

# CardiologyRounds™

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## Restenosis: Is the cure finally here?

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**More than 1 million percutaneous coronary intervention (PCI) procedures are performed annually worldwide to relieve the symptoms of coronary artery disease. Coronary stenting has reduced the restenosis rate for select groups of patients, resulting in stent implantation in greater than 85% of those undergoing PCI. Yet, clinical challenges remain. Depending on patient and lesion characteristics, up to 50% of patients still develop restenosis after stenting, leading to repeat target vessel revascularization (TVR). In the United States alone, more than 150,000 cases of restenosis occur annually, accounting for 10-20% of total PCI procedures, and estimated to cost \$3 billion.<sup>1</sup> In this issue of *Cardiology Rounds*, we will review the mechanisms and pathophysiology of restenosis and highlight strategies for preventing and treating it, focusing on inflammation as a therapeutic target.**

### Definition and mechanisms of restenosis

Various clinical and angiographic criteria are used to define restenosis. The most common angiographic definition is a dichotomous distinction based on a stenosis diameter of >50% at the site of intervention. There are also continuous measures of restenosis, such as late loss or the loss index (defined as the ratio of late loss to acute gain).<sup>2</sup> Over a broad range of devices, including balloon angioplasty, atherectomy, and stenting, the loss index is approximately 0.4 to 0.5. Since late loss is only a fraction of acute gain, this suggests that the bigger the acute gain, the better the late lumen and less restenosis. Clinical trials use a composite endpoint of death, MI, and the need for TVR to define the success of PTCA. Symptom driven TVR or "clinical restenosis" occurs at a rate of approximately one-half of angiographic restenosis.

Restenosis is the healing response to mechanical injury comprised of 4 processes: elastic recoil, thrombus incorporation, neointimal hyperplasia (ie, smooth muscle cell migration/proliferation, extracellular matrix deposition), and vessel remodeling. Negative remodeling or vessel shrinkage is the principal restenosis mechanism following balloon angioplasty, while neointimal hyperplasia predominates after in-stent restenosis (ISR). Stenting results in an exaggerated neointimal proliferative response with little vessel remodeling due to the rigid scaffolding effect of the stent. In intravascular ultrasound (IVUS) studies of stent deployment, lumen loss is due almost entirely to neointimal thickening with little change in stent cross sectional area. Animal and clinical studies indicate that stents result in a greater degree of neointimal proliferation compared to balloon angioplasty alone.



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**Table 1: Effects of minimum lumen diameter, lesion length, and diabetes mellitus on risk of angiographic restenosis.**

POST-PROCEDURE In-Stent MLD	LESION LENGTH			
	10 mm	15 mm	20 mm	25 mm
<b>Diabetics</b>				
2.5 mm	35%	39%	43%	46%
3.0 mm	23%	26%	30%	33%
3.5 mm	15%	17%	19%	22%
4.0 mm	9%	10%	12%	14%
<b>Non-diabetics</b>				
2.5 mm	27%	30%	33%	37%
3.0 mm	17%	19%	22%	25%
3.5 mm	10%	12%	14%	16%
4.0 mm	6%	7%	8%	10%

\* Model based on 1,555 patients in C-DAC stent trials (Courtesy of Dr. Richard Kuntz)

### Restenosis risk factors

Clinical, angiographic, and procedural risk factors for restenosis include diabetes mellitus, unstable angina/myocardial infarction presentation, lesion length, severity of stenosis at baseline, location (left anterior descending artery, saphenous vein graft), vessel size, and post-procedural residual stenosis (minimum lumen diameter, MLD). In a multivariate analysis of 1555 patients receiving coronary stents, Kuntz and co-workers identified 3 variables – diabetes, lesion length, and MLD – as powerful independent predictors of angiographic restenosis risk. Risk ranges from 6% in large, non-diabetic vessels to 46% in small, diabetic vessels with long lesions (Table 1).

### Pathophysiology of restenosis

PCI results in deep crush- and stretch-induced injury of the vessel wall. This is followed by platelet deposition and thrombus formation, recruitment and activation of inflammatory cells, and proliferation and migration of smooth muscle cells, which produce neointimal thickening. The key players involved in vascular injury and repair are platelets, leukocytes, and smooth muscle cells (Figure 1).

### Platelets and restenosis

Platelets have been incriminated in contributing to neointimal hyperplasia via the release of platelet-derived growth factor (PDGF) that induces smooth muscle cell proliferation and migration. By virtue of the ability of platelets to facilitate the generation of thrombin, they may also act as a smooth muscle cell mitogen. Additionally, as will be discussed below, platelets express multiple counter-receptors for leukocytes, thereby providing a nidus for vessel wall inflammation. Studies with platelet glycoprotein IIb-IIIa receptor antagonists – that potently inhibit

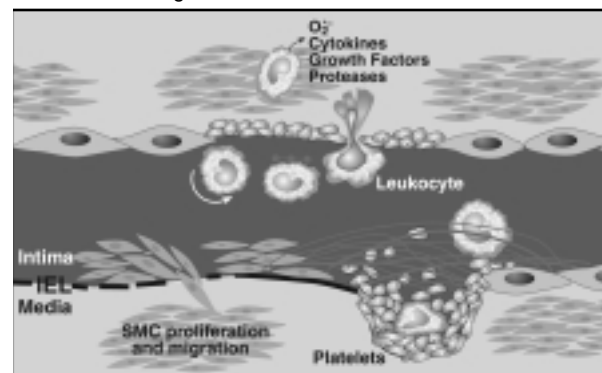
platelet aggregation – have shown mixed effects on vascular repair, reducing TVR or clinical restenosis in some trials (eg, EPIC,<sup>1</sup> ADMIRAL), but not in others (EPILOG, CAPTURE, ERASER, RAPPORT, EPISTENT, PRISM-PLUS, ESPRIT). For an explanation of these acronyms, see Table 2. Abciximab cross-reacts and inhibits  $\alpha V\beta 3$  and Mac-1 in addition to GP IIb-IIIa. The  $\alpha V\beta 3$  receptor has also been implicated in neointimal hyperplasia since smooth muscle cells express  $\alpha V\beta 3$  receptors that are upregulated further after vascular injury.<sup>3</sup> Moreover, in a number of different animal models, inhibition of  $\alpha V\beta 3$  receptors has resulted in decreased neointimal thickening. The clinical significance of abciximab's receptor cross-reactivity is unknown.

### Inflammation and restenosis

Inflammation plays an essential role in the initiation and progression of atherosclerosis, as well as atherosclerotic plaque rupture that culminates in acute ischemic syndromes.<sup>4</sup> Emerging experimental and clinical data indicate that leukocytes may be central to intimal growth after mechanical arterial injury (ie, angioplasty or percutaneous coronary intervention, PCI). In animal models of vascular injury, neutrophil and monocyte recruitment precedes intimal thickening<sup>5,6</sup> and inflammatory cell number within the vessel wall is associated with the extent of cellular proliferation and intimal thickening.<sup>6</sup> Infiltration and accumulation of monocyte/macrophages is a dominant pathophysiological response after stent-induced arterial injury,<sup>6</sup> with inflammatory cells comprising up to 60% of neointimal cells in rabbit, porcine, and non-human primate models and in human autopsy specimens. Meticulous examination after balloon injury alone also demonstrates

**Figure 1: Key players in vascular injury and repair.**

Balloon- and stent-induced injury denude the endothelial lining leading to platelet deposition that is followed rapidly by leukocyte recruitment. Cytokines, chemokines, and growth factors secreted by platelets and leukocytes promote the proliferation and migration of smooth muscle cells.



**Table 2: Clinical Trials<sup>1</sup>**

ADMIRAL	Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up
CAPTURE	Chimeric c7E3 AntiPlatelet Therapy in Unstable Refractory Angina
EPIC	Evaluation of c7E3 for the Prevention of Ischemic Complications
EPILOG	Evaluation in PTCA to Improve Long Term Outcome with Abciximab GPIIb/IIIa Blockade Study Group
EPISTENT	Evaluation in PTCA to Improve Long Term Outcome with Abciximab GPIIb/IIIa Blockade Study Group- <b>Stent</b>
ERASER	The Evaluation of Reo-Pro And Stenting to Eliminate Restenosis
ESPRIT	Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy
PRESTO	Prevention of RESTenosis with Tranilast and its Outcomes
PRISM-PLUS	Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
RAPPORT	ReoPro for Acute Myocardial Infarction and Primary PTCA Organization and Randomized Trial
RAVEL	A RAnomized Study with the Sirolimus-Coated BX VELOCITY Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions
SIRIUS	Sirolimus-Coated BX Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Coronary Artery Lesions

that neutrophils are present in abundance within hours of balloon injury and accumulate in the arterial media for several days after injury with a paucity of monocyte/macrophages.<sup>7</sup> Clinical studies have shown that angioplasty is associated with leukocyte activation and increased expression of the  $\beta$ 2-integrin Mac-1 (CD11b/CD18) both systemically and locally across the injured vessel that predicts clinical restenosis<sup>8-10</sup> and angiographic late lumen loss.<sup>11</sup>

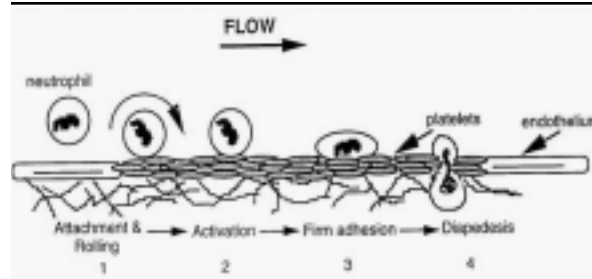
Leukocyte recruitment and infiltration occur rapidly at sites of vessel injury following balloon angioplasty or stenting where the lining endothelial cells have been denuded and platelets and fibrin have been deposited. A sequential adhesion model of leukocyte attachment to and transmigration across surface-adherent platelets has been proposed (Figure 2).<sup>12</sup> The initial tethering and rolling of leukocytes on platelet P-selectin<sup>13-15</sup> are followed by their firm adhesion and transplatelet migration, processes that are dependent on the leukocyte integrin Mac-1<sup>12</sup> and several platelet receptors, including GP Iba<sup>16</sup> and ICAM-2.<sup>17</sup> The bridging interaction between platelet GPIIb/IIIa and leukocyte Mac-1 bridged by fibrinogen is also possibly

relevant.<sup>18</sup> In addition to promoting the accumulation of leukocytes at sites of platelet coverage within the vasculature, the binding of platelets to leukocytes induces neutrophil and monocyte activation, upregulates cell adhesion molecule expression, and generates signals that promote integrin activation, chemokine synthesis, and production of reactive oxygen intermediates.

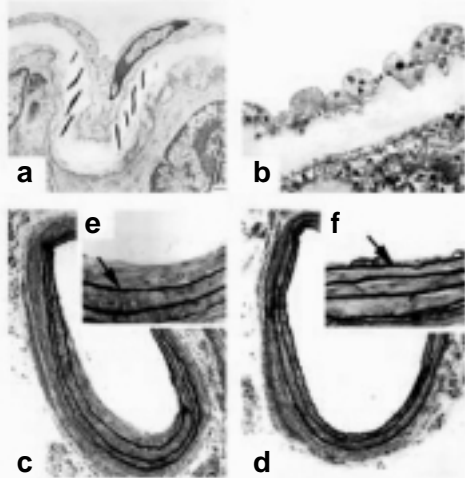
It was previously uncertain whether the relationship between inflammation and experimental and clinical restenosis was causal or simply due to co-variation with other factors. Experimental observations by our laboratories and others now support a central role for inflammation in the biological repair response to vascular injury. We found that antibody-mediated blockade<sup>19</sup> or selective absence<sup>20</sup> of Mac-1 (Figure 3) impaired transplatelet leukocyte migration into the vessel wall, diminishing leukocyte accumulation and neointimal thickening after experimental angioplasty or endovascular stent implantation. Targeting the more upstream selectin-mediated interactions between platelets and leukocytes also markedly reduces leukocyte recruitment and neointimal thickening in a variety of animal models.<sup>21-25</sup>

Critical to the transplatelet migration of leukocytes at sites of vascular injury are chemokines and their receptors, most notably the neutrophil and monocyte chemoattractants, interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1), respectively. Stenting in experimental models is associated with sustained elevation of MCP-1 post-injury (~14 days) compared to balloon-injured arteries (<5 days).<sup>26</sup> Antibody-mediated blockade of MCP-1<sup>27</sup> and its receptor, CCR2, have reduced neointimal thickening after experimental angioplasty. MCP-1 is upregulated

**Figure 2: Sequential adhesion cascade at sites of vascular injury.** Leukocytes attach loosely and roll on platelets in an interaction mediated by leukocyte PSGL-1 and platelet P-selectin. This initial tethering is followed by leukocyte activation, which promotes firm adhesion and transplatelet migration and vessel wall invasion (ie, diapedesis) mediated by the leukocyte integrin Mac-1 and platelet GP Iba and ICAM-2. (Reprinted from Diacovo et al. *Blood* 1996;88:146-57, with permission.)<sup>12</sup>



**Figure 3: Neointimal thickening is reduced in Mac-1-deficient mice.** Photomicrographs of mouse carotid arteries after arterial dilation and endothelial denudation. Transmission electron micrograph from wild-type (*Mac-1<sup>+/+</sup>*) mice: (a) uninjured and (b) 24h post-injury (original magnification: x3000). VerHoeff elastin stain 28d after vascular injury: (c) *Mac-1<sup>+/+</sup>* (x38); (d) Mac-1-deficient (*Mac-1<sup>-/-</sup>*) mice (x38); (e) *Mac-1<sup>+/+</sup>* (x150); (f) *Mac-1<sup>-/-</sup>* (x150). Neointima separates the internal elastic lamina (arrows) from the lumen. (Reprinted from Simon et al. *J Clin Invest* 2000;105:293-300, with permission.)<sup>16</sup>



following PCI in humans and elevated levels are associated with an increased risk of restenosis.<sup>28</sup>

The mechanisms by which leukocytes modulate vascular repair are likely multifactorial. These inflammatory cells contribute to neointimal thickening due to their direct bulk within the intima, generation of injurious reactive oxygen intermediates, elaboration of growth and chemotactic factors, or production of enzymes (eg, matrix metalloproteinases, cathepsins G and S) capable of degrading extracellular constituents and thereby facilitating cell migration.

### **Inflammation and restenosis: Clinical evidence**

Despite compelling experimental and clinical data indicating that leukocytes may directly drive the restenosis process, clinical trials are needed to test whether inhibiting this inflammation will reduce restenosis. To date, there is only indirect and conflicting evidence that this may be the case. Targeting reactive oxygen intermediates (the source of which is most likely leukocytes) with the anti-oxidant probucol has been effective at reducing restenosis after balloon angioplasty in two randomized trials.<sup>29,30</sup> Tranilast, an anti-allergy compound with anti-proliferative and

anti-inflammatory properties, has reduced restenosis in 2 smaller randomized trials in Japan, but appears to have failed to impact restenosis in the multi-center, randomized PRESTO trial, according to preliminary reports from the study's sponsor. Anti-inflammatory therapeutics, including prednisone and colchicine, have uniformly failed in preventing restenosis after balloon angioplasty.

Such pharmacological approaches to reduce restenosis possibly may have failed due to insufficient local drug concentrations. Delivering medication directly to the site of vascular injury via polymeric-coated stents is a rational approach to achieve adequate local drug delivery. Rapamycin, a natural macrocyclic lactone, is a potent immunosuppressive agent approved by the Food and Drug Administration for the prophylaxis of renal transplant rejection.<sup>31</sup> Rapamycin binds to an intracellular receptor protein and elevates p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes and, ultimately, induces cell-cycle arrest in the late G1 phase. It inhibits the proliferation of smooth muscle cells *in vitro*, reduces intimal thickening in models of vascular injury, and, perhaps most importantly, reduces vessel wall inflammation.

The safety and efficacy of the rapamycin-coated BX Velocity stent were reported recently by Sousa and co-workers.<sup>31</sup> Thirty patients with angina pectoris were electively treated with 2 different formulations of rapamycin-coated stents (slow release [SR], n=15, and fast release [FR], n=15). At 8-month follow-up, there was minimal neointimal hyperplasia in both groups ( $11.0 \pm 3.0\%$  in the SR group and  $10.4 \pm 3.0\%$  in the FR group) by ultrasound and quantitative coronary angiography (in-stent late loss,  $0.09 \pm 0.3$  mm [SR] and  $-0.02 \pm 0.3$  mm [FR]). No in-stent or edge restenosis (diameter stenosis  $\geq 50\%$ ) was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, or death) had occurred by 8 months in this small trial. A single case of stent thrombosis was reported, however, at 13 months. Phase 2 and 3 placebo-controlled trials (RAVEL and SIRIUS), designed to confirm these promising results, have completed enrollment.

Stents coated with a variety of agents, such as paclitaxel, actinomycin D, anti-sense myc, dexamethasone, and matrix metalloproteinase inhibitors, aimed at altering inflammatory and smooth muscle actions in the biological repair response to vascular injury, are being evaluated.

## Conclusion

Major advances in pharmacology and device technology have improved the safety and efficacy of percutaneous coronary interventions, yet treating physicians confront the predicament of restenosis on a daily basis. Most therapies, with very few exceptions, have failed to prevent restenosis. We have reviewed data supporting the concept that, much like atherosclerosis, inflammatory cells directly drive the restenosis process:

1) Leukocytes are recruited rapidly following balloon angioplasty and stenting;

2) Markers of inflammation (eg, CRP and Mac-1 expression) predict restenosis;

3) Targeting inflammation reduces neointimal thickening in animal models.

Novel anti-inflammatory agents specifically targeting leukocyte cell adhesion molecules or interrupting the actions of inflammatory cytokines are being developed for clinical restenosis trials.

We agree with Dr. Donald S. Baim's prediction that "it seems likely that a biologic agent will be found that can reduce the loss index below 0.3, thereby reducing restenosis to single digits and replacing brachytherapy for that indication." Is the cure for restenosis finally here? Perhaps.

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