A Randomized Comparison of Intravenous Heparin With Oral Aspirin and Dipyridamole 24 Hours After Recombinant Tissue-Type Plasminogen Activator for Acute Myocardial Infarction

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Background. This study addressed the need for heparin administration to be continued for more than 24 hours after coronary thrombolysis with recombinant tissue-type plasminogen activator (rt-PA).

Methods and Results. A total of 241 patients with acute myocardial infarction were treated with 100 mg rt-PA and a bolus of 5,000 units i.v. heparin followed by 1,000 units/hr i.v. heparin for 24 hours. At 24 hours, 202 patients were randomized to continue intravenous heparin therapy (n=99) in full dosage or to discontinue heparin therapy and begin an oral antiplatelet regimen of aspirin (300 mg/day) and dipyridamole (300 mg/day) (n=103). On prospective recording, there were no differences in the pattern of chest pain, reinfarction, or bleeding complications. Coronary angiography on cardiac catheterization at 7–10 days showed no differences in patency of the infarct-related artery. The proportion of patients with total occlusion (TIMI grade 0-1) of the infarct-related artery was 18.9% in the heparin group and 19.8% in the aspirin and dipyridamole group. In the patients with an incompletely occluded infarct-related artery, the lumen was reduced by 69±2% of normal in the heparin group and 67±2% in the aspirin and dipyridamole group. Left ventricular function assessed on cardiac catheterization and radionuclide study at day 2 and at 1 month showed no differences between the two groups. Left ventricular ejection fraction on radionuclide ventriculography at 1 month was 52.4±1.2% in the heparin group and 51.9±1.2% in the aspirin and dipyridamole group.

Conclusions. We conclude that heparin therapy can be discontinued 24 hours after rt-PA therapy and replaced with an oral antiplatelet regimen without any adverse effects on chest pain, reinfarction, coronary patency, or left ventricular function. (Circulation 1991;83:1534–1542)

Recombinant tissue-type plasminogen activator (rt-PA) has been shown to be an effective thrombolytic agent in acute myocardial infarction.1–4 Because of its short half-life and the likelihood of early rethrombosis after successful thrombolysis,5,6 most of the clinical experience to date with this agent has been in conjunction with heparin. Despite this experience, the role of heparin in thrombolytic therapy in general7,8 and with rt-PA

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in particular is not clear. Heparin may increase the risk of bleeding complications after rt-PA administra-
tion.9 As a result, a series of investigations on heparin and rt-PA were recently conducted. One
published report showed that heparin administered at the same time as rt-PA had no significant ad-
ditional effect on coronary artery patency at 90 min-
utes.10 Two reports have indicated that heparin given in the period immediately after rt-PA will improve
coronary artery patency.11,12 A recently completed
international study showed no advantage in patient
survival or reinfarction for heparin administration
(12,500 units b.i.d. s.c.) starting 12 hours after throm-
botic therapy.13

In the current trial, we administered an intrave-
nous bolus of heparin as the infusion of rt-PA was
begun, and when the rt-PA infusion was finished, we
immediately began an intravenous infusion of hepa-
arin. We then assessed the need for heparin admin-
istration to continue after the first 24 hours after
rt-PA administration by comparing its continued
intravenous administration with an oral anti-platelet
regimen of aspirin and dipyridamole.

Patient Selection

Patients 75 years old or less with suspected acute
myocardial infarction were included in the trial if they
had no prior history of myocardial infarction, were
admitted to the hospital within 4 hours of symptom
onset, had cardiac pain of typical character and loca-
tion, and if the electrocardiogram showed ST segment
elevation in two or more leads (>2 mm in suspected
anterior infarction or >1 mm in suspected inferior
infarction). Patients were excluded from the trial if they
had at least one contraindication to thrombolytic ther-
apy, such as previous cerebrovascular disease, active
peptic ulceration or history of gastrointestinal hemor-
rhage, recent trauma, recent surgery, or hypertension.
After informed consent was obtained, patients were
administered rt-PA and heparin.

rt-PA and Heparin Infusion

rt-PA (Boehringer Ingelheim Pty. Ltd. Australia)
was administered as a 10-mg bolus i.v. followed by a
50-mg infusion in the next hour and by 20 mg/hr
during the subsequent 2 hours. Heparin 5,000 units
i.v. was administered at the start of the rt-PA
infusion, and after the infusion, heparin was continued in
a dose of 1,000 units/hr for an additional 24 hours.

Randomization to Heparin or Aspirin
and Dipyridamole

Patients were randomized to receive heparin or
aspirin and dipyridamole 24 hours after completion
of the rt-PA infusion. Patients in the heparin group
continued to receive an intravenous infusion of hepa-
arin for 7–10 days; the dose was adjusted to maintain
the activated partial thromboplastin time (APTT) at
2–2.5 times the normal range. The APTT was
checked 6 hours after the commencement of the
heparin infusion and then at least twice daily. Hep-
arin was diluted in 100 ml 5% dextrose and was
infused by a metered infusion pump during 24 hours.
Patients who were allocated to the aspirin and dipy-
ridamole group received soluble aspirin 300 mg/day
and dipyridamole 100 mg t.i.d. In the heparin group,
the intravenous line was maintained continuously,
whereas in the aspirin and dipyridamole group, it was
removed when no longer needed for administration of
intravenous drugs, usually on the second or third
hospital day.

Blood and Electrocardiographic Monitoring

Blood was sampled for serum creatine kinase
before infusion, then every 4–8 hours for the next 24
hours, and then every 12 hours up to 72 hours. Blood
was taken for measurement of plasma fibrinogen
levels at the start of the infusion, immediately after
the infusion, and 4 and 24 hours later. Twelve-lead
electrocardiograms were recorded daily, and contin-
uous electrocardiographic monitoring was performed
during the entire coronary care stay.

Recording of Complications

Postinfarction chest pain was recorded with a chest
pain diary. Chest pain was categorized as cardiac
ischemic, cardiac nonischemic, and noncardiac. Isch-
emic pain was graded according to severity, and the
scale ranged from 10 (very severe, most severe pain
experienced) to 1 (very mild discomfort). Reinfar-
ction was recorded if the patient experienced typical
cardiac ischemic pain lasting more than 15 minutes
with elevation of cardiac enzymes to more than twice
the normal range or a reelevation of more than 20%
in the abnormal range. Hemorrhagic complications
were recorded using a hemorrhage observation sheet
that allowed the grading of the severity of bleeding
from venous and arterial puncture sites, subcutane-
ous bruising or hematoma, and gastrointestinal and
urinary tract bleeding. Urinalysis for hematuria was
performed on all urine samples.

Laboratory Procedures

Serum enzyme levels, plasma fibrinogen levels, and
APPTs were measured in each center. The 12-lead
electrocardiogram was used to categorize the infarc-
tion as Q wave or non-Q wave and the location as
anterior, inferior, or indeterminate. Detailed analyses
of Q wave, ST segment, and T wave changes were
performed to allow separate recording of anterior,
inferior, and lateral lead groups.

Radionuclide Studies

Radionuclide estimates of ventricular function were
performed on the first day after admission and then at
28 days. Both right and left ventricular ejection frac-
tions were analyzed. Previous studies showed good
correlation (r=0.85) for estimates of ejection fraction
between the centers participating in the trial.3
Cardiac Catheterization and Coronary Angiography

Cardiac catheterization including selective coronary angiography and left ventriculography was performed before hospital discharge at 7–10 days after myocardial infarction. Coronary angiograms were analyzed by investigators who were not aware of the patient’s clinical course or treatment allocation. The infarct-related artery was identified from the serial postinfarction electrocardiograms. Two independent observers measured the caliber of coronary vessels proximal to and at the point of maximum narrowing in both the right and left anterior oblique views. Percent luminal narrowing was estimated from the average of electronic caliper measurements at these points. In addition, the absolute degree of narrowing was measured in millimeters, deriving measurements from the known external diameter of the angiographic catheter.

Global ejection fraction and regional wall motion were measured both by the radial coordinate method of Rickards et al.14 and the long-axis chordal method of Sheehan et al.15 Systolic and diastolic ventricular silhouettes were traced in two independent cycles that were free of ventricular ectopy. Ventriculograms were considered unsuitable for analysis when the entire outline of the ventricle could not be displayed.

Trial Administration and Ethical Supervision

The overall conduct of the trial was supervised by a management committee on which was represented the senior investigators from each participating center, the director of the National Heart Foundation, and a representative of Boehringer Ingelheim. The data from the trial were monitored by a data monitoring and ethics committee that received regular reports on the progress of the trial from an independent statistician.

Data Management

Data were forwarded from each center to the coordinating center. The data base was managed by the dBase III system and analyzed by use of PC-SAS in the Department of Cardiovascular Medicine of the Sir Charles Gairdner Hospital and the Unit of Clinical Epidemiology of the University of Western Australia.

Results

During the course of the trial (from February 1988 to December 1988), 1,464 patients with suspected acute myocardial infarction were admitted to the participating centers. Of these patients, 941 did not fulfill the inclusion criteria because of previous infarction, delays in excess of 4 hours, atypical chest pain, or insufficient electrocardiographic criteria. The remaining 523 patients fulfilled all inclusion criteria, but 265 had one or more exclusion criteria, predominantly a contraindication to thrombolytic therapy. Of these, 17 patients were eligible but did not enter the trial because they withheld informed consent or because the admitting physician did not agree to the patients’ entering the trial. A total of 241 patients received rt-PA and then heparin for 24 hours. Of these, 202 patients were randomized, 103 had their regimen changed to oral aspirin and dipyridamole, and 99 continued intravenous heparin therapy. Thirty-nine patients were not randomized. The reasons for non-randomization were death (nine patients), bleeding complications (six), major cardiac complications (two), cerebrovascular accidents (two, one of which was fatal), transient cerebral ischemic attacks (two), protocol violations (14), and exclusion at the supervising physician’s discretion (five). Overall, there were 16 in-hospital deaths (6.6%) in the 241 patients who received rt-PA.

Results were analyzed with the intention-to-treat principle. Seven patients in the aspirin and dipyridamole group had their trial medications stopped and were treated with anticoagulants because of proven apical left ventricular thrombus (one patient), headaches attributed to dipyridamole (one), recurrent chest pain (four), and medication error (one). Heparin therapy was discontinued in three patients in the heparin group because of anticoagulant complications.

Baseline characteristics in the two groups of patients were similar (Table 1), and the severity of infarction assessed by enzyme and electrocardiographic criteria was similar. There was a similar proportion of patients with non-Q wave infarction in the two groups (six of 41 versus three of 38 in the anterior-anterolateral infarction subset and eight of 54 versus six of 51 in the inferior infarction subset). During the period of hospital treatment after randomization, there was one stroke (14 days after infarction, nonhemorrhagic on computed tomography scan) in the aspirin and dipyridamole group and none in the heparin group. Other major events (death and reinfarction) in the two groups are summarized in Table 2. There was an increased number of events in the heparin group compared with that in the aspirin and dipyridamole group, but none of these were significant. Overall, there were 10 major events in the heparin group and five in the aspirin and dipyridamole group ($p$=0.09). The pattern of bleeding complications was similar in the two groups (Table 3). There were more cases of significant phlebitis of the intravenous site in the heparin group than in the aspirin and dipyridamole group ($p$=0.15). One patient in the heparin group developed thrombocytopenia (minimum platelet count, 120,000/ml).

The overall pattern of chest pain indicative of myocardial ischemia after infarction was similar in the two groups (Table 3), and there were no differences in the timing of these episodes (Figure 1). Overall, 196 patients underwent coronary angiography at 7–10 days, 95 in the heparin group and 101 in the aspirin and dipyridamole group. Reasons for failing to undergo coronary angiography at 7–10 days were death (five patients) and infection in the arm due to phlebitis (one).

The angiographic findings concerning the infarct-related artery are summarized in Figures 2 and 3.
<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Patients Randomized at 24 hours After Recombinant Tissue-Type Plasminogen Activator</th>
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<tr>
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<td></td>
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<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Women ((n))</td>
</tr>
<tr>
<td>Previous history ((n))</td>
</tr>
<tr>
<td>Exertional angina</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Status on admission</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Chest radiography ((n))</td>
</tr>
<tr>
<td>Edema/congestion</td>
</tr>
<tr>
<td>Cardiothoracic ratio (&gt;0.50)</td>
</tr>
<tr>
<td>Electrocardiogram (location and extent of infarction ((n)))</td>
</tr>
<tr>
<td>Anterior-anterolateral</td>
</tr>
<tr>
<td>Q wave</td>
</tr>
<tr>
<td>Non-Q wave</td>
</tr>
<tr>
<td>Inferior</td>
</tr>
<tr>
<td>Q wave</td>
</tr>
<tr>
<td>Non-Q wave</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Time to infusion of rt-PA ((min))</td>
</tr>
<tr>
<td>Cardiac enzymes</td>
</tr>
<tr>
<td>Peak CK ((IU/l))</td>
</tr>
<tr>
<td>Time to peak CK ((hr))</td>
</tr>
<tr>
<td>LD total ((IU/l))</td>
</tr>
<tr>
<td>LD1 ((IU/l))*</td>
</tr>
<tr>
<td>LD2 ((IU/l))</td>
</tr>
<tr>
<td>Complications between rt-PA and randomization ((n))</td>
</tr>
<tr>
<td>Complete AV block</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>4–30 beats</td>
</tr>
<tr>
<td>&gt;30 beats</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>Left ventricular failure</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Pericarditis</td>
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</tbody>
</table>

Values are mean±SEM, where applicable.
BP, blood pressure; rt-PA, recombinant tissue-type plasminogen activator; CK, creatine kinase; LD, lactate dehydrogenase; AV, atrioventricular.
*p<0.05.
The grades of narrowing of the infarct-related artery averaged on two views are subdivided into five groups in Figure 2. There were no significant differences in the distribution of incomplete occlusions; the number of patients with total occlusion was similar in the two groups: 19 of 95 (20.0%) in the heparin group and 20 of 101 (19.8%) in the aspirin and dipyridamole group. The degree of occlusion in the incompletely occluded infarct-related arteries was almost identical. In the heparin group, 76 patients had incomplete occlusion of 69±2%, and in the aspirin and dipyridamole group, 81 patients had incomplete occlusion of 67±2%.

Figure 3 shows the TIMI (Thrombolysis in Myocardial Infarction study) flow rates in the two groups showing that there was no difference in the distribution of TIMI flow rates in the infarct-related arteries in the two groups.

The left ventricular ejection fractions calculated from the contrast ventriculogram at the time of cardiac catheterization are shown in Table 4; there were no differences between the groups. The data for radionuclide estimates of left ventricular ejection fraction in the two groups are also shown in Table 4. There were no differences in the two groups in ventricular ejection fractions measured on day 2. There was a slight improvement in left ventricular ejection fractions at 1 month in both groups compared with day 2, but there were no differences between groups. Right ventricular ejection fractions showed a similar pattern. Patients with both Q wave and non-Q wave infarctions were combined in the ventriculographic analyses because conclusions from the analysis of the combined groups were not different from those of the separate groups.

The APTT in the heparin group is summarized in Figure 4, which shows that the mean APTT levels were maintained within the therapeutic range of 2–2.5 times normal.

### Table 2. Major In-Hospital Events in the Two Groups of Patients Randomized at 24 Hours After Recombinant Tissue-Type Plasminogen Activator and Heparin

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin-dipyridamole (n=103)</th>
<th>Heparin (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (1.9)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>2 (1.9)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (1.0)</td>
<td>0 ...</td>
</tr>
<tr>
<td>Total</td>
<td>5 (4.8)</td>
<td>10 (10.1)</td>
</tr>
</tbody>
</table>

Statistical analysis by χ² test; p=0.091.

### Table 3. Bleeding Complications in the Two Groups of Patients Randomized at 24 Hours After Recombinant Tissue-Type Plasminogen Activator and Heparin

<table>
<thead>
<tr>
<th>Bleeding complications</th>
<th>Aspirin-dipyridamole (n=103)</th>
<th>Heparin (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV line seepage</td>
<td>5 (4.9)</td>
<td>11 (11.1)</td>
</tr>
<tr>
<td>Venepuncture seepage</td>
<td>6 (5.8)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Arterial seepage</td>
<td>22 (21.3)</td>
<td>18 (18.2)</td>
</tr>
<tr>
<td>Bruising</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV site</td>
<td>43 (41.7)</td>
<td>51 (51.5)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (12.6)</td>
<td>13 (13.1)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (1.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IV line complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant phlebitis</td>
<td>4 (3.9)</td>
<td>10 (10.1)</td>
</tr>
<tr>
<td>Cardiac ischemic chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with chest pain</td>
<td>24 (23.3)</td>
<td>24 (24.2)</td>
</tr>
<tr>
<td>Chest pain events</td>
<td>52 (50.5)</td>
<td>66 (66.7)</td>
</tr>
<tr>
<td>Total duration (min)</td>
<td>1,734</td>
<td>1,672</td>
</tr>
</tbody>
</table>

IV, intravenous.
ment of coronary thrombosis. The major finding was that there was no benefit on coronary artery patency at 1 week in continuing heparin therapy after 24 hours. In addition, there were no differences in left ventricular function or clinical outcome between patients treated with continuing heparin and those treated with oral aspirin and dipyridamole.

Although the unblinded comparison of the intravenous regimen of heparin and the oral regimen of aspirin and dipyridamole could have introduced a bias in recording of hemorrhagic and other complications, we consider this unlikely. The comparison of the two regimens was very much an open question during the course of the study: The apparent logic of combining heparin with rt-PA as suggested by earlier reports was balanced by knowledge of the benefits of oral aspirin in combination with thrombolytic therapy as demonstrated in the International Study of Infarct Survival (ISIS) trial. Clearly, there was no opportunity for bias in the reading of the coronary angiograms and ventriculograms because the physicians who read them were unaware of treatment groups.

The heparin dosage in this study maintained the APTT on average 2–2.5 times the normal range in the treated patients for the duration of heparin administration. Although this may be at the upper end of the dosage range, it confirms that the patients in the heparin group were indeed receiving therapeutic doses of heparin. Thus, the trial can be taken as a valid comparison between a regimen of intravenous heparin and a regimen of oral antiplatelet agents. The data do not indicate that one regimen is more effective than another. The choice of treatment regimen will depend on other factors, such as convenience and patient acceptance. The disadvantages of continuing intravenous heparin therapy compared with oral antiplatelet therapy are obvious. The intravenous route can cause significant morbidity; although not of statistical significance in this study, the intravenous route did cause an increased incidence of phlebitis in the heparin-treated patients. The alternative subcutaneous route can cause distress and discomfort for the patient. Bleeding attributable to heparin is a widely recognized complication and of particular concern when invasive vascular procedures are performed soon after thrombolysis. Heparin-induced thrombocytopenia is an additional complication of prolonged heparin therapy; one such case occurred in this study.

A conceivable interpretation of our results is that reduced platelet-initiated thrombosis with unaffected coagulation in the oral antiplatelet group was balanced by the reduced coagulation and unaffected platelet-initiated thrombosis in the heparin group. Inclusion of a third group in which heparin therapy would continue in addition to antiplatelet therapy might have clarified this issue and might have dem-
achieved without accompanying a with necessary. was to determine whether continued heparin therapy was necessary. We would be concerned about the potential for hemorrhage, particularly intracranial, with a combined full-dose heparin and antiplatelet regimen. The report from the European cooperative study group showed that when heparin was continued in full dosage for 10–21 days in combination with aspirin the cerebral hemorrhage rate was 1.4%, which is considerably higher than that reported in other studies using less-aggressive antithrombotic regimens after rt-PA.

A limitation of our study is the potential for a type II error. The size of our trial was designed to demonstrate a difference of 15% in the degree of coronary artery patency at a confidence level of 0.05 and a power of 0.8. The hypothesis under test was that heparin would have an advantage of this extent and that this would have been demonstrable in a trial size of approximately 200 patients. This hypothesis was not confirmed when the study was conducted as planned. It is conceivable that a larger study would demonstrate a difference of lesser magnitude in coronary artery patency and left ventricular function, but such a study would have to include many thousands of patients, and whether the results would be clinically relevant is doubtful.

Whether the addition of dipyridamole to aspirin was necessary is not clear from our results. Although this is an antiplatelet regimen that has been effective in several clinical situations, no clear advantage over therapy with aspirin alone has been shown. Our intention was to compare the need for heparin with a potent antiplatelet regimen, but this trial was designed primarily to examine the need to continue heparin administration after 24 hours rather than establish the most appropriate antiplatelet regimen for continued antithrombotic therapy. The ISIS II trial has shown convincingly that the addition of aspirin to streptokinase will improve the survival and reinfarction rate (from 3.7% to 1.8%, p<0.001) of patients with suspected acute myocardial infarction. Although the experience of thrombolysis with streptokinase is not directly applicable to that with rt-PA, the ISIS II findings suggest that oral aspirin is a highly effective antiplatelet regimen as an adjunct to thrombolytic treatment.

The main rationale for antithrombin anticoagulant therapy with heparin after thrombolytic therapy is the prevention of coronary reoclusion and reinfarction. With streptokinase, the meta-analysis of Yusuf et al in 1985 showed no support for the use of adjunct anticoagulant regimens, and the clear-cut benefits of streptokinase in reducing mortality in the ISIS and Gruppo Italiano per lo Studio della Streptokinasi nell’Infarto Miocardico (GISSI) studies were achieved without accompanying formal regimens of anticoagulant therapy. With rt-PA, a higher rate of rethrombosis would be anticipated because of its shorter effective thrombolytic duration, and early reports with rt-PA, particularly from Gold et al, suggested a very high rate of reocclusion and reinfarction after rt-PA therapy. Wider clinical experience since then has strongly suggested that these early reports exaggerated the risk of clinically significant reinfarction after rt-PA. There was no increase in reinfarction after rt-PA in the European cooperative study group (5.9% versus 6.2%, rt-PA versus placebo) or in the Anglo-Scandinavian Study of Early Rethrombosis (ASSET) study (3.9% versus 4.5%, rt-PA versus placebo). In the present study, the late reinfarction rate was 3.5% (1.9% in the aspirin and dipyridamole group), and the coronary artery patency rate was approximately 80% at 1 week after randomization at 24 hours. These observations suggest that late reinfarction and reocclusion are not as frequent as suggested by the earlier reports, and thus, the need for continuing aggressive anticoagulant therapy after thrombolysis with rt-PA may not be as great as originally thought.

This study, together with other recent reports, helps to clarify the role of antithrombin anticoagulant regimens after thrombolytic therapy with rt-PA. A recent report by Topol et al showed that when heparin was administered at the same time as rt-PA, there was no additional effect on coronary artery patency at 90 minutes. After rt-PA administration, the experimental evidence favors early administration of heparin, which has been recently supported in randomized clinical trials. Preliminary reports from two studies showed that heparin therapy started immediately after rt-PA results in improved coronary artery patency. Bleich et al studied the patency of the infarct-related artery at an average of 55 hours and showed that rt-PA alone resulted in patent in 44% of patients (n=41), whereas rt-PA combined with heparin resulted in patent in 71% (n=42). Hsia et al used a very low dosage of aspirin (80 mg/day) in comparison with heparin (1,000 units/hr) and subsequently titrated the dosage of heparin to achieve an APTT of 1–1.5 times the control value for 7 days; they showed that the early use of heparin had an advantage in patency of the infarct-related artery at 7–24 hours (82% in the heparin-treated group and 52% in the aspirin-treated group, p<0.0001). The two studies together strongly confirm a role for heparin early after thrombolysis with rt-PA. The International Study Group examined the role of heparin on outcome after thrombolytic therapy and showed no benefit when heparin was given in a dosage of 12,500 units b.i.d. s.c., starting 12 hours after administration of rt-PA. The results of that study would be consistent with those of the present study, that is, that late administration of heparin confers no benefit. However, as mentioned earlier, our study did not address the issue of whether heparin or other antithrombin agents combined with antiplatelet agents would be more beneficial than either alone.

From this trial, we conclude that intravenous heparin therapy can be stopped at 24 hours after...
the administration of rt-PA and that oral regimens of antiplatelet agents can be substituted for heparin without any clinically significant adverse effects on coronary artery patency, left ventricular function, or clinical outcome. The following approach for adjunctive antithrombotic therapy with rt-PA can be synthesized from this and other recently completed clinical trials: Heparin may not be necessary before the administration of rt-PA because it does not improve patency at 90 minutes. However, it should be administered immediately after rt-PA and continued for 24 hours because it does improve patency. Thereafter, it can be stopped and replaced with an oral regimen of aspirin or other oral regimens of antiplatelet agents because the present study has shown no advantage in continuing heparin after 24 hours.

Appendix

**Participating Centers**


**Angiography reading.** Greg Nelson, Warren Walsh, Phillip Harris.

**Ventriculography reading.** Greg Nelson, Mark Nidorf.

**Coordinating Center.** Department of Cardiovascular Medicine, Sir Charles Gairdner Hospital and Unit of Clinical Epidemiology, University of Western Australia. Trial Coordinator: Margherita Veroni. Statistical Consultant: Richard Parsons.

**National Heart Foundation Liaison.** Director: Robert Hodge. Chairman, Medical and Scientific Advisory Committee: Philip Barter.


**Protocol Development.** Chairman: Peter Thompson. Philip Aylward, Jack Federman, Phillip Harris, Robert Hodge, Andrew Thomson, Andrew Tonkin.

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