Prevention of restenosis after percutaneous transluminal coronary angioplasty: The search for a "magic bullet"

Walter R. M. Hermans, MD, Benno J. Rensing, MD, Bradley H. Strauss, MD,* and Patrick W. Serruys, MD, PhD. Rotterdam, The Netherlands

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted treatment for providing relief of angina pectoris in patients with single- and multi-vessel disease. Increased experience and advances in technology have resulted in a high primary success rate (90% to 95%) and a lower complication rate (4% to 5%). Despite the therapeutic success of coronary angioplasty, the exact mechanisms of dilatation remain speculative and involve multiple processes including stretching of the vessel at the site of the dilatation and disruption and fissuring of the plaque.

Angiographic renarrowing at the site of PTCA, frequently accompanied by recurrence of symptoms of angina, is a common phenomenon (30%) and has a negative bearing on the long-term results of PTCA. Although many of the risk factors for restenosis have been identified (Table 1), most of these are difficult to influence. Until now we have not found a technical or pharmacologic cure, and we are unable to predict which patients or vessel segments will have restenosis. The reason why a clinically significant restenosis occurs in only a minority of the dilated vessels (30%) remains an enigma. Although the typical restenotic lesion differs from the usual atherosclerotic plaque in architecture and lipid content, both contain smooth muscle cells and fibrous tissue, and it is even likely that the factors responsible for restenosis are similar to those that effect de novo atherosclerosis. In some cases of "restenosis" it is conceivable that it is caused by progression of the preexisting atherosclerotic plaque.

An important step in the restenosis process is activation of the hemostatic system with platelet adhesion, platelet aggregation, and fibrin formation. This is followed by smooth muscle cell proliferation, which is mediated by growth factors produced by cellular constituents in the blood and damaged vessel wall. Each of these steps could be sites of intervention that might halt the restenosis process. The drugs that could reduce or prevent restenosis in the animal model are listed in Table II. Some of these have been investigated in prospective randomized angioplasty trials and although efficacy has not been demonstrated, they continue to be used and prescribed in daily routine. In this review we will concentrate on the drugs (Fig. 1) that have been tested to prevent restenosis in the animal model (Table III) and in postangioplasty patients (Table IV).

Animal models are of limited value in restenosis research because it is impossible to create arterial stenoses in animals (e.g., pigs, rabbits, or dogs) that resemble human coronary artery disease (Table V). Most models use an inflated balloon to "injure" the intimal and medial layers of the vessel wall, although infused air has also been used. Some investigators have performed experiments in iliac or carotid arteries rather than in coronary arteries; others have fed the animals an atherogenic diet for brief periods of time to induce an "atherosclerotic lesion." Several studies in animals have examined the degree of platelet deposition after arterial injury to test the hypothesis that platelet aggregation and platelet-derived substances are responsible for the restenosis process. Other studies use angiographic or histologic findings in damaged arteries to assess restenosis (Table IV). Recently a model of human restenosis...
Table I. Variables associated with higher restenosis rates in patients with follow-up angiography

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of patients</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al.(^4)</td>
<td>1984</td>
<td>557</td>
<td>Male sex, Male sex, Canadian class III-IV, No previous MI, Angina onset &lt;2 mo, Diabetes mellitus</td>
</tr>
<tr>
<td>Cowley et al.(^5)</td>
<td>1985</td>
<td>557</td>
<td>Male sex, Male sex, Male sex, Angina onset &lt;2 mo</td>
</tr>
<tr>
<td>Leimgruber et al.(^6)</td>
<td>1986</td>
<td>998</td>
<td>Male sex, Old age, Unstable angina, Angina onset &lt;2 mo, Medication (^7)</td>
</tr>
<tr>
<td>Kaltenbach et al.(^7)</td>
<td>1985</td>
<td>333</td>
<td></td>
</tr>
<tr>
<td>Levine et al.(^8)</td>
<td>1985</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Bertrand et al.(^9)</td>
<td>1986</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>Uebis et al.(^10)</td>
<td>1986</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>David et al.(^11)</td>
<td>1984</td>
<td>191</td>
<td>Variant angina</td>
</tr>
<tr>
<td>Hollman et al.(^12)</td>
<td>1986</td>
<td>536</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Scholl et al.(^13)</td>
<td>1981</td>
<td>45</td>
<td>Variant angina</td>
</tr>
<tr>
<td>Margolis et al.(^14)</td>
<td>1984</td>
<td>216</td>
<td>Insulin-dependent diabetes mellitus</td>
</tr>
<tr>
<td>Marante et al.(^15)</td>
<td>1984</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Mata et al.(^16)</td>
<td>1985</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Probst et al.(^17)</td>
<td>1985</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Serruys et al.(^18)</td>
<td>1985</td>
<td>20</td>
<td>High cholesterol, Current smoker</td>
</tr>
<tr>
<td>Roubin et al.(^19)</td>
<td>1986</td>
<td>411</td>
<td></td>
</tr>
<tr>
<td>Shaw et al.(^20)</td>
<td>1986</td>
<td>97</td>
<td></td>
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<tr>
<td>Clark et al.(^21)</td>
<td>1986</td>
<td>124</td>
<td></td>
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<tr>
<td>Powelson et al.(^22)</td>
<td>1986</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Urban et al.(^23)</td>
<td>1987</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Bertrand et al.(^24)</td>
<td>1989</td>
<td>437</td>
<td></td>
</tr>
<tr>
<td>Ellis et al.(^25)</td>
<td>1989</td>
<td>308</td>
<td></td>
</tr>
</tbody>
</table>

BIP, balloon inflation pressure; CABG, coronary artery bypass graft; DS, diameter stenosis; MI, myocardial infarction; TSG, transstenotic gradient; CWP, coronary wedge pressure.

\(^*\)In patients with totally occluded vessel.

\(^\dagger\)Early restenosis (<2 days).

was developed in the domestic crossbred swine fed a standard nonatherogenic diet. Metallic foreign bodies were implanted percutaneously in porcine coronary arteries with oversized PTCA balloons inflated to high pressure. Results of histologic examination of lesions showed a marked proliferation of medial smooth muscle cells. This may be a useful animal model to test drugs used for treatment of restenosis, since it more closely resembles the response in human restenosis.
ANTICOAGULANTS AND ANTIPLATELET AGENTS

Platelets play an important role in the development of restenosis after PTCA. Intact endothelium prevents platelet aggregation; however, after superficial injury a thin layer of thrombocytes attach themselves to the endothelium (platelet adhesion). If, however, there is deeper damage to the vessel wall, blood is exposed to collagen and other substances of the subintima, which is a potent stimulus for platelet aggregation that is mediated by the release of adenosine diphosphate, serotonin, thromboxane A2, fibrinogen, fibrinectin, and von Willebrand factor. These substances activate neighboring platelets via different metabolic pathways (thromboxane A2, adenosine diphosphate, and a platelet-activating factor) and promote thrombosis. In addition, the release of several growth factors, including platelet-derived growth factor, epidermal growth factor, and transforming growth factor beta from thrombocytes, smooth muscle cells, endothelium, and macrophages, stimulates smooth muscle cells and fibroblasts to proliferate and migrate from the medial layer into the intima of the vessel wall. In some patients this response is excessive and is associated with formation of abundant amounts of connective tissue. This results in hyperplasia of the intima with a reduction in luminal diameter.

To prevent platelet deposition (which occurs within minutes of the procedure) and the associated release of smooth muscle cell mitogenic factors, antiplatelet therapy appears to be a logical approach. Experimental studies have demonstrated that the use of antiplatelet agents can decrease the extent of platelet deposition and acute thrombosis after angioplasty, with some agents reducing the rate of restenosis in the pig model (dipyridamole [2.5 mg/day] + acetylsalicylic acid [20 mg/kg/day], low-dose acetylsalicylic acid [1 mg/kg/day], anagrelide, intravenous nitroglycerin, and intravenous ibuprofen). Because only one of three pathways of platelet activation is blocked by current platelet-inhibitor therapy, it is not surprising that these agents are insufficient to prevent restenosis when tested in patients (Fig. 1).

Heparin. For many years heparin has been an integral aspect of the PTCA procedure since it binds reversibly with antithrombin, which results in increased activity of antithrombin. The antithrombin-heparin complex then binds with factor Xa and factor IIa resulting in an anticoagulant effect (believed to be the result of its IIa effect) and an antithrombotic effect (through its anti-Xa activity). Early discontinuation of heparin after angioplasty is associated with acute occlusion of the dilated arterial segment, suggesting that anticoagulation is important in the early stages after PTCA. However, the optimum duration of heparin therapy is still unknown.

A prospective trial conducted by the M-HEART study group35 with 209 patients showed an inverse relationship between the duration of heparin therapy and the incidence of restenosis. This was not con-
Fig. 1. Simplified schematic presentation of how the different drugs act on the different processes involved in the restenosis process (Modified from Fuster V et al. Prog Cardiovasc Dis 1987;22:325-46.) ASA, Acetylsalicylic acid; NSAID, nonsteroidal antiinflammatory drugs; TxA2, thromboxane A2; 7E3, antiplatelet glycoprotein receptor 2B/3A; ADP, adenosine diphosphate; LMWH, low molecular weight heparin; cAMP, cyclic adenosine monophosphate; IGF, insulin-like growth factor; FGF, fibroblastic growth factor; SMC, smooth muscle cell.

Table II. Mechanisms to prevent restenosis

<table>
<thead>
<tr>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin, hirudin, coumadin, acetylsalicylic acid, dipyridamole, sulfinpyrazone, thromboxane A2 synthetase inhibitor, thromboxane A2 receptor blocker, ticlopidine, prostacyclin, ciprostene, 7E3. fish oil. NSAID. ridogrel</td>
</tr>
<tr>
<td>Cell proliferation</td>
</tr>
<tr>
<td>Low-molecular-weight heparin, platelet-derived growth factor antagonist (trapidil), angiotensin-converting enzyme inhibitor (cilazapril), colchicine, cytostatic agents, serotonin antagonist (ketanserin), angiopeptin</td>
</tr>
<tr>
<td>Inhibitor of inflammation</td>
</tr>
<tr>
<td>Corticosteroids, nonsteroidal antiinflammatory drugs</td>
</tr>
<tr>
<td>Coronary vasospasm</td>
</tr>
<tr>
<td>Nifedipine, diltiazem</td>
</tr>
<tr>
<td>Lipid regulators</td>
</tr>
<tr>
<td>Fish oil, lovastatin</td>
</tr>
</tbody>
</table>

In only 58.4% of the patients treated with heparin and 64.5% of the patients given placebo. More bleeding complications were seen in the group of patients who were treated with heparin (8.2% vs 3.8%). Acute total closure was seen more frequently in the group given placebo (2.4%) than in the group treated with heparin (1.8%), and the restenosis rate was 41.2% with heparin and 36.7% with placebo.

Because low-molecular-weight heparin affects platelet aggregation and platelet-dependent thrombin generation to a lesser extent than "regular" heparin, it has fewer side effects and yet both forms are known to inhibit the proliferation of vascular smooth muscle cells (dose dependent) and thrombosis after endothelial injury in the rat. The mechanism of this inhibition is not clear. Recently low-molecular-weight heparin has been used after transluminal angioplasty of rabbit iliac arteries. Two groups were studied: the first group (n = 9) received low-molecular-weight heparin (10 mg/kg/day subcutaneously) immediately before transluminal angioplasty until follow-up angiography 1 month later, whereas the second group (n = 12) received a placebo. After 4 weeks all rabbits in the placebo group and three of nine rabbits in the group treated with low-molecular-weight heparin had a loss of more than 50% of the gain in diameter after transluminal angioplasty.
angioplasty. Histologic findings showed reduced intimal hyperplasia and no formation of thrombus in the group treated with low-molecular-weight heparin. A multicenter double-blind control trial with low-molecular-weight heparin (Enoxaparin) is currently underway in the United States. Patients without prior PTCA or recent myocardial infarction (within 5 days) are randomly assigned to placebo or low-molecular-weight heparin (30 mg subcutaneously) for 1 month, and all patients will undergo repeat angiography at 6 months. This will provide important information about whether long-term administration of low-molecular-weight heparin can decrease the rate of restenosis.

Hirudin. Newer anticoagulant drugs such as recombinant hirudin are becoming available. Hirudin prevents fibrinogen clotting, thrombin-catalyzed activation of factors V, VIII, and XIII, and thrombin-induced platelet activation. Hirudin has been shown to be more effective in preventing thrombosis than heparin (by quantifying the deposition of platelets and fibrinogen by means of the method of Dewanje in a swine model). This latter effect is probably due to the fact that hirudin is a more potent and specific thrombin antagonist. Trials designed to test the efficacy of hirudin on early and late complications of PTCA are currently in the planning stages in Europe and the United States.

Coumadin. Before Gruentzig began his work at Emory University in Atlanta in 1980, he had been administering coumadin (a vitamin K antagonist responsible for inhibiting thrombin formation) to his patients after balloon dilatation. In Atlanta his view was challenged since there was evidence that antiplatelet drugs were effective in preventing thrombosis in venous bypass grafts. To test this new therapeutic approach a trial was begun in which 248 patients were randomly assigned to either 325 mg acetylsalicylic acid daily or coumadin at a dose that resulted in a prothrombin time that was 2 to 2.5 times the normal value. In the group treated with acetylsalicylic acid (126 patients) restenosis was angiographically documented in 27% of the patients versus 36% of the patients treated with coumadin. A loss of >50% of the gain achieved at the time of PTCA or an increase in the stenosis of more than 30% (NHLBI IV criterion was used). Although the incidence of angiographic restenosis tended to be lower with coumadin, none of the differences were significant. A randomized trial to evaluate the efficacy of coumadin in the prevention of restenosis should be performed that would ensure adequate medication compliance with reliable and safe monitoring of prothrombin time.

Acetylsalicylic acid. Acetylsalicylic acid is a "popular drug" in restenosis prevention trials. In the animal model it reduces platelet-thrombus deposition in a dose of 1 mg/kg/day when given in addition to heparin. Angiographic restenosis has also been shown to be reduced when acetylsalicylic acid is used in addition to dipyridamole. Acetylsalicylic acid has the ability to inhibit platelet thromboxane A2 synthetase and subsequent platelet activation by irreversibly blocking the enzyme cyclooxygenase, which is responsible for the conversion of arachidonic acid to thromboxane A2. At high doses acetylsalicylic acid may be less effective, since it inhibits the production of prostacyclin (which prevents platelet aggregation) by endothelial cells. However, it only partially inhibits platelet aggregation induced by adenosine diphosphate, collagen, or thrombin. Consequently platelet-derived growth factor and other mitogens may still affect proliferation of smooth muscle cells (Fig. 1).

Acetylsalicylic acid has been studied in several prospective randomized trials. The first trial showed a reduction in the restenosis rate of 25% when acetylsalicylic acid (325 mg) was compared with coumadin. Three trials compared different dosages of acetylsalicylic acid. In a trial in Homburg/Saar, 203 patients were randomly assigned to either 1500 mg/day or 320 mg/day. In a preliminary report 25% of these patients had been restudied (6 months after PTCA). Results of follow-up angiography showed restenosis (>50% diameter stenosis) in 13 of 44 (31%) patients in the group treated with the lower dose compared with 9 of 42 patients (21%) in the group given the higher dose. However, in a randomized trial in Atlanta with 495 patients, the effectiveness of two doses of acetylsalicylic acid (90 mg vs 1500 mg daily started the day before PTCA) in the prevention of restenosis and acute complications af-
Table III. The effect of drug therapy in the animal model for prevention of restenosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Model</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clowes and Karnowsky</td>
<td>1977</td>
<td>Rat</td>
<td>Heparin</td>
<td>5-14 days</td>
</tr>
<tr>
<td>Gordon et al.</td>
<td>1987</td>
<td>Rabbit aorta</td>
<td>LMWH</td>
<td>2.5 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A. carotis</td>
<td>Placebo</td>
<td>1 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rabbit aorta</td>
<td>Hydrocortisone</td>
<td>LMWH + hydrocortisone Placebo</td>
</tr>
<tr>
<td>Pow et al.</td>
<td>1989</td>
<td>Rabbit</td>
<td>LMWH</td>
<td>10 mg/kg/day</td>
</tr>
<tr>
<td>Heras et al.</td>
<td>1989</td>
<td>Pig</td>
<td>Hirudin</td>
<td>1 mg/kg/hr</td>
</tr>
<tr>
<td>Faxon et al.</td>
<td>1984</td>
<td>Rat</td>
<td>Heparin</td>
<td>6 different doses</td>
</tr>
<tr>
<td>Sanborn et al.</td>
<td>1986</td>
<td>Rabbit</td>
<td>ASA + D</td>
<td>1 mg/kg/day</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>1990</td>
<td>Rabbit</td>
<td>TXA2 synthetase inhibitor</td>
<td>500 U/kg</td>
</tr>
<tr>
<td>Currier et al.</td>
<td>1989</td>
<td>Rabbit</td>
<td>Heparin</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A. iliaca</td>
<td>ASA</td>
<td>0.02 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rabbit</td>
<td>Colechicine</td>
<td>0.02 mg/kg</td>
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<tr>
<td>Barath et al.</td>
<td>1989</td>
<td>Rabbit aorta</td>
<td>Vincreistine + actinomycin</td>
<td>0.075 mg/kg</td>
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<tr>
<td>Powell et al.</td>
<td>1989</td>
<td>Rats</td>
<td>Captopril</td>
<td>100 mg/kg/day</td>
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<tr>
<td>Müller et al.</td>
<td>1990</td>
<td>Rabbit</td>
<td>Hydralazine</td>
<td>0.015 mg/kg</td>
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<td>A. carotis</td>
<td>Verapamil</td>
<td>100 mg/kg/day</td>
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<td></td>
<td></td>
<td>Rabbit</td>
<td>Angiopeptin</td>
<td>100 mg/kg/day</td>
</tr>
<tr>
<td>Faxon et al.</td>
<td>1994</td>
<td>Rabbit</td>
<td>Nifedipine</td>
<td>Placebo</td>
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<td></td>
<td></td>
<td>A. femoralis</td>
<td>Placebo</td>
<td>40 mg/day</td>
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<td></td>
<td>Rabbit cardiac transplant</td>
<td>Placebo</td>
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<td>Rats</td>
<td>Placebo</td>
<td>6 mg/kg/day</td>
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<td>A. carotis</td>
<td>Lovastatin</td>
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<td></td>
<td></td>
<td>Rabbit</td>
<td>Placebo</td>
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</table>

ASA, acetylsalicylic acid; D, dipyridamole; LMWH, low-molecular-weight heparin; TXA2, thromboxane A2.

Results of follow-up angiography were available in only 166 patients (34%). In the group treated with the low dose of acetylsalicylic acid, 47% of the patients had restenosis >50% diameter stenosis in one or more sites) compared with 51% in the group treated with the high dose. There were no differences in success or acute complication rates. Thus restenosis was not influenced favorably by the use of a higher dose of acetylsalicylic acid.

A smaller trial compared the effects of acetylsalicylic acid in doses of 100 mg/day versus 1000 mg/day, started 1 day before PTCA until 6 months after PTCA. In addition, all patients received calcium channel blockers and long-acting nitrates. Restenosis (clinically significant stenosis requiring repeat PTCA or coronary artery bypass graft) occurred in 7 of the 40 patients in the group treated with 100 mg acetylsalicylic acid (18%) and in 8 of the 39 patients in the group treated with 1000 mg acetylsalicylic acid (21%). The investigators concluded that restenosis is not favorably influenced by the use of high-dose versus low-dose acetylsalicylic acid. Another trial designed to compare the effects of 100 mg acetylsalicylic acid with those of placebo was stopped prematurely after 40 patients (single blind) were enrolled because of reports showing the benefit of acetylsalicylic acid (combined with dipyridamole) in preventing acute thrombosis in dilated vessels and the need for urgent bypass surgery. Results of follow-up angiography at 6 months (95% of the patients) in this particular trial showed an incidence of restenosis (>50% diameter stenosis) that was two times higher in the group treated with acetylsalicylic acid (33%) compared with the group given a placebo (14%). Although the difference seems impressive, it was not statistically significant because of the small numbers.
In a well-designed trial at the Montreal Heart Institute and Toronto General Hospital,\(^{51}\) 376 patients were randomly assigned to a combination of acetylsalicylic acid (990 mg daily) and dipyridamole (225 daily) or to placebo starting the day before PTCA until follow-up angiography 4 to 7 months later. More acute complications were seen in the placebo group, including 13 periprocedural myocardial infarctions in the placebo group versus three in the treated group (\(p < 0.05\)). However, no differences were observed in the restenosis rate (increase in diameter stenosis from \(<50\%\) after PTCA to \(>50\%\) at follow-up): 39\% (127 patients) in the placebo group compared with 38\% (122 patients) in the treated group. All patients received heparin until 12 hours after the procedure (500 U/hr) and diltiazem until follow-up angiography.

Chesebro et al.\(^ {52}\) randomly assigned 207 patients (297 stenoses) to either acetylsalicylic acid (975 mg/day) and dipyridamole (225 mg/day) or to placebo from the day before PTCA until 6 months later. There was no difference in the restenosis rate defined in a linear model based on the minimum lumen diameter obtained by quantitative angiography. There were fewer acute complications (occlusion, myocardial infarction, repeat PTCA, coronary artery bypass graft <48 hours) in the group treated with acetylsalicylic acid and dipyridamole (11\% vs 20\% in the placebo group) confirming the results of the Montreal/Toronto trial. It is clear from these data that although acetylsalicylic acid does not influence the incidence of restenosis, it definitely has a positive influence on acute complications during or immediately after angioplasty.

Dipyridamole. In a rabbit model treatment with acetylsalicylic acid and dipyridamole decreased
### Table IV. The effect of drug therapy on restenosis in patients after successful coronary angioplasty

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Drug</th>
<th>Dose</th>
<th>Patients Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirshfeld et al.</td>
<td>1987</td>
<td>Heparin Different duration</td>
<td></td>
<td>209</td>
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<tr>
<td>Ellis et al.</td>
<td>1989</td>
<td>Heparin (18-24 hr)</td>
<td>&lt;2.5 normal PTT</td>
<td>416</td>
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<tr>
<td>Thornton et al.</td>
<td>1984</td>
<td>Coumadin</td>
<td>2-2.5 normal PTT</td>
<td>248</td>
</tr>
<tr>
<td>Urban et al.</td>
<td>1988</td>
<td>Coumadin + Verapamil</td>
<td>&gt;2.5 normal PTT</td>
<td>110</td>
</tr>
<tr>
<td>Dyckmans et al.</td>
<td>1988</td>
<td>ASA</td>
<td>1,500 mg/day</td>
<td>203</td>
</tr>
<tr>
<td>Mufson et al.</td>
<td>1988</td>
<td>ASA</td>
<td>1,500 mg/day</td>
<td>453</td>
</tr>
<tr>
<td>Schanzenbacher et al.</td>
<td>1988</td>
<td>ASA</td>
<td>1,000 mg/day</td>
<td>79</td>
</tr>
<tr>
<td>Finci et al.</td>
<td>1988</td>
<td>ASA</td>
<td>100 mg/day</td>
<td>40</td>
</tr>
<tr>
<td>Schwartz et al.</td>
<td>1988</td>
<td>ASA + D</td>
<td>990-225 mg/day</td>
<td>249</td>
</tr>
<tr>
<td>Chesebro et al.</td>
<td>1989</td>
<td>ASA + D</td>
<td>975-225 mg/day</td>
<td>207</td>
</tr>
<tr>
<td>White et al.</td>
<td>1987</td>
<td>ASA + D</td>
<td>650-225 mg/day</td>
<td>238</td>
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<tr>
<td>Yabe et al.</td>
<td>1989</td>
<td>TXA₂ synthetase inhibitor</td>
<td>600 mg/day</td>
<td>33</td>
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<tr>
<td>Kitazume et al.</td>
<td>1988</td>
<td>ASA</td>
<td>300 mg/day</td>
<td>280</td>
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<tr>
<td>Knudtson et al.</td>
<td>1990</td>
<td>ASA + Ticlodipine</td>
<td>+300 mg/day</td>
<td>270</td>
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<tr>
<td>Raizner et al.</td>
<td>1988</td>
<td>Ciprostene</td>
<td>120 mg/kg/min</td>
<td>311</td>
</tr>
<tr>
<td>Klein et al.</td>
<td>1989</td>
<td>Ketanserin</td>
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<td>Corcos et al.</td>
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<td>Steroid</td>
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<td>Steroid for restenosis</td>
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<td>Pepine et al</td>
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*Pop follow up (%) of successful PTCA; DS, diameter of stenosis; PTT, prothrombin time; NS, not significant; ASA, acetylsalicylic acid; TXA₂, thrombox-ane A₂; D, dipyridamole.*
<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Method</th>
<th>Definition</th>
<th>Restenosis (%)</th>
<th>Drug vs placebo significance</th>
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<td>&gt;50% DS Fup</td>
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platelet-thrombus deposition and restenosis after transluminal angioplasty by increasing platelet cyclic adenosine monophosphate. However, in clinical trials no effect has been shown on the restenosis rate after angioplasty.

**Sulfinpyrazone.** In contrast to acetylsalicylic acid, sulfinpyrazone is a competitive (reversible) inhibitor of platelet cyclooxygenase, but the exact mechanism of its antithrombotic activity is not well understood. Faxon et al. showed a reduction in restenosis with the use of a rabbit model. There is no clinical evidence to date to support a role for sulfinpyrazone in the prevention of restenosis after coronary angioplasty.

**Thromboxane A2 synthetase inhibitor.** Thromboxane A2 is a potent aggregating agent and vasoconstrictor. A specific inhibitor of thromboxane A2 can antagonize these actions while at the same time leaving prostacyclin production of the vascular endothelium unaffected. In rabbits it was shown that a selective thromboxane synthetase inhibitor was more effective than heparin or acetylsalicylic acid in inhibiting platelet deposition after balloon angioplasty. Another thromboxane A2 synthetase inhibitor was tested in a small number of patients to prevent restenosis after PTCA. It was given a minimum of 5 days before PTCA and was continued until follow-up angiography (>3 months later). Restenosis was defined as >50% loss of the initial gain in luminal diameter. The results showed that 4 of the 18 patients (22%) given thromboxane A2 synthetase inhibitor had restenosis versus 8 of the 15 patients (53%) in the placebo group. Besides inhibiting thromboxane A2 synthetase, it is also possible to block the receptor of thromboxane on the platelet. Soon results will be available from a prospective European trial (Coronary Artery Restenosis Prevention On Repeated Thromboxane Antagonism) involving more than 700 patients treated with either a thromboxane A2 receptor blocker or placebo until follow-up angiography 6 months after PTCA.

**Ticlopidine.** The mechanism of action of ticlopidine is not exactly known, but it is a potent platelet inhibitor. The optimum effect occurs 3 days after the first administration and lasts for at least several days. In a multicenter trial in the United States, patients were randomly assigned to ticlopidine (750 mg/day), to a combination of acetylsalicylic acid (650 mg/day) and dipyridamole (225 mg/day), or to placebo. Restenosis was defined as a diameter stenosis of 70% or more at follow-up angiography (6 months). There was no difference in the restenosis rate; in the 65 patients who received ticlopidine the restenosis rate was 29% compared with 18% in the 57 patients who received acetylsalicylic acid and dipyridamole. Among the 54 patients who received placebo, the restenosis rate was 20%. There was no difference in the acute complication rate. In Japan data collected retrospectively showed a lower restenosis rate when patients received a combination of ticlopidine (200 mg/day), nicorandil (30 mg/day), and aspirin (300 mg/day).

**Prostacyclin or prostacyclin analogue.** Prostacyclin is a potent naturally occurring platelet inhibitor and vasodilator. In a Canadian trial 270 patients were randomly assigned to placebo (136 patients) or prostacyclin (5 to 7 mg/min intravenously) (134 patients) just before PTCA up to 48 hours after PTCA. All patients received 325 mg acetylsalicylic acid and 225 mg dipyridamole beginning before angioplasty until follow-up angiography 6 months later. Short-term administration of prostacyclin did not significantly lower the risk of restenosis: 27% in the treated group compared with 32% in the placebo group. Restenosis was defined as >50% or more narrowing at follow-up angiography or >50% loss of the immediate gain after angioplasty. Acute vessel closure and ventricular tachyarrhythmias were more common in the control group than in the patients who received prostacyclin.

**Ciprostene.** Ciprostene is a chemically stable analogue of prostacyclin. To study the effect of ciprostene during PTCA, 311 patients were randomly assigned shortly before PTCA (40 ng/kg/min) to ciprostene until 48 hours after PTCA (120 ng/kg/day) or to placebo. Acute closure occurred in three patients.
in the placebo group and none in the ciprostene-treated group. Restenosis, defined as a diameter stenosis of 50% or more at the time of follow-up angiography, was present in 52 of the 126 patients (41%) treated with ciprostene and in 65 of the 122 patients (53%) given placebo. The clinical end points of this trial included death, myocardial infarction, repeat PTCA, or coronary artery bypass graft. In 30 of the 149 patients (20%) treated with ciprostene, one of these clinical end points was observed compared with 55 of the 147 patients (33%) in the placebo group. Although the clinical results were more favorable with ciprostene, there was no effect on the incidence of angiographic restenosis.\(^{58}\)

**Prostaglandin E\(_1\).** Inasmuch as the deposition of platelets after angioplasty in porcine carotid arteries was reduced significantly after infusion with prostaglandin E\(_1\) even more than with prostacyclin or dipyridamole, a study was attempted to determine the effect of intracoronary followed by intravenous prostaglandin E\(_1\) on restenosis. Eighty patients were randomly assigned to an infusion of 20 to 40 ng/kg/min 12 hours before PTCA or placebo. Clinical follow-up showed abrupt occlusion in 3 of 40 patients in the placebo group compared with none in the prostaglandin E\(_1\) group. An additional repeat PTCA was necessary in 4 of 40 given placebo compared with none in the group treated with prostaglandin E\(_1\). No angiographic study has assessed the effect of prostaglandin E\(_1\) on restenosis.\(^{59}\)

**ANTIPROLIFERATIVE DRUGS**

Restenosis is characterized by migration and proliferation of smooth muscle cells in response to balloon injury. Although the mechanisms responsible for proliferation and migration of smooth muscle cells are not completely understood, it has been postulated that they are controlled by the balance between growth factors and growth inhibitors released from circulating blood cells, at local tissue sites, or both.\(^{28, 60, 61}\) Interference with growth factor-mediated, cellular hyperplasia may be beneficial in inhibiting smooth muscle cell proliferation and thereby reduce restenosis (Fig. 1).

**Platelet-derived growth factor antagonist.** Trapidil (triazolopyrimidine) has been shown to inhibit cellular proliferation induced by platelet-derived growth factor in cell culture and intimal thickening in damaged carotid arteries. In a model of atherosclerosis, rabbits were assigned to placebo (n = 8) or traidil (60 mg/kg/day) (n = 9). The medication was started 2 days before balloon dilatation of the external iliac artery and continued for 4 weeks. Follow-up angiography showed a greater luminal reduction in the control group than in the trapidil group (p < 0.001) compared with similar baseline values. Histologic findings showed significantly less intimal hyperplasia in the trapidil group compared with the placebo group.\(^{62}\) A clinical trial in angioplasty patients seems warranted.

**Serotonin antagonist.** Serotonin, similar to platelet-derived growth factor, is released during platelet degranulation at the time of vessel injury and appears to directly stimulate proliferation of smooth muscle cells in addition to potentiating the effects of platelet-derived growth factor.\(^{63}\) Therefore administration of a serotonin antagonist such as ketanserin may inhibit smooth muscle cell proliferation. Klein et al.\(^{64}\) studied the effects of ketanserin on the incidence of early and late restenosis. Ketanserin was given intravenously (0.1 mg/min/24 hr) for 24 hours after PTCA to 21 patients. After 24 hours three patients in the placebo group had an occlusion compared with none in the control group. Follow-up angiography 4 to 6 months later showed no difference in restenosis rates: 29% in the control group and 33% in the ketanserin group. A large multicenter interventional trial (Post-Angioplasty Restenosis Ketanserin trial) with ketanserin has recently been started and will elucidate the question of whether a longer administration (6 months) has a beneficial effect on the incidence of restenosis.

**Colchicine.** Colchicine inhibits the proliferation and migration of smooth muscle cells and the release of chemotactants by leukocytes.\(^{65}\) To study the effect of colchicine on restenosis, rabbits with atherosclerosis with >50% diameter stenosis underwent iliac transluminal angioplasty. Colchicine was started 2 days before transluminal angioplasty (0.02 mg/day or 0.2 mg/day) until follow-up angiography at 4 weeks. The high dose of colchicine significantly decreased the diameter stenosis at follow-up, although no effect was seen with the low dose. Clinical trials with colchicine are currently in progress. However, it is likely that the efficacy of the drug will be limited by a high incidence of side effects (abdominal pain, vomiting, diarrhea, and bone marrow depression).

**Cytostatic agents.** After the disruptive action of balloon dilatation, a change in differentiation of smooth muscle cells (with a shift from the contractile to synthetic phenotype) is observed and accompanied by cell proliferation and extracellular matrix production, which is the basis for the restenosis process. Barath et al.\(^{66}\) hypothesized that cytostatic agents may prevent restenosis by selective injury to active and proliferating smooth muscle cells without damaging the normal smooth muscle cells. In their study rabbits were divided into four groups: the first
group was a control group, the second group had only a balloon dilatation of the aorta, the third group received the cytostatic agents (vincristine, 0.075 mg/kg, and actinomycin D, 0.015 mg/kg), and the fourth group underwent balloon dilatation and received cytostatic agents. All rabbits were killed 3 days later. Electron microscopic findings showed that the cytostatic agents prevented smooth muscle cell proliferation without damaging the "normal" smooth muscle cells. The principle concern with these agents is the potential for serious side effects, because they are capable of damaging other rapidly dividing cells, for example, those in the gastrointestinal tract, bone marrow, and reproductive system. Recently it has become possible to administer the drug locally with a specifically designed infusion catheter, which should limit systemic toxicity.

Angiotensin-converting enzyme inhibitors. Several organs contain local angiotensin-converting enzyme (ACE) systems. It appears that both the production of angiotensin II and its interaction with specific angiotensin II receptors may take place in these tissues independent of the plasma renin-angiotensin system. ACE is a membrane-bound enzyme present in the walls of large arteries and veins. Angiotensin II receptors are present in the smooth muscle cells in the media of the vessel wall. In chronic hypertension it has been shown that long-term administration of an ACE inhibitor can reduce medial hypertrophy. It has been postulated that the local ACE system plays an important role in the remodeling process after arterial injury. There is also evidence to support the role of angiotensin II as a mitogen responsible for intimal hyperplasia after PTCA. In rats, neointima formation was reduced by 80% 14 days after balloon dilatation of the left carotid artery when an ACE inhibitor was given either 6 days before, 1 hour before, or 2 days after angioplasty and continued until 14 days after angioplasty. This effect seems to be dose dependent and is synergistic with the effect of heparin. There was no effect with administration of a single dose or when it was discontinued 2 days after balloon dilatation. Further study has shown that captopril (100 mg/kg/day) also reduced intimal hyperplasia to almost the same extent. Two other vasodilators, verapamil and hydralazine, demonstrated a lesser effect. These results indicate that hemodynamic effects on the vascular walls may influence the formation of intimal hyperplasia after balloon catheterization and that ACE inhibitors may reduce intimal hyperplasia through additional mechanisms related to inhibition of the angiotensin system. Currently a large multicenter randomized trial in Europe (Multicenter European Research Trial with Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis) is underway to determine the effect of cilazapril on the incidence of restenosis. More than 700 patients have been randomly assigned to cilazapril or placebo starting 4 to 6 hours after PTCA, in addition to the standard therapy of 200 mg acetylsalicylic acid. After 6 months (or earlier if indicated by symptoms) follow-up angiography is performed. A similar trial with 1400 patients has recently begun in the United States, but with a different dosage schedule.

Angiopeptin. It has been known for a long time that hypophysectomy inhibits neointimal plaque formation in response to endothelial injury. This suggests that an endocrine factor may be involved in plaque formation. Recently the effect of a newly synthesized class of pituitary growth hormone–inhibiting agents on vascular smooth muscle cell hyperplasia after endothelial cell injury in vivo has been investigated. These compounds are peptide analogues of somatostatin and have a high affinity for somatostatin receptors on pituitary cells and inhibit release of pituitary growth hormone. One of these agents, angiopeptin, was shown to inhibit vascular smooth muscle cell proliferation in response to a variety of vascular injuries. This seems to be due to a local effect directly on smooth muscle cells. This new group of agents is currently undergoing investigation as an inhibitor of several variants of "accelerated atherosclerosis" (postangioplasty, cardiac transplantation, and coronary bypass surgery).

**CALCIUM ANTAGONIST**

Coronary spasm is frequently seen during and shortly after PTCA and may have a role in the pathogenesis of restenosis. Calcium antagonists by inhibiting vasospasm may reduce the incidence of restenosis in an animal model, and in two randomized trials calcium antagonists have not been shown to influence the incidence of restenosis.

**Diltiazem.** In a study from the Montreal Heart Institute, 92 patients received diltiazem (270 mg) for 3 months, and all underwent recatheterization 5 to 10 months after balloon angioplasty or earlier if symptoms returned. All patients also received acetylsalicylic acid (650 mg) and dipyridamole (225 mg) for 6 months. Patients treated with diltiazem had a restenosis rate of 15% versus 22% in the patients not treated with diltiazem (restenosis was defined as stenosis of 70% or more at the time of the follow-up
angiography). The average decrease in diameter during follow-up was 4% in the diltiazem group and 7% in the control group. It was concluded that diltiazem had no effect on restenosis and that coronary spasm is not a major mechanism of restenosis.

**Nifedipine.** In a 6-month follow-up trial at Emory University in Atlanta,241 patients were randomly assigned to either nifedipine (40 mg/day) or placebo. All patients also received acetylsalicylic acid (325 mg/day). Restenosis was defined as a loss of more than 50% of the gain achieved at the time of PTCA. In patients who were compliant and underwent follow-up angiography (84 patients in both groups) there was no difference in restenosis rates: 29% in the nifedipine group and 33% in the placebo group.

**LIPID-LOWERING DRUGS**

Epidemiologic trials have shown that a diet rich in (n-3) polyunsaturated fatty acids (present in high concentrations in most salt water fish) may account for the low incidence of coronary disease in Eskimos. Animal research has shown that these polyunsaturated fatty acids inhibit atherosclerosis in general. This can be partly explained through a lowering of serum lipid levels and decreased aggregation of platelets by altering the balance between prostacyclin and thromboxane. In the last few years several trials have studied the effects of n-3 fatty acids in the prevention of restenosis after PTCA.

Slack et al.76 showed that adding 2.4 gm of fish oil each day (rich in eicosapentaenoic acid) to the usual post-PTCA regimen of calcium channel blocker, nitrates, acetylsalicylic acid, and dipyridamole could reduce the incidence of clinical restenosis in patients with single-vessel disease (33% in the placebo group vs 16% in the group treated with fish oil). In 49 patients with multivessel disease, no influence could be shown. Reis et al.76 showed that supplementing the normal diet with 6.0 gm of fish oil daily starting just before PTCA until 6 months later had no influence on the restenosis rate in 186 patients in whom PTCA was successful. Angiographic restenosis (70% diameter stenosis at a site previously dilated to less than 50%) was present in 34% of the group taking fish oil and 23% of the control group. However, repeat angiography was performed in only 68 patients (37%); almost all patients had a recurrence of chest pain, which contributed to selection bias at follow-up angiography. Milner et al.77 found that the addition of 4.5 gm of fish oil each day to a normal diet in 194 patients had a positive influence on the clinical restenosis rate with 19% (16 of 84 patients) in the fish oil group versus 35% (35 of 99 patients) in the placebo group having a recurrence of chest pain. However, in the first week 11 of 95 patients stopped taking the medication because of side effects.

In Dallas76 82 patients were randomly assigned to acetylsalicylic acid and dipyridamole with and without 3200 mg (18 capsules) of eicosapentaenoic acid. Treatment was started 7 days before PTCA and was discontinued 6 months after PTCA. In all 82 patients a second angiogram (on average 3 to 4 months after PTCA) was obtained. Restenosis was defined as 50% or more narrowing of the dilatation site at follow-up angiography. Restenosis was seen in 46% in the placebo group and 19% in the treatment group. This trial suggests that n-3 fatty acids may effectively reduce restenosis in high-risk patients provided they comply with the treatment and are pretreated starting 7 days before PTCA. In Melbourne78 108 patients were randomly assigned to 10 capsules of fish oil or placebo. Medication was started the day before angioplasty and continued until 4 months after angioplasty. All patients also received acetylsalicylic acid and verapamil. Restenosis was defined as loss of >50% of the gain in luminal diameter at angioplasty (using caliper measurement). No difference in angiographically defined restenosis rates was observed: 34% in the group treated with fish oil versus 33% in the placebo group.

It is clear that a consensus cannot be reached. These conclusions are in part related to differences in the design of the individual studies. Although all studies were randomized, only in two studies were patients and investigators blinded to the n-3 supplement. Different dosages and formulations were used and patient compliance varied in the studies. There were also differences in the timing of initiation of therapy and variable methods (coronary angiography, stress test, or symptoms) for the detection of restenosis.

**Cholesterol-lowering drugs.** Hypercholesterolemia is a well-known risk factor for ischemic heart disease. Lipid modification is an important goal in secondary prevention in halting the progression of atherosclerosis in general and possibly after angioplasty. Recently it was shown that lovastatin reduces intimal hyperplasia after balloon angioplasty in rabbits with hypercholesterolemia.90 However, two trials with postangioplasty patients in which the effects of lipid lowering on the incidence of restenosis81,82 after PTCA were tested yielded conflicting results.

In the first trial81 157 patients were randomly assigned to lovastatin or placebo for an unstated period of time. Only 50% of the patients underwent follow-up angiography at an average of 4 months after
PTCA (50 patients in the lovastatin group and 29 patients in the control group). Restenosis was defined as narrowing of 50% or more at follow-up angiography. Restenosis was seen in 14% of the sites in the lovastatin group and in 47% in the placebo group, suggesting a beneficial effect of lovastatin in this select group. In the second trial aggressiveness was used in 55 consecutive patients to lower cholesterol levels, including diet, colestipol, and lovastatin, starting on the day of PTCA. After 2 weeks the cholesterol level was reduced by 50%. To date 44 of the 55 patients have been restudied with a restenosis rate of 34%. There was no difference in cholesterol levels between patients with and without restenosis.

INHIBITORS OF INFLAMMATION

Corticosteroids. Corticosteroids have been suggested as a potential restenosis inhibitor. Hydrocortisone can inhibit growth of vascular smooth muscle in culture. However, in a randomized trial in which patients received placebo or corticosteroids from 48 hours before to 5 days after PTCA, there was no difference in restenosis rates (33% in both groups). The same results were achieved when steroids were given as treatment to 102 patients with restenosis after PTCA. In addition to acetylsalicylic acid, dipyridamole, and a calcium antagonist, patients received 125 mg methylprednisolone intramuscularly 1 day before the repeat PTCA and 240 mg prednisone for 1 week. Only the 54 patients undergoing follow-up angiography were analyzed. Restenosis was defined as >50% diameter narrowing at the site. Restenosis was found in 36% of the stenoses in the group treated with steroids compared with 40% in the group receiving standard treatment.

In a recent multicenter trial in the United States, 850 patients were randomly assigned to methylprednisolone or placebo 2 to 24 hours before PTCA. In 71% of the patients follow-up angiography was performed. There was no difference between the two groups in the incidence of restenosis (defined as >50% diameter stenosis): 43% in the group treated with steroids compared with 40% in the group receiving placebo. These trials showed that administration of corticosteroids has no influence on the incidence of restenosis.

Nonsteroidal antiinflammatory drugs. Ibuprofen is known to decrease platelet-thrombus deposition in polytetrafluoroethylene (PTFE)* arterial grafts. In a study of normal porcine common carotid arteries pretreated with heparin, balloon angioplasty was performed and followed by a bolus (12.5 mg/kg) and infusion (75 to 100 μg/kg/min) of ibuprofen or placebo. Quantitative In-labeled autologous platelet deposition at the site of angioplasty was significantly reduced by ibuprofen. Whether this will affect the risk of late restenosis is not known.

FUTURE DEVELOPMENTS

Until now we have not found a drug that prevents restenosis in patients undergoing angioplasty. In the near future the results will be known of currently ongoing multicenter trials with a new ACE-inhibitor (cilazapril), serotonin antagonist (ketanserin), hirudin, low molecular weight heparin, angiopentin and fish oil. Other promising drugs such as thrombin blockers, antagonists of smooth muscle cells, growth factor blockers, prostacyclin analogues, and monoclonal antibodies against platelet membrane receptors (GP IIb/IIIa) and the von Willebrand factor will be tested in clinical trials and may bring us closer to the solution of the restenosis problem.

CONCLUSION

Despite 13 years of clinical experience and research in the field of restenosis after PTCA, there have been no major breakthroughs in pharmacologic interventions. Assessment of the value of drug trials that have been performed in the past is extremely difficult because of differences in selection of patients, methods of analysis, and definition of restenosis. Recently our group has reviewed the influence of these three factors on the outcome and conclusion of restenosis studies. Although there is no scientific proof that the tested drugs are effective, many clinicians continue prescribing them to "prevent restenosis."

Clinical and experimental research must continue to look for the elusive "magic bullet" that can prevent aggregation of thrombocytes, spasm, proliferation of smooth muscle cells, and atherosclerosis without any side effects and, if possible, in only one tablet! Moreover, the cost of this potential drug solution must be less expensive than repeating PTCA in 30% of all patients. It is clear that this magic drug has not been found, and in the meantime we will continue (re)dilating while we search for a pharmacologic or technical solution to the problem of restenosis.

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