neointima formation with systemic or local administration of exogenous NO following balloon-induced arterial injury.<sup>137</sup> The recently published ACCORD (Angioplastie Coronaire Corvasal Diltiazem) study<sup>44</sup> was the first to examine the utility of adjunctive therapy with a nitric oxide donor following coronary angioplasty. Seven hundred patients undergoing elective angioplasty were randomized to receive either (i) intravenous linsidomine, begun at least 3 hours prior to the procedure, followed by oral molsidomine for 6 months (both of these agents are direct nitric oxide donors); or (ii) oral diltiazem for 6 months (the "placebo" arm). Angiography immediately prior to, immediately following, and 6 months following angioplasty demonstrated significantly greater vessel reference diameters in patients treated with the nitric oxide donors, presumably as a result of the potent vasodilatory properties of these agents. Consistent with this greater

reference vessel size, the minimal luminal diameter both immediately following angioplasty and at 6 months was significantly greater in the nitric oxide donor compared with the diltiazem group, which translated into a decreased binary restenosis rate (38.0% vs 46.5%,  $P=0.026$ ). However, neither the extent of late luminal narrowing (which excludes the effects of the initial differences in reference vessel size) nor the rate of combined clinical events (32.2% vs 34.4%) differed significantly between the groups. Therefore, the beneficial angiographic effects of the nitric oxide donors used in this study appeared to result from an improvement in the pre- and immediate postprocedure lumen size rather than from beneficial effects on later events such as neointima formation or remodeling. Further clinical trials should clarify the issue.

## CONCLUSION

An important lesson that is evident from the myriad of basic research and clinical trials performed to date is that restenosis is a multifactorial process. For example, while stent placement may eliminate vessel recoil and remodeling, clinically significant neointimal hyperplasia can still occur within the stent. Consequently, it appears that the ultimate solution to restenosis may require a combination of therapies for these disparate processes, such as a mechanical device to eliminate early recoil and late vessel constriction with concomitant therapy aimed at preventing neointima growth (eg, local radiation, gene-based therapy, or a systemically or locally administered pharmacologic agent). Furthermore, as the cost and potential toxicity of putative adjunctive therapies increase, the necessity for developing better indices (perhaps at the genetic level) to predict which of the minority of patients who undergo angioplasty are at greatest risk for restenosis becomes paramount.

The question of which therapeutic approach holds most promise in eliminating restenosis is given more focused scrutiny in the following pages. **Is mechanical intervention the answer?** Ulrich Sigwart expounds potential refinements of the mechanical approach. **Is pharmacological intervention the answer?** Michel Bertrand looks at what role drugs can be expected to play in the future. **Is gene therapy the answer?** Martin Bennett sizes up the promises and difficulties of this exciting approach.

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# Restenosis

*Expert Answers to Three Key Questions*

①

Restenosis:  
are mechanical interventions the answer?

*U. Sigwart*

②

Restenosis:  
is pharmacological intervention the answer?

*M.E. Bertrand, E. Van Belle, E. McFadden*

③

Will gene therapy be the answer  
to restenosis?

*M.R. Bennett*



# Restenosis: are mechanical interventions the answer?

**Ulrich Sigwart, MD, FRCP, FACC, FESC**

*Department of Invasive Cardiology - The Royal Brompton Hospital - Sydney Street - London SW3 6NP - UK*

*The remarkable drop in restenosis rates is largely attributable to the use of stents as an adjunct to angioplasty, which has contributed to making the results of angioplasty more predictable and reliable. The flexibility of devices has significantly improved and stents now conform to most clinical targets. Suboptimal results after balloon angioplasty now account for 80% of all stent procedure indications. Aspirin and ticlopidine are now used universally in stent patients. Refinements of the mechanical approach give restenosis rates of the order of 10%, but further reductions will be possible by combining optimized stent design with active modulation of intimal hyperplasia. Local drug delivery and radiotherapy appear to be promising approaches, at least as far as medium-term results are concerned, but very long-term results are another issue.*

Restenosis, an iatrogenic disease? Certainly not! However, the fact that the term restenosis has become an important keyword in medicine bears witness to our inability to cope with a number of issues related to transluminal interventions. This could mean either of two things: (i) that we are not efficient enough in dealing with atherosclerotic plaques in the first place; or (ii) the target gives way only briefly and returns after a short period of time. I tend to the belief that in the majority of cases we are not meticulous enough in our technique and that only a small minority of plaques are genuinely recurrent. The fact that, by using the most appropriate tools, rates are now as low as 10% in selected indications obviously means that we have learned a great deal about improving angioplasty.

This remarkable drop in restenosis rates is largely attributable to the use of stents, which have contributed to making the results of angioplasty more predictable and reliable. A dramatic increase in the use of stents has occurred in the decade since their introduction in clinical medicine.<sup>1</sup> This is all the more surprising, as only a few years ago, serious doubt was cast on the role of stents in cardiology: in an editorial following the publication of results on the early Wallstent series, Peter Block expressed his disbelief in stenting as a means of reducing

restenosis and called this approach “futile.”<sup>2</sup> Why then the resurgence of stents as the only rational means of reducing the number of recurrences after angioplasty?

## HISTORY

The concept of placing scaffolding into injured blood vessels—or other conduits—is so simple that it is not surprising to find traces of such thinking long ago. It is generally believed that Alexis Carrel was the first to attempt such an operation when he tried to place glass tubes into the arteries of dogs in the hope of treating traumatic injury to blood vessels and improving surgical anastomoses.<sup>3</sup> Carrel predicted that “smooth-edged tubes or tubes lined with a vein” would be used as reinforcement inside arteries in “human surgery.” However, Carrel had neither the right materials nor the right technology to insert these tubes into blood vessels with a minimally invasive procedure. And yet, although he was unable to find his way around the complexities of the problem, the basic concept was sound.

Fifty years later, Dotter attempted unsuccessfully to implant plastic tubes into arteries. Having recognized that the problem lay with the use of nonporous structures in this context, he subsequently implanted metal spirals into dog arteries.<sup>4</sup> Dotter used the term “stent,” which vascular surgeons later employed in the 1970s when they

placed synthetic tubes into vessels to facilitate suturing. The word stent dates back to at least the 14th century.<sup>5</sup> As a noun, it refers to a stake for stretching out fishing nets upon a river; as a verb, it describes the act of stiffening a garment.

### **MECHANICAL SOLUTIONS**

Mechanical solutions for biological problems such as replacement of missing limbs and teeth have been used for thousands of years. Nowadays these include mechanical joints and prosthetic heart valves. Stents are not "prostheses" in the strict sense; they do not replace organs but support existing biological structures.

Internal scaffolding is used in non-vascular applications, such as the bronchial tree and the gastrointestinal and genitourinary tracts. Where the vascular system is concerned, failing venous and arterial blood conduits can be made to regain their function thanks to the internal mechanical support provided by stents. The situations where this type of intervention may be of benefit include degenerative changes resulting in loss of wall integrity, accumulation of material reducing the luminal diameter, or external compression.

The first indications that stents could reduce the incidence of restenosis triggered an incredible amount of interest and research. Immense progress has been made over the past 10 years in the design of stents. The indications for their use and the management of patients with a stent implant have also considerably evolved.

### **DEVICES**

Intraluminal stents undergo important geometrical changes between their introduction into the target

vessel and their final state after deployment. This metamorphosis from "small" to "big" without loss of structural integrity remains a major technological challenge that has only partly been resolved. There are limits to material stress and it is not easy to force geometrical structures to deploy into a desired shape that is so vastly different from the miniaturized state necessary for "keyhole" surgery. Computer modeling has helped enormously in determining the optimal shape to keep material stress at an acceptable level. Computer-controlled laser edging techniques permit the crafting of literally any desired stent shape from metal tubing. This technique is applicable to a variety of metal alloys ranging from stainless steel to nickel/titanium and is used for balloon-expandable and self-expanding stents. The flexibility of devices has significantly improved and stents now conform to most clinical targets. The handling characteristics of stents in terms of user-friendliness have undergone very significant improvements over the past few years. Stents premounted on angioplasty balloons perform so well that even operators unaccustomed to the use of stents have little difficulty in using them.

### **INDICATIONS**

The indications for stenting in 1986 were restricted to restenosis, abrupt closure, and graft disease.<sup>1</sup> The primary implantation of stents was deliberately excluded. Ten years ago it was considered unwise—if not unethical—to use stents in situations where the benefit was doubtful, eg, in the event of suboptimal results after balloon angioplasty. Today, this indication has taken the lead and accounts for 80% of all stent procedures. The demonstration that stents made

angioplasty a predictable procedure has given operators a hitherto unknown degree of confidence in transluminal techniques and has opened up a whole array of new indications, such as complicated and diffuse lesions, stenoses in last remaining conduits, and involvement of two or more vessels. Comparison of the results of stenting in these new indications with those of surgical revascularization is under way.<sup>6</sup>

### **MANAGEMENT**

Great progress has been made in the management of patients after stenting. The dreaded complication of subacute stent thrombosis resulted in the disastrous habit of over-anticoagulation during the late 1980s.<sup>6,7</sup> The crucial role of platelets in the thrombogenic process observed after stenting was not recognized until relatively recently.<sup>8,9</sup> Despite aggressive medication, subacute stent thrombosis occurred in more than 1 patient in 10, and a prolonged hospital stay of about 6 to 7 days was the rule. Furthermore, large hematomas at the site of puncture and the need for blood transfusion or surgical revision occurred in a significant number of patients.<sup>10</sup> It was only in 1993 that the propensity to thrombosis was linked to suboptimal implantation techniques.<sup>11</sup>

On the basis of these observations, suspicion grew that warfarin might be counterproductive. A small randomized trial comparing aspirin alone and a combination of aspirin and ticlopidine showed no significant difference between the regimens; the subacute occlusion rate in the aspirin-only arm was 3.9% in 103 patients, as compared to 0.8% in the 123 patients treated with the combination of aspirin and ticlopidine ( $P=0.2$ ).<sup>12</sup> A large randomized trial (STARS) has reproduced these



figures (3.7% versus 0.6%) using an adequate sample size (M. Leon et al, personal communication).

These clinical results underline the role of stents in platelet activation. There is no doubt that stents favor the expression of markers of platelet activation.<sup>13,14</sup> The combination of a metal surface and turbulent flow created by numerous struts opposed to the vascular surface is responsible for the development of shear forces and other previously unknown mechanisms of platelet activation. Neither heparin nor the inhibition of thromboxane A<sub>2</sub> by aspirin are effective in this respect, but the added inhibition of ADP-induced aggregation with drugs like ticlopidine appears to be the answer. The role of IIb/IIIa monoclonal antibodies has not yet been defined in this context, not to mention the prohibitive cost.

Aspirin and ticlopidine are now used universally in stent patients. As bleeding complications are no more frequent with this regimen than with balloon angioplasty alone, patients can be discharged after minimal hospital stay; even outpatient stenting is now possible. Although ticlopidine has side effects, primarily leukocytopenia in about 1% of cases if given for longer than 3 weeks, it remains the drug of choice until better compounds become available. One potential candidate is clopidogrel, which has a faster action and milder side effects.

### IN-STENT RESTENOSIS

One unresolved issue is the worrying rate of recurrence of narrowing by uncontrolled *intimal hyperplasia* that occurs in 1 or 2 out of every 10 patients. Even if the average rate of restenosis after stenting is significantly reduced compared

with balloon angioplasty, and even if stents with good flow characteristics and homogeneous structural support have been demonstrated to further reduce the amount of repair tissue,<sup>15</sup> restenosis has not been eliminated yet. When measured according to standard criteria, restenosis rates with the classic Johnson & Johnson Palmaz-Schatz 153 articulated stent were found to be of the order of 20% to 30% on both sides of the Atlantic.<sup>16-18</sup> Newer stents (H. Emanuelsson et al, on behalf of the WEST study group, submitted for publication) have halved this rate of restenosis simply by using a more refined stent geometry but without changing any other parameter. The BENESTENT II data<sup>19</sup> have suggested that coating the stent with heparin may also reduce restenosis rates, but this is by no means clear.

Present-day stent technology thus gives restenosis rates of the order of 10%. In other words, restenosis has been reduced to less than a third of earlier figures. This has been achieved by means of comparatively simple technology without any biological intervention. It seems likely that further reductions will be possible by combining refined stent design with active modulation of hyperplasia. Coatings, hybrid stents, or radioactive stents are already under clinical investigation.

Several observations indicate that the principal goal is not the lowest possible metal-to-artery ratio, but the smoothness of the wall lining and the absence of turbulent flow. Animal experiments have shown that flat, porous, self-expanding rolled sheets of nitinol, which are introduced into the vessel and then unrolled, will result in a very thin lining,

and are associated with low thrombogenicity. Since the pore size of such linings can easily be varied, it is possible to experimentally determine the optimal metal-to-artery ratio.

Drugs that suppress exuberant healing response and intimal hyperplasia cannot always be used systemically, and local drug delivery may be useful. With restenosis rates of the order of 10%, very large trials will be required to determine their value. Physical energy ( $\gamma$ - or  $\beta$ -radiation as well as ultrasound) may be effective in reducing intimal hyperplasia. Radiotherapy inside arteries, using either a removable radiation source<sup>20,21</sup> or very low irradiation from metallic stents,<sup>22</sup> has been shown to be effective in animals and may prove to be effective in humans in the medium term.

### CONCLUSION

In summary, it appears that "plugging" fissures in disrupted plaques, creating a smoother lumen, and avoiding elastic recoil results in a substantial reduction in the rate of restenosis. This reduction can reach about 60% when restenosis is defined as a 50% reduction in luminal diameter.

Refinements of the mechanical approach may yield even lower restenosis rates. Local drug delivery, either by dedicated devices or on the stents themselves should reduce the restenosis rate even further. Radiotherapy inside stents appears to be an equally promising approach, at least as far as medium-term results are concerned; very long-term results are another issue. The use of stents as an adjunct to angioplasty seems promised to go on for at least another decade.

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# Restenosis: is pharmacological intervention the answer?

**Michel E. Bertrand, MD, FRCP, FESC, FACC; Eric Van Belle, MD; Eugene McFadden, MD, MRCP, FESC, FACC**

*Lille Heart Institute - Service de Cardiologie B - Hôpital Cardiologique - Bd du Professeur Leclercq - 59037 Lille - FRANCE*

*Restenosis is a multifactorial process involving remodeling, neointimal hyperplasia, and thrombosis. Restenosis following balloon angioplasty is mainly due to remodeling, whereas tissue growth and hyperplasia are the predominant phenomena after stent implantation. The pharmacological approach alone is unable to prevent restenosis. Stents have significantly decreased the rate of restenosis without abolishing it altogether, and adjunctive treatment remains necessary to block the detrimental hyperplasia resulting from this foreign body. Four trials suggested a beneficial effect of trapidil, verapamil, probucol, and a nitric oxide donor, although most of these results need confirmation. Gene therapy and radiation are promising, but it will probably take a long time before these methods are available in combination with stenting. The goal of a limited residual risk of 5% to 6% is still far away.*

Twenty years after the first percutaneous transluminal coronary angioplasty (PTCA) performed by A. Gruntzig in September 1977, restenosis remains an important and significant problem. Every year, millions of people undergo percutaneous coronary intervention involving a whole range of different techniques; 20% to 50% of them develop significant recurrent stenosis within 6 months. Physicians, scientists, technicians, engineers, and the pharmaceutical industry have all made a remarkable effort to overcome this problem, but have only been partially successful. This is probably related to the fact that for more than 15 years attention was focused on a single mechanism of restenosis, ie, neointimal hyperplasia. From 1977 to 1994, restenosis was considered to be related to an exaggeration of the healing process induced by vascular injury. More recently, two other important mechanisms have been described that explain the negative results in most of the clinical trials.

## MECHANISMS OF RESTENOSIS

It is now well established that restenosis is a multifactorial process involving three major mechanisms.

### Remodeling

In 1987, Glagov et al<sup>1</sup> demonstrated that human coronary arteries were

able to adapt to the atherosclerotic process through compensatory enlargement, thus preventing luminal narrowing.

Eight years later, Lafont et al<sup>2</sup> showed that this concept could be applied to experimental restenosis. In elegant studies performed in a rabbit atherosclerotic model, they demonstrated that lumen narrowing was correlated with the degree of chronic arterial constriction, but not with the extent of neointimal proliferation.

In 1996, Mintz et al<sup>3-7</sup> used serial intravascular ultrasound (IVUS) imaging to confirm the importance of arterial remodeling. An important finding was their observation that arterial remodeling after PTCA was a bidirectional phenomenon. Twenty-two percent of the lesions after angioplasty show a positive remodeling (adaptive or expansive remodeling) similar to the phenomenon described by Glagov.<sup>1</sup> In other words, the patients who do not develop restenosis respond to wall injury in the same way as some patients respond to the development of atherosclerosis, namely by compensatory enlargement.

Unfortunately, in most cases (78%), there is negative remodeling (constrictive or restrictive remodeling). In such patients, a decrease in lumen area occurs (from  $6.6 \pm 2.5$  to  $4.0 \pm 3.7$  mm<sup>2</sup>,  $P < 0.0001$ ),

which reflects a decrease in vessel area (from  $20.1 \pm 6.4$  to  $18.2 \pm 6.4$  mm<sup>2</sup>,  $P < 0.0001$ ).

The SURE (Serial Ultrasound REstenosis) study,<sup>8</sup> a cooperative study carried out at the Washington Hospital Center and the Kokura Memorial Hospital, examined the time-course of this phenomenon over a 6-month follow-up (Figure 1): serial IVUS imaging performed before and immediately after, and 24 hours, 1 month, and 6 months after PTCA in the same patients showed there was an early enlargement of the vessel (within 24 hours and between 24 hours and 1 month) and a late constriction (1 to 6 months). In addition, a significant increase in the plaque + media area was observed both within 24 hours and between 24 hours and 6 months. The early increase in the plaque + media area may reflect thrombus formation, while the early enlargement of the vessel observed after 24 hours is probably related to resolution of vasospasm. Between 1 and 6 months, constriction of the vessel contributed to lumen loss more than the increase in plaque + media area.

Thus, the major finding of the SURE study<sup>8</sup> was that constriction of the vessel is a late event and completely different from the early passive elastic recoil, which is a minor phenomenon in the genesis of restenosis. This late event could be related to adventitial fibrosis.

To summarize, the relative contributions of remodeling and increase in the plaque + media area vary widely among individuals. Moreover, the mechanism of late lumen loss is heterogeneous, as the contributions of remodeling and increase in plaque + media area vary over time after the procedure.

#### Neointimal hyperplasia

This phenomenon has been extensively described. After wall injury, which includes endothelial denudation, overstretching of the wall, and rupture of the internal elastic membrane, a cascade of events leads to the stimulation, proliferation, and migration of smooth muscle cells. The first event is oncogene production (*c-myc*, *c-jun*, and *c-fos*) leading to cell replication. This phenomenon is induced by

the release of cytokines and various growth factors from platelets and endothelial cells. Inflammatory cells and release of angiotensin II also contribute to neointima formation, following the transformation of vascular smooth muscle cells (VSMCs) from the adventitia and media to the intima. It has recently been shown that among the cells migrating from the adventitia to the lumen are adventitial fibroblasts with an intermediate structure between fibroblasts and VSMCs. The secretory phenotype of the VSMCs produces a loose extracellular matrix which represents 90% of neointimal hyperplasia. Thus, the healing process leads not only to tissue growth, but also to fibrotic constriction of the adventitia, which is responsible for constrictive remodeling.

#### Role of thrombosis

Previous pathological studies have suggested that thrombus formation could play a role in restenosis. Specimens obtained from restenotic lesions by directional atherectomy have been found to contain a higher proportion of layers of incorporated thrombus than atherosclerotic lesions.

More recently, two human studies confirmed these findings. The first was published by Bauters et al<sup>9</sup> who studied 117 patients using angiography. Among the various characteristics of the plaque, a protruding thrombus after angioplasty was an important predictor of restenosis at 6 months<sup>9</sup> follow-up. In the second study, Violaris et al,<sup>10</sup> analyzing a large cohort of patients who had participated in different restenosis trials, found that angiographically identifiable thrombus was a predictor of restenosis. Although angiography has a lower sensitivity than angiography in the

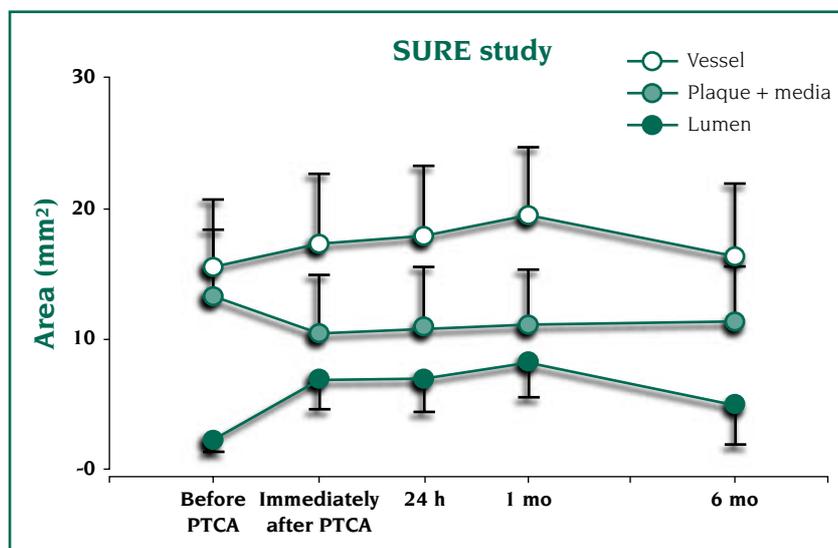


Figure 1. Results from the SURE study.<sup>8</sup>



identification of intracoronary thrombus, it provides additional evidence of the potential role of a thrombus. However, these findings were not supported by various trials with antithrombotic or antiplatelet regimens, which, with the exception of the EPIC trial,<sup>11</sup> all failed to prevent restenosis.

### Respective role of these different mechanisms

The technical aspects of presently available coronary interventions can be summarized as follows. In most cases (50% to 70% and up to 85% in some countries), a stent is implanted after balloon predilatation. The indications are abrupt closure, significant dissection, suboptimal results (a highly subjective notion), or for prevention of restenosis of lesions at higher risk.

In 20% to 40% of cases, the intervention is performed with a balloon; it is seldom performed with a Rotablator, rarely with directional atherectomy, and almost never with a laser.

Thus, the interventional cardiologist now has to deal with two different sorts of restenosis, because the mechanisms of restenosis after balloon angioplasty alone or after stent implantation are completely different. *Table I* shows the respective mechanisms of restenosis in these two conditions.

Restenosis following balloon angioplasty is mainly due to remodeling (78% of cases), whereas neointimal proliferation plays a relatively minor role. Thrombus may also play a role, but to a lesser extent.

Restrictive remodeling is now very rare after stent implantation, although some stent compression has been described. In contrast, tissue growth and hyperplasia are

	Balloon angioplasty	Stent
Remodeling	+++++	0
Hyperplasia	++	+++++
Thrombus	+	0

**Table I.** Respective roles of remodeling and hyperplasia in balloon angioplasty and stenting.

the predominant phenomena: angiographic and serial IVUS imaging studies have shown that all in-stent restenosis is due to hyperplasia.

This response to the foreign body implanted in the artery is even greater than after balloon angioplasty. In addition, recent angioscopic data have shown that thrombosis is not involved in the in-stent restenosis process.

### Therapeutic consequences

The better understanding of the major mechanisms involved in restenosis calls for the following considerations:

1. We should prevent restrictive remodeling: since no drug available today is capable of preventing constrictive remodeling, coronary stenting is the only method that can achieve this goal.
2. Intimal hyperplasia is greater after stent implantation and should be prevented. This can be achieved in various ways, including local or systemic administration of drugs, gene therapy, or use of radiation.
3. We should promote expansive, positive remodeling. Unfortunately no adequate solution has yet been found that mimics mother nature and induces a compensatory enlargement at the dilated site.

### IS PHARMACOLOGICAL INTERVENTION ALONE THE ANSWER?

The answer to this question is certainly "No" and there is much experimental and clinical evidence for such an assertion. More than 50 randomized multicenter, double-blind and open trials have been performed, almost all of them with negative results.

### Most of the drugs able to prevent thrombus formation fail to prevent restenosis

Unfractionated heparin and low-molecular-weight heparin (ERA, EMPAR, FACT, REDUCE) have been shown to be unable to significantly decrease the rate of restenosis. Hirudin (Helvetica trial) has also given negative results.

Trials conducted with various antiplatelet drugs have also been negative. Aspirin at different doses or ticlopidine (White, TACT) did not significantly decrease the rate of restenosis. Only one group of antiplatelet agents has shown a positive effect on clinical restenosis. In the EPIC study<sup>11,12</sup> abciximab, administered as a bolus followed by a 12-hour infusion significantly decreased the rate of clinical restenosis. Clinical restenosis at 6 months' follow-up was reduced by 23% with abciximab. This was essentially the result of a 26% decrease in repeat target vessel

revascularization in the bolus + infusion group. These results were not confirmed by the EPILOG trial since the target vessel revascularization was identical ( $P=0.23$ ) in the three groups treated. We are still waiting for the results of the angiographic substudy of EPILOG.

However, even if the results of the EPIC trial have potentially important implications for patients, clinical restenosis does not really prove the efficacy of the treatment, because clinical restenosis is a composite end point, including death (which is very rare), myocardial infarction (which is usually unrelated to the thrombosis of the dilated lesion), and target lesion revascularization (which is most often based on the subjective appreciation of the investigator, ie, visual estimation rather than a careful quantitative assessment).

#### **Drugs suppressing or preventing vasospasm**

Although vasospasm is a proven risk factor for restenosis, drugs that suppress or prevent it, such as the calcium antagonists nifedipine or verapamil, have failed to demonstrate any beneficial effect. High doses of verapamil may have a positive effect, but the trial<sup>13</sup> indicating this was less than satisfactory from the methodological standpoint, and results from a new ongoing trial are awaited before any firm conclusion can be drawn. Thromboxane A<sub>2</sub> inhibitors or blockers are also ineffective. Prostacyclin and its analogs may be able to slightly prevent restenosis, but only a trend has been demonstrated, without reaching statistical significance.

#### **Inhibitors of cell proliferation and migration**

Angiotensin II is a very powerful agent that induces and promotes neointimal hyperplasia. However,

despite high initial expectations with the angiotensin-converting enzyme (ACE) inhibitors, two large randomized trials undertaken both in Europe (MERCATOR) and in the USA (MARCATOR) failed to show any significant difference between the ACE inhibitor cilazapril and placebo.

Angiopeptin, a somatostatin analog, showed promising results in a small trial conducted in the United Kingdom and Denmark. However, a larger trial (1241 patients) performed in the USA reported no clinical or angiographic benefit with this drug.

Trapidil also appeared promising and the STARC study,<sup>14</sup> published in 1994, showed a positive effect. A larger ongoing trial is seeking to demonstrate the real benefit of this compound.

#### **Anti-inflammatory agents**

These could be of benefit, owing to the role of inflammation in the atherosclerotic process and the onset of acute ischemic syndromes. Unfortunately, steroids have completely failed to demonstrate any beneficial effect.

Similarly, colchicine has been shown to be ineffective. In a small trial of 80 patients, ebselen, a nonsteroidal anti-inflammatory agent, appeared to be effective, and tranilas, a Japanese compound used to prevent skin keloid formation, was associated with a decrease in the rate of restenosis in two small randomized trials. These results require further confirmation.

#### **Lipid-lowering drugs**

Various studies have been performed with fish oils and have yielded conflicting results. The HART trial was completely negative.

Statins were demonstrated to have an important action in the primary and secondary prevention of coronary events and were studied in two major trials: the LRT trial (with lovastatin) and the PREDICT trial with pravastatin. Both trials yielded negative results regarding prevention of restenosis.

More recently, probucol was shown to be beneficial<sup>15</sup> but there are still some gray zones requiring clarification before the beneficial effect of this compound can be confirmed.

#### **Nitric oxide donors**

Endothelial cells play an important role not only because they form a barrier between blood and the vessels, but also because they secrete different compounds that inhibit smooth muscle cell proliferation and have vasodilatory or antithrombotic and anti-inflammatory effects. One of these compounds is endothelium-derived relaxing factor (EDRF) or nitric oxide. The ACCORD study<sup>16</sup> examined the effect of linsidomine followed by molsidomine in comparison to diltiazem. At 6 months' follow-up, minimal lumen diameter (MLD) in the nitric oxide donor group was significantly greater than in the other group, leading to a significant decrease from 46.5% to 38% ( $P=0.026$ ) in the number of patients with >50% stenosis.

To summarize this long list of failures, it appears that most of the drugs described are ineffective in preventing restenosis after angioplasty with balloon (or other devices). Only four trials suggested a beneficial effect in preventing restenosis: STARC (with trapidil)<sup>14</sup>; ACCORD with a nitric donor oxide<sup>16</sup>; the verapamil trial<sup>13</sup>; and the study with probucol.<sup>15</sup> However, most of these results need further investigation and confirmation.



### IS THERE ANY HOPE FOR THE PHARMACOLOGICAL APPROACH?

The answer is clearly "YES": a great future is in store for them.

This paradoxical answer—in view of the above—is based on the following observations.

None of the abovementioned drugs could prevent constrictive remodeling or promote a positive compensatory enlargement. Since constrictive remodeling is by far the most important phenomenon in the development of restenosis after balloon angioplasty, the failure of these drugs was therefore logical.

The only method capable of preventing constrictive remodeling to date is coronary stenting. Two trials (BENESTENT and STRESS) have clearly shown that stents significantly decrease the restenosis rate compared with conventional balloon angioplasty. Initially, these good results were obtained at the cost of a significantly higher rate of bleeding due to the aggressive anticoagulation therapy. This problem has since been resolved with the use of a combination of aspirin and ticlopidine, so that the risk of subacute thrombosis no longer exists. It has been suggested that the BENESTENT and STRESS populations represent only selected populations that were therefore not truly representative. However, in BENESTENT II, a large cohort of patients with unstable angina was enrolled and the benefit of stenting was even more obvious. Furthermore, some groups of patients with lesions traditionally more prone to restenosis benefit from stent implantation (diabetics, patients with lesions in infarct-related vessels, or complete chronic occlusion).

It has been suggested that the long-term prognosis after stenting was uncertain, but the angiographic

10-year follow-up as studied by the group of Lausanne or Jacques Puel was very reassuring.

Thus, stenting is here to stay and is not likely to be dethroned in its role of prevention of remodeling.

However, the downside is the fact that stents are the best experimental model of human hyperplasia. This means that coronary stenting should be complemented by treatment for hyperplasia. Aside from gene therapy and radiation, drugs have here again a role to play.

Coronary stenting requires adjunctive therapy to prevent in-stent hyperplasia. The drug (yet to be determined) could be delivered locally (although preliminary trials of local drug delivery remain unconvincing) or given systemically.

Taking into account our recent knowledge of the mechanisms of restenosis, it may be useful to consider repeating all the trials performed in the past, this time with systematic stent implantation. It may also be useful to identify patients who are more prone to develop in-stent restenosis and to treat or pretreat them with one of the many drugs that have been proposed, particularly those most likely to block neointimal proliferation, eg, the ACE inhibitors.

As mentioned above, angiotensin II is a powerful stimulating factor for hyperplasia. Plasma levels of ACE are genetically regulated and there is a strong correlation between angiotensin levels and the different allele genotypes. Patients homozygous for the *DD* allele have the highest levels of plasma ACE, while patients with the *II* genotype have the lowest levels; *ID* heterozygotes have intermediate levels. No relationship exists between gene polymorphism and the rate of restenosis after balloon angioplasty.<sup>17</sup>

However, in patients with stent implantation there is a strong correlation between *DD* gene polymorphism, late loss of minimal lumen diameter, and rate of in-stent restenosis—the human experimental model of hyperplasia.<sup>18</sup>

This observation has two important clinical implications. First, it is possible to identify patients with the *DD* genotype who are at greater risk of restenosis compared with patients with the *II* genotype. Second, these high-risk patients could benefit from pretreatment or treatment with ACE inhibitors.

### CONCLUSIONS

From these various observations, it is possible to conclude that, to the best of our knowledge, the pharmacological approach alone is unable to prevent restenosis, unless a miraculous compound is discovered. However, stents have significantly decreased the rate of restenosis, without abolishing it altogether. Therefore, adjunctive treatment is needed to block the detrimental hyperplasia resulting from this foreign body. Gene therapy is promising but it will probably be a long time before it is available. Furthermore, the long-term follow-up is still uncertain. The same remark applies to radiation where initial results when it is combined with stenting are very promising. Finally, current research suggests that the prospects for the pharmacological approach combined with stent implantation are still bright. Over the past 4 years, significant ground has been gained in the fight against restenosis. By combining these various approaches we can hope to achieve a limited residual risk of 5% to 6%, at best, but there is still a long way to go to reach that goal.

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# Will gene therapy be the answer to restenosis?

**Martin R. Bennett MD, PhD, MRCP**

*BHF Clinician Scientist / Honorary Consultant Cardiologist - University of Cambridge School of Clinical Medicine,  
Box 157 - Addenbrooke's Hospital - Cambridge CB2 2QQ - UK*

*Gene therapy designates both the introduction of new DNA as replacement for absent or defective genes and the suppression of endogenous gene products. Introduction of new DNA by plasmid or virus vectors as well as suppression of gene expression by antisense oligonucleotides have been shown to inhibit neointima formation after arterial injury. However, present vectors and oligonucleotides have significant limitations in terms of efficiency of gene transfer and maintenance of expression of introduced DNA. Furthermore, our lack of knowledge regarding the appropriate targets for gene therapy in restenosis makes this approach speculative.*

The failure of conventional pharmacological approaches to suppress angioplasty restenosis has prompted research into new therapies. In particular, recent research has shown that gene therapy for the prevention of restenosis is possible in animal models, and clinical trials for gene-based therapeutics are presently under way. Gene therapy embraces two basic strategies. First, introduction of new genes can replace or augment absent or defective genes. This is the approach taken for replacement of genes in hereditary disorders, such as cystic fibrosis or familial hypercholesterolemia, where the defective or absent gene is known. Indeed, delivery of the hepatic lipase gene to deficient animals results in a significant reduction in serum cholesterol and triglycerides.<sup>1</sup> This approach can also be used to augment a normally expressed gene product in order to achieve an increased therapeutic effect. An example of this is the delivery of vascular endothelial growth factor (VEGF), an angiogenic factor and endothelial cell mitogen, to promote endothelialization and new vessel formation in an atherosclerotic region of an ischemic limb.<sup>2</sup> Second, gene therapy can be used to suppress a gene whose function is deemed undesirable. Examples of this approach are suppression of oncogenes in cancer, and of genes associated with cell

proliferation or matrix synthesis in wound healing or restenosis.

## SELECTING A TARGET

Selection of the target for gene therapy of restenosis obviously requires extensive knowledge of the gene products expressed in the disease state and their pathogenetic roles. The ideal target for replacement therapy would be a gene product expressed in the healthy vessel, with reduced expression in the diseased vessel, which promotes favorable remodeling of the vessel or reduced neointima formation after angioplasty. For suppression therapy, the target would be expressed after angioplasty (but at no other times), be critical for the response to injury, and its expression would be deleterious to the maintenance of vessel lumen size.

As described in the lead article of this issue, restenosis comprises the summation of both geometric remodeling of the vessel wall and neointima formation. In remodeling and neointima formation, individual processes such as cell proliferation, cell migration, extracellular matrix formation and degradation, apoptosis, and organization of thrombus all contribute to the final wall thickness and vessel caliber. It is therefore likely that no single agent targeted against one of these processes is likely to succeed in preventing restenosis, and combination therapy may be

required. To date, gene therapy approaches to restenosis have focused predominantly on smooth muscle cell proliferation. This focus on proliferation reflects several issues. First, cell proliferation has several key steps. Blocking any one of these steps is sufficient to halt the whole cascade leading to DNA synthesis. Thus, many genes can be chosen whose inhibition would be predicted to block cell proliferation. In contrast, the other processes described are either poorly defined at a mechanistic level (remodeling) or lack any single molecular target that could stop the entire process (migration, matrix synthesis). Second, suppression gene therapy approaches are most effective when the mRNA being targeted is of low abundance. Many mRNAs required for replication are of low abundance and therefore make good targets. Finally, replication may be an early, transient event following angioplasty. This proposal is based on the absence of replication in human atherectomy specimens at late time points<sup>3</sup> and on results from animal studies using both gene therapeutics and conventional drugs in which blockade of replication early in the response to injury had surprisingly long-term effects on neointimal mass seen weeks later. All these factors make replication easier to target than the other more poorly defined components of the response. However, it should be borne in mind that if proliferation is only a small part of restenosis after angioplasty in humans, as suggested by some studies,<sup>3</sup> then a gene therapy approach targeting proliferation alone may not work in humans.

### REPLACEMENT STRATEGIES

Replacement gene therapy requires the insertion of complementary DNA encoding the gene of interest into an expression vector, and delivering

this vector, either alone or using viruses, to the proposed site. Genes have been delivered to the vascular system using naked DNA, DNA complexed to cationic liposomes, or retro- or adenovirus vectors. Of these, virus vectors are the most efficient means of gene transfer, but only retroviruses can integrate DNA into target cells, resulting in long-term expression of the introduced DNA. The limitations of delivery systems are discussed below.

Targets for replacement therapy in restenosis have focused on delivery of genes that suppress neointima formation, in particular those suppressing cell proliferation. For example, delivery of the growth arrest gene p21 by adenovirus vector reduces neointima formation after injury in the rat carotid and pig iliac arteries.<sup>4,5</sup> Alternatively, therapeutic delivery of genes that promote cell death achieves the same end. For example, delivery of the herpes virus thymidine kinase gene to replicating cells by adenovirus after injury renders them susceptible to cell death induced by systemic delivery of ganciclovir, with a markedly reduced total neointima.<sup>6,7</sup>

### SUPPRESSION STRATEGIES

In contrast, the ideal target for suppression gene therapy in restenosis would be a gene product only expressed in the diseased vessel after injury and which is critical at an early stage for the whole process of restenosis to occur. Such a gene product would be expressed at low levels (which are therefore amenable to low efficiency suppression strategies), and transiently, so that a single application would suffice. Suppression gene therapy has mostly used antisense oligonucleotides, ie, genetic sequences designed to bind to the messenger RNA of a

target, resulting in mRNA degradation or inhibition of translation of the target protein.

Again, because of our profound ignorance of the remodeling process, most suppression strategies have focused on neointima formation, and particularly on using antisense oligonucleotides to suppress genes associated with cell proliferation. Cell proliferation is stimulated when the artery is injured, and there is a cascade of expression of genes required for cells to undergo successful division.<sup>8</sup> Inhibition of the expression of almost any of these genes is sufficient to arrest the process. Furthermore, if the stimulus to cell proliferation is transient, then inhibition of proliferation for a few days may be sufficient to prevent cell division completely. The effectiveness of this strategy has been demonstrated by numerous studies showing that antisense oligonucleotides to cell cycle genes (*c-myc*, *c-myb*, proliferating cell nuclear antigen [PCNA], *cdk-2*, etc) block neointima formation in rat, rabbit, and pig models of injury (reviewed in reference 9). Antisense oligonucleotides to cell surface receptors, such as the platelet-derived growth factor- $\beta$  (PDGF- $\beta$ ) receptor, also inhibit neointima formation. In many of these studies, a single administration at the time of injury was sufficient to maintain long-term patency of the vessel. Whether the inhibition of the gene product was truly responsible for inhibiting neointima formation is debatable, however, as random oligonucleotides can also effectively inhibit neointima formation (see below).<sup>10</sup>

### ADVANTAGES OF GENE THERAPY

In a disease process as complex as restenosis, what are the potential advantages of gene therapy, other than the possibility of an effective



treatment when all other treatments have failed? The first major advantage of gene therapy, at least in theory, is the potential for the design of a wide variety of agents with target specificity. Thus, agents can be designed that inhibit receptors, second messenger pathways, or nuclear gene products, and as the hybridization of base sequences between nucleic acids is very specific, only the complementary base (C-G, A-T) should be bound. Because the mRNAs of related proteins often have areas lacking significant homology, this specificity of base pairing means that an antisense sequence of bases should target only a single mRNA, without affecting the mRNAs of other genes. This specificity of binding is greater than can be achieved with most conventional pharmacological inhibitors, which frequently act on a variety of proteins with different binding affinities. For gene replacement strategies, the specificity is almost absolute—only the gene product delivered should be expressed. In practice, such specificity is achieved neither with antisense oligonucleotides nor with gene replacement, and nonspecific effects of gene therapeutics and vectors are a particular problem, such as inflammatory reactions to the virus vector or transgene.

The second major advantage is that gene therapeutics to suppress specific target mRNAs are much easier to design and synthesize than any previous class of drugs, resulting in much faster identification of effective drugs. The structures of oligonucleotides are relatively simple, consisting only of possible polymers of the four base pairs. Since the target sequence is known, rational drug design against a target is theoretically obvious, without the necessity of screening thousands of products

as occurs with pharmacological agents. Third, genetic therapeutics have the potential for permanently altering the target tissue. Constitutive expression of a therapeutic RNA or antisense RNA in the target tissue can be achieved by inserting DNA into the host chromosome. Retrovirus vectors, in particular, can be used to integrate the therapeutic DNA into the host cell. Finally, if delivered properly, the effects of polynucleotide-based drugs should be highly localized. Nucleotides are taken up into cells and are trapped in the intracellular compartment. Any polynucleotide that remains outside the cell or undergoes exocytosis is likely to be rapidly degraded by serum nucleases. This mechanism may help to restrict delivery of DNA-based therapeutics to the target site. Indeed, oligonucleotides have good systemic bioavailability, rapid distribution to tissues, and little first-pass loss into the urine. Furthermore, despite the impracticality of chronic administration with a parenteral agent for restenosis, the slow metabolism of oligonucleotides in tissues means that active drug can be present for several days after a single administration.

#### **LIMITATIONS AND RISKS OF GENE THERAPY**

The major limitation to gene therapy for restenosis is our lack of knowledge of the critical regulators of restenosis, in particular, the regulators of remodeling. This makes target gene selection a partly informed guess at best. Furthermore, delivery of genes has specific problems, particularly targeting the vascular tissue alone, enhancing entry to cells into nonlysosomal compartments, nuclear import, percentage of cells transduced with the therapeutic gene, sustained expression of the transgene in

human tissues, and immunogenicity of the transduced cells expressing the recombinant or viral proteins. Present vectors for gene delivery are of low efficiency, with naked DNA or liposome-based delivery to the vasculature resulting in expression in less than 1% of cells, although higher efficiencies may be obtained with newer combinations of liposomes. These low levels of transfer may be adequate if a secreted protein is encoded, which can affect other cells locally, or if massive amounts of DNA are delivered, but this is unlikely to be useful for routine clinical use. Efficiency can be improved with virus vectors, although none of the present vectors are ideal. The most effective virus vectors are adenoviruses, but even these infect less than 25% of smooth muscle cells, result in profound inflammation at the site of delivery, and demonstrate only transient expression of the gene product (less than 4 to 8 weeks). In contrast, retrovirus vectors can integrate DNA into host cells, resulting in long-term expression. However, retrovirus vectors have even lower gene transfer rates and, because of random integration of DNA, have the potential for insertional mutagenesis.

There are also major limitations to the use of antisense oligonucleotides. Parenteral administration of oligonucleotides is required, and uptake of oligonucleotides is inefficient, requiring large doses to be used. Even so, suppression of the target gene is usually incomplete, and long-term suppression is not achieved. A further problem relates to the nonspecific activity of oligonucleotides. Degradation of a number of nontargeted mRNAs has been demonstrated after oligonucleotide use, and nonspecific induction of cellular signaling pathways and cytokine production has also been shown (reviewed in reference 9).

**Will gene therapy be the answer to restenosis? - Bennett**

Indeed, as mentioned above, random oligonucleotides are often as potent in reducing neointima formation as oligonucleotides targeted against specific gene products. This means that the oligonucleotides may have a number of unpredictable, undesirable effects on the vasculature.

The other major problem of gene therapy relates to the fact that the targets selected are unlikely to be truly specific to the diseased vessel during restenosis. In fact, all of the targets to date are also expressed in normal vessels, and many other tissues. This means that delivery of gene therapeutics must be extremely localized, and agents must have a good therapeutic index when compared with normal tissues. Fortunately, catheter-based delivery systems have now been developed to allow very localized delivery of oligonucleotides or virus-based genes to the vasculature, and little expression of genetic or virus material is found outside the vasculature. Furthermore, oligonucleotides are remarkably nontoxic when delivered to cells in high concentration in vitro, or systemically in vivo. Formal toxicity testing of oligonucleotides or of gene transfer vectors in man is still incomplete, and this issue needs to be resolved before large-scale clinical trials are carried out. However, recent approval for two double-balloon catheters has been given for clinical use for local drug delivery, which should result in an increased transfer of potential gene therapeutics to the clinical arena.

### CONCLUSIONS

Gene therapy for restenosis offers great promise. To date, studies have shown that localized delivery of genetic material to the vessel wall is possible, with reduction in neointima formation in injured arteries. The challenge for future

development of gene therapy lies in identifying critical targets for such therapy, improving the efficiency and longevity of gene expression or suppression, and minimizing local inflammation or toxicity. Vector design may prove crucial for optimizing local delivery of gene products, and nonvirus vectors or viruses targeted to specific receptors on target tissues may improve transfer efficiency. For once in angioplasty research, it is not improvements in equipment design that are required, but an increased understanding of the pathogenesis of the restenosis process.

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# Restenosis

## Summaries of Ten Seminal Papers

①

Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy  
**Kuntz RE and others.** *J Am Coll Cardiol.* 1993

⑥

Proliferation in primary and restenotic coronary atherectomy tissue: implications for antiproliferative therapy  
**O'Brien ER and others.** *Circulation.* 1993

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Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months  
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A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease  
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**Topol EJ and others, for the CAVEAT Study Group.** *N Engl J Med.* 1993

④

Inhibition of vascular smooth muscle cell proliferation in vitro and in vivo by *c-myc* antisense oligodeoxynucleotides  
**Bennett MR and others.** *J Clin Invest.* 1994

⑨

Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study  
**Mintz GS and others.** *Circulation.* 1996

⑤

Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near-Gaussian distribution: a quantitative angiographic study in 1445 successfully dilated lesions  
**Rensing BJ and others.** *J Am Coll Cardiol.* 1992

⑩

A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease  
**Serruys PW and others, for the BENESTENT Study Group.** *N Engl J Med.* 1994

Summaries prepared by **M.R. Bennett, MD, PhD, MRCP**  
BHF Clinician Scientist / Honorary Consultant Cardiologist - University of Cambridge School of Clinical Medicine, Box 157  
Addenbrooke's Hospital - Cambridge CB2 2QQ - UK  
Events selected by **Dr P.B. Garlick** - Division of Radiological Sciences - Guy's Hospital - London SE1 9RT - UK

## Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy

Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS

*J Am Coll Cardiol.* 1993;21:15-25

The demonstration that stenosis after angioplasty, minimal lumen diameter (MLD), or change in MLD are all continuous variables—and not divided into a bimodal population representing restenosis or no restenosis—produced a profound change in the thinking behind the restenosis process. The fact that the artery has a limited response to injury, based primarily on neointima formation, recoil, and geometric remodeling, implies that other interventions used to treat atherosclerosis, such as atherectomy or stenting, may also result in a continuous distribution of angiographic variables. As atherectomy and the use of other devices also result in a continuous distribution of stenosis of vessels, with no improvement in restenosis rates over conventional angioplasty, the authors have examined whether this lack of benefit of the newer modalities was due to the classification of patients into restenosis or nonrestenosis at follow-up.

To address these questions, the authors enrolled 524 patients to undergo Palmaz-Schatz stenting, directional coronary atherectomy (DCA), or angioplasty, with follow-up angiography at 3 and 6 months. The DCA and stenting procedures were performed in the USA, and the conventional angioplasty in Japan. Because of this, and the nonrandom allocation of patients to treatment groups, there were differences in patient characteristics (age, sex), anatomy (preponderance of left anterior descending artery lesions), or percentage of restenotic lesions treated, although it is unlikely that these would affect interpretation of the data. The results show that DCA or stenting resulted in a larger initial gain following the procedure. At 6 months, conventional angioplasty showed a smaller MLD than the other two modalities. Interestingly, stenting provided the highest final MLD at 6 months, although it was associated with the highest overall loss of MLD. This implies that the reason stents perform better than the other two treatments is that a wider lumen can be achieved with stents immediately after the procedure. In fact, there was a good positive correlation between initial gain and late loss, implying that the more damage is done to the vessel, the greater the arterial response in terms of late narrowing.

This study has important implications for the actual clinical practice of these interventions. First, it suggests that the best way to improve restenosis following any intervention would be to minimize immediate stenosis (maximize postprocedural MLD). However, this implies that unless postprocedural MLDs for angioplasty can be achieved similar to the other modalities, conventional angioplasty will always have a higher restenosis rate. Second, the concept of “bigger is better” is applicable to all modalities, and should be practiced clinically. Third, as the results (late percentage stenosis, immediate gain, and late loss) all follow normal distributions for continuous variables, the ability to detect small differences in outcome among experimental treatments is far greater if selected continuous variables are used rather than binary models of restenosis based on an arbitrary cutoff point for restenosis. Finally, although the late loss was related to the immediate gain, treatments which interrupt this relationship, allowing a smaller late loss despite a large initial gain, should still provide further improvements in rates of restenosis.

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1993

Rolls Royce opens its first Russian  
showroom in Moscow;  
Bill Clinton has a controversial \$200 haircut;  
and Audrey Hepburn dies, aged 63



## Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months

*Topol EJ, Califf RM, Weisman HF, et al, on behalf of the EPIC Investigators*

*Lancet.* 1994;343:881-886

Numerous studies have used antiplatelet agents to prevent restenosis. In fact, angioplasty is routinely performed using heparin and aspirin, although neither treatment reduces long-term restenosis. This may be due to the fact that both these agents have weak antiplatelet actions, and platelet stimulation can occur in the presence of aspirin therapy. The final common path for platelet aggregation involves the platelet receptor for the glycoprotein IIb/IIIa integrin, and earlier studies have shown that treatment of vessels with an antibody to this receptor can render them unable to activate platelets after injury. The antibody 7E3 is a humanized murine monoclonal chimeric antibody Fab fragment that selectively binds the platelet IIb/IIIa receptor, and thus represents a more potent method of inhibiting platelet function than conventional pharmacological agents. The present study was based on the premise that platelets are important in both acute vessel closure after angioplasty and long-term restenosis. The study evaluated the efficacy of profound suppression of platelet activity using 7E3 on these clinical end points.

This study included nearly 2100 patients; all patients were of a high-risk type (evolving or recent myocardial infarction, unstable angina, or high-risk angiographic lesion morphology or clinical characteristics). All patients received aspirin and heparin, but were then divided into three groups: (i) placebo bolus (>10 minutes before coronary procedure) + placebo infusion for 12 hours; (ii) 7E3 bolus + placebo infusion; or (iii) 7E3 bolus + 7E3 infusion for 12 hours. Patients underwent either coronary angioplasty or directional atherectomy. The primary end points were the composite 30-day or 6-month incidence of death from any cause, myocardial infarction, the need for repeat revascularization (30 days and 6 months), or the need for stent or intra-aortic balloon pump insertion for ischemia (30 days only).

The main clinical findings were that at 30 days there was significant reduction in all events in patients who received the 7E3 bolus and infusion compared with placebo bolus and infusion. This reduction was accounted for predominantly by a reduced need for revascularization of the target vessel by repeat angioplasty. At 6 months of follow-up,

there was still a significant difference in all events in the 7E3 bolus + 7E3 infusion group compared with placebo bolus + infusion, again made up primarily by the reduction in need for repeat angioplasty. This reduction in need for repeat angioplasty was evident at 48 hours, indicating that 7E3 treatment reduces acute closure of the artery. Interestingly, there was no reduction in events at any time with the 7E3 bolus alone. In contrast to these favorable outcomes, 7E3 treatment, either as a bolus or as a bolus + infusion, was associated with a significant increase in bleeding complications requiring approximately twice the volume of blood transfusion in the first 48 hours.

This study is remarkable as it shows a favorable outcome for a therapeutic agent in the suppression of restenosis. In fact, figures for 3-year follow-up are now available that show a maintained benefit of the 7E3-treated patients. However, the trial actually tells us more than this.

The success of 7E3 in the suppression of acute closure is not unexpected; platelets are well known to play a significant role in the acute thrombotic events precipitating vessel occlusion. However, it is less clear why an antiplatelet agent given for only 12 hours has a beneficial effect on restenosis. If restenosis is primarily due to remodeling (see page 166), why should antiplatelet agents affect long-term remodeling? The answer may lie in the nonspecific nature of the antibody used. There is now good evidence that 7E3 also binds to other integrins, many of which are involved in the cell-matrix interactions which mediate wound contracture or chronic recoil. This may be the true mechanism of 7E3 in restenosis, although, as the trial did not use follow-up angiography, this is only speculation at present.

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1994

Cambridge beats Oxford  
in the 140th University boat race;  
Quentin Tarantino's "Pulp Fiction" wins  
the Palme d'Or at the Cannes film festival;  
and Melina Mecouri, Greek actress and politician,  
dies, aged 68

## Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients

Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Yokoi H, Hamasaki N, Horiuchi H, Ohishi H

*J Am Coll Cardiol.* 1988;12:616-623

**A**ngioplasty results in overexpansion of the vessel, with dissection of the intimal plaque, often extending into the media. This injury induces a characteristic reparative response, with both neointima formation and geometric remodeling (see Narins and Topol's article in this issue). Both of these processes result in lumen narrowing, but the natural history of lumen changes was largely unknown prior to the study of Nobuyoshi et al. The timing of lumen narrowing is critically important for prevention of restenosis, as animal studies have underlined the fact that treatment immediately after angioplasty, extending only for a few days, can affect long-term arterial patency. However, the failure of pharmacological agents that are effective in animals to inhibit restenosis in humans raised the prospect that restenosis in humans was due to low-grade, chronic processes over the months following intervention.

To address this problem, Nobuyoshi et al performed angioplasty on 229 patients with angiography at day 1 and at 1, 3, 6, and 12 months following angioplasty. Success rates for the initial procedure were approximately 80%. Quantitative angiography was used to assess the diameter of the reference and stenotic segments of the artery, and restenosis was classified as more than 50% of the loss of gain immediately after the procedure (change in diameter from postprocedure to follow-up). The study managed to follow up 219 patients at 3 months, 149 patients at 6 months, and 73 patients at 1 year. The main reason for the reduced numbers of patients at follow-up was restenosis of the target lesion requiring further angioplasty. Symptom status was recorded by the patients subjectively.

Using the definition of restenosis outlined above, 15% of patients had restenosed by day 1, with no change to 1 month. However, thereafter there was a rapid increase in restenosis to 43% at 3 months, and then very gradual increases to 6 and 12 months (50% and 53%, respectively). Subgroup analysis of patients who had previous angioplasty, multivessel angioplasty, and acute myocardial infarction showed a similar time course of restenosis. Recurrence of symptoms paralleled restenosis, with most symptoms recurring within 3 months. However, there was

a poor correlation between patients' symptoms and angiographic restenosis. Similar to the STRESS and BENESTENT studies (see pages 164 and 167), a small number of lesions (<4%) showed regression during the follow-up period.

Although this study does not analyze the separate processes contributing to the restenotic process, the time course of changes which have been accurately established in this study do give clues as to the processes involved. Thus, the immediate "restenosis" seen at day 1 is likely to be due to elastic recoil of the artery, possibly superimposed with thrombus on the lesion. More recent definitions of restenosis have in fact excluded this early time point and these processes from the classification. However, most of the restenosis occurs within 3 months, with little change between 3 and 12 months. This has profound implications for the prevention of restenosis, implying that a short-term treatment, with effects possibly only for a few weeks, can suppress restenosis. The study by O'Brien et al (see page 163) has identified that there is no peak of cell proliferation between 1 and 3 months. However, the study by Mintz et al (see page 166) demonstrates that geometric remodeling accounts for most of the changes in lumen diameter over this period. The implications of this are that any treatment that induces favorable arterial remodeling short-term can suppress restenosis. The success of 7E3 in the EPIC trial (see page 159), which was only given for 12 hours after the procedure, further endorses the scientific validity of this concept.

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1988

Enzo Ferrari, Italian racing car magnate, dies aged 90;  
Sir Alexander Issigonis, British designer of  
the "Mini" motor car, dies aged 81;  
and George Bush wins the US presidential election



## Inhibition of vascular smooth muscle cell proliferation in vitro and in vivo by *c-myc* antisense oligodeoxynucleotides

Bennett MR, Anglin S, McEwan JR, Jagoe R, Newby AC, Evan GI

*J Clin Invest.* 1994;93:820-828

The failure of conventional pharmacological agents to inhibit restenosis has spawned a whole series of studies dedicated to using gene therapy to prevent restenosis.

The premise for these studies is that interruption of the cascade of gene expression in vascular smooth muscle cells (VSMCs) following arterial injury can prevent those cells undergoing cell proliferation or cell migration and thus inhibit neointima formation. A number of techniques have been tried, with variable success. However, the majority have made use of antisense oligonucleotides—short sequences of DNA that irreversibly bind to the mRNA of a chosen gene, and thereby inhibit formation of a specific protein product critical to cell proliferation or migration.

The study by Bennett et al examined the use of antisense oligonucleotides to *c-myc*, a proto-oncogene that regulates cell proliferation, in the proliferation of rat VSMCs. The authors first used antisense oligonucleotides to *c-myc* and showed that these oligonucleotides could inhibit VSMC proliferation. To control for nonspecific toxic effects of the oligonucleotides, the authors used control oligonucleotides encoding the sense *c-myc* sequence, irrelevant oligonucleotides (to glyceraldehyde-phosphate dehydrogenase (GAPDH) and actin, both genes whose function is unrelated to proliferation), and a 2-base pair mismatch antisense sequence which had been shown to be ineffective in other studies in cancer cells. None of these control oligonucleotides affected rat VSMC proliferation. To demonstrate that the antisense oligonucleotides were acting on the *c-myc* target, the authors showed inhibition of *c-myc* mRNA and protein with the antisense oligonucleotide, but not with any of the other sequences. As a further control, the study used overexpression of *c-myc* to block the effect of the antisense oligonucleotides. Thus, rat VSMCs were engineered with very high levels of *c-myc*; the antisense oligonucleotides to *c-myc* had no effect on the cell proliferation or *c-myc* expression of these cells.

The authors then used antisense oligonucleotides to *c-myc* to inhibit cell proliferation in the rat carotid artery model

of injury. Sense or antisense oligonucleotides to *c-myc* were applied in a gel to the adventitia of the artery immediately after injury. Northern blots demonstrated that after injury, *c-myc* mRNA peaks in the vessel wall at 2 to 4 hours. Application of the antisense oligonucleotide inhibited this induction of *c-myc* expression. Arterial morphometry was analyzed at 2 weeks after injury. This showed that there was a significant inhibition on neointima formation in the antisense treated group, with the effect limited to the segment of the vessel which had been treated.

The study by Bennett et al was not the first to use antisense oligonucleotides in vivo to inhibit neointima formation. However, it differs from other studies in several important aspects. First, while there is considerable debate about the specificity of antisense oligonucleotides, particularly as used here containing specific 4 G motifs, this study provides extensive controls to show that at least some of the effect observed is specific. Furthermore, the study shows that suppression of gene expression at very early times (2 to 4 hours after injury) is sufficient to inhibit neointima formation in this model. While it is debatable how representative this model is of human disease, the long-term efficacy of a single agent applied immediately after angioplasty is an essential prerequisite of any treatment aimed at inhibiting restenosis. Finally, this and subsequent studies demonstrate that gene therapy for restenosis is feasible, if the correct target can be found.

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1994

Canada wins the World Ice-hockey  
Championship in Milan;  
Manchester United beats Chelsea  
4-0 to win the FA cup;  
and shops in Britain open legally on Sundays

## Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near-Gaussian distribution: a quantitative angiographic study in 1445 successfully dilated lesions

Rensing BJ, Hermans WRM, Deckers JW, de Feyter PJ, Tijssen JGP, Serruys PW

*J Am Coll Cardiol.* 1992;19:939-945

Clinical classifications of restenosis are based on a number of criteria; primarily, the patient has a return of symptoms, with demonstrable narrowing of the previously dilated vessel. About 30% of patients in clinical practice present again after angioplasty with this scenario. The 70% of patients who do not have a return of symptoms (and may or may not have a similar re-narrowing), are classified as not having restenosed. Thus, the perception has grown of two populations of patients, those who do and those who do not undergo restenosis. Such a division would have profound significance. If patients had similar clinical and angiographic characteristics of the lesion, then a (presumed genetic) susceptibility would predispose a subset of patients to restenosis. While this may partly still be true, the study by Rensing et al debunked the idea that “restenosis” and “nonrestenosis” were distinct entities, and were actually part of an overlapping spectrum of disease. Thus, like most landmark studies, this changed the way we view the disease process.

Rensing et al performed angioplasty on 1445 lesions in 1427 patients, with a primary success rate of 94.8%, defined as <50% residual stenosis and no in-hospital complications (death, acute myocardial infarction, coronary artery bypass grafting, repeat angioplasty, or symptom recurrence). Patients with both stable and unstable angina were included. Follow-up angiograms were performed at 6 months, and quantitative angiography with edge detection in a central core laboratory was performed for all angiographic measurements.

Minimal lumen diameter (MLD) preangioplasty, immediately after angioplasty, and at 6 months of follow-up all followed a normal (Gaussian) distribution with no evidence of a bimodal distribution. The change in MLD between the immediately postangioplasty and follow-up angiograms also showed a Gaussian distribution, including some lesions which appeared to regress. Percentage diameter stenosis at follow-up also showed a Gaussian distribution. This study yielded other interesting and valuable results. First, if the data were analyzed to exclude the lesions that progressed to total occlusion, then the distribution of

change in MLD more closely followed the Gaussian plot. This suggests that the lesions that progress to occlusion are not necessarily those with the poorest angiographic result post procedure, and occlusion may be associated with other variables. The authors suggest that as lesion diameters below 0.5 mm are impossible to sustain because of unphysiologically high blood pressures required to maintain flow, the last reduction in lumen size, from 0.5 mm to zero, occurs due to thrombosis. Second, only a very small percentage (approx. 1%) of lesions showed evidence of angiographic regression, indicating that, without adjunctive therapy, the healing response of the vessel is only to narrow the lumen back towards its pretreatment size.

This study is important as it emphasizes the continuous variation in response to the angioplasty, rather than an “all or none” response. This underlines the fact that the incidence of angiographic restenosis in a population of patients is critically dependent upon which arbitrary cutoff point one uses for percentage reduction in lumen size. Continuously distributed variables in medicine are always difficult to interpret, as the arbitrary cutoff point not only defines the disease incidence, it also usually decides when to intervene. For coronary stenosis, the cutoff point has usually been 50%, because it represents the approximate point at which coronary flow reserve is reduced in animal arteries. However, restenosis is the tail end of a near-Gaussian distribution, with some lesions crossing an arbitrary cutoff point, rather than representing a specific disease entity that only occurs in some lesions, or some patients. This fact also means that the change in MLD rather than percentage restenosis should be used when comparing the efficacy of new antirestenosis treatments.

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1992

Boutros Boutros Ghali becomes  
UN Secretary-General;  
Agassi wins the Mens' Singles at Wimbledon;  
and the last survivor of the Titanic,  
Marjorie Robb, dies aged 103



## Proliferation in primary and restenotic coronary atherectomy tissue: implications for antiproliferative therapy

O'Brien ER, Alpers CE, Stewart DK, Ferguson M, Tran N, Gordon D, Benditt EP, Hinohara T, Simpson JB, Schwartz SM

*Circulation.* 1993;73:223-231

For the last 20 years, vascular smooth muscle cell proliferation has been considered to be an indispensable part of the pathogenesis of atherosclerosis, and more recently, of angioplasty restenosis. Consequent upon this premise and encouraging data from animal models of both diseases, numerous trials of antiproliferative agents have been done, particularly to prevent restenosis. These agents have universally been unsuccessful. This failure has led many investigators to question the preeminent role of smooth muscle cell proliferation in either disease.

The study by O'Brien et al follows up a study from the same group which showed that there are very low levels of cell proliferation in primary atherosclerotic plaques (<0.5%) (Gordon et al. *Proc Natl Acad Sci USA.* 1990;87:4600-4604). O'Brien et al used directional atherectomy to examine primary (118 specimens) and restenotic (100 specimens) lesions from human coronary arteries, including those from aortocoronary-saphenous vein bypass grafts. These specimens were obtained from a range of patients, with stable or unstable angina, from various sites within the coronary tree, and at various times after angioplasty (to 1 year). Specimens were stained with an antibody to proliferating cell nuclear antigen (PCNA), which stains cells in the cell cycle, and cell type-specific antibodies to recognize vascular smooth muscle cells, macrophages, and endothelial cells. Over 4000 cells/slide were counted for both primary and restenotic specimens.

The study found that the vast majority of primary or restenotic specimens had no evidence of cell proliferation, and where this was present, it was at very low levels. Proliferating cells were smooth muscle cells (approximately 70%), macrophages (approximately 20%), and endothelial cells (approximately 10%). Furthermore, there was no difference in cell proliferation in restenotic specimens when analyzed 0 to 3, 4 to 6, 7 to 9, or >9 months after angioplasty.

This study occupies a very important place in the development of knowledge regarding restenosis. In particular, as there is no difference in rates of

proliferation between primary and restenotic tissues, it provides prima facie evidence disputing the preeminent role of smooth muscle cell proliferation in restenosis. Indeed, subsequent studies have found that neointima formation per se plays only a minor role in restenosis, and the major player appears to be geometric remodeling of the artery. The study by O'Brien et al changes the paradigm for the pathogenesis of restenosis, and redirects our studies to different biological processes and different therapeutic opportunities. In addition, the lack of evidence of a wave of proliferation following human angioplasty corresponding to that seen in animal models further underlines the growing feeling that animal models of restenosis—which involve traction withdrawal of balloon catheters in normal arteries—do not accurately reflect the human disease. This means that better models of restenosis need to be developed before therapeutic trials are extended to humans.

It should be borne in mind that this study is at odds with a similar study on human restenosis material (Pickering et al. *J Clin Invest.* 1993;91:1469-1480), which showed levels of proliferation of 15% to 20% in restenotic lesions. A number of technical differences may account for these discrepancies, as well as the fact that most of the tissue obtained in the study by Pickering et al was from peripheral arteries. It may well be therefore that different biological processes have different contributions to restenosis in the coronary or peripheral circulations.

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1993

“The Piano” wins the Palme d’Or  
at the Cannes film festival;  
Toni Morrison becomes the first black American  
to win the Nobel prize for literature;  
and Alfred Butts, American inventor of  
the boardgame Scrabble, dies aged 93

## A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease

Fischman DL, Leon MB, Bairn DS, et al, for the STent REStenosis Study Investigators

*N Engl J Med.* 1994;331:496-501

Restenosis following angioplasty has been the Achilles' heel of the technique since its inception. As described in the CAVEAT trial (page 165), newer devices such as directional coronary atherectomy (DCA), excimer laser, or rotablation have not been associated with lower incidences of restenosis. This is likely to be because all these techniques induce arterial injury, with no way of preventing late contraction of the vessel by constrictive remodeling. The advent of coronary stents, metal scaffoldings that brace the vessel in an open and, in many cases, an overdilated state, offer the prospect of directly tackling constrictive remodeling. The findings of two trials (here and Serruys et al, see page 167), which were direct comparisons of stenting versus angioplasty, were thus eagerly awaited.

The STRESS trial, conducted in the USA, randomly assigned 410 patients with symptomatic coronary artery disease to receive elective placement of a Palmaz-Schatz stent or standard balloon angioplasty. Lesions needed to be primary, with no previous intervention, in vessels >3 mm in diameter and producing at least a 70% stenosis. Angiography was performed before, immediately after, and 6 months after the procedure. Procedural success rates were high for both stent placement and angioplasty, although stents were significantly better and produced fewer dissections. In contrast, stenting had more vascular and bleeding complications than angioplasty, with patients staying over twice as long in hospital.

At 6 months' follow-up, stent restenosis was significantly lower than after balloon angioplasty (31.6% to vs 42.1%, respectively). When the authors studied the mechanisms by which improved outcome occurred after stenting, it appeared that stenting results in a greater minimal lumen diameter after the procedure. Although the stented group also had a larger loss of lumen, the higher initial gain resulted in an overall greater lumen diameter in the stented group at 6 months. Indeed, the most important predictor of lumen diameter at 6 months was the lumen after the procedure, whatever the procedure itself. Smaller vessels and left anterior descending lesions

tended to fare worst, whatever the intervention chosen. The angiographic benefits of stenting also translated into clinical events for the patients. Stented patients required less revascularization, and had less angina than the angioplasty group. There was, however, no difference in mortality or rates of myocardial infarction between stented and angioplasty groups at 6 months.

In addition to demonstrating that elective stenting reduces restenosis, this trial also partly suggests the mechanism of this effect. The concept of "bigger is better" in minimal lumen diameter post intervention was mentioned in the discussions of the papers by Kuntz et al and Topol et al (see pages 158 and 165). One major reason why stenting appears to be advantageous is that larger lumens can be achieved safely with this procedure. A larger lumen, with less constrictive remodeling, appears to be the secret of the stent's success.

A word of caution is, however, necessary with this trial. A significant number of stents thrombosed. Indeed, over 20% of stents used as a bailout after failed angioplasty were associated with stent thrombosis. This thrombosis occurred despite the intense anticoagulation regimens employed, regimens which themselves were associated with bleeding complications and a longer hospital stay. Thus, stenting buys a reduction in restenosis; there is, however, a morbid and economic price to pay.

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1994

Austria, Sweden, and Finland join the EU;  
Queen Elizabeth II and Boris Yeltsin  
attend the Bolshoi Ballet;  
and Burt Lancaster dies, aged 80



## A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease

Topol EJ, Leya F, Pinkerton CA, et al, for the CAVEAT Study Group

*N Engl J Med.* 1993;329:221-227

The high rate of restenosis following balloon angioplasty has acted as a driving force for the development of a number of different interventions in an attempt to improve overall long-term patency rates.

Directional coronary atherectomy (DCA) was invented by Simpson in 1984 and involves the introduction of a catheter-based cutting blade across the atherosclerotic plaque, and with a combined closure of the blade and retraction, part of the plaque is excised. If one considers that restenosis is due to neointima formation, then removal of the plaque mass from which the neointima arises is a conceptually elegant solution to the problem of restenosis. Indeed, from 1988, there was a rapid expansion of the use of DCA, due mainly to its high procedural success rate. However, until this study by Topol et al, there was no randomized comparison of the long-term outcome of DCA versus angioplasty. This study effectively puts the nail in the coffin for routine DCA.

Topol et al recruited 1012 patients in a multicenter study in the USA and Europe, and randomly assigned them to DCA or angioplasty. Patients had symptomatic coronary artery disease (although most had unstable angina), without previous intervention, in vessels at least 3 mm in diameter, and >60% stenosis on angiography. Both DCA and angioplasty had good initial procedural success rates, with a slight but significant benefit of DCA over angioplasty. This was due to the increased lumen diameter achieved with DCA versus angioplasty. However, there was a marked difference in the rates of myocardial infarction, with 19% of DCA patients suffering a clinical, ECG, and biochemical infarct. This resulted in higher hospital cost for DCA versus angioplasty.

Angiography was performed in 90% of the original patients at 6 months. This showed no significant difference in restenosis for DCA versus angioplasty patients. However, for either procedure, the single most important determinant of restenosis was the minimal lumen diameter after the procedure, with a larger diameter being associated with a lower restenosis rate. Other minor predictors of restenosis included smaller

vessels, the presence of diabetes mellitus, and a lesion located in the proximal left anterior descending (LAD) artery. There was no significant difference in survival or the need for revascularization between DCA and angioplasty groups at 6 months, although all of the deaths in the DCA group occurred shortly after the procedure. There was still a significant increase in myocardial infarction rates in the DCA group at 6 months.

So what does this study tell us? The main finding of this study is that DCA, despite its conceptual simplicity, does not reduce restenosis, and can produce high levels of procedural complications, including early myocardial infarction and death. Although there is a small subgroup of patients with LAD disease who do better with DCA, most patients do not, and overall, routine DCA in unselected cases increases the total costs of the intervention. However, one important concept has come from this study. Until this time, it had been difficult to assess what size of vessel one should aim to produce with any intervention. This study endorsed the concept that "bigger is better," in that the greater the final minimal lumen diameter, the lower the restenosis. This concept has now been adopted with the advent of stent technology (see page 164).

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1993

The Canadian and Turkish governments are headed  
by women for the first time;  
A Turner landscape is sold to the Getty museum  
for a record £11 million;  
and Rudolf Nureyev dies, aged 54

## Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study

Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong SC, Hong MK, Kovach JA, Leon MB

*Circulation.* 1996;94:35-43

The emerging viewpoint over recent years has been that human angioplasty restenosis is attributable to a number of processes, specifically, neointima formation, subacute recoil, and geometric remodeling.

While suppression of neointima formation has been addressed by numerous animal models, and found to be a poor predictor of clinical efficacy of therapeutics, the role of arterial remodeling has not been studied in depth. In fact, it was not until animal models used angioplasty of diseased arteries that arterial remodeling became apparent. Arterial remodeling is defined as a change in overall arterial size, as measured from the internal or external elastic lamina, without necessarily a change in arterial lumen size. It has been known for many years that an artery can expand to accommodate increasing amounts of atherosclerotic intima. However, equally important is the concept that constrictive remodeling of an artery can reduce lumen size with no change in neointima. While this concept has been proven in animal arteries after angioplasty, the study by Mintz et al was the first demonstration that remodeling is the predominant reason that human arteries restenose.

Mintz et al used intravascular ultrasound to measure lumen size, and the proportion of the vessel area occupied by plaque + media (P+M). In addition, they measured the area of the vessel circumscribed by the external elastic lamina. Thus, changes in P+M (or tissue mass) could be discriminated from changes in overall vessel size without changes in mass. These measurements were made prior to angioplasty, immediately after angioplasty, and at an average interval of 6 months after angioplasty. In addition, other forms of vessel manipulation were studied including directional coronary atherectomy, rotational atherectomy, or excimer laser angioplasty.

The results of this study are highly illuminating. The authors found that whatever the nature of the initial procedure, 75% of the restenosis (lumen narrowing) was due to a decrease in the total cross-sectional area of the vessel, ie, due to constrictive remodeling. Only 25% of restenosis could be attributed to neointima formation.

In fact, there was no difference between the amount of neointima found in the vessels that restenosed compared with those that did not. There was a correlation between increasing neointima and lumen loss, but the degree of correlation was far less than that between the reduction in vessel cross-sectional area and lumen loss. Interestingly, there was also a correlation between increase in neointima and increase in vessel cross-sectional area, confirming observations that vessels compensate for atherosclerosis by expanding. When the authors examined the role of remodeling in each of the separate interventions, remodeling accounted for most of the restenosis if the procedure was angioplasty, rotablation, atherectomy, or excimer laser.

This study represents a huge increase in our understanding of restenosis. It may explain why therapies aimed at blocking neointima formation have consistently failed to inhibit restenosis. The study thus provides the rational basis for testing drugs which promote favorable remodeling of arteries. It may also explain why stenting, which is not associated with chronic recoil, does inhibit restenosis, despite the almost universal presence of neointima in stents. Furthermore, it suggests that the range of arterial responses to injury is very limited. We are dealing with a small number of biological processes involved in restenosis, which are similar irrespective of how the artery is injured. This underscores the clinical finding that predictors of restenosis relate more to the vessel characteristics at the time of the procedure than to the nature of the procedure itself.

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1996

The statue of Liberty celebrates its 110th birthday;  
China agrees to lend San Diego Zoo  
two giant pandas for 12 years;  
and Claudette Colbert dies, aged 90



## A comparison of balloon-expandable–stent implantation with balloon angioplasty in patients with coronary artery disease

Serruys PW, de Jaegere P, Kiemeneij F, et al, for the BENESTENT Study Group

*N Engl J Med.* 1994;331:489-495

As the STRESS trial (see page 164) was being conducted, an almost identical European trial was also recruiting, and the results of both STRESS and BENESTENT were published back to back in the *New England Journal of Medicine*. This is appropriate, since the overall message from both is identical: that elective stenting improves clinical and angiographic outcomes versus conventional angioplasty, but at a cost of increased vascular complications. However, there are some very interesting findings to be made in the comparison of the two trials.

BENESTENT recruited 520 patients with stable angina and single-vessel disease, and randomly assigned them to elective stent implantation or balloon angioplasty. Small numbers of patients (approximately 5%) crossed over from each treatment, primarily due to failure to cross the lesion with a stent, or dissection following angioplasty. Angiographic and procedural success rates were similar. The primary clinical end points were death, cerebrovascular accident, myocardial infarction, and need for subsequent revascularization (by coronary artery bypass graft or percutaneously). As in STRESS, quantitative angiography was used to assess minimal lumen diameter (MLD) at follow-up at 7 months. No difference was found in the clinical events between the two groups in hospital, with small numbers of patients suffering myocardial infarctions or requiring revascularization. Stent thrombosis and vessel closure after angioplasty were also similar. However, as in STRESS, stent implantation was associated with a higher risk of bleeding or vascular complications, predominantly groin hematomas or pseudoaneurysms). At 7 months, clinical events were significantly lower in the stented group, due again to a reduction in revascularization of the target vessel. Furthermore, MLD at follow-up was significantly reduced by stenting compared with conventional angioplasty, with a significant reduction in restenosis (defined as >50% stenosis) in the stented patients.

Comparison with STRESS reveals some interesting results. Although lesion characteristics were similar in both trials (>15 mm in length, in a vessel that was at least 3 mm in diameter), lesions were significantly severer in the STRESS

trial (75% vs 64% stenosis). Despite this, US operators achieved significantly greater lumen diameters compared with European operators, although, paradoxically, the percentage stenosis actually calculated after the procedure is similar for both angioplasty and stenting in both studies. In both studies, stenting achieved a far greater MLD after the procedure compared with angioplasty, which, despite an increased late loss in the stented group, still produced a larger vessel overall following stenting.

BENESTENT and STRESS thus lay the foundations for the modern practice of elective stenting. However, both trials offset the clinical reduction in end points (from approximately 30% to 20% with stents) against a longer hospital stay, and a higher incidence of bleeding and vascular complications in the stented group. The bleeding complications are due to the aggressive anticoagulation regimens in stented patients, with both heparin and warfarin after the procedure, with the latter continuing for 3 months. This predictable increase in complications after stenting can be reduced by minimal anticoagulation, and many units now anticoagulate their patients with a similar regimen to that used for angioplasty (heparin during the procedure and aspirin thereafter). This policy has reduced vascular complications, with no significant reduction in the efficacy of stents to prevent restenosis. A word of caution is still necessary, however. Restenosis after angioplasty can be successfully treated with further angioplasty, accepting an approximately 30% restenosis risk of the second procedure. Although the initial rate of restenosis is lower after stenting, we are creating a disease (stent stenosis) with a high subsequent restenosis rate (>50%), and also making surgical access for bypass grafting difficult. Thus, the incidence of restenosis is lower after stents, but the ones that do restenose are harder to deal with.

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1994

The Blackpool Tower is 100;  
 “Schindler’s List” wins 7 Oscars; and Marcel Bich,  
 inventor of the Bic ballpoint pen dies, aged 79



# Restenosis

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