

Acute Coronary Thrombolysis with Recombinant Human Tissue-Type Plasminogen Activator: Initial Patency and Influence of Maintained Infusion on Reocclusion Rate

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An intravenous infusion of 40 mg of recombinant tissue-type plasminogen activator (rt-PA) was given intravenously over 90 minutes to 123 patients with acute myocardial infarction (AMI) of less than 4 hours' duration. A coronary angiogram was recorded at the end of the infusion in 119 patients. Central assessment of the angiograms revealed a patent infarct-related artery in 78 patients (patency rate 66%, 95% confidence limits 57 to 74%). Patients with a patent infarct-related artery at the first angiogram were randomized in a double-blind manner to receive a subsequent 6-hour infusion of either 30 mg of rt-PA or placebo. All patients had received an initial bolus of 5,000 IU of heparin and then 1,000

IU/hour until a second angiogram was recorded 6 to 24 hours after the start of the second perfusion. At central assessment of the second coronary angiogram the reocclusion rate was 2 of 36 patients who received rt-PA at the second infusion and 3 of 37 patients not receiving this drug (or the 2 groups combined 7%, 95% confidence limits 2 to 15%). Three of 60 patients (5%, 95% confidence limits 1 to 14%) with patent arteries on both previous angiograms had a later occlusion as judged on the angiogram recorded at hospital discharge. No difference in late reocclusion rates between the 2 treatment groups was observed.

(Am J Cardiol 1987;60:231-237)

Acute coronary thrombolysis with recombinant human tissue-type plasminogen activator (rt-PA) has been shown to be practicable and effective,¹⁻⁵ but uncertainty persists about the most effective dosage schedule, both in terms of total dosage and distribution in time.⁶ To be clinically relevant, thrombolysis requires not only early recanalization, but also long-term maintenance of patency of the infarct-related artery. Different studies have shown widely varying rates of coronary reocclusion during the first hours or days after thrombolysis as documented by repeat angiography.⁷⁻²⁴ The present trial was performed to determine

the early and late predischARGE reocclusion rates after patency of the infarct-related artery had been shown by coronary angiography in patients with acute myocardial infarction (AMI) treated with intravenous rt-PA. Because reocclusion was reported to occur within 1 hour after cessation of the rt-PA infusion,⁶ an early repeat catheterization was planned at the end of the second infusion: 6 hours after start of the second infusion, the latest after 24 hours. A second aim was to assess whether a continued infusion with rt-PA over 6 hours could prevent early and late reocclusion and further reduce residual stenosis as measured by quantitative coronary angiography. The results of the quantitative angiography, performed with a computer-assisted cardiovascular angiography analysis system (CAAS), are reported separately.²⁵

Methods

Patients and management: Inclusion and exclusion criteria were the same as for the first 2 European

Committees and Participation Institutions are listed in the Appendix. Manuscript received December 23, 1986; revised manuscript received and accepted April 10, 1987.

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trials^{2,3} except that a previous myocardial infarction in a different location did not disqualify the patient for the present study and that all patients had to enter the trial within 4 hours of the onset of pain.

All consenting patients were registered by telephone at a central allocation service. After blood sampling for coagulation and other assays, an intravenous bolus of 5,000 IU of heparin was given and was followed by an intravenous infusion over 90 minutes of 40 mg rt-PA (G-11021, Genentech Inc., supplied by Boehringer Ingelheim International GmbH). Cardiac catheterization was performed as previously reported³ and the first selective coronary angiogram was recorded between 75 and 90 minutes after the start of the rt-PA infusion. Coronary angiograms were recorded on 35-mm cine film in all patients except in 10 for whom high-resolution videotape was used for the 90-minute angiogram. After angiography, the local cardiologists made a decision as to whether they regarded the infarct-related vessel as patent or occluded. Patients with a patent infarct-related artery were given heparin as a continuous intravenous infusion of 1,000 IU/hour for at least 24 hours or until the second angiogram was recorded and were randomized to receive in a double-blind manner either an additional infusion of 30 mg rt-PA or placebo over 6 hours. Numbered treatment packages contained either rt-PA or an indistinguishable placebo. Allocation was balanced at each clinic.

Serial electrocardiograms and blood samples for cardiac enzyme analysis were taken to confirm the diagnosis of myocardial infarction. Blood samples for central assessment of coagulation factors and rt-PA activity were collected. Coronary angiography was repeated between 6 to 24 hours after start of the second infusion and at the time of hospital discharge.

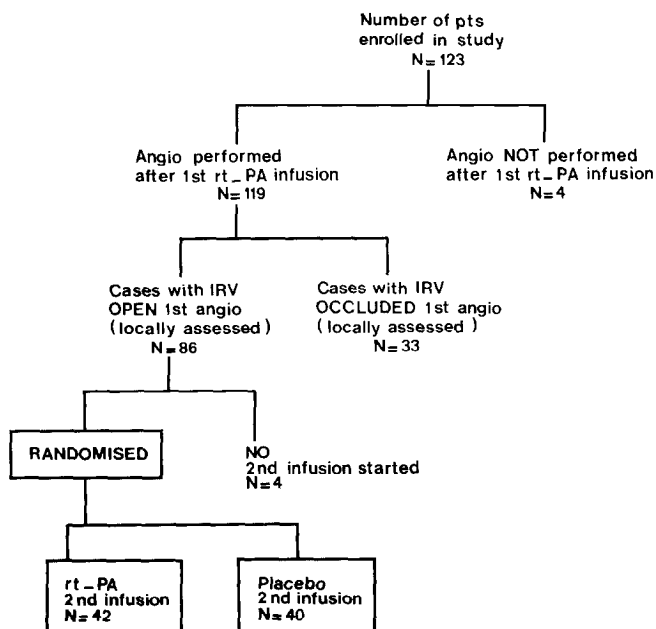


FIGURE 1. Flow diagram of patients in whom rt-PA infusion was given. Subsequent randomization based on local assessment of the patency of the infarct-related artery at first angiogram. IRV = infarct-related vessel.

Assessment of coronary arteriograms: For the angiograms at 6 to 24 hours and before discharge the x-ray system was repositioned in projections corresponding as closely as possible to those recorded during the initial angiogram. Angiograms were recorded in multiple views, including hemiaxial views for the left coronary artery. The infarct-related segment was identified for all films on the basis of electrocardiographic and angiographic evidence during a central assessment by teams of 3 assessors (D de B and PS), 2 of whom were always present to maintain consistency.

Qualitative assessment of patency was performed using a predetermined code: 0 = normal vessel with complete filling of distal vessels within 3 cardiac cycles; 1 = less than 50% diameter stenosis with complete filling of distal vessels within 3 cycles; 2 = diameter stenosis between 50% and 90% with complete filling of distal vessels, not through collaterals, within 3 cardiac cycles; 3 = severe stenosis greater than 90%, but distal vessels fill completely, not through collaterals, within 3 cardiac cycles; 4 = subtotal occlusion, no distal filling within 3 cardiac cycles; 5 = total occlusion with or without collateral distal filling. Patency of an infarct-related artery was assessed at the first technically adequate contrast injection and classified as patent in case of grade 0, 1, 2 or 3 and as occluded in case of grade 4 and 5.

Blood coagulation and fibrinolytic assays: Blood samples for analysis in the central coagulation laboratory were collected in all patients admitted to the trial before and 60 and 90 minutes after the start of rt-PA infusion. In randomized patients, further blood samples were obtained 2, 4, 6 and 24 hours after the start of the second infusion (rt-PA or placebo). Tubes for blood collection were provided containing 0.5 ml sodium citrate (final concentration 0.01 M/liter). Processing and storage of blood samples and methods to assess coagulation and fibrinolytic components were as described previously.^{3,4} The normal values for fibrinogen in plasma is 2 to 4 g/liter and for fibrinogen degradation products in serum less than 8 mg/liter.

Trial size, data acquisition and statistical analysis: Data collection and analysis were performed by an autonomous data center, independent of the investigators and the sponsor Boehringer Ingelheim International. Continuous data are presented as medians and ranges; 95% confidence interval of the differences between proportions are given.²⁶

Results

Eleven European centers entered 123 patients in the study over a 6-month period. Mean age was 56 years and median duration from onset of symptoms to initiation of rt-PA infusion was 2.5 hours (range 0.9 to 4.2). Enzyme data at admission were normal. The full dose of rt-PA was administered in all patients except in 1 because the catheterization laboratory was being used for an emergency. Technical or vascular problems prevented coronary angiography in 3 patients. Thus, angiography at 90 minutes after the start of the rt-PA infusion was completed in 119 patients (Fig. 1).

Patency rate at 90 minutes: Central assessment of the 119 coronary angiograms revealed a patent infarct-related artery in 78 patients (patency rate 66%, 95% confidence intervals 57 to 74%). Figure 2 shows the disagreement between locally and centrally assessed patency of the first angiogram. The local cardiologists considered the infarct-related artery to be patent in 8 patients who were randomized to receive a second infusion of rt-PA (5 patients) or placebo (3 patients). According to the central angiography evaluation group, the criteria for patency in these 8 patients were not fulfilled either because of sluggish flow in a distal vessel (grade 4 in 3 patients allotted to rt-PA for second infusion), because the vessel only became patent during later contrast injections (3 patients receiving placebo for second infusion), or because of complete occlusion (1 patient allotted to rt-PA for second infusion).

Of the 86 patients locally judged to have a patent infarct-related artery at initial catheterization, 82 received further heparin and were randomized to either an additional rt-PA infusion (n = 42) or placebo (n = 40). Four patients were not randomized: 2 because of emergency coronary bypass surgery, 1 because of immediate percutaneous transluminal coronary angioplasty (PTCA) and 1 because of hemodynamic deterioration (Fig. 1). Analysis of baseline characteristics shows that randomization was successful in segregating similar groups for the second infusion given in a blinded manner (Table I). Among patients receiving rt-PA the infusion was stopped in 3 because of a large hematoma in the groin, in 1 patient because of emergency PTCA for clinical signs of reocclusion 5 hours after start of the second infusion, and in 1 patient for an unreported reason. In the placebo group 2 patients did not receive the full dose, 1 patient because of hemodynamic deterioration and 1 because of reappearance of chest pain subsequently treated with acylated streptokinase-plasminogen complex intravenously.

Reocclusion rate at 6 to 24 hours after start of the second infusion: Between 6 to 24 hours after the start of the second infusion, angiography was performed in 79 of 82 patients allocated to a second infusion of either rt-PA or placebo. In 3 patients coronary angiography was not performed because of coronary artery bypass grafting, hypotension and impossibility to pass the aorta bifurcation. The median interval between the start of second infusion to 6- to 24-hour angiography was 13 hours, 30 minutes (90% range 6 hours 28 minutes to 24 hours 12 minutes) for the rt-PA group and 15 hours, 6 minutes (90% range 6 hours 9 minutes to 24 hours) for the placebo group.

At the end of the initial rt-PA infusion the number of patients with a patent infarct-related vessel (assessment of angiographic review panel) who showed at the 6- to 24-hour angiogram an occluded infarct-related artery was identical in both treatment arms (Fig. 2): 2 of 36 patients (6%, 95% confidence interval 1 to 19%) randomized to rt-PA at second infusion and 2 of 23 in the placebo group showed an occluded infarct-related artery (5%, 95% confidence interval 10 to 19%). One of the 2 patients who had a patent-infarct related artery at the first angiogram and did not receive a second infu-

TABLE I Baseline Characteristics (Median and Range)—Cases in Which the First Angiogram was Performed and Found to be Open as Locally Assessed and Second Infusion Started

	rt-PA at 2nd Infusion (n = 42)	Placebo at 2nd Infusion (n = 40)	All Others (n = 41)
Male	35	33	32
Age (yr)	56 (33-68)	55 (31-70)	56 (34-69)
Time from onset AMI to start of 1st infusion (hr)	2.3 (0.9-4.2)	2.7 (1.2-4.0)	2.4 (1.3-4.5)
Previous AMI	3	1	2
Pulmonary rales	11	4	8
Medication within 6 hrs before start of 1st rt-PA infusion			
Nitrates (sublingual)	9	11	6
Nitrates (intravenous)	11	10	14
Beta blockers	1	0	2
Calcium antagonists	9	11	5

AMI = acute myocardial infarction.

sion underwent repeat catheterization at 6 to 24 hours and had an occluded coronary artery. This resulted in an overall 6- to 24-hour reocclusion rate of 7% (5 of 73 patients, 95% confidence interval 2 to 15%).

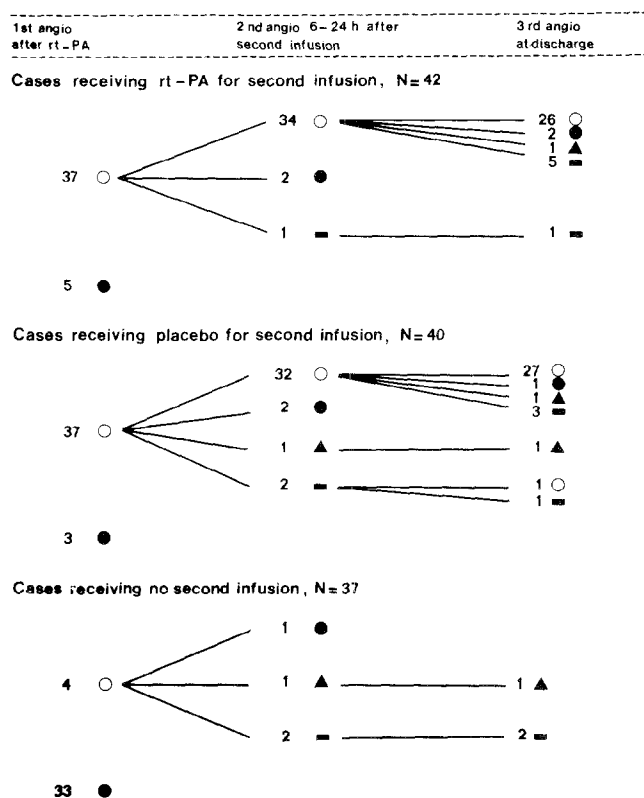


FIGURE 2. Status of infarct-related coronary artery at the first, second and third coronary angiogram as assessed by the angiographic evaluation group. Status of the infarct-related vessel: circles, open, dots, closed; triangles, patent after intervention; and dash, missing film. Results of the follow-up angiograms performed in patients with an occluded infarct-related vessel are not reported in this figure.

TABLE II Patients with an Event During Entire Hospital Stay

	rt-PA at 2nd Infusion (n = 42)	Placebo at 2nd Infusion (n = 40)	All Others (n = 41)
Ventricular fibrillation	8	2	3
Ventricular tachycardia (exceeding 100 beats/min)	13	10	5
Chest pain or exacerbation of chest pain at rest	7	6	13
Definite reinfarction	1	1	2
Fall in systolic BP <90 mm Hg	5	9	8
Pulmonary edema	3	2	2
Mortality	1	1	4
Bleeding*			
Hematoma (>5 cm diameter) and/or prolonged bleeding at puncture sites	12	9	7
Retroperitoneal bleeding	1	-	-
Hematuria	3	-	1
Gum bleeding	-	1	1
Blood or plasma transfusion given	1	3	3
Additional interventions			
at 1st angio:			
Intracoronary SK	-	-	17
Intracoronary SK+PTCA	-	-	9
Intracoronary SK+mechanical perforation	-	-	1
Mechanical perforation + PTCA	-	-	2
PTCA alone	-	-	2
PTCA after first catheterization	7	4	5
Coronary artery bypass grafting	3	1	5

*One patient had hematuria and prolonged bleeding at puncture site, and 1 patient had gum bleeding and hematuria. these patients were classified twice.

BP = blood pressure; PTCA = percutaneous transluminal coronary angioplasty; SK = streptokinase.

At the predischARGE angiography, 1 of the 5 patients with reocclusion at 6 to 24 hours had a patent infarct-related vessel, 1 patient had a patent vessel after angioplasty, which was performed immediately after second catheterization, 1 patient still had an occluded infarct-related artery and 2 patients did not undergo a catheterization before discharge.

Reocclusion rate at one to four weeks: At the time of hospital discharge, coronary angiography was performed in 69 of the 82 patients who received a second infusion. It was not performed in 13 patients, due to patient refusal (n = 6), coronary artery bypass grafting (n = 6) and death (n = 1). In 2 of 29 patients (7%, 95% confidence interval 1 to 23%) in the group receiving rt-PA as a second infusion and in 1 of 30 (3%, 95% confidence interval 0 to 17%) in the group receiving placebo, late reocclusion occurred (Fig. 2). In the group that did not receive a second infusion, repeat catheterization before discharge was performed in 1 patient; the infarct-related vessel was patent (Fig. 2). Thus, in all groups combined, a late occlusion was found in 3 of 60 patients (5%, 95% confidence interval 1 to 14%). The median interval from start of the first infusion to the predischARGE catheterization was 10 days (90% range 7 to 26) for the rt-PA group and 14 days (90% range 7 to 26) for the placebo group. This resulted in a 1- to 4-week occlusion rate of 7 + 5 = 12%. Only 4 of the 8 patients with reocclusion (5 early, 3 late) had clinical symptoms of reocclusion.

Outcome of further recanalization attempts in patients with occluded vessel at 90 minutes: The local

angiographic assessment was confirmed in the 33 patients with an occluded infarct-related vessel by the central reading. Twenty-eight patients had a completely occluded infarct related artery (grade 5) and 5 patients had subtotal occlusion (grade 4). Intracoronary streptokinase was given to 27 patients; 4 patients with grade 4 and 23 with complete occlusion. Although the protocol required intracoronary streptokinase, 1 patient with complete occlusion was treated with intravenous acetylated streptokinase-plasminogen complex (15 mg in 15 minutes). Thus, 5 patients were not treated with streptokinase even though they did not have a patent infarct-related vessel (1 patient refusal, 1 patient with arrhythmias, 1 protocol violation: immediate mechanical perforation, 1 hemodynamic instability, 1 subtotal occlusion). The median dose of intracoronary streptokinase was 120,000 IU (range 4,000 to 262,500) and median time of administration 30 minutes (range 15 to 90).

Immediate angioplasty was performed in 2 of the patients with an initially subtotal occlusion (in 1 case with streptokinase) and in 10 of 28 patients with an initially occluded vessel (in 2 cases without streptokinase). In 1 patient with a completely occluded infarct-related vessel, streptokinase was followed by mechanical perforation.

Local assessment revealed a patent infarct-related vessel in 4 of the 14 patients with a complete occlusion and in 2 of the 3 with subtotal occlusion who were treated with intracoronary streptokinase without mechanical perforation or PTCA. Angioplasty in 12 pa-

tients and mechanical perforation without PTCA in 1 patient were successful in all but 2 occasions (85%).

Complications: The initial infusion of 40 mg of rt-PA administered over 90 minutes was well tolerated and hemodynamic or other complications were rare in 122 patients who received the full dose. The incidence of bradycardia that formed an indication for temporary pacing, ventricular tachycardia and ventricular fibrillation combined was 17 of 123 patients (14%). These arrhythmias occurred equally frequent in patients who had a patent infarct-related artery at 90 minutes as in those with an occluded vessel. Pyrexia or allergic reactions were not reported, although 1 case of shivering was observed. The events and complications during the entire hospitalization phase are listed in Table II. There were no differences between those randomized to a second infusion of rt-PA and those allotted to placebo.

During the first rt-PA infusion hemorrhagic complications were limited to 2 patients, 1 with a hematoma at a puncture site and 1 with hematuria. After the first catheterization, bleeding around the sheath was observed in 3 patients; at that time 1 patient received additional streptokinase because of persistent coronary occlusion. During the second infusion, 1 patient had hematuria and 4 others randomized to rt-PA had a large hematoma at the catheter site, while the latter was noted in only 1 patient randomized to placebo infusion. Heparin was stopped in 3 of these patients; 1 received protamin. The second infusion of rt-PA was stopped in 1 patient.

Table II lists patients with bleeding during the hospital stay. All bleeding events not yet described were observed between the second catheterization and hospital discharge. One patient required surgical arterial repair because of prolonged bleeding that occurred 24 hours after the second rt-PA infusion. A retroperitoneal bleeding developed 1 day after the end of the second rt-PA infusion but did not require special measures. Two patients had hematuria 2 days after rt-PA allocation. No cerebral or gastrointestinal bleeding was seen. The number of patients with 1 or more bleeding sites was slightly higher in the rt-PA group (± 16) than in the placebo group (± 10). Blood transfusions were given to 1 patient in the rt-PA group and to 3 patients in the placebo group, all because of large hematoma.

There were 6 in-hospital deaths. In the group of patients without a second infusion, 4 died: 1 from reinfarction, 1 from cardiogenic shock, 1 from asystole and 1 perioperatively. Among the patients who had received rt-PA as a second infusion, 1 patient died during pre-discharge catheterization due to asystole followed by electromechanical dissociation. Among the patients receiving placebo as a second infusion, 1 patient died due to a myocardial rupture. The first catheterization was complicated in 1 patient with aortic root dissection, which was treated conservatively. The second catheterization in 1 patient was complicated by right ventricle perforation by a pacemaker catheter; cardiac surgery was required.

Central assessments of electrocardiograms: All electrocardiograms were reevaluated by 2 indepen-

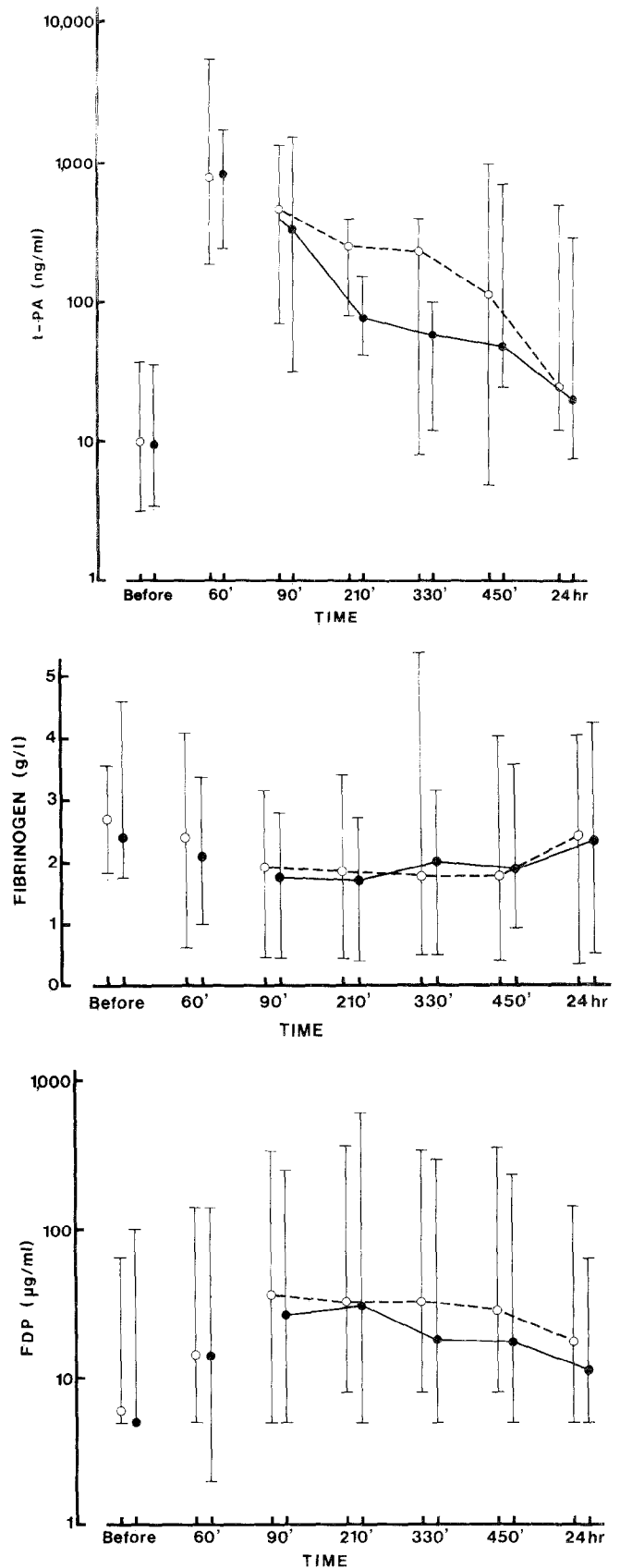


FIGURE 3. Levels of rt-PA antigen, fibrinogen and fibrinogen degradation products (FDP) in plasma during the initial infusion of rt-PA (40 mg in first 90 minutes) in all randomized patients and during subsequent rt-PA infusion (30 mg over 6 hours) (circles) or placebo infusion (6 hours) (dots).

dent readers. The admission electrocardiograms of 3 patients could not be retrieved for central analysis. Of 120 patients, 106 showed more than 0.2 mV of ST-segment elevation in 2 limb leads or more than 0.3 mV in 2 precordial leads as required by the protocol (anterolateral in 64 patients, inferoposterior in 42). In 14 patients ST-segment elevation was present but of lesser magnitude (anterolateral in 2 patients, inferoposterior in 11 and undefined in localization in 1 patient). The final diagnosis of myocardial infarction was confirmed by electrocardiographic criteria and enzyme elevation exceeding twice the upper limit of normal in 116 patients and by electrocardiogram alone in 7 (in 2 patients no diagnostic enzyme increase, in 5 patients insufficient enzyme data).

Blood coagulation and rt-PA assay: The median radioimmunoactive rt-PA levels for patients ($n = 100$) analyzed at 60 minutes after the start of the 1st rt-PA infusion was 800 ng/ml (range 189 to 5,440) (Fig. 3). The median fibrinogen concentration of all patients analyzed decreased from 2.6 g/liter (range 1.7 to 4.6) to 1.8 g/liter (range 0.1 to 3.2) (23%) at the end of the first infusion (90 minutes), without further reduction during the maintenance infusion of 30 mg of rt-PA over the next 6 hours. The median level of fibrinogen was 72% of the starting value at the end of the first infusion and 65% as lowest value during subsequent maintenance infusion.

Discussion

Reocclusion is a major problem after coronary recanalization in the setting of acute myocardial infarction. Two weeks after intracoronary streptokinase, the reocclusion rate varies between less than 10% to 29%.^{8,9,11,14-20} Pooling the data of all these studies, 61 of 311 patients had an angiographically documented reocclusion (17%, 95% confidence limits 13 to 21%). The first studies^{5,6} that evaluated the early reocclusion rates after successful recanalization with intravenous rt-PA reported rates of 33% (95% confidence limits 15 to 57%)⁵ and 46% (95% confidence limits 23 to 83%).⁶ However, the wide range of the 95% confidence limits made definite conclusions impossible. The present study suggests a reocclusion rate comparable to the reocclusion rate after intracoronary streptokinase.

It could be argued that due to our strict criteria for patency, we excluded from analysis the patients with subtotal occluded vessels (grade 4) and the patients in whom the infarct-related vessel opened during later contrast injections who could be prone for reocclusion on the short term. Repeat analysis including these patients ($n = 4$ in the group receiving rt-PA as second infusion and $n = 3$ in the group randomized to placebo) added 1 patient with a reocclusion at 6 to 24 hours, resulting in a 6- to 24-hour reocclusion rate of 6 of 80 patients (8%, 95% confidence limits 3 to 16%). At 1 to 4 weeks, no more patients with reocclusion were found (3 of 65 patients with patent vessels at both previous films). Hence, we conclude that our definition of patency does not have a major influence on the results. A second possible explanation for the low reocclusion rate in the present study is that patients with already patent vessels before treatment (21% according to one

of our previous studies using very similar selection criteria)² are less susceptible to reocclusion, perhaps because the cause of the initial occlusion was transient coronary spasm.²⁷

Finally, the reocclusion rate reported here could be underestimated because of the missing angiograms at 6 to 24 hours in 5 patients and at hospital discharge in 12 (Fig. 2). To determine the magnitude of the bias that has been introduced thereby, we recalculated the occlusion rates assuming that patients who did not undergo recatheterization because of coronary bypass operation or death were patients with reocclusion. Applying this definition to the 6- to 24-hour angiogram, 1 patient was added in the group receiving rt-PA as second infusion and 2 patients in the group without a second infusion, resulting in a reocclusion rate at 6 to 24 hours of 11% (8 of 76 patients). Regarding the pre-discharge angiogram, 3 patients were added in the group receiving rt-PA as second infusion and 2 patients in the group receiving placebo as second infusion (1 to 4 weeks reocclusion rate 12%, 8 of 65 patients). Thus, the overall reocclusion rate, applying the assumption mentioned above, was 23%. This indicates that patients lost to follow-up cannot completely account for the disparity between the reocclusion rate of the present study and that of previous studies.^{5,6}

We failed to show a further reduction of the reocclusion rate by an additional 6 hours infusion of rt-PA. Nevertheless, quantitative analysis of the angiograms showed a greater reduction in residual stenosis in the group receiving rt-PA as a second infusion.²⁵ It has been suggested^{23,28} that the presence of residual thrombus after recanalization is a major cause of reocclusion. Furthermore, several studies show that reocclusion mainly occurs in patients with severe residual stenoses.^{6,7,12,16} This is not confirmed by the present study. Agnelli et al,²⁹ using a venous thrombosis model in the rabbit, showed that the thrombolytic activity of rt-PA persists within the thrombus for several hours after rt-PA was cleared from the circulation. This may explain the low reocclusion rate in our patients.

Notwithstanding the fibrinogen sparing properties of rt-PA, bleeding was the most frequent complication after thrombolysis with rt-PA. Most bleeding complications were related to the 90-minute catheterization. There was a tendency of more frequent bleeding in the group receiving rt-PA as a second infusion, although no difference in fibrinogen levels was seen during the first 24 hours. Also, most other events mentioned in Table II were more frequently seen in the group receiving rt-PA as second infusion.

Intracoronary streptokinase appeared effective in only 35% of the patients in whom the initial treatment with rt-PA was not successful. This means that additional interventions are needed. PTCA and mechanical perforation were successful in 85% of the cases.

This study also shows that clinically silent reocclusion occurs in many patients with recanalization and that silent reocclusion may be transient. The latter finding shows that recanalization alone is not a clinically relevant achievement. Harder endpoints such as left ventricular function and mortality to assess clinical benefits of thrombolysis with rt-PA are needed.

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Appendix

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