A Controlled Trial of Corticosteroids to Prevent Restenosis After Coronary Angioplasty

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A multicenter, double-blind, placebo-controlled trial was conducted to determine if corticosteroids influence the development of restenosis after successful percutaneous transluminal coronary angioplasty (PTCA). Either placebo or 1.0 g methylprednisolone (steroid) was infused intravenously 2–24 hours before planned PTCA in 915 patients. The PTCA patient success rate was 87% (mean) in the eight centers. There were no differences in clinical or angiographic baseline variables between the two groups. End-point analysis (angiographic restenosis, death, recurrent ischemia necessitating early restudy, and coronary artery bypass graft surgery) showed that there was no significant difference comparing placebo- with steroid-treated patients. Angiographic restudy showed the lesion restenosis rate to be 39% (120 of 307 lesions) after placebo and 40% (117 of 291) after steroid treatment ($p=NS$). We conclude that pulse steroid pretreatment does not influence the overall restenosis rate after successful PTCA. (Circulation 1990;81:1753–1761)

Successful treatment of patients with stenotic coronary arteries by percutaneous transluminal coronary angioplasty (PTCA) is associated with restenosis in approximately 25–55% of cases.1–3 Despite advances in techniques, the occurrence of restenosis does not seem to have been altered. This is, in part, related to the fact that although the primary cause of restenosis must be associated with the vascular response to balloon-induced injury, the exact mechanisms have not been identified.

Restenosis is believed to be a multifactorial process involving certain clinical, anatomic, and procedural factors.3 Balloon-induced vascular injury damages the endothelium and deeper plaque structures, so within several days, inflammatory cells are present.4 Recurrent narrowing can be identified angiographically at certain sites approximately 12 weeks after PTCA.5 This process probably involves the vessel wall and blood elements, as well as factors that influence cellular proliferation.3,6–9 One natural model for coronary artery plaque injury may be found in patients dying after hospitalization for unstable angina. Mononuclear cells and edematous changes have been found in the subendothelium of proximal coronary arteries, with edematous changes at sites of naturally occurring plaque injury.10 These mononuclear cells are transformed from monocytes to macrophage types and later to foam cells.10 Other studies have suggested that endothelial damage, caused by migration of blood-borne mononuclear cells, may be an early change of atherosclerosis.11 These mononuclear cells are known to release vasoactive substances that influence platelet aggregation, other leukocyte properties, and proliferation of exposed vascular smooth muscle.

The effects of corticosteroids on mononuclear cells are well known.12 Some animal studies have shown that corticosteroids may modify induced athero-
sclerosis. Results of a small study in humans, in which corticosteroids were used to control restenosis, were interpreted as suggesting a beneficial trend, but a larger sample was required to reach more definitive conclusions.

Accordingly, we conducted a large, prospective, multicenter, double-blind, placebo-controlled trial to evaluate the role of corticosteroids in reducing the rate of restenosis in patients after successful PTCA and also to identify factors predictive of restenosis.

**Methods**

**Patient Selection**

During a 19-month period, 915 patients were enrolled from eight centers (see "Appendix"). All patients presenting for PTCA and who had at least one eligible stenosis (see definitions) were considered candidates. Patients undergoing PTCA for the specific purpose of revascularizing acute myocardial infarction, as well as those with left main coronary artery stenosis (≥50% luminal diameter reduction), contraindication to steroid use, anticipated need for corticosteroids or other immunosuppressive agents, renal failure, and those receiving corticosteroids within the preceding 30 days were specifically excluded. The study protocol was approved by institutional review boards at each center.

**Study Design (Figure 1)**

**Drug assignment and administration.** After eligibility was evaluated, the patients gave written informed consent, which included intention to undergo angiographic restudy at 6 months, and they were randomly assigned to either a placebo or a methylprednisolone group. In double-blind fashion, either 1 g methylprednisolone in 200 cc of 5% dextrose and water, or 200 cc of 5% dextrose and water alone was given by venous infusion during a 30–45 minute interval, 2–24 hours before the planned PTCA. Patients also received their usual antianginal medications, which in most instances included nitrates in addition to a calcium antagonist and/or a β-adrenergic blocker.

**Angioplasty procedure.** Aspirin (325 mg orally) and heparin (10,000 units intravenously) were given before the PTCA procedure. Heparin was supplemented by an additional 1,000 units/hr during the procedure. Nitroglycerin was given intravenously just before the pre-PTCA (baseline) angiogram. This angiogram was filmed in a view revealing the stenosis in its maximum degree of narrowing. The PTCA was performed with standard balloons and guidewires.

After the procedure, aspirin was continued, but an attempt was made to withdraw antianginal drugs over several weeks, provided no other indication (e.g., hypertension, arrhythmia, or recurrent ischemia) for the drugs existed. Patients with successful PTCA (see below) were followed up and after 6±2 months, were scheduled for restudy. The restudy angiogram was filmed after nitroglycerin in the same projection used for the baseline angiogram. Follow-up was terminated either after an early end point had been attained or the restudy angiogram had been performed.

**Definitions**

**Eligible stenosis.** For a patient to qualify for entry into the study, PTCA had to be performed on at least one stenosis with a 60% or greater luminal diameter reduction within 2–24 hours of completion of study drug infusion. The screening percent diameter stenosis on the baseline angiogram was determined as the greatest diameter reduction observed in the "worst" single view. This "optimal" view was recorded. Initial visual assessment required confirmation by caliper measurement of the site of maximal narrowing and adjacent noninvolved segment from the baseline angiogram, recorded just before PTCA. From the optimal view, a frame near end diastole, when artery motion blurring, lesion foreshortening, and overlapping were minimal, was selected for measurement. The PTCA result was considered successful when a diameter stenosis of less than 50% was observed after the dilation by the angiographic technique noted above. The restudy angiogram was repeated with the same worst view recorded at baseline. Physicians who performed the angiograms both initially and at restudy, those who made the caliper measurements, and those who followed up the patients were blinded as to therapy.

**End points.** The following end points were prospectively defined. Angiographically documented restenosis was the primary end point. Restenosis was defined as a diameter stenosis of at least 50% measured on the restudy angiogram by the same technique outlined for the baseline angiogram. The patient was considered to have reached an early end point before the protocol-directed restudy (6±2 months) when recurrent chest pain or ischemia, occurring before 4 months after PTCA, necessitated a repeat coronary angiogram that showed no restenosis, and a 6-month restudy was not available (Figure 1). Other early end points included acute myocardial infarction, need for coronary artery bypass surgery, and death. All patients with an early end point were assumed to have restenosis for the intention-to-treat analysis. Since the primary dilated lesion has clinical relevance, it was used in the analysis of patient restenosis rate, and all dilated lesions were used in the analysis of lesion restenosis rate.

**Statistical Analysis**

**Sample size considerations.** We assumed that the restenosis rate would be approximately 20% at 6 months (best case), and that a 50% reduction would be necessary to justify, for ethical and clinical reasons, a pharmacotherapeutic intervention to prevent restenosis. Thus, a truly effective approach would be associated with a restenosis rate of approximately 10%. A two-armed trial would require approximately 300 patients (assuming at least one lesion per patient) in each arm to provide adequate conclusions with an α or Type I error of 0.05 and a β or Type II
error of 0.90 by a two-tailed test. A sample of this size would also provide sufficient numbers for analysis of factors relating to restenosis. Assuming an immediate success rate for PTCA of 80% at our centers (worst case) and assuming that approximately 25% of patients would be unavailable for angiographic restudy, we determined that a sample size of approximately 1,000 patients would be required (assuming one lesion per patient). This sample size would be expected to provide the required 800 successfully dilated patients eligible for follow-up, further yielding approximately 600 patients available for final angiographic analysis.

Data collection and analysis. Data were collected on standardized forms and sent to the Data Coordinating Center. Reports relative to enrollment and restudy rates, as well as dates for individual patient restudy, were sent to each center on a monthly basis. For quantitative data, unpaired t tests were used, and for qualitative data, $\chi^2$ analyses were performed. All tests were two-tailed and were completed with the SAS statistical software package (Statistical Analysis Systems, Inc., Cary, North Carolina). The analyses were performed using the first or primary dilated lesion and also using all dilated lesions.

To better characterize the restenosis process and the possible effect of methylprednisolone, we prospectively chose to examine the influence of a number of patient- and lesion-related characteristics.\textsuperscript{20,21} It was also recognized that the balloon-induced injury produced in certain lesions might not be extensive enough to be modified by methylprednisolone. Thus, we chose to examine the effect on lesions according to their risk for development of restenosis. We performed this examination retrospectively, using the hypothesis that methylprednisolone would be effective in attenuating restenosis in patients identified as being at high risk for restenosis. The four continuous variables that showed statistically significant differences between lesions that were and those that were not restenosed were used to classify lesions into low-, high-, and intermediate-risk groups for restenosis as follows. Lesions in the worst three quartiles of three of four of these factors were assigned a high-risk rank, and those in the best three quartiles of three of four factors were assigned a low-risk rank for restenosis. The remaining lesions were assigned to the intermediate-risk group. Since restenosis risk probably represents a multifactorial process, this hypothesis was also tested by multiple stepwise logistic regression analysis, with an $\alpha$ to enter of $p$ less than 0.10 and an $\alpha$ to remove of $p$ more than 0.10, with the risk of restenosis as the dependent variable. The $\alpha$ represents the probability that the variable makes an independent contribution to the explanatory power of the model. Restenosis rates in placebo and methylprednisolone groups were then examined as a function of restenosis risk, and appropriate corrections were made for multiple comparisons.

A random sample of 100 patient studies (two films, one pre-PTCA and one restudy angiogram from each of 50 patients) was submitted to the Quantitative Coronary Angiography (QCA) Laboratory. Comparison of caliper measurements of stenosis severity (percent diameter reduction) made at all eight centers was performed at the QCA by a computer-based analysis of stenosis geometry.\textsuperscript{22} Correlation between the two methods gave an $r=0.891$, $y=0.945x+1.621$ ($p<0.001$). Additionally, on-site caliper measurements were compared with those made by a panel of three expert angiographers not involved in the study who were blinded to treatment. No significant differences were noted between on-site measurements and those made by either the computer-based QCA analysis or the panel.

Results

Of the 915 patients enrolled in the study, 457 were randomized to receive methylprednisolone and 458 to receive placebo (Figure 2). Forty-eight patients in the methylprednisolone group and 41 in the placebo group were excluded. Thirty-four patients in the methylprednisolone group and 22 in the placebo group were excluded because they did not have PTCA performed within 24 hours of the study drug infusion. This event occurred either because planned surgical backup could not be obtained or the coronary anatomy had changed between the referring angiogram and the baseline angiogram completed just before planned PTCA. In the latter situation, the investigator no longer believed that PTCA was the most appropriate intervention. Included in this category were cases in which the disease had progressed, as well as cases in which a stenosis of more than 60% could not be identified after nitroglycerin administration, and the previously identified stenosis was assumed to represent spasm. Thirty-three patients

\begin{figure}
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\includegraphics[width=\textwidth]{flowchart}
\caption{Flow chart of study design. PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; CABG, coronary artery bypass grafting.}
\end{figure}
Successful dilation occurred in 722 patients, and 75% of these had a result that was considered optimal, with a stenosis of less than 30% after PTCA. Successful dilation resulted in 355 patients randomized to methylprednisolone and 367 patients randomized to placebo (Figure 2). There were no significant differences in either clinical or angiographic characteristics comparing treatment groups at baseline (Table 1). Ninety-three patients in the methylprednisolone group and 100 in the placebo group had multiple vessels dilated. This difference was not statistically significant. There were no differences in success rates comparing the two treatment groups. Success rates for the 722 patients were uniform for all eight centers (mean, 87%), and the number of patients entered into the study by center ranged from 50 to 124. No significant difference in the number of patients requiring emergency coronary artery bypass surgery (5% in the methylprednisolone group and 3% in the placebo group) was found. During follow-up of the 722 successfully dilated patients, 28 patients had events that met the study criteria for early endpoints. Event distribution between the two study groups appears in Figure 2. Of these, 15 died, seven underwent coronary artery bypass surgery, and six had signs and/or symptoms suggesting early (<4 months) recurrent ischemia but were found not to have restenosis on restudy and did not undergo repeat restudy. Thus, 340 patients randomized to methylprednisolone and 354 randomized to placebo were available for restudy. A final angiogram was evaluated for outcome in 250 patients randomized to methylprednisolone and 260 randomized to placebo. Thus, the restudy rate was 73.5% of available patients, and comparison of those who were restudied with those who were not appears in Table 2. The only significant differences noted were with respect to age (2.2 years) and sex (7% more men), as fewer elderly women appeared in the restudied patients. In the 510 restudied patients, there were 598 dilated lesions, 291 in the methylprednisolone group and 307 in the placebo group, available for final angiographic analysis.

![Figure 2. Patient flow chart. PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ANGIO, angiogram.](http://circ.ahajournals.org/)
Overall, lesion restenosis rates were 40% (117 of 291) of lesions in the methylprednisolone group and 39% (120 of 307) of lesions in the placebo group (p=0.78). No significant difference occurred in the patient restenosis rates, as restenosis occurred in 43% (108 of 250) of patients after methylprednisolone administration and 43% (111/260) of patients after placebo administration. Likewise, the occurrence of restenosis, death, recurrent ischemia necessitating early restudy, and coronary artery bypass grafting in all qualifying patients was not significantly different comparing the methylprednisolone (34%, 141 of 409) and placebo (33%, 136 of 417) groups. There were no significant differences regardless of whether the analysis was done with all dilated lesions or only with the first or primary lesion dilated. Thus, to simplify presentation, the remainder of this section will focus on the analysis of all dilated lesions.

Univariate predictors of restenosis that were identified included stenosis location (p<0.005), baseline percent stenosis (p<0.005), stenosis length (p<0.01), diameter of the adjacent artery (p<0.03), and post-PTCA percent diameter (p<0.01). No differences were found comparing placebo group and methylprednisolone group restenoses rates according to stenosis location. Lesions falling within any of the three lowest-risk quartiles (baseline percent stenosis ≤88%, stenosis length ≤7.0 mm, adjacent artery diameter ≥2.5 mm, and post-PTCA percent stenosis ≤30%) and any three of the four highest-risk quartiles (baseline percent stenosis ≥80%, stenosis length ≥4.8 mm, adjacent artery diameter ≤2.89 mm, and post-PTCA percent stenosis >22%) for each of the latter four predictors were ranked as low- and high-risk lesions, respectively. The remaining lesions were ranked as intermediate risk. A significant difference (corrected for multiple comparisons) in restenosis rates was found in the low-risk restenosis subset comparing methylprednisolone (20%, 15 of 75 lesions) and placebo (37%, 37 of 99 lesions; p=0.013) groups. No significant differences were found in either the intermediate- or high-risk restenosis subsets.

These same four covariates were also identified by multivariate analysis as important independent predictors of restenosis. The model using percent stenosis (p<0.01), stenosis length (p<0.001), adjacent artery diameter (p<0.012), and post-PTCA percent stenosis (p<0.005) was used to create subsets of lesions at deciles of increasing risk for restenosis (Figure 3). Again, the lesions at lowest risk for restenosis showed a trend toward a reduced observed restenosis rate, comparing methylprednisolone and placebo groups. Thus, for the majority of lesions (55%, 331 of 598) in the lowest-risk categories defined by multivariate analyses, there was a trend, not statistically significant, toward a reduced restenosis rate after methylprednisolone administration.
TABLE 2. Description of Patients Restudied and Those Not Restudied

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients restudied (n)</th>
<th>Patients not restudied (n)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>510</td>
<td>184</td>
<td>...</td>
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<tr>
<td>Age (mean yr)</td>
<td>57.8</td>
<td>60.0</td>
<td>0.013</td>
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<tr>
<td>Men</td>
<td>403 (80)</td>
<td>13.8 (72.6)</td>
<td>0.038</td>
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</table>

**Clinical findings**

<table>
<thead>
<tr>
<th>Angina class (Canadian)</th>
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</thead>
<tbody>
<tr>
<td>I and II</td>
<td>151 (33.5)</td>
<td>43 (26.9)</td>
<td>0.123</td>
</tr>
<tr>
<td>III and IV</td>
<td>300 (66.5)</td>
<td>117 (73.1)</td>
<td>0.123</td>
</tr>
<tr>
<td>Angina duration (mean mo)</td>
<td>12.56</td>
<td>9.27</td>
<td>0.087</td>
</tr>
<tr>
<td>Rest angina</td>
<td>256 (52.8)</td>
<td>96 (53.0)</td>
<td>0.953</td>
</tr>
<tr>
<td>Previous MI</td>
<td>117 (23.2)</td>
<td>52 (27.4)</td>
<td>0.256</td>
</tr>
<tr>
<td>Diabetes</td>
<td>68 (13.8)</td>
<td>25 (13.9)</td>
<td>0.975</td>
</tr>
<tr>
<td>Smoking (within 1 mo)</td>
<td>128 (26.6)</td>
<td>56 (32.9)</td>
<td>0.115</td>
</tr>
<tr>
<td>Nitrates</td>
<td>384 (77.7)</td>
<td>149 (82.8)</td>
<td>0.154</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>421 (85.1)</td>
<td>153 (84.1)</td>
<td>0.752</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>241 (50.3)</td>
<td>78 (44.8)</td>
<td>0.215</td>
</tr>
</tbody>
</table>

**Angiographic findings**

| Mean pre-PTCA stenosis (%)  | 82.2                    | 83.1                      | 0.316|
| Mean stenosis length (mm)   | 5.69                    | 5.41                      | 0.411|

**Lesion location**

| LCA                        | 249 (49.5)              | 99 (52.7)                 | 0.460|
| LCx                        | 112 (22.3)              | 42 (22.3)                 | 0.983|
| RCA                        | 122 (24.3)              | 45 (23.9)                 | 0.931|
| Graft                      | 20 (4.0)                | 2 (1.1)                   | 0.052|

MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; LCA, left coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

**Discussion**

Several studies of induced atherosclerosis have suggested less severe atherosclerosis in cortisone-pretreated rabbits,13-17 but other studies have not reported a beneficial effect.23-25 This steroid has been reported to inhibit vascular smooth muscle growth and also inhibit vascular smooth muscle proliferation after balloon-induced endothelial injury.26 Stone et al18 randomized 52 patients to receive 125 mg methylprednisolone intramuscularly the night before and morning of repeat PTCA. These patients also took 60 mg prednisone daily for 1 week while 50 control patients received no steroids. All of these patients had restenosis following a prior PTCA. Angiographic follow-up was limited to only 53% of patients, and the restenosis rate was 36% in the steroid group and 40% in controls. Occurrence of restenosis, death, or angina class III-IV was 38% in the steroid group and 46% in controls. These differences were not statistically significant but were interpreted as suggesting a trend in favor of steroid treatment to reduce restenosis, which would require larger trials for confirmation.

Our results, from the largest, prospective, controlled trial dealing with restenosis, indicate that infusion of methylprednisolone before PTCA does not significantly influence the overall restenosis rate. No significant differences in baseline characteristics in the study groups occurred that may have obscured...
a possible overall beneficial effect on restenosis. Several factors, most relating to the severity of stenosis, were found to be highly correlated with restenosis. Additional analyses were performed to identify possible trends relating to the effect of treatment within subsets of lesions stratified according to the risk of restenosis. Both univariate and multivariate analyses suggested that methylprednisolone pretreatment may be associated with a trend toward a reduced restenosis rate in lesions not characterized as high risk for restenosis. This finding suggests the possibility that different mechanisms may be operative in the restenosis process of different lesions. We emphasize that such retrospective analysis must be interpreted with caution and cannot provide definitive results; however, we believe that these data and methods can provide some useful insights for future trials.

It is somewhat surprising that no randomized, controlled trial of adequate size has investigated the possible role of pharmacotherapy in preventing restenosis. As far as we know, no trials have been reported with as many as 500 subjects. A number of smaller trials have been conducted with the use of various therapies, and it is not surprising that the results are conflicting. Although our study population was sufficiently large, there are several limitations that deserve mention. First, we did not use computerized angiographic analysis in a central laboratory. We used caliper measurements to determine the percent diameter reduction as an index of stenosis severity. These measurements offer more precise, objective data than do simple, visual estimates and can be extrapolated to clinical practice. Agreement with computerized measurements was excellent. On-site caliper measurements are also being used in the National Heart, Lung, and Blood Institute-sponsored Balloon Angioplasty Revascularization Trial. Second, we used a restudy measurement made at one time point. Therefore, it is possible that an apparent beneficial effect on lesion growth at 2 months, for example, might not be present at 6 months. Third, only 73.5% of study patients had a repeat angiogram. Our restudy rate was similar or better than most published studies of restenosis intervention. Since the restudy rate was very similar in both groups (260 of 354 in the placebo group vs. 250 of 340 with the methylprednisolone group) and there were no clinically important differences or differences in lesion characteristics related to restenoses comparing those who were re-studied with those who were not, the restudy rate would not have been expected to influence the comparison between steroid and placebo groups. Finally, methylprednisolone was given as a pulse dose before angioplasty to provide a maximal effect at the time when we believed the balloon-induced injury would be expected to influence migrating cellular effects. The effects of the pulse dose on mononuclear cell function are known to persist for several weeks and probably for 1 month in other models in which inflammatory and immunologically mediated responses to injury with a prominent vascular component are present. Since serial angiographic studies of restenosis show near-maximal obstruction is present at 3 months, the cellular processes responsible for this obstruction must be initiated early after PTCA. Nonetheless, it is possible that different results might have been obtained with continued short-term steroid therapy.

Although mechanisms responsible for restenosis remain unknown, a likely possibility is the response to balloon-induced injury at the site of dilation. We can assume that the magnitude of injury is directly related to the extent of damage caused by the balloon. This injury should be most intense when the stenosis is most severe. We found that most of the factors predictive of restenosis are related to lesion severity. It is likely that balloon dilation caused more extensive arterial damage at sites of severe stenoses within smaller vessels than in less severe stenoses within larger vessels. The effect of the single-pulse fixed dose of methylprednisolone may not have been adequate to modify the response to the greater damage caused at sites of severe lesions compared with lesser damage caused at sites with less severe lesions. Similar reasoning may explain the widely divergent results of fish oil pretreatment in preventing restenosis.

One may also hypothesize that restenosis results from an imbalance between responses attempting to repair the injury and natural counterregulating responses. As a result of localized injury, platelets adhere to the subendothelial surface and release a number of substances that promote thrombus formation and cell growth. In addition, mononuclear cells migrate to sites of endothelial injury and are probably transformed to macrophages and foam cells. Regional accumulations of T cells, macrophages, and smooth muscle cells have been identified in human plaque. Fibroblasts form collagen, which will further stimulate platelet and clotting activation. The monocyte-macrophage within the atherosclerotic plaque may also be immunologically active and secrete platelet-derived and fibroblast-derived growth factors. Fibrocellular proliferation and vessel remodeling, on one hand, controlled and leading to continued patency, and on the other hand, intense and uncontrolled and leading to restenosis, would determine the outcome of PTCA.

Glucocorticoids have the potential to modify these processes. They reduce influx of mononuclear cells and diminish the role of lymphocytes in perpetuating injury by causing lymphopenia and inhibiting production of interleukin-1 and interleukin-2, as well as release of arachidonic acid from cell membranes. They inhibit phospholipase A, which releases arachidonic acid from phospholipid-bearing membranes through stimulation of an inhibitory protein, lipocortin. Generation of products of the cyclooxygenase and lipoxygenase systems are inhibited (e.g., prostaglandins, thromboxanes, and leukotrienes). The platelets may be relatively unaffected by gluco-
corticoids, but the aspirin used in our study should have inhibited platelet-derived thromboxane.

In summary, pulse methylprednisolone did not reduce the overall restenosis rate after successful PTCA, but a beneficial effect in less severe lesions could not be definitely excluded. Different mechanisms may dominate in the repair process after PTCA, depending on the degree of arterial injury caused by the balloon. In future trials designed to study restenosis, perhaps patients should be stratified, relative to restenosis risk, to permit those with differing stenosis and artery characteristics to be evaluated independently.

Appendix
M-HEART Study Group

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