Clinical Trials of Restenosis After Coronary Angioplasty

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Since its introduction more than 10 years ago, coronary angioplasty has been limited by a 30–40% incidence of restenosis, typically developing within 3–6 months of the procedure. The interactive biological processes responsible for restenosis have generally been attributed to varying degrees of three pathomorphological mechanisms. First, depending on the relative fibrocellular, sclerotic, and calcium contents of the atherosclerotic lesion, passive vascular recoil may result in progressive diminution of the maximal coronary dimensional improvement imparted by balloon dilatation. Second, balloon-induced vascular barotrauma, resulting in severe intimal and medial disruption, platelet deposition, and thrombus formation, may provide a potent nidus on which mural thrombus organization, collagen matrix formation, and myointimal proliferation can occur. Last, mitogenic factors released as a result of vascular injury at the time of coronary angioplasty may induce smooth muscle cell hyperplasia, culminating in excessive myointimal proliferation and luminal compromise in some patients. Unfortunately, multiple pharmacological strategies aimed at prevention of restenosis have thus far failed to demonstrate a convincing reduction in its incidence.

The profound economic importance of the identification of an agent or combination of agents that will reduce restenosis after coronary angioplasty has led to an impressive investment of resources into clinical restenosis trials. Because the number of agents that can be tested in this setting is exceptionally large, for descriptive purposes, these agents can be divided into those that primarily inhibit platelet-specific receptors, platelet mediators, and thrombus formation at the site of coronary angioplasty; smooth muscle cell proliferation; and growth factors (Figure 1). Currently, at least 11 placebo-controlled clinical restenosis trials are ongoing, each varying in preclinical investigation, timing and duration of dosing, and clinical and angiographic end points. The study designs of these 11 clinical restenosis trials, their strengths and limitations, and the direction of future clinical restenosis trials are discussed.

Selection of a Preclinical Model

To simulate the hemodynamic, hematologic, and rheological processes of vascular repair after balloon-induced barotrauma in human coronary atherosclerosis, several experimental models have been used. In rats, quantitation of the degree of neointimal thickening after carotid artery injury is relatively easy and inexpensive and provides a predictable proliferative response to air- or balloon-induced endothelial denudation. Several agents have been shown to effectively limit myointimal proliferation after endothelial injury in the rat model, although the age-dependence and short time course of fibroproliferation after endothelial injury (14–21 days) and relative resistance of the rat to atherogenesis may limit the applicability of this model to human restenosis.

When rabbits are fed cholesterol-rich diets sufficient to result in a serum cholesterol of 1,000 mg/dl, they develop intimal lipid-laden atherosclerotic lesions within the aorta and iliac vessels. After balloon injury, these lesions consist of loose, lipid-rich connective tissue and thrombus, which is in marked contrast to the predominantly fibrointimal hyperplasia demonstrated in human restenotic lesions obtained by coronary atherectomy. Similar to the rat model, several agents have demonstrated efficacy in preventing intimal hyperplasia after balloon injury in the rabbit iliac, but the disparate histopathological findings in human restenosis remain a significant concern in this model.

The less extensively studied nonhuman primates develop spontaneous atherosclerosis and fibromuscular lesions after balloon injury in some but not all species. The expense and impracticalities of maintaining nonhuman primates limit their use as a model of restenosis.

After balloon injury with or without intracoronary stent implantation in the porcine coronary artery, restenotic lesions have been observed that are histologically similar to those seen in humans. Although the major limiting feature of the porcine model has been the relatively high cost of maintain-
Platelet-derived growth sensitivity for preclinical testing of agents aimed at reducing restenosis after coronary angioplasty is lacking. Furthermore, after experimental arterial injury, smooth muscle cell receptor sensitivity and proliferative response to platelet-mediated growth factors may each vary depending on the species used for study. Thus, it remains to be proven whether the results of any of these experimental models of arterial injury can be accurately extrapolated to arterial injury after coronary angioplasty in humans.

Preclinical Evaluation of Agents Used in Clinical Restenosis Trials

Most but not all agents used in current clinical restenosis trials have undergone at least some preclinical testing (Table 1). In only a few cases has the preclinical testing been extensive or performed in animal models of intimal proliferation after balloon injury. Some preclinical investigations have relied solely on the demonstration of in vitro platelet inhibition; others have simulated balloon-induced vascular injury in a variety of animal models, examining the ability of the agent to inhibit smooth muscle cell migration and proliferation.

Platelet and Thrombus Inhibitors

In a canine coronary occlusion model, specific thromboxane A₂ receptor blockade partially inhibits platelet aggregation and cyclic flow variation after endothelial injury. Furthermore, single- and multipledose GR32191, a specific thromboxane A₂ receptor antagonist, reduced thromboxane A₂–, arachidonic
Inhibitors of oxygenase may relate platelet-derived growth has and diminish triene metabolism sufficient effects vascular smooth muscle providing an antagonistic, sulotroban, normal volunteers and serotonin-stimulated platelet activation.

Furthermore, after the demonstration of serotonin-stimulated DNA synthesis in vascular smooth muscle cells in vitro, ketanserin was shown to block the mitogenic effect of serotonin, providing an additional pathway for the inhibition of myointimal proliferation independent of its effects on platelet aggregation.

Eicosapentanoic acid may reduce the fibroproliferative response to vessel injury by a number of differing mechanisms. Alteration of prostaglandin and leukotriene metabolism sufficient to decrease platelet aggregability and diminish leukotriene responsiveness has been demonstrated after dietary supplement of ω-3 fatty acids. Furthermore, cod-liver oil supplementation has been shown to prevent intimal hyperplasia in autogenous vein grafts, potentially by reducing local platelet-derived growth factor–like protein production. These latter findings suggest that the beneficial effects of ω-3 fatty acid supplementation on restenosis may relate to factors other than alterations in cyclooxygenase metabolism.

Inhibitors of Smooth Muscle Cell Proliferation

In addition to its effects on thrombin inhibition, heparin sulfate suppresses smooth muscle cell migration and proliferation in experimental models. Fractionation of heparin into anticoagulant and nonanticoagulant components allowed the demonstration of the antiproliferative effects of nonanticoagulant fragments. In rat carotid arteries injured by air drying, nonanticoagulant heparin caused a 77% decrease in myointimal proliferation compared with controls. Furthermore, although the biological efficacy of the heparin fragments is approximately half that of a similar dose of heparin, both heparin and nonanticoagulant heparin decrease intimal hyperplasia after experimental arterial injury in a dose-dependent fashion. The exact mechanism of the inhibition of cell growth by nonanticoagulant heparin has not been established, but it appears that similar to heparin, these fragments are internalized, preventing cell division by S-phase inhibition. Importantly, heparin and heparin fragments are effective in reducing myointimal proliferation only when administered within the first 3 days after arterial injury. These agents are ineffective in reducing myointimal proliferation when administered 4–7 days after arterial injury, suggesting that heparin may inhibit the migration of smooth muscle cells into the intima as well as inhibiting subsequent proliferation. Although these heparin fragments may provide similar or greater antithrombin activity than standard heparin, heparin fragments have a much less profound effect on systemic anticoagulation and a lesser tendency toward spontaneous bleeding than do similar doses of standard heparin.

Recent demonstration of angiotensin II receptor, angiotensinogen messenger RNA, and converting enzyme activity within the vascular wall have supported the role of angiotensin II as a regulator of smooth muscle cell myointimal proliferation.
that occurs after balloon injury.24 After balloon injury in rat carotid arteries, the angiotensin converting enzyme inhibitor cilazapril has been shown to inhibit myointimal hyperplasia by as much as 80% compared with control balloon-injured arteries.23 Although continuous administration of 10 mg/kg/day cilazapril beginning either 1 hour before injury or 2 days after injury was effective in preventing myointimal proliferation in the subsequent 14 days, neither single-dose cilazapril 1 hour before injury nor treatment with cilazapril 6 days before until 2 days after balloon injury was effective in inhibiting delayed myointimal proliferation.23 The dosage of cilazapril used in this experimental model was much higher than that used clinically; however, significant blood pressure reductions, presumably results of lowered angiotensin II levels, have been noted in patients using these lower dosing regimens. Similar experimental inhibition of myointimal proliferation was noted with 100 mg/kg/day captopril but not with 100 mg/kg/day verapamil. Conversely, in porcine carotid arteries,55 in a preliminary report 10 mg/kg/day cilazapril was ineffective in preventing myointimal proliferation after balloon injury.

Finally, in a rabbit iliac model, the combination of balloon injury and hypercholesterolemia has been shown to result in abnormal vasoactive regulation and more pronounced macrophage infiltration than either balloon injury or hypercholesterolemia alone.56 By lowering serum cholesterol level, lovastatin, a competitive 3-hydroxy-methylglutaryl coenzyme A reductase inhibitor, may exert a beneficial effect on endothelial vasodilator dysfunction and lessen macrophage infiltration after balloon injury. Furthermore, lovastatin has been shown to reduce intimal hyperplasia in a rabbit model of balloon injury.27 Direct cytotoxic activity against murine fibroblasts has also been demonstrated with lovastatin.57

**Growth Factor Inhibitors**

A variety of growth factors have been identified as potentially important mediators for the development of restenosis after coronary angioplasty.58–60 Epidermal growth factor, somatomedin-C, and insulinlike growth factor I have each been identified as essential growth factors with biological effects that are accentuated by platelet-derived growth factor.59,60 Angiopeptin, an analogue of somatostatin, may nonspecifically inhibit the mitotic effect of these growth factors and indirectly alter responsiveness to platelet-derived growth factor. After arterial injury in a rat carotid model, angiopeptin has been shown to inhibit intimal hyperplasia 14 days after balloon injury.24 Similar results have been noted in the rabbit and primate models.28,61,62 Notably, for maximal effect, the first dose of angiopeptin must be administered within 8 hours of arterial injury.62

**Randomization and Dose Duration**

Available experimental evidence suggests that platelet activation immediately after arterial injury culminates in the release of several mitogenic factors responsible for subsequent cellular proliferation. Within 24–48 hours after arterial injury, these mitogenic factors and possibly others released by smooth muscle cells4 stimulate migration and subsequent proliferation of smooth muscle cells located in the media.63 Interestingly, less than half of the smooth muscle cells that migrate from the media into the intima undergo subsequent proliferation.63 The fibroproliferative response is initiated within hours of balloon injury, usually peaking within the subsequent 10–14 days.22 Notably, once stimulated, the fibroproliferative response continues for at least 28 days, albeit at a much reduced rate.22 Thus, to moderate the biological processes occurring after vascular injury, agents aimed at reducing myointimal proliferation would need to be active at the time of or soon after balloon injury.

The optimal timing and duration of dosing of these agents after coronary angioplasty have not been determined and may vary significantly depending on the agent administered. For example, agents directed principally at the inhibition of platelet aggregation and activation would need to be “on board” at the time of coronary angioplasty, necessitating some duration of treatment before coronary angioplasty. Furthermore, depending on their mechanism of action, some antplatelet agents may require somewhat extended periods of pretreatment. For example, to allow incorporation of eicosapentanoic acid into platelet, leukocyte, and smooth muscle cell membranes, pretreatment for 7 days or longer may be required.10 Conversely, agents directed principally at inhibition of smooth muscle cell proliferation may be given soon after coronary angioplasty, although delay of more than 8 hours may substantially reduce the effectiveness of the agent.22,28

As a result of these issues, clinical trials of restenosis vary considerably with regard to the timing and duration of dosing (Table 2). All agents directed at platelet inhibition are begun before coronary angioplasty. Agents aimed principally at inhibiting the fibroproliferative response, such as low-molecular-weight heparin, cilazapril, and angiopeptin, may be begun just before or soon after coronary angioplasty. Presumably, longer delays in therapy may affect subsequent inhibition of fibrocellular proliferation.

Considerable variability also exists in the duration of dosing after coronary angioplasty, with treatment ranging from 10 days to 6 months. Preclinical trials have suggested that dosing for more than 10 days of a nonselective growth factor antagonist, angiopeptin, does not significantly alter the degree of inhibition of late intimal proliferation, but insufficient data are available to determine the optimal duration of therapy with other agents after coronary angioplasty. Furthermore, whether therapy duration of only 10 days prevents or simply delays the fibroproliferative response after coronary angioplasty is not known.
Table 2. Randomization and Dosing Duration in Clinical Restenosis Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Time of randomization (before or after PTCA)</th>
<th>Timing of first dose</th>
<th>Dosage and duration</th>
<th>Doses tested (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GR32191</td>
<td>Before</td>
<td>1-12 hours before PTCA</td>
<td>20 or 40 mg b.i.d. x6 months</td>
<td>2</td>
</tr>
<tr>
<td>Sulotroban</td>
<td>Before</td>
<td>After PTCA</td>
<td>800 mg q.i.d. x6 months</td>
<td>1</td>
</tr>
<tr>
<td>Ketanserin</td>
<td>Before</td>
<td>1 hour before PTCA</td>
<td>40 mg p.o. b.i.d. x6 months</td>
<td>1</td>
</tr>
<tr>
<td>Fish oil</td>
<td>Before</td>
<td>14 days before PTCA</td>
<td>5.4 g q.d. x6 months</td>
<td>1</td>
</tr>
<tr>
<td>Smooth muscle cell proliferation inhibitors</td>
<td>EMPAR Trial Before EPA 7 days before PTCA</td>
<td></td>
<td>5.4 g q.d. x4 months</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin 2 hours after sheath removal</td>
<td>30 mg s.q. b.i.d. x6 weeks</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-10 days before PTCA</td>
<td>40 mg b.i.d. x6 months</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hours after sheath removal</td>
<td>40 mg s.q. x28 days</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After PTCA</td>
<td>Not reported</td>
<td>&gt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 hours after PTCA</td>
<td>1, 5, 10 mg b.i.d. x6 months</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 hours before PTCA</td>
<td>40 mg q.d. x6 months</td>
<td>1</td>
</tr>
<tr>
<td>Growth factor inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiopeptin</td>
<td>Before</td>
<td>Before PTCA</td>
<td>b.i.d. x10 days</td>
<td>3</td>
</tr>
</tbody>
</table>

EMPAR, Enoxaparin/Max-EPA for Prevention of Angioplasty Restenosis Trial; RD, reconstituted depolymerized; EPA, eicosapentanoic acid; PTCA, percutaneous transluminal coronary angioplasty; q.d., daily; q.i.d., four times daily.

These categories are set up for the purpose of simplification. Agents such as fish oil may also have important inhibitory effects on smooth muscle cell proliferation and growth factor production.

Patient Inclusion Criteria

In general, the need for homogeneity has been stressed in clinical trials, leading to narrow entry criteria and the exclusion of many patients. The assumption has been that this type of trial design would lead to the safest conclusions about exactly which patients would benefit from the intervention because the results could then be extrapolated to a specific subgroup of patients. A second reason for such an approach has been fear of adverse events in the early phase of development of a new therapeutic agent. If high-risk patients are enrolled in the studies, the impact of the illness itself could be mistaken for a negative consequence of the therapeutic approach, thereby lessening the chances of regulatory approval or acceptance by the clinical community.

This philosophy regarding clinical trials has recently come under controversy. All too often, the narrow entry criteria of clinical trials have led to enrollment of a low-risk group with little chance of showing benefit and little applicability to a large proportion of patients seen in practice. Clinical trials designed to exclude fewer patients may provide a full range of therapeutic benefit and toxicity before regulatory approval or clinical acceptance. Ironically, such an approach can lead to rapid adoption of a therapy in a convincing manner as demonstrated by the recent “megatials” of thrombolytic therapy.

Another problem with current restenosis trials is that they may not be representative of typical patients undergoing angioplasty. Prior studies have shown that only 25% of patients screened for restenosis trials are actually randomized in the study.7-8 This low recruitment-to-screening ratio may be explained in part by the exclusion of patients at highest risk for restenosis, such as patients with a previous history of restenosis, unstable angina, diabetes mellitus, or saphenous vein grafts lesions.7,8 Furthermore, patients at highest risk for a subsequent clinical event, such as those with congestive heart failure or recent myocardial infarction, often are also excluded. Personal physicians and patients often refuse randomization because of the risk, expense, or inconvenience of clinical and angiographic follow-up. Once the safety of the agent has been demonstrated, liberalization of the entry criteria may allow these high-risk subgroups access to future trials of restenosis, thereby broadening the spectrum of patients undergoing coronary angioplasty in clinical trials.

Issues in End Point Selection

Therapeutic efficacy has been evaluated using either angiographic or clinical end points (Table 3). Traditionally used as a surrogate end point for clinical failure,7-17 angiographic restenosis, defined using a variety of objective criteria, remains an important end point in clinical restenosis trials. In addition to providing a site-specific index of vessel wall dynamics immediately after arterial injury, core angiographic laboratory review using quantitative techniques allows documentation of the degree of intimal hyperplasia and recoil that occurs from the periprocedural period through follow-up, although the relative contribution of each cannot be determined using current study designs. In general, a computer-assisted automated edge detection algorithm has been used to determine the absolute changes in coronary dimensions before, immediately after, and 6 months after
balloon dilatation. With the use of these continuous variables, smaller sample sizes may be used, but transferability to practicing cardiologists and clinical interpretation of these criteria may be limited. Quantitation of luminal dimensional changes over time may provide insight into the biological and mechanistic effects of treatment after coronary angioplasty. Despite these advantages, application of angiographic end points alone has certain important limitations. Varied definitions of angiographic restenosis, including 50% or greater loss of the initial gain in luminal diameter, a 30% or greater increase over final percent diameter stenosis, an increase from less than 50% to 70% or greater diameter stenosis, a return to within 10% or less of the preangioplasty diameter stenosis, or a 50% or greater diameter stenosis at follow-up, have resulted in differing restenosis rates depending on the criteria used and underscore the importance of standard predetermined criteria for restenosis. In addition, asymptomatic angiographic restenosis has been documented in as many as 33% of patients after coronary angioplasty, often with a benign long-term outcome. Thus, angiographic failure alone may not truly indicate clinical failure in patients after coronary angioplasty. For these reasons, recent emphasis by clinical investigators as well as by the Food and Drug Administration Clinical Advisory Panel has been appropriately placed on demonstrating clinical improvement after coronary angioplasty. For example, an agent that prevents angiographic restenosis by inhibiting platelet aggregation but is associated with an increased propensity to life-threatening hemorrhage resulting from thrombocytopenia would not be an attractive agent for widespread use.

Our clinical restenosis trial experience suggests that in an elective angioplasty population, cumulative "hard" clinical events, such as death, nonfatal myocardial infarction, or the need for repeat coronary angioplasty or bypass surgery, occur in only 20% of patients within 6 months after coronary angioplasty (Table 4), necessitating extremely large sample sizes to demonstrate significant differences; such trials may be prohibitively expensive if large numbers of agents are to be tested. To provide a forecast of an agent's effect in pilot or phase 2 trials with smaller numbers of patients, surrogate clinical end points are desirable. Recurrence of angina, exercise test duration, and back-to-work status have each been used to evaluate clinical improvements after coronary angioplasty, but the subjective nature of some of these end points may limit their overall clinical applicabilities. Stress testing protocols have included standard exercise testing or resting dipyridamole, adenosine, or dobutamine stress tests with or without adjunctive echocardiography or thallium scintigraphy. A pos-

<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary end point</th>
<th>Angiographic criteria</th>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR32191 Platelet inhibitors</td>
<td>Angiographic</td>
<td>Change MLD after follow-up</td>
<td>Death, MI, repeat PTCA, CABG, +ETT, exercise time, quality of life</td>
</tr>
<tr>
<td>Sulotroban</td>
<td>Clinical</td>
<td>&gt;50% follow-up diameter stenosis</td>
<td>Recurrence of angina, death, MI, repeat PTCA, CABG</td>
</tr>
<tr>
<td>Ketanserin</td>
<td>Angiographic and clinical</td>
<td>Change MLD after follow-up</td>
<td>Death, MI, repeat PTCA, CABG</td>
</tr>
<tr>
<td>Fish oil</td>
<td>Angiographic</td>
<td>&gt;50% follow-up diameter stenosis</td>
<td>Recurrent angina</td>
</tr>
</tbody>
</table>

Smooth muscle cell proliferation inhibitors

- EMPAR Trial: Angiographic, Loss >50% gain, Periprocedural complications, recurrent ischemia
- Lovastatin: Angiographic, >50% follow-up diameter stenosis, Death, MI, repeat PTCA, CABG, recurrence of angina, +ETT
- Enoxaparin: Angiographic, Loss >50% gain, +ETT
- RD heparin: Angiographic, Not reported, Recurrent ischemia, +ETT, repeat PTCA, CABG
- Cilazapril: Angiographic, Change MLD after follow-up, Repeat PTCA, CABG; freedom from death, MI, repeat PTCA, CABG
- Fosinopril: Angiographic, Loss >50% gain, Congestive heart failure, recurrent angina
- Recurrent angina, +ETT
- Growth factors inhibitor
- Angiopeptin: Angiographic, >50% follow-up diameter stenosis, Recurrence of angina, ischemia, +ETT

EMPAR, Enoxaparin/Max-EPA for Prevention of Angioplasty Restenosis Trial; RD, reconstituted depolymerized; MLD, minimal luminal diameter; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass surgery; ETT, exercise test.
TABLE 4. Composite Ordinal Ranking of Major, Hard, and Soft End Points Developing Within 6 Months of Index Angioplasty Procedure

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency of event</th>
<th>Cumulative frequency</th>
<th>Composite ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.7</td>
<td>2.7</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.5</td>
<td>6.2</td>
<td>2</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>0.9</td>
<td>7.1</td>
<td>3</td>
</tr>
<tr>
<td>Elective CABG</td>
<td>1.3</td>
<td>8.4</td>
<td>4</td>
</tr>
<tr>
<td>Emergency PTCA</td>
<td>1.4</td>
<td>9.8</td>
<td>5</td>
</tr>
<tr>
<td>Elective PTCA</td>
<td>9.6</td>
<td>19.4</td>
<td>6</td>
</tr>
<tr>
<td>Recurrent typical angina</td>
<td>15.5</td>
<td>34.9</td>
<td>7</td>
</tr>
<tr>
<td>+ETT</td>
<td>12.6</td>
<td>47.5</td>
<td>8</td>
</tr>
<tr>
<td>Angiographic restenosis only</td>
<td>10.9</td>
<td>58.4</td>
<td>9</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass surgery; PTCA, percutaneous transluminal coronary angioplasty; ETT, exercise stress test.

In this hierarchical analysis, each patient is counted only once. From Duke University Medical Center and University of Michigan Medical Center, unpublished observations.

Table 4.

The relative response would be interpretable only if each test were weighted for its relative sensitivity and specificity. Although difficult, ideally paired stress tests (baseline and soon after coronary angioplasty) could be obtained; otherwise, the interpretation of an ischemic exercise test 6 months after angioplasty may be more difficult, particularly in patients with multivessel coronary artery disease. Depending on the combination of symptoms, exercise test results, and angiographic findings, multiple clinical outcomes are possible (Figure 2).

Life-table analysis of freedom from an adverse clinical event or a weight-adjusted clinical event index may also provide increased discriminating power in detecting the therapeutic profile of an agent. Using the former method, however, each event would carry similar weight, giving death the same clinical importance as the recurrence of angina. Alternatively, clinical outcome measures could be ranked by their relative clinical importance such that death, for example, would carry significantly more weight than recurrence of angina. With the relative weight of these events admittedly somewhat arbitrary, a weighted index would account for the relative value of survival compared with the finding of a positive exercise test for ischemia in a patient who is clinically asymptomatic. Such methods have been standard in the field of decision analysis. We have proposed a composite clinical end point index for patients with acute myocardial infarction who are receiving thrombolytic therapy;56 a similar composite end point is proposed for late follow-up after coronary angioplasty (Table 4). Although such an approach should not be considered “definitive” and would require prospective validation, it clearly provides the ability to combine both clinical and angiographic end points and may be useful in early, phase 2 clinical trials to improve statistical power.

Sample Size Calculations

Most current trials of restenosis have predetermined sample sizes that are sufficient to detect a 33–50% reduction in the primary study end point (Table 5), obtaining significantly more power than prior restenosis trials.8-15,17 Most trial sample sizes, however, are still not sufficient to detect a 25% difference in restenosis rates between treatment and placebo. In addition, most but notably not all studies have accounted for patient “drop out” in their sample size calculations. Drugs requiring pretreatment necessitate randomization before the patient is even brought to the catheterization laboratory. Once randomized, at least 1% of patients will not undergo angioplasty, and 10% will have an unsatisfactory angiographic result (University of Michigan, unpublished data). Furthermore, an additional 4–6% will develop a periprocedural ischemic complication. Although these factors may be eliminated for some agents by deferring randomization until after a successful angioplasty has been performed, other events, such as adverse drug reactions and lack of angiographic follow-up at completion of the study, may result in the loss of an additional 10–20% of patients.

Sample size determination may be further influenced by the type of statistical end point analysis used. Using the preferred method—the intention-to-treat analysis—treatment group assigned at the time of randomization is used to analyze statistical significance, regardless of whether therapy was discontinued. All patients enrolled in the study would be
followed to the end of the trial period and thus be included in the statistical analysis. Alternatively, the end point analysis can be based on only those patients who actually completed the protocol as designed. Such an analysis would lend little insight into overall drug efficacy. Notably, even larger sample sizes will not compensate for bias introduced by patient dropout after randomization. Because some agents could make restenosis worse, most clinical restenosis trials have appropriately chosen a two-tailed test of significance.

In restenosis trials, angiographic end points can be analyzed by either lesion or patient. Because angioplasty may be performed in multiple vessels, more than one lesion could be approached per patient, potentially lowering the number of patients needed in the study if per-lesion analysis were used. Statistical methods to compare treatment groups assume that the probability of events in each unit of measurement is independent, whereas available data suggest that the probabilities of restenosis in multiple lesions in the same patients are interdependent. Furthermore, because clinical symptoms and end points usually develop in patients, the majority of current clinical trials of restenosis are justifiably being performed using per-patient analysis. Although per-patient analysis would be particularly useful for clinical end points, it may adversely bias the analysis of angiographic end points. For example, using per-patient analysis, the occurrence of restenosis in one of five lesions undergoing dilatation could be given the same weight in the analysis as restenosis developing in five of five lesions, thereby underestimating the true biological efficacy of the agent.

Finally, the sample size required for statistical analysis is critically dependent on both the estimated frequency of the end point without treatment and the reduction of the end point with drug therapy. Using the estimated frequency of composite end points outlined in Table 4, 6,510 and 3,664 patients would be required to demonstrate 25% and 33% reductions of death or myocardial infarction, respectively. With the inclusion of all hard clinical end points (i.e., death, recurrent myocardial infarction, repeat revascularization using coronary angioplasty or bypass surgery), the sample sizes would be reduced to 1,924 and 1,102 patients, respectively. However, whether repeat coronary revascularization is performed is a decision often left to the individual practitioner and is dependent on subjective variables not entirely related to restenosis. The additional inclusion of “soft” clinical end points would reduce the sample size required for 25% and 33% reductions in statistical significance to 604 and 350 patients, respectively. Notably, however, using these broadly inclusive end points, an effective antiangiinal agent may be shown to be beneficial after coronary angioplasty by reducing angina and improving exercise performance yet have little or no effect on intimal hyperplasia after balloon-induced vascular injury. Angiographic restenosis trials would require inclusion of 638 and 368 patients to demonstrate 25% and 33% reductions in restenosis, respectively. One advantage of prospectively evaluating patients using ordinally ranked end points is that multiple tiers of outcome could be evaluated simultaneously.

Determining “Ideal” Therapy After Coronary Angioplasty

An extraordinary number of agents are available for evaluation of the prevention of restenosis after coronary angioplasty. Because of limited applicability

<table>
<thead>
<tr>
<th>Agent</th>
<th>Assumed event rate control (%)</th>
<th>Assumed event rate treatment (%)</th>
<th>Event reduction (%)</th>
<th>Recruit size</th>
<th>Sample size</th>
<th>End point unit</th>
</tr>
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<tbody>
<tr>
<td>Platelet inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GR32191</td>
<td>0.05</td>
<td>0.20</td>
<td>20</td>
<td>10</td>
<td>50</td>
<td>1,200</td>
</tr>
<tr>
<td>Sulotroban</td>
<td>0.05</td>
<td>0.20</td>
<td>30</td>
<td>15</td>
<td>50</td>
<td>800</td>
</tr>
<tr>
<td>Ketanserin</td>
<td>0.05</td>
<td>0.10</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>600</td>
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<td>33</td>
<td>400*</td>
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<td>NR</td>
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<td>NR</td>
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*Assumes one-tailed test; all others, two-tailed.
of experimental results in single animal models and the tremendous expense of clinical restenosis trials, agents with purported benefit in preventing restenosis should undergo extensive preclinical testing in a variety of experimental models, including those after balloon-induced or equivalent endovascular injury (Figure 3). At least two animal species should be tested because of extensive interspecies heterogeneity to vascular injury response; a porcine model, albeit more expensive and inconvenient, may provide particularly relevant data. Furthermore, an attempt to define a reasonable pretreatment period and required duration of therapy should be performed during the preclinical phase.

After demonstration of preclinical efficacy, an open-labeled pilot trial with or without control patients should be performed to establish drug safety in the setting of coronary angioplasty. This may be particularly important with agents that exert their primary effects by inhibiting platelets and thrombin; potential pharmacological interactions with other agents, such as aspirin, should be especially scrutinized. Angiographic studies may lend preliminary insight into the beneficial effects of the agent on the reduction of intimal hyperplasia after angioplasty using continuous end points.

Once the preliminary safety trials have been completed, larger clinical trials should be performed, primarily evaluating the clinical and angiographic benefits of the agent. Using both angiographic and soft clinical end points, such trials may be completed with as few as 600 patients. As noted previously, an agent may have an important benefit in improving soft clinical end points after coronary angioplasty, independent of its effect on angiographic restenosis. If clinical improvement were demonstrated, such an agent could certainly be recommended for patients after angioplasty.

For trials testing multiple-dose regimens, large sample sizes would be needed. These dose–response trials are especially critical for agents with potential adverse effects at higher dosing ranges. Furthermore, the most robust method of demonstrating additive or even synergistic effects of combination drug therapy is a 2×2 factorial design, such as that currently used with the eicosapentanoic acid and low-molecular-weight heparin trial. Such factorial design trials could expeditiously identify effective therapies, thereby using limited patient and industry financial resources efficiently. Such a factorial design may require substantial interindustry and regulatory agency cooperation because current guidelines prohibit the simultaneous evaluation of two investigational agents under most circumstances.

Once benefit in soft clinical end points has been established, a larger trial should be performed to demonstrate reduction in hard clinical end points such as death, myocardial infarction, and the need for repeat revascularization using coronary angioplasty or bypass surgery. Although such trials would include 1,000–2,000 patients, the need for clinical monitoring would be minimal, and a large amount of follow-up could be performed by telephone contact alone.

Finally, the tremendous cost burden of these clinical restenosis trials has been variably provided by industry, third-party payers, and patients. Although some early trials of restenosis were performed with little industry support, increasing pressure from hospitals, third-party payers, and patients has shifted many of the costs of these trials back to industry. In our experience, industry-sponsored reimbursements have ranged from $4,500 to $12,100 per patient. Thus, depending on the end points and sample size selected, between $1.8 and $16.8 million would be required from industry to reimburse institutional costs alone, underscoring the critical importance of preclinical testing before embarking on a clinical restenosis trial.

An increased understanding of the factors contributing to the development of restenosis after coronary angioplasty has resulted in the development and clinical testing of a variety of novel agents. With adequate sample size and statistical power of the current restenosis trials, the usefulness of platelet, smooth muscle cell, and growth factor inhibition in preventing restenosis will be defined. Ideally, future clinical trials of restenosis will include a combination of clinical and angiographic end points, lending insight into the efficacy of these agents directed at restenosis at both the affected coronary artery and the clinical level.

**Acknowledgments**

We gratefully acknowledge the assistance of the following individuals in the preparation of the manu-

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**Figure 3.** Proposed scenario of sequential demonstration of efficacy in clinical trials of restenosis. Sample size is based on a 25–30% reduction of angiographic and hard and soft clinical end points.
script and in providing information about clinical trials in progress: Marie Foegh, MD (Henri Beaufour Institute, Inc.), Mark Zimmerman, PhD (Glaxo, Inc.), Alexander Leaf, MD (Massachusetts General Hospital), Bruce Davidson, MD (Wyeth-Ayerst), Jeffrey Granett, MD (Smith-Kline Beecham), Yale Mitchell, MD (Merck, Sharp & Dohme), Theodore E. Sprio, MD (Rhone-Poulenc Rorer), Jack Preibisz, MD (Hoffman-LaRoche), Hans deRuyter, MD (Bristol-Meyers), Sin Sit, PhD (Janssen Research), and Michael Gent, PhD (Hamilton Civic Research Center).

References


