Aspirin Versus Coumadin in the Prevention of Reocclusion and Recurrent Ischemia After Successful Thrombolysis: A Prospective Placebo-Controlled Angiographic Study

Results of the APRICOT Study

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Background. Successful coronary thrombolysis involves a risk for reocclusion that cannot be prevented by invasive strategies. Therefore, we studied the effects of three antithrombotic regimens on the angiographic and clinical courses after successful thrombolysis.

Methods and Results. Patients treated with intravenous thrombolytic therapy followed by intravenous heparin were eligible when a patent infarct-related artery was demonstrated at angiography <48 hours. Three hundred patients were randomized to either 325 mg aspirin daily or placebo with discontinuation of heparin or to Coumadin with continuation of heparin until oral anticoagulation was established (international normalized ratio, 2.8–4.0). After 3 months, in which conservative treatment was intended, vessel patency and ventricular function were reassessed in 248 patients. Reocclusion rates were not significantly different: 25% (23 of 93) with aspirin, 30% (24 of 81) with Coumadin, and 32% (24 of 74) with placebo. Reinfarction was seen in 3% of patients on aspirin, in 8% on Coumadin, and in 11% on placebo (aspirin versus placebo, p<0.025; other comparisons, p=NS). Revascularization rate was 6% with aspirin, 13% with Coumadin, and 16% with placebo (aspirin versus placebo, p<0.05; other comparisons, p=NS). Mortality was 2% and did not differ between groups. An event-free clinical course was seen in 93% with aspirin, in 82% with Coumadin, and in 76% with placebo (aspirin versus placebo, p=0.001; aspirin versus Coumadin, p<0.05). An event-free course without reocclusion was observed in 73% with aspirin, in 63% with Coumadin, and in 59% with placebo (p=NS). An increase of left ventricular ejection fraction was only found in the aspirin group (4.6%, p<0.001).

Conclusions. At 3 months after successful thrombolysis, reocclusion occurred in about 30% of patients, regardless of the use of antithrombotics. Compared with placebo, aspirin significantly reduces reinfarction rate and revascularization rate, improves event-free survival, and better preserves left ventricular function. The efficacy of Coumadin on these end points appears less than that of aspirin. The still-high reocclusion rate emphasizes the need for better antithrombotic therapy in these patients. (Circulation 1993;87:1524–1530)

KEY WORDS • reinfarction • coronary angiography • antithrombotics • revascularization

Thrombolytic therapy for suspected acute myocardial infarction reduces both short-term and long-term mortality.1,2 Reperfusion leads to better residual left ventricular function,1 which is the most important determinant of prognosis after myocardial infarction.

A major problem in patients successfully treated with thrombolytic therapy is the recurrence of myocardial ischemia caused by coronary reocclusion. Reocclusion may lead to worsening of left ventricular function and, subsequently, prognosis. The routine use of coronary angioplasty has not been shown to be effective in terms of preservation of vessel patency, left ventricular function, or survival.3 Many believe that some form of antithrombotic therapy is mandatory after coronary thrombolysis. As comparative studies in this field are relatively scarce, there is not much scientific support for a particular type of antithrombotic treatment. After the Second International Study of Infarct Survival (ISIS-2),4 aspirin has become the standard because it is effective in terms of reducing recurrent myocardial infarction and mortality after thrombolysis. The results of another small placebo-controlled study suggest that aspirin may also be effective in preventing angiographic
reocclusion. Studies of either intravenous or subcutaneous heparin have yielded conflicting results regarding improvement of early patency, risk of recurrent ischemia, and bleeding complications.\textsuperscript{6-12} Comparative data concerning long-term follow-up antithrombotic therapy after heparin are not available.

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Therefore, the multicenter Antithrombics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT) Study was designed to compare aspirin, Coumadin, and placebo in patients with a patent infarct-related vessel after thrombolysis regarding the patency of the infarct-related vessel at 3 months, recurrent ischemic events, and changes in left ventricular function.

Methods

Study Protocol

Patients who presented with chest pain of <4 hours and >30 minutes of duration and a minimum of 0.2 mV ST-segment elevation in two contiguous ECG leads, suggestive of acute myocardial infarction, were treated with thrombolytic therapy (see Figure 1). Thrombolytic agents used were streptokinase and anisoylated plasminogen streptokinase activator complex (APSAC). Streptokinase was given intravenously in a dose of 1.5 million units in 30–60 minutes. APSAC was given intravenously in a dose of 30 units in 5 minutes. Thrombolytic treatment was followed by the immediate administration of intravenous heparin in a fixed dose of 20,000 units/24 hours. No bolus was given. Only downward dose adjustments were made when the activated partial thromboplastin time exceeded 2.5 times the control value. Patients received standard coronary care treatment,\textsuperscript{13} including intravenous atenolol according to the ISIS-I protocol\textsuperscript{14} (see “Appendix”). Cardiac catheterization was performed within 48 hours after the start of thrombolytic treatment.

Patients were eligible to enter the study when the infarct-related artery was patent, as described below. Patients were randomized to either continuation of intravenous heparin and start of Coumadin (open label) or to discontinuation of heparin and follow-up treatment with 325 mg aspirin daily or a matched placebo (double blind). In the Coumadin group, the initial dose was chosen by the attending physician, and dose adjustments were made until the international normalized ratio (INR) was between 2.8 and 4.0. Intravenous heparin then was discontinued. After hospital discharge, follow-up lasted 3 months, when a second cardiac catheterization was scheduled to assess patency of the infarct-related artery.

A conservative strategy was intended, implicating that revascularization was to be performed only for reasons of recurrent ischemia not responsive to medical anti-ischemic treatment.

Study Patients

Patients older than 70 years, those with a history of coronary surgery, those already on antithrombotic therapy, and those with a contraindication to antithrombotics were not eligible. Patients with normal coronary arteries, those with significant left main stem stenosis, and those with an occluded infarct-related coronary artery were not eligible. Patients gave oral informed consent. The study was approved by the ethics committees of the participating hospitals (see “Appendix”).

Cardiac Catheterization

The infarct-related artery was identified by correlating the coronary anatomy with the distribution of wall motion abnormality on the 30° right anterior oblique and the 60° left anterior oblique ventriculograms. When necessary, coronary anatomy was also correlated with the site of ST-segment elevation on the admission ECG. Lead V\textsubscript{3R} was used for discrimination between the circumflex artery and the right coronary artery as the infarct-related vessel in patients with inferior myocardial infarction.\textsuperscript{15} Residual stenosis severity of the infarct-related artery was classified according to the criteria of the European Cooperative Study Group\textsuperscript{16}: grade 0: normal coronary artery; grade 1: <50% diameter stenosis; grade 2: 50–90% diameter stenosis; grade 3: 91–99% diameter stenosis, complete filling within three cycles; grade 4: 91–99% diameter stenosis, no complete filling within three cycles; grade 5: 100% diameter stenosis. Lesions were analyzed with the angiographic view in which the stenosis was most severe. Patients with a grade 1–3 stenosis were eligible for the study. Reclosure was defined as a grade 4–5 stenosis at follow-up coronary angiography. When angioplasty was performed during follow-up, the preangioplasty patency state was scored as the follow-up coronary angiogram. In patients undergoing angioplasty, no second ventriculography was done. All angiographic assessments were done by an angiography committee of three experienced angiographers who were blinded to the treatment allocation and to the clinical course of the patients. Decisions were made by consensus.

Left ventricular ejection fraction was calculated from the 30° right anterior oblique ventriculogram by the area–length method.

Study End Points

The primary end point was patency of the infarct-related artery at follow-up angiography. Secondary end points were the incidence of recurrent myocardial infarction, of coronary surgery or coronary angioplasty, and the change of left ventricular ejection fraction between the first and the second cardiac catheterization. The combination of a clinical course free of reinfarction, revascularization, or death and the combination of a clinical course both free of these events and

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart}
\caption{Chart of study design. IRV, infarct-related vessel.}
\end{figure}
a patent vessel at follow-up coronary angiography were also prespecified as secondary end points. Recurrent myocardial infarction was defined as chest pain accompanied by typical ECG changes followed by a rise of creatine kinase higher than twice the upper normal limit. All clinical end points, including the presence of recurrent ischemia resulting in revascularization, were reviewed by a data monitoring committee.

Randomization and Statistics
Randomization was done in blocks of six, stratified per center, by a central telephone service that was available 24 hours per day. The sample size that was projected initially was 200 patients per treatment group. However, as angiographic reocclusion rate after 3 months was unknown, adequate calculation of statistical power was not possible. However, this sample size would have enabled us to detect a 40% reduction of the reocclusion rate of an assumed 30% in the placebo group to 18% on either active treatment with a power of 80%, presuming two-sided significance levels. The assumed reocclusion rate of 30% on placebo was based on the upper limit of the reported range of in-hospital reocclusion rates after thrombolysis with tissue plasminogen activator and streptokinase. The expected 40% reduction of this end point by antithrombotics was based on the reported efficacy of aspirin in the setting of unstable angina, consistently showing a reduction of the incidence of myocardial infarction and death by about 50%. Interim analysis was performed after randomization of 300 patients to allow change of the sample size or of the protocol. Stopping rules were not formally prespecified. The study was discontinued after a total of 300 patients were enrolled, when interim analysis disclosed a significantly more favorable clinical outcome in one of the treatment arms while only small differences in reocclusion rates were observed. This decision was based on the consideration that larger differences in reocclusion rates between the treatment groups would only be achievable at the expense of more reinfarctions and revascularizations in the Coumadin and placebo groups.

For comparisons between groups, χ² and Student’s t tests were used whenever appropriate. Statistical significance was defined as two sided (p < 0.05). Analysis was performed on the basis of the intention-to-treat principle.

Results
Of the total 300 randomized patients, 16 were excluded from analysis because the infarct-related artery at prerandomization coronary angiography was retrospectively judged to be occluded by the angiography committee. Five of these patients were allocated to treatment with aspirin, six to Coumadin, and five to placebo. One of these patients had recurrent myocardial infarction. None of these patients died or underwent revascularization during the follow-up period.

Clinical follow-up was complete in all patients. Angiographic follow-up was available in 248 patients (82%) but was lacking in nine patients on aspirin because of refusal, in 11 patients on Coumadin (refusal in nine, coronary surgery in one, death in one), and in 16 patients on placebo (refusal in 10, coronary surgery in five, death in one). Patients without second angiography were slightly older (60±7 versus 56±9 years, p < 0.01), were more often female (31% versus 17%, p < 0.05), and more often had previous infarcts (17% versus 6%, p < 0.025). There were no statistical differences with respect to the other clinical or angiographic baseline variables (data not shown). Analyzable left ventriculography at both catheterizations was available in 170 patients. The main reason for ventriculograms not being analyzable was the presence of extrasystole. One center did not perform second ventriculography. The treatment groups were well balanced with respect to demographic, clinical, and angiographic baseline criteria (Table 1).

The study medication was discontinued in 20 patients in the aspirin group, in eight patients in the Coumadin group, and in 27 patients in the placebo group. In five patients who had aspirin and in six patients who had placebo, Coumadin was prescribed because of left ventricular thrombosis, deep venous thrombosis, or atrial fibrillation. Seven patients from the aspirin group received regular aspirin, as did seven patients on Coumadin and 20 patients on placebo because of suspected recurrent ischemic symptoms. Three patients assigned to aspirin treatment were switched to regular aspirin because of refusal to further participate in the trial. So, in total, in 37 of the 55 patients in whom study medication was discontinued, regular aspirin was the substitute. For several reasons, no alternative antithrombotic treatment was given to five patients in the aspirin group, to one patient in the Coumadin group, and to one patient on placebo. According to the principle of intention to treat, patients continued to be assessed by originally allocated therapy.

Angiographic Results
Overall, reocclusion occurred in 71 of 248 patients (29%; 95% confidence limits, 23–34%) (see Figure 2). Thirteen of these patients had grade 4 stenosis, and 58 patients had grade 5 stenosis. The reocclusion rate in patients on aspirin was 23 of 93 patients (25%; 95% confidence limits, 16–34%); in those on Coumadin, 24 of 81 (30%; 95% confidence limits, 20–40%); and in those on placebo, 24 of 74 (32%; 95% confidence limits, 22–34%). Neither of the comparisons was statistically significantly different. The reocclusion rate of either of the three coronary arteries was also not significantly different (Table 2).

There was a slight increase in ejection fraction in the patient group that underwent follow-up ventriculography from 51.0±11.1% to 53.4±12.6% (p = 0.006). This is explained by the significant increase of left ventricular ejection fraction of 4.1±10.3 absolute percent (baseline ejection fraction, 50.6±10.5%) in 119 patients with persistent patency (Figure 3). In contrast, there was no recovery of left ventricular ejection fraction in 51 patients with reocclusion (baseline ejection fraction, 52.0±12.6%; change, −1.7±11.1%) (Figure 3). Differences between follow-up left ventricular ejection fractions within the treatment groups were small, but by paired analysis, ejection fraction increased significantly in patients on aspirin (change, +4.6±10.8%; p < 0.001), whereas there was no significant increase in the other treatment groups (Coumadin group: change, +1.4±11.2%; placebo group: change, +0.8±11.8%).
TABLE 1. Baseline Demographic, Clinical, and Coronary Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=102)</th>
<th>Coumadin (n=92)</th>
<th>Placebo (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56±9</td>
<td>56±9</td>
<td>58±8</td>
</tr>
<tr>
<td>Male sex</td>
<td>84 (82%)</td>
<td>76 (83%)</td>
<td>71 (79%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>7 (7%)</td>
<td>7 (8%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Time to thrombolysis</td>
<td>2.1±0.9</td>
<td>2.1±1.1</td>
<td>1.9±1.0</td>
</tr>
<tr>
<td>Intravenous atenolol</td>
<td>44 (43%)</td>
<td>40 (43%)</td>
<td>38 (42%)</td>
</tr>
<tr>
<td>Thrombolytic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>87 (85%)</td>
<td>83 (90%)</td>
<td>81 (90%)</td>
</tr>
<tr>
<td>Anistreplase</td>
<td>15 (15%)</td>
<td>9 (10%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Peak creatine kinase (units/L)</td>
<td>1,437±1,215</td>
<td>1,560±1,623</td>
<td>1,549±1,461</td>
</tr>
<tr>
<td>Acute complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>7 (7%)</td>
<td>9 (10%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Total AV block</td>
<td>9 (9%)</td>
<td>3 (3%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Time to thrombolysis—first angiography (hours)</td>
<td>25±15</td>
<td>24±12</td>
<td>22±14</td>
</tr>
<tr>
<td>Infarct-related vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>42 (41%)</td>
<td>41 (45%)</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>LCx</td>
<td>16 (16%)</td>
<td>14 (15%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>RCA</td>
<td>44 (43%)</td>
<td>37 (40%)</td>
<td>40 (44%)</td>
</tr>
<tr>
<td>Residual stenosis grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>8 (8%)</td>
<td>7 (8%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>51–90%</td>
<td>65 (64%)</td>
<td>58 (63%)</td>
<td>58 (64%)</td>
</tr>
<tr>
<td>91–99%, filling &lt;3 cycles</td>
<td>29 (28%)</td>
<td>27 (29%)</td>
<td>23 (26%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>49±10</td>
<td>52±12</td>
<td>51±11</td>
</tr>
</tbody>
</table>

AV, atrioventricular; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery.

Clinical Results

There was a significantly lower incidence of both reinfarction and revascularization in patients on aspirin compared with placebo (Table 3). Patients on Coumadin had an intermediate incidence of these end points. Of the 36 patients without a second angiogram, two patients sustained a nonfatal reinfarction. They were both allocated to Coumadin. In this group, six patients underwent coronary surgery; five of these were allocated to placebo and one to Coumadin. Three of these patients died: Two were on placebo, and one was on Coumadin. None of these patients underwent angioplasty. All patients in this group on aspirin had an uneventful course. There was no difference in the timing of the reinfarctions between the treatment groups. Of the seven reinfarctions in the Coumadin group, five occurred during heparin infusion.

Death was related to symptomatic recurrent ischemia after anterior wall myocardial infarction in three patients (cardiogenic shock after recurrent infarction, cardiogenic shock 1 hour after successful angioplasty, and electromechanical dissociation 1 day after angioplasty). In these patients, recurrent ischemia occurred 5, 8, and 3 days, respectively, after thrombolysis. One other patient died in refractory pulmonary edema not preceded by evidence of recurrent ischemia. The fifth patient died after surgical repair for ventricular septal rupture.

We did not observe a correlation between the adequacy of anticoagulation at the time of discontinuation of heparin and the number of clinical events or the occurrence of reocclusion (Table 4). In the 20 patients who did not achieve adequate oral anticoagulation, the duration of heparin infusion was left to the discretion of the attending physician in order not to interfere with

![Bar graph shows reocclusion rates at coronary angiography after 3 months in the three treatment groups.](image-url)
mobilization or extend hospitalization. Bleeding related to the cardiac catheterization puncture site and not requiring transfusion occurred in 11 of 102 patients (11%) assigned to aspirin, in nine of 92 of those on Coumadin (10%), and in eight of 90 of those on placebo (9%). One patient in the Coumadin group required transfusion after retroperitoneal bleeding after cardiac catheterization. No cerebral or other bleeding was reported in any group.

**Combined End Points**

The proportion of patients without reinfarction, revascularization, or death was significantly higher in patients treated with aspirin than in patients on Coumadin or on placebo (Figure 4). A similar pattern was observed in patients with both an event-free clinical course and an open infarct-related vessel at 3 months.

**Discussion**

This study is the first to report a comparison of three antithrombotic regimens in the prevention of recurrent ischemia and reocclusion after successful thrombolysis for acute myocardial infarction: intravenous heparin followed by aspirin, Coumadin, or placebo. The main finding is that at 3 months, reocclusion rates are very high (mean, 29%) and not significantly different between patients allocated to aspirin, heparin/Coumadin, and placebo. The study further demonstrates a statistically significant reduction of reinfarction and revascularization in patients on aspirin compared with placebo and a lower rate of the combined outcomes of revascularization, reinfarction, and death on aspirin than on placebo or heparin/Coumadin. The importance of the superior efficacy of aspirin on these clinical end points is stressed by the fact that, of the five patients who died in this trial, death was related to symptomatic recurrent ischemia in three. The efficacy of aspirin on recurrent ischemia is corroborated by the fact that only in the aspirin group, a significant recovery of left ventricular function was observed. Heparin/Coumadin–allocated patients did no better on any end point than those on aspirin, but there were trends toward better efficacy than placebo.

**Heparin and Coumadin After Thrombolysis**

The role of heparin in thrombolytic therapy remains controversial. In recent studies, intravenous heparin was used as an adjunct to alteplase. Three of these studies demonstrate improvement of patency of the infarct-related artery by heparin with coronary angiography at 7–120 hours after thrombolysis, at the expense of increased bleeding rates in two. However, this was not seen at angiography after 90 minutes or after 7–10 days. The additional value of intravenous heparin in thrombolysis with streptokinase or APSAC is unclear. The lytic state that these agents induce may increase the risk of bleeding when full-dose heparin is started early. For that reason, in the International Study Group trial and in ISIS-3, subcutaneous heparin (12,500 units b.i.d.) was started no earlier than 4–12 hours after thrombolysis. In a combined analysis of these trials, the addition of heparin to aspirin slightly reduced the incidence of death during the scheduled treatment period from 7.3% to 6.8%, with loss of this mortality advantage at 35 days or 6 months. In ISIS-3, the same pattern was observed regarding the reinfarction rates. In both trials, there was a definite increase of major bleeding. In our study, in patients who were assigned to Coumadin treatment, the timing of reinfarction did not differ from the other treatment groups.Apparently, the stimulus for rethrombosis is strongest during the first days after thrombolysis and is neither reduced or delayed by our heparin regimen. It cannot be excluded that the relatively low dose of heparin we gave (started

![Bar graph shows paired analysis of left ventricular (LV) ejection fraction at baseline and follow-up ventriculography in patients without and in those with reocclusion.](http://circ.ahajournals.org/)

**TABLE 3. Clinical and Combined End Points**

<table>
<thead>
<tr>
<th>Clinical end points</th>
<th>Aspirin (n=102)</th>
<th>Coumadin (n=92)</th>
<th>Placebo (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>3 (3%)</td>
<td>7 (8%)</td>
<td>10 (11%)*</td>
</tr>
<tr>
<td>Revascularization</td>
<td>6 (6%)</td>
<td>12 (13%)</td>
<td>14 (16%)†</td>
</tr>
<tr>
<td>Coronary surgery</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>6 (6%)</td>
<td>9 (10%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Both</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Combined end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event free</td>
<td>95/102 (93%)</td>
<td>75/92 (82%)</td>
<td>68/90 (76%)‡</td>
</tr>
<tr>
<td>Event free and no reocclusion</td>
<td>68/93 (73%)</td>
<td>51/81 (63%)</td>
<td>44/74 (59%)</td>
</tr>
</tbody>
</table>

*Aspirin vs. placebo, p<0.025; †aspirin vs. placebo, p<0.05; ‡aspirin vs. placebo, p<0.001; aspirin vs. Coumadin, p<0.025.
without a bolus) has contributed to a less favorable outcome in the heparin/Coumadin group.

The value of Coumadin against recurrent ischemia and reocclusion has not been tested earlier. Although the present study suggests a small effect of Coumadin treatment with respect to recurrent myocardial infarction and need for revascularization, this becomes less relevant given the superior effects of aspirin, with its additional advantage of greater convenience to the patient, lower costs, and lower long-term bleeding risk. The fact that in at least 20 of the 92 patients, the target INR of 2.8–4.0 was not established during hospital stay is in accordance with earlier studies.21 Apparently, initial dosing problems are inherent to oral anticoagulation as an antithrombotic strategy.

**Aspirin After Thrombolysis**

In the ISIS-2 trial, the immediate addition of aspirin to streptokinase significantly reduced the reinfarction rate from 3.7% to 1.8% and the 5-week vascular mortality rate from 10.4% to 8.0%. In the HART trial, a small number of patients with successful reperfusion at 7–24 hours underwent second angiography on day 7 to compare the efficacy of intravenous heparin with 80 mg aspirin per day. These investigators also reported lower rates of recurrent ischemia (3% versus 12%, p=NS) and reocclusion (5% versus 12%, p=NS) in patients on aspirin with a patent vessel at baseline coronary angiography. In contrast to ISIS-2, in the present study, aspirin was started in patients with proven patency of the infarct-related vessel. Although in the present study the reinfarction rate was also reduced with aspirin, in patients with a follow-up coronary angiogram, no significant reduction in angiographic reocclusion rate was observed. This may in part be explained by the dilution of the treatment effect of aspirin that may have occurred by the relatively large number of patients in both the Coumadin and placebo groups that crossed over to aspirin. Furthermore, of the 36 patients without follow-up angiography, none who died, underwent revascularization, or experienced a reinfarction was allocated to aspirin. One may thus speculate that the actual reocclusion rate in the Coumadin- and placebo-allocated patients was higher than could be observed angiographically. However, even if aspirin were more effective than our data show, patients with successful thrombolytic reperfusion face a considerable risk of reocclusion.

Why patients without reocclusion allocated to aspirin have a lower event rate than similar patients on Coumadin or placebo remains speculative. This may relate to the occurrence of transient rethrombosis. Data from animal studies indicate that reocclusion may be mediated by a platelet-rich, fibrin-poor thrombus that may be less resistant to early spontaneous lysis on aspirin than on heparin/Coumadin or placebo. Thus, on aspirin, the balance of rethrombosis versus rethrombolysis may be shifted toward the latter more frequently before critical flow reduction causes symptoms of recurrent ischemia.

**Reocclusion After Thrombolysis**

The present study is the first to report reocclusion rates at 3 months of follow-up in a large group of patients. Although the observed overall reocclusion rate is high, it is within limits reported earlier.17,22 This can be explained by the study design and the timing of follow-up coronary angiography. The wide range of reocclusion rates that have been reported previously were mainly derived from studies in which reocclusion was not a primary end point, as it was in our study. Moreover, earlier studies reported in-hospital reocclusion rates based on early angiography after thrombolytic treatment.6,17–19 In contrast, in our study, follow-up coronary angiography was done after 3 months, allowing a greater time window for reocclusion to occur.

**Reocclusion and Left Ventricular Function**

Our data strongly suggest that there is no recovery of left ventricular function after successful thrombolysis when reocclusion occurs, although these data may be subject to selection bias. If this finding is confirmed by other studies, this may indicate that the benefits of thrombolysis for left ventricular function are limited to the estimated 35–55% of patients with both successful thrombolysis and persistent patency of the infarct-related vessel. Consequently, better prevention of reocclusion may result in further reduction of mortality after thrombolysis.

**Study Limitations**

A limitation of our study imposed by the study design is that only patients who survived the acute phase and

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**TABLE 4. Angiographic Outcome and Clinical Events in Relation to Quality of Oral Anticoagulation**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adequate (INR &gt; 2.8) (n=57)</th>
<th>Inadequate (INR &lt; 2.8) (n=20)</th>
<th>Unknown (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reocclusion</td>
<td>35 (61%)</td>
<td>12 (60%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Reocclusion</td>
<td>16 (28%)</td>
<td>5 (25%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>No angiography</td>
<td>6 (11%)</td>
<td>3 (15%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>4 (7%)</td>
<td>2 (10%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>9 (16%)</td>
<td>1 (5%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

INR, international normalized ratio.
were fit to undergo cardiac catheterization within 48 hours, showing a patent infarct-related vessel, entered the study. This selection will have contributed to the low mortality figure that we observed and makes our study population less comparable to other study populations without proven patency of the infarct-related vessel.

After interim analysis, the small differences that were found in reocclusion rates and the significantly more favorable clinical outcome in one of the treatment arms prompted us to discontinue the trial. This will have affected the statistical power of the trial to detect differences in the primary end point.

Conclusions

We conclude that at 3 months after successful thrombolysis, reocclusion occurs in almost one third of the patients and that reocclusion interferes with left ventricular recovery. When heparin is given in the acute phase, this should be followed by aspirin treatment because aspirin reduces recurrent myocardial infarction and the need for revascularization and tends to reduce angiographic reocclusion. Because the reocclusion rate is high even with aspirin, the search for better prevention of reocclusion should continue.

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Appendix

Participating Centers and Investigators

Academic Hospital, Groningen (59 patients, see “Study Protocol”): Kong I. Lie, Erwin Goebell, Albert van der Galen.

Groot Ziekenhuis, s’Hertogenbosch (34 patients): Joop M.J. van der Pol, Aaf Kuiper.

Catharina Hospital, Eindhoven (seven patients, see “Study Protocol”): H. Rolf Michels.

Free University Hospital, Amsterdam (200 patients, see “Study Protocol”): Freek W.A. Verheugt, Albert Meijer, Christ J.P.J. Werter, Machiel J. van Eenige, Jan P. Roos.

References

11. The International Study Group: In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. Lancet 1990;336:76–76
23. de Bono D: Coronary thrombolysis. Br Heart J 1987;57:301–305
Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Results of the APRICOT Study.

A Meijer, F W Verheugt, C J Werter, K I Lie, J M van der Pol and M J van Eenige

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