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Lessons From the European Cooperative Recombinant Tissue-Type Plasminogen Activator (rt-PA) Versus Placebo Trial*

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A new European Cooperative Study Group trial of 721 patients has recently found recombinant tissue-type plasminogen activator (rt-PA) to positively affect infarct size, left ventricular function, cardiovascular morbidity and early survival. In this 26 center trial, patients were randomized to receive either placebo or 100 mg rt-PA intravenously over 3 h. Heparin (5,000 U bolus injection and then 1,000 U/h) and aspirin (250 mg initially, then 75 to 125 mg every other day) were given to all patients until angiography was performed (10 to 22 days after allocation).

Enzymatic infarct size was found to be 20% smaller in the rt-PA group (2p = 0.0018) than in the control group. At angiography, 83% of rt-PA–treated patients had a patent infarct-related vessel compared with 77% of the placebo-treated patients. Ejection fraction was 2.2% points higher (2p = 0.04) and end-diastolic and end-systolic volumes were ±6 ml smaller (2p = 0.003) than in the control group, indicating an improved left ventricular pump function in the thrombolysis group. Cardiovascular complications such as shock, ventricular fibrillation and pericarditis were markedly fewer in patients treated with rt-PA, but bleeding complications occurred more frequently. An intracranial hemorrhage within 3 days after the infusion of rt-PA was observed in five patients (1.4%). None of these bleeding episodes was causally related to death. Although this European Cooperative trial was not designed primarily as a mortality study, important reductions in early mortality rates were observed. At 14 days, the death rate among rt-PA–treated patients was 2.8%, which is 51% (95% confidence interval −76% to +1%, 2p = 0.053) lower than the 5.7% mortality rate of the control group. At 3 months, the mortality rate was 5.1% in the rt-PA group, which is 36% (95% confidence interval −63% to +13%, 2p = 0.121) lower than the 7.9% in the control group. In patients treated within 3 h of symptoms, the European Cooperative Study Group reported mortality reductions of 82% (95% confidence interval −95% to −31%, 2p = 0.009) at 14 days and 59% (95% confidence interval −83% to −2%, 2p = 0.045) at 3 months. The early mortality rates observed in this trial were very similar to those reported previously by the same European Cooperative Study Group for a similarly selected and treated group of patients and are the lowest so far published in large trials with intravenously administered thrombolytic agents.

The results of these European multicenter trials, together with the recent findings of large studies conducted in the United States (Johns Hopkins Hospital trial, Thrombolysis and Angioplasty in Myocardial Infarction [TAMI], Thrombolysis in Myocardial Infarction [TIMI]), further add to evidence that early thrombolytic treatment with rt-PA in addition to antithrombotic and antiplatelet medication is of major benefit for patients with an acute myocardial infarction.

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Intravenous administration of thrombolytic agents after acute myocardial infarction has been shown to limit infarct size, preserve left ventricular function and, most important, improve survival (1–16). The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial (1), a randomized, controlled study of nearly 12,000 patients, was the first to show improved in-hospital survival after intravenous infusion of a thrombolytic agent (streptokinase), particularly when administered within the first 3 h after the onset of symptoms. The improved survival after intravenous streptokinase has been confirmed recently in an even larger multicenter study, the Second International Study of Infarct Survival (ISIS-2) trial (8), which reported a significant reduction in 5 week vascular mortality. Improved early survival

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was also demonstrated for a streptokinase-derived thrombolytic agent, anisoylated plasminogen streptokinase activator complex (APSAC) (9), and very recently also for recombinant tissue-type plasminogen activator (rt-PA) (16).

The mechanism responsible for these beneficial effects is most probably related to coronary artery recanalization with salvage of ischemic myocardium. In this respect, rt-PA, a more physiologic and fibrin-specific agent, has been shown to have greater thrombolytic efficacy than streptokinase (17–19). Indeed, combining the results of two multicenter trials—the European Cooperative Study Group trial (19) and the Thrombolysis in Myocardial Infarction (TIMI) phase I trial (18)—the patency rate of the infarct-related vessel was significantly greater with rt-PA than with streptokinase, irrespective of whether treatment was applied in the first 3 h or at 3 to 6 h (17). The European Cooperative Study Group has recently conducted a large prospective placebo-controlled trial to study the effect of intravenous rt-PA on enzymatic infarct size, left ventricular function and clinical follow-up (20). A full list of collaborating hospitals and assessment groups is given in the main report (20). The most striking results of this study and the insights we have gained are presented here.

Methods

Selection of patients. The entry criteria of the trial included: age <71 years; chest pain typical of myocardial ischemia for ≥30 min and <5 h unrelieved by nitroglycerin; ST segment elevation ≥2 mm in two or more electrocardiographic (ECG) limb leads or leads V_5 and V_6, ≥3 mm in at least two precordial leads or ≥1 mm in two limb leads or leads V_5 and V_6 together with ≥2 mm of ST segment depression in two or more precordial leads. Exclusion criteria were previous myocardial infarction at the same site or previous coronary artery bypass surgery, previous myocardial infarction at any site during the preceding 2 weeks and contraindications for thrombolytic therapy.

Protocol. Every patient was given 250 mg of aspirin intravenously followed by 75 to 125 mg of oral aspirin every other day and 5,000 U of heparin administered as a bolus followed by 1,000 U/h. The patients were then randomized by a telephone answering service and allocated to either 100 mg single-chain rt-PA or placebo. The total individual dose of 100 mg powdered rt-PA was dissolved in 100 ml solvent and the undiluted product was administered (10 mg as a bolus followed by 50 mg over 1 h and 40 mg over the next 2 h). In patients allocated to conventional treatment, placebo was given in exactly the same way as rt-PA. After 3 days heparin could be replaced by oral anticoagulants. Any other treatment was given only if clinically indicated. At discharge, a beta-adrenergic blocker was given to both groups unless contraindicated.

Blood samples were drawn before and at 12, 24, 36, 48, 72 and 96 h after the start of the experimental infusion for local assessment of cardiac enzymes and for central analysis of alpha-hydroxybutyrate dehydrogenase (HBDH) activities in plasma. The cumulative myocardial release of HBDH into plasma was determined centrally as previously described (21,22). The value at 72 h was used as an estimate of infarct size.

No pretreatment angiography was performed. Between 10 to 22 days after allocation, coronary arteriography and left ventricular angiography were performed and recorded on 35 mm film. All films were centrally analyzed by the Angiography Assessment Group. Patency of the infarct-related vessel was assessed according to the TIMI criteria (18). Left ventricular volumes and ejection fraction were measured from the 30° right anterior oblique projection using the area-length method.

Table 1. Baseline Characteristics of 721 Patients

	Placebo (n = 366)	rt-PA (n = 355)
Age (yr)	58 (43 to 69)	58 (41 to 69)
Men	304 (83)	313 (88)
History of previous infarction	26 (7.1)	27 (7.6)
Anterior infarction	129 (35)	145 (41)
Mild heart failure (Killip class II)	78 (21)	71 (20)
Overt heart failure/shock (Killip classes III and IV)	17 (4.6)	11 (3.1)
Ventricular fibrillation	12 (3.3)	8 (2.3)
3rd° AV block	11 (3.0)	11 (3.1)

The actual numbers of patients are shown. Continuous variables are presented as median and 90% range. Percent of patients in each treatment group or 90% ranges are shown in parentheses. AV = atrioventricular; 3rd° = third degree; rt-PA = recombinant tissue-type plasminogen activator.

Results

Patient characteristics (Table 1). A total of 721 patients entered the trial in 26 participating hospitals. Of these patients, 366 were allocated to placebo and 355 to rt-PA. In eight patients the experimental infusion was not given because of protocol violation in three patients and various clinical reasons in five patients. These eight patients were included in the analysis according to their treatment allocation ("intention to treat" principle).

Baseline characteristics on admission were similar in the two treatment groups (Table 1). The delay between the onset of symptoms and the start of the experimental infusion was 2.8 h (90% range 1.3 to 4.5) in the placebo group and 2.9 h (90% range 1.4 to 4.6) in the rt-PA group.

Clinical follow-up (Table 2). The administration of rt-PA was associated with an improved short-term survival. Compared with the placebo group, the reduction in mortality rate in patients treated with rt-PA was from 5.7% to 2.8% at 14

Table 2. Clinical Follow-Up

	Placebo (n = 366)	rt-PA (n = 355)	Rate Ratio	95% Confidence Interval
Mortality at 14 days				
Total group	21 (5.7)	10 (2.8)	0.49	0.24 to 1.01
Treated <3 h of symptoms onset*	13 (6.3)	2 (1.1)	0.18	0.05 to 0.69
Bleeding complications and stroke	27 (7.4)	104 (29.3)	3.97	2.69 to 5.91
Documented hemorrhagic stroke	—	6 (1.7)		
Documented nonhemorrhagic stroke	—	1 (0.3)		
Nondocumented stroke	2 (0.6)	—		
Gastrointestinal bleeding	4 (1.1)	5 (1.4)		
Macroscopic hematuria	4 (1.1)	16 (4.5)		
Local hematoma	9 (2.5)	68 (19)		
Other bleeding	15 (4.1)	30 (8.5)		
Blood transfusion given	7 (1.9)	13 (3.7)	1.92	0.80 to 4.62
Cardiac complications during hospital stay				
Reinfarction	15 (4.1)	14 (3.9)		
Shock	22 (6.0)	9 (2.5)	0.37	0.17 to 0.83
Pulmonary edema	24 (6.6)	22 (6.3)		
Pericarditis	40 (11)	22 (6.3)	0.57	0.35 to 0.93
Ventricular fibrillation	23 (6.3)	12 (3.4)	0.54	0.28 to 1.05
3rd° AV block	18 (5.0)	11 (3.1)	0.63	0.31 to 1.29
Supraventricular tachyarrhythmia	38 (10.4)	27 (7.6)	0.73	0.46 to 1.17
Angioplasty	9 (2.5)	9 (2.5)		
CABG	1 (0.3)	10 (2.8)	10.3	1.72 to 62.0
Angioplasty and CABG	1 (0.3)	1 (0.3)		
Status at 3 months				
Mortality				
Total group	29 (7.9)	18 (5.1)	0.64	0.36 to 1.13
Treated <3 h of symptoms onset*	17 (8.2)	6 (3.4)	0.41	0.17 to 0.98
Reinfarction	23 (6.2)	21 (5.9)	0.94	0.53 to 1.66
Angioplasty	16 (4.4)	22 (6.2)	1.42	0.77 to 2.64
CABG	17 (4.6)	32 (9.0)	1.94	1.11 to 3.41
Angioplasty and CABG	2 (0.5)	2 (0.6)	1.03	0.18 to 5.82

*207 patients allocated to placebo, 179 patients allocated to rt-PA. The actual number of patients with an event is given; percent of patients in each treatment group is shown in parentheses. Rate ratio and 95% confidence interval are given when appropriate. CABG = coronary artery bypass grafting.

days (a 51% reduction, 95% confidence interval −76% to +1%, 2p = 0.053) and from 7.9% to 5.1% (a 36% reduction, 95% confidence interval −63% to +13%, 2p = 0.121) at the 3 month follow-up. In patients treated within 3 h of the onset of symptoms, the reduction in mortality rate was 82% (95% confidence interval −95% to −31%, 2p = 0.009) at 14 days (from 6.3% in the placebo-treated group to 1.1% in the group receiving rt-PA) and 59% (95% confidence interval −83% to −2%, 2p = 0.045) at 3 months (from 8.2% to 3.4%).

Cardiovascular complications during the hospital stay were less frequent in patients treated with rt-PA. For example, a 63% reduction in the incidence of cardiogenic shock and a 40 to 50% reduction in the incidence of ventricular fibrillation and pericarditis were observed. Angioplasty was performed in a similarly low percent of patients in both groups (2.5%). Coronary bypass surgery was performed in 10 rt-PA–treated patients and in only one control patient.

Bleeding complications were more frequent in patients treated with rt-PA. Intracranial bleeding was observed in six patients allocated to rt-PA. In one of these six patients neurologic symptoms and death occurred on the 15th day, 12 h after treatment with angioplasty and intravenous streptokinase for reocclusion. In the remaining five patients (1.4% of the rt-PA–treated patients), the neurologic symptoms occurred within 3 days after the infusion of rt-PA. In none of these five patients was the bleeding causally related to death. One patient died of cardiogenic shock and ventricular fibrillation due to reinfarction a few hours after the interruption of the heparin infusion. Gastrointestinal and other major bleeding episodes were relatively infrequent. Blood transfusions were required in 3.7% of the rt-PA–treated patients.

After 3 months the incidence of reinfarction was very similar in both groups. Angioplasty or coronary artery bypass surgery, or both, was performed in a greater proportion of patients allocated to rt-PA–(15.8% versus 9.6%, respectively).

Table 3. Enzymatic Infarct Size and Left Ventricular Function

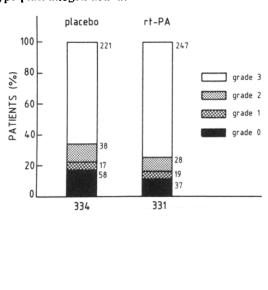
	Placebo	rt-PA
HBDH-Q72*	867 (123-2143)	697 (119-1889)
(U/liter)	(n = 314)	(n = 305)
Ejection fraction†	48.5 (±11.3)	50.7 (±10.9)
(%)	(n = 288)	(n = 289)
Left ventricular volumes (ml)		
End-diastolic‡	124.2 (±34.6)	118.2 (±35.2)
End-systolic‡	65.6 (±29.7)	59.8 (±28.1)
	(n = 283)	(n = 282)

*$2p = 0.0018$; †$2p = 0.04$; ‡$2p = 0.003$. Data are given as median or mean values; 90% ranges or standard deviations are shown in parentheses. HBDH-Q72 = cumulative release of alpha-hydroxybutyrate dehydrogenase into plasma up to 72 h; rt-PA = recombinant tissue-type plasminogen activator.

Infarct size and angiographic findings (Table 3, Fig. 1). The cumulative myocardial release of HBDH into plasma up to 72 h was 20% higher in the control group than in patients treated with rt-PA; 867 U/liter (90% range 123 to 2,143) versus 697 U/liter (90% range 119 to 1,889). These results indicate a significant reduction in infarct size in the thrombolysis group ($2p = 0.0018$).

Angiography could not be performed in 22 patients (6.2%) allocated to thrombolysis and in 30 patients (8.2%) allocated to conventional treatment, including the patients who died before catheterization. The infarct-related coronary artery could not be identified in 26 rt-PA–treated and in 11 placebo-treated patients in whom angiography was performed. A high percent of patent (TIMI grades 2 and 3) coronary arteries was found in both groups 10 to 22 days after the experimental treatment: 77% in the placebo group and 83% in the rt-PA group (Fig. 1). In 80% of the recruited patients (n = 577) the left ventricular angiogram was adequate for quantitative analysis. Global ejection fraction was 2.2 percentage points higher and left ventricular volumes ±6 ml smaller in patients allocated to rt-PA than in control patients. All these differences were statistically significant.

Figure 1. Patency (according to Thrombolysis in Myocardial Infarction [TIMI] criteria) of the infarct-related coronary artery, 10 to 22 days after allocation. The number of patients in the different subgroups are shown next to the bars. rt-PA = recombinant tissue-type plasminogen activator.



Discussion

Effect on infarct size and ventricular function. The European Cooperative rt-PA versus placebo trial (20) is the first trial to show a beneficial effect of intravenous thrombolytic therapy on infarct size, left ventricular function, cardiovascular morbidity and mortality within the same study population. The intravenous administration of rt-PA within 5 h of onset of an acute myocardial infarction significantly reduced infarct size by 20%. A reduction in infarct size measured by enzymatic methods was also demonstrated for intravenous streptokinase in the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) trial (2). The reduction in enzymatic infarct size in the European trial was associated with a preserved left ventricular function. Global ejection fraction was 2.2 percentage points higher in patients allocated to rt-PA than in the placebo group. As in two other studies with streptokinase (5,23), end-diastolic and end-systolic volumes were significantly smaller in patients allocated to rt-PA. These findings suggest that early reperfusion not only improves contractile function but also prevents or at least limits infarct expansion and cardiac dilation. The latter effect might be of great clinical importance because it has been shown that ventricular volumes may have a greater predictive value for late survival after infarction than does the ejection fraction (24). However, it seems unlikely that this improvement, albeit moderate, in left ventricular pump function is the sole mechanism responsible for the major clinical benefit observed in the trial.

Infarct-related arterial patency rates. The patency rates (TIMI grades 2 and 3) of the infarct-related vessel at 10 to 22 days after admission were remarkably high: 83% in the rt-PA group and 77% in the control group. This late patency rate of 77% in the control group is higher than those reported by Rentrop et al. (25) at 10 to 14 days (67%) and White et al. (5) at 3 weeks (54%) in patients not receiving thrombolytic treatment. It can be assumed that the very early intravenous administration of aspirin and heparin, followed by oral aspirin and continuous anticoagulation, in the European Cooperative study was beneficial by enhancing both endogenous and rt-PA–induced thrombolysis and also by preventing rethrombosis of the infarct-related vessel.

Mortality. Although not designed primarily as a mortality study, the trial demonstrated that the administration of rt-PA for acute myocardial infarction is associated with an improved short-term survival. Despite very low mortality rates in the control group, a reduction in mortality rate at 14 days of 51% was observed in the total group of patients allocated to rt-PA (from 5.7% to 2.8%). In patients in whom the rt-PA infusion was started within 3 h of onset of symptoms, the reduction in mortality rate at 14 days was 82% (from 6.3% to

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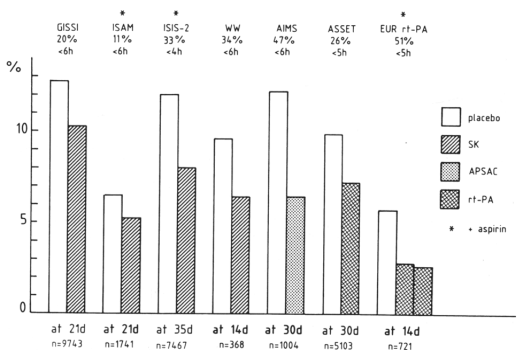

Figure 2. Early mortality rates in large placebo-controlled trials with intravenously administered thrombolytic agents. The time window for treatment and the percent mortality reduction observed in each trial are shown at the **top of the bars.** The number of patients allocated within the given time window are shown below. The **third bar on the right side** indicates the 14 day mortality rate in 184 rt-PA-treated patients from the previously reported European trial (ref. 26). AIMS = AIMS trial (ref. 9); APSAC = anisoylated plasminogen streptokinase activator complex; ASSET = ASSET trial (ref. 16); Eur rt-PA = European Cooperative trials with rt-PA (present study and ref. 26); GISSI = GISSI trial (ref. 1); ISAM = ISAM trial (ref. 2); ISIS-2 = ISIS-2 trial (ref. 8); SK = streptokinase; rt-PA = recombinant tissue-type plasminogen activator; WW = Western Washington trial (ref. 4).

1.1%). At 3 month follow-up the reductions in mortality rate were 36% for the total group (from 7.9% to 5.1%) and 59% for patients treated within 3 h (from 8.2% to 3.4%). These mortality rates are nearly identical to those recently reported by the European Cooperative Study Group for a similarly selected and treated group of patients (26) and are the lowest published so far in large thrombolysis trials.

Mortality rates in the placebo group were very low when compared with those in other studies of intravenous thrombolytic therapy (Fig. 2). It is unlikely that this is caused by selection of a low risk group of patients because the ECG criteria were more stringent than in the other studies and because patients with cardiogenic shock or previous infarction were not excluded. In view of the recent findings of the ISIS-2 trial it is very likely that the administration of low dose aspirin and heparin in the European Cooperative trial may have contributed not only to the high patency rates of the infarct-related vessel (previously mentioned) but also to the lower mortality rates when compared with the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial (16). The 51% reduction in mortality rate found in the European Cooperative trial despite a very low mortality rate in the placebo group undoubtedly supports the efficacy of rt-PA.

Complications. In addition to the mortality reduction, the incidence of cardiovascular complications (e.g., shock, pericarditis, ventricular fibrillation) was markedly lower in the thrombolysis group. On the other hand, bleeding complications occurred more frequently in rt-PA–treated patients. The incidence of intracranial bleeding after rt-PA of 1.4% (5 of 355 patients) in this trial contrasts with the 0.3% incidence (only 1 of 367 patients) in the other recently reported trial from the European Cooperative Study Group (26) in which entry criteria, treatment regimens with rt-PA, heparin and aspirin were identical. When the data of these two European trials are combined, the total incidence of intracranial hemorrhage was 0.8% (6 of 722 patients). Among 3,768 patients treated with 80 to 120 mg rt-PA from Genentech Inc. and Boehringer Ingelheim GmbH up to the summer of 1987, an intracranial bleeding episode occurred in 0.4% (95% confidence interval 0.2% to 0.6%) of the patients (27). The number of gastrointestinal or other major bleeding episodes was small. Blood transfusions were required in 3.7% of the rt-PA–treated patients and in 1.9% of the placebo-treated patients. On the basis of the available data it is impossible to establish the relative frequency of cerebral bleeding with streptokinase, APSAC or rt-PA because cerebrovascular accidents in large thrombolysis trials are most often reported as strokes and because computed tomography scans have not been performed systematically.

Bleeding complications after thrombolytic therapy possibly consist of two groups (28): In the first group hemorrhagic complications are caused by the dissolution of a fibrin-stabilized hemostatic plug of a vascular lesion. The incidence of this type of bleeding is probably related to the efficacy of the thrombolytic agent. In the other group bleeding might be due to impaired primary hemostasis. In these patients the incidence of bleeding complications will be related to the degree of systemic fibrinolytic activation and will be influenced by adjunctive antithrombotic and antiplatelet treatment. The most severe bleeding complications are expected to occur when the life-saving hemostatic plug of a vascular lesion is dissolved in the setting of a defective hemostasis due to severe hypofibrinogenemia. In view of these considerations, a careful evaluation not only of the incidence but also of the severity of the bleeding complications after different thrombolytic treatment regimens seems to be warranted.

Conclusions. The European Cooperative Study Group has clearly shown that the intravenous infusion of rt-PA after an acute myocardial infarction in addition to heparin and aspirin exerts a beneficial effect on infarct size, left ventricular function, early survival and cardiovascular morbidity, but at the cost of an increased risk of bleeding. The observed beneficial effects indicate a substantial salvage of ischemic myocardium due to the early administration of rt-PA. Treatment with rt-PA can therefore be recommended in patients with acute myocardial infarction. Most likely, such treatment will be cost-effective (29). However, definite choice between the newer thrombolytic agents must await the results of ongoing (GISSI-2 and the International rt-PA/streptokinase mortality trial) and future (ISIS-3 trial) multicenter trials directly comparing the relative efficacy, safety and clinical benefit (including survival) of these drugs.

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