JACC Vol. 12, No. 3
September 1988:581–7

COOPERATIVE STUDIES

Intravenous Recombinant Tissue Plasminogen Activator (rt-PA) and Urokinase in Acute Myocardial Infarction: Results of the German Activator Urokinase Study (GAUS)

KARL-LUDWIG NEUHAUS, MD, ULRICH TEBBE, MD, MARTIN GOTTWIK, MD, MICHAEL A.J. WEBER, MD, WERNER FEUERER, MD, WALTER NIEDERER, MD, WINFRIED HAERER, MD, FRANK PRAETORIUS, MD, KLAUS-DIETER GROSSER, MD, WOLFGANG HUHMANN, MD, HANS-WILHELM HOEPP, MD, GUENTER ALBER, MD, ABDOHLHAMID SHEIKHZADEH, MD, BERTHOLD SCHNEIDER, MD

Kassel, West Germany

The effects of recombinant tissue plasminogen activator (rt-PA) and urokinase on patency and early reocclusion of infarct-related coronary arteries were investigated in a single blind, randomized multicenter trial in 246 patients with acute myocardial infarction of <6 h duration. Both 70 mg of single chain rt-PA with an initial bolus of 10 mg and 3 million units of urokinase with an initial bolus of 1.5 million units were given intravenously over 90 min. The first angiographic study at the end of the infusion revealed a patent infarct-related artery (Thrombolysis in Myocardial Infarction trial [TIMI] grade 2 or 3) in 69.4% of 121 patients given rt-PA versus 65.8% of 117 patients given urokinase (p = NS). Among patients treated within 3 h from symptom onset a patent infarct-related artery was found in 63.9% of 72 patients given rt-PA versus 70% of 70 patients given urokinase (p = NS).

There were five cardiac deaths in each group and one fatal intracranial hemorrhage in the rt-PA group. The in-hospital reinfarction rate was 8.9% versus 13.2% for patients treated with rt-PA and urokinase, respectively. There was no difference in left ventricular function at baseline and follow-up catheterization studies. Both drugs were well tolerated and there was no significant difference in cardiovascular or bleeding complications between the two groups.

It is concluded that rt-PA and urokinase in the dosages used provide similar efficacy and safety in the treatment of acute myocardial infarction. Reocclusion during the first 24 h may be less frequent after urokinase treatment.

(J Am Coll Cardiol 1988;12:581–7)

Recent studies (1,2) have reported recombinant tissue plasminogen activator (rt-PA) to be more effective in early recanalization of infarct-related coronary artery occlusion than streptokinase. The risk of bleeding, however, which had been thought to be reduced with the new fibrin-specific agent, was significantly less in one study (1) but similar to that of streptokinase in another (2) despite a lesser degree of fibrinogenolysis with rt-PA (1,2). Furthermore, the short half-life of rt-PA may lead to a high incidence of early reocclusions unless the infusion is prolonged to ≥3 h (3), which in turn increases the risk of bleeding (4). Because intravenous urokinase is both effective in early reperfusion (5) and possibly associated with a lesser incidence of reocclusion than rt-PA as a result of a longer half-life and an extended systemic fibrinolysis, the effects of rt-PA and urokinase on patency and early reocclusion of infarct-related arteries were compared in a randomized single-blind multicenter trial (German Activator Urokinase Study [GAUS]).

Methods

Study patients. From March 1986 to February 1987, 246 patients aged 25 to 75 years with an acute myocardial infarction of >30 min and <6 h duration were enrolled into

From the Medizinische Klinik II, Staedtische Kliniken Kassel, Kassel, West Germany. This study was supported by a grant from Dr. Karl Thomae, Inc., Biberach, West Germany.

Manuscript received December 1, 1987; revised manuscript received April 13, 1988, accepted April 28, 1988.

Address for reprints: Karl-Ludwig Neuhaus, MD, Medizinische Klinik II, Staedtische Kliniken Kassel, Moenchebergstrasse 41-43, D-3500 Kassel, West Germany.

0735-1097/88/$3.50

the study. Inclusion criteria consisted of typical symptoms of acute myocardial infarction and ST segment elevation in ≥2 of the 12 leads of the standard electrocardiogram (ECG), >1 mm in standard leads and >2 mm in precordial leads. Exclusion criteria were a known bleeding disorder, oral anticoagulation, peptic ulcer during the last 3 months, inflammatory bowel disease, esophageal varices, aortic aneurysm, uncontrolled hypertension (systolic blood pressure ≥200 mm Hg or diastolic blood pressure ≥110 mm Hg), external cardiac massage, complicated puncture of deep veins, trauma or operation within the last 6 months, short-term headache of unknown origin, cancer, bacterial endocarditis, pregnancy or any other condition posing an increased risk of bleeding during fibrinolysis as judged by the physician in charge. Patients who were unable to give informed consent were also excluded.

After informed consent, written or witnessed, was obtained, the patient's identification was transmitted by phone to the data center for randomization, and the code number of the prepackaged lytic substance to be given to that patient was obtained. The sample size of the study was computed to be 434 patients (α = 5%, β = 10%) assuming a 70% patency rate of the infarct-related artery in the rt-PA group and 55% in the urokinase group at the 90 min-angiographic study. It was decided to have data analysis performed at predefined sample sizes of 100, 200 and 300 patients by an independent statistician to report to the ethics committee and stop the study before the preset sample size, in case a significant difference in patency rates or complications would be observed or no significant difference could be extrapolated for the preset maximal sample size. Accordingly, the trial was stopped on January 31, 1987 on the basis of the last interim analysis of 190 patients, which at the 90 min coronary angiographic study revealed a 0.2% difference in perfusion (Thrombolysis in Myocardial Infarction trial [TIMI] grade 3) and a 6.2% difference in perfusion TIMI grade 2 between rt-PA and urokinase.

Treatment protocol. Patients randomized to rt-PA treatment (n = 124) received a bolus of 5,000 U heparin followed by a sequence of intravenous rt-PA infusions, 10 mg by bolus injection, 50 mg over 1 h and another 10 mg over 30 min (predominantly single-chain rt-PA, Genentech Inc., supplied by Thomae). Patients randomized to urokinase (n = 121) received a bolus of 5,000 U heparin followed by a bolus of 1.5 million units of urokinase and another 1.5 million units over 90 min (Alphakinase, Alpha Therapeutic GmbH). Pretreatment angiographic study was not performed. During infusion of the fibrinolytic drugs, the patients were transferred to the catheterization laboratory, and the first angiographic study was started by opacification of the presumed infarct-related artery 90 min (range 90 to 105) after the onset of fibrinolytic therapy, followed by the opacification of the remaining coronary arteries in at least two projections of the right and three projections of the left coronary artery. Angiographic study was followed by left ventriculography, either single plane in the 30° right anterior oblique projection or biplane in 30° right anterior oblique and 60° left anterior oblique projections.

The investigators were free to perform further recanalization procedures at the end of the 90 min angiographic study such as intracoronary or prolonged intravenous thrombolysis or coronary angioplasty, which had to be documented by cineangiographic study and in the protocol. When the Judkins technique was used, the investigators were asked to repeat the coronary angiographic studies of the infarct-related artery after 24 h (range 12 to 36) before removal of the introducer sheaths. A second complete coronary and ventricular angiographic study was performed 10 to 28 days later or before hospital discharge when indicated.

Twelve lead ECGs were recorded before treatment, after 3, 24 and 48 h and before the last angiographic study or at hospital discharge. Creatine kinase-MB fraction (MB CK) serum levels were measured before treatment and at 4 h intervals up to 48 h; fibrinogen levels were measured before treatment and after 3 and 24 h.

A detailed analysis of hemostatic and fibrinolytic variables was undertaken in a large subset of patients; it will be reported separately.

Anticoagulation was instituted after fibrinolysis with intravenous heparin when the thrombin time had returned to 2.5 times normal or the partial thromboplastin time to 1.5 times normal values and was maintained during the hospital stay either by intravenous or subcutaneous heparin or by an oral anticoagulant agent.

Reinfarction was defined as an anginal episode of >30 min duration unresponsive to nitrates and associated with significant ST segment elevation, regardless of new Q waves and a significant increase of cardiac enzymes.

Assessment of coronary and ventricular angiograms. Each angiogram was graded for patency and perfusion of the infarct-related artery by two experienced investigators (K.L.N. and U.T.) according to the classification criteria of the TIMI study group (2). The investigators were unaware of the treatment mode. The infarct-related artery was identified from the sequential angiograms and the ST segment changes in the ECG. Left ventricular ejection fraction was assessed from the 30° right anterior oblique single plane ventriculogram with the use of the formula of Sandler and Dodge (7).

All angiocardiograms were then sent to the central angiographic study analysis at Erlangen for quantitative assessment of the infarct-related artery (7) and regional and global ventricular function.

In this report, only data of the central evaluation in Goettingen will be reported. A total of seven angiograms at 90 min could not be analyzed (three from patients receiving rt-PA and four from patients receiving urokinase): three were missed for technical reasons and in two patients (one

Table 1. Selected Baseline Variables of 245 Patients on Admission

	rt-PA (n = 124)	UK (n = 121)
Men (%)	83.1	87.6
Age (yr)	57 ± 10	57 ± 10
Time from onset of symptoms to infusion (h)		
0 to 2	27 (21.8%)	34 (28.1%)
>2 to 4	74 (59.7%)	60 (49.6%)
>4 to 6	23 (18.5%)	27 (22.3%)
Systolic blood pressure (mm Hg)	134 ± 22 (80 to 190)	128 ± 23* (60 to 180)
Diastolic blood pressure (mm Hg)	83 ± 11 (50 to 105)	80 ± 14 (20 to 105)
Heart rate (beats/min)	77 ± 18 (43 to 130)	79 ± 21 (20 to 182)
Pulmonary rales	15 (12.1%)	25 (20.7%)
MB CK (U/liter)	8.7 ± 10.4 (n = 90)	8.2 ± 8.4 (n = 86)
Anterior MI	65 (52.4%)	53 (43.8%)†
Previous MI	18 (14.5%)	20 (16.5%)
Diabetes mellitus	13 (10.5%)	16 (13.2%)

*p = 0.04; †p = 0.08. MB CK = serum creatine kinase, MB fraction; MI = myocardial infarction; rt-PA = recombinant tissue plasminogen activator; UK = urokinase.

rt-PA and one urokinase) the first angiographic study was not performed for clinical reasons; one patient refused angiographic study after randomization and one angiogram was lost in the mail.

Statistical analysis. The proportion of events in the two treatment groups were compared by standard methods. Ordered variables were compared by the Mann-Whitney U test; where appropriate, chi-square and *t* tests were used. The chi-square test was corrected according to Yates, when the number of events was <5 in at least one group.

Results

Clinical features and events. Two-hundred forty-five patients received the study medication (rt-PA in 124 and urokinase in 121). One patient allocated to rt-PA did not receive the study medication because a contraindication (oral anticoagulant therapy) was detected before the start of infusion. With respect to baseline variables, there was no major difference between the two treatment groups (Table 1). Systolic blood pressure was slightly higher and the proportion of anterior infarction was slightly larger in the rt-PA than in the urokinase group (52.4 versus 43.8%, p = 0.08). Treatment groups did not differ with respect to medical therapy before thrombolysis including pretreatment with intravenous nitroglycerin.

Two major incidents occurred between the onset of thrombolysis and the end of the first angiographic study. In the rt-PA group, one patient died in cardiogenic shock as a consequence of an extended anterior myocardial infarction and one patient had a cerebrovascular ischemic event with subsequent complete recovery.

Table 2. Patency of Infarct-Related Artery* in 238 Patients

	rt-PA	UK	p Value (chi-square test)
Angiogram at 90 min	n = 121	n = 117	
TIMI grade 2 or 3	84 (69.4%)	77 (65.8%)	0.56
Angiogram at 24 h	n = 105	n = 105	
TIMI grade 2 or 3	82 (78.1%)	77 (73.3%)	0.43
Angiogram after >10 days	n = 86	n = 83	
TIMI grade 2 or 3	63 (73.3%)	59 (71.1%)	0.75

*Angiograms at 24 h and after >10 days were performed after various interventions (see Table 4). TIMI = Thrombolysis in Myocardial Infarction trial. Other abbreviations as in Table 1.

Cardiovascular complications including atrioventricular (AV) block and ventricular tachyarrhythmias were similar in both groups. A systolic blood pressure <90 mm Hg was seen more frequently in the urokinase group (13 versus 7 patients). Both thrombolytic agents were well tolerated; no definite allergic reaction was reported with either drug.

Angiographic findings. The patency of the infarct-related coronary artery as assessed from the angiograms by two independent observers unaware of other patient data is listed in Table 2 for both treatment groups. A 90 min angiogram (performed at a mean of 97 ± 10 min in either group) was evaluated in 98% of the rt-PA group and in 97% of the urokinase group, a 24 h angiogram in 85 and 87%, respectively and a ≥10 day angiogram in 69% of both groups. The patency rate of the infarct-related artery in both treatment groups did not differ significantly at 90 min, at 24 h or after 10 days.

Left ventricular angiograms suitable for interpretation were available in 89, 56 and 64% of patients at the first, second and third angiographic study, respectively. Left ventricular ejection fraction at the first, second and third angiographic study was 54 ± 15 versus 53 ± 14% (NS), 54 ± 12 versus 52 ± 12% (NS) and 53 ± 12 versus 52 ± 14% (NS) for the rt-PA and the urokinase group, respectively.

Interventions during first angiographic study (Table 3). Additional revascularization procedures in the patients with high grade residual stenosis or persisting occlusion of the infarct-related artery were left to the decision of the investigating physician. Thus, coronary angioplasty was attempted in both treatment groups in a total of 52 patients (32 rt-PA and 20 urokinase), intracoronary thrombolysis in 32, intravenous thrombolysis in 13 and emergency surgical bypass grafting in five patients.

Reocclusion of the infarct-related artery (Table 4). In 102

Table 3. Interventions After Thrombolytic Therapy

	rt-PA		UK	
	Total	Success	Total	Success
A. Interventions During First Angiographic Study				
CABG	2	—	3	—
PTCA only	17	13	9	9
PTCA and i.c. lysis	11	6	11	5
PTCA and i.v. lysis	4	3	0	—
i.c. lysis only	6	3	5	2
i.v. lysis only	9	2	0	—
B. Interventions After the First Angiographic Study				
CABG	7	—	12	—
PTCA only	13	10	10	8
PTCA and i.c. lysis	3	2	0	—
PTCA and i.v. lysis	0	—	1	1
i.c. lysis only	1		0	—
i.v. lysis only	1	1	0	—

CABG = coronary artery bypass grafting; i.c. = intracoronary; i.v. = intravenous; PTCA = percutaneous transluminal coronary angioplasty. Other abbreviations as in Table 1.

of the 124 patients treated with rt-PA the infarct-related artery was patent at completion of the first angiographic study, with or without additional recanalization procedures, compared with 87 of the 121 patients in the urokinase group. In 14 patients treated with rt-PA and 10 of the urokinase group, 24 h films were not obtained, leaving 88 and 77 patients, respectively, with a patent artery who were restudied. A reocclusion rate of 14.8% was observed after rt-PA treatment as compared with a rate of 6.5% with urokinase treatment. In patients with a patent artery at the 90 min angiographic study and no additional intervention, early reocclusion rate as assessed from the 24 h angiogram was 10.5% in the rt-PA group and 1.6% in the urokinase group ($p = 0.08$). Comparison of late reocclusions as listed in Table 4 did not show a significant difference between the rt-PA and urokinase groups.

Events during hospital stay. There were 11 deaths (4.5%) during the study period, 6 in the rt-PA and 5 in the urokinase group; all were due to cardiac causes with the exception of one fatal intracranial hemorrhage in the rt-PA group. Reinfarction occurred in 27 patients, 11 (8.9%) in the rt-PA and 16 (13.2%) in the urokinase group; this was not associated with a re-elevation of CK levels to >100 U/liter in 11 of the 27 patients.

Apart from a slightly greater rate of bleeding at puncture sites in the urokinase group (22.3 versus 14.5%) and a slightly greater rate of angina pectoris after rt-PA treatment (35 versus 27%), bleeding and cardiovascular complications were evenly distributed in the two treatment groups.

Table 4. Reocclusion Rate of Patent Infarct-Related Arteries in 238 Patients

	rt-PA (n=121)	UK (n=117)	p Value (chi-square test)
Patient artery (TIMI 2 or 3) after first angiographic study (including successful interventions)	102 (84.3%)	87 (74.4%)	0.06
Reoccluded at 24 h (TIMI 0 or 1)	13/88 (14.8%)	5/77 (6.5%)	0.09
No angiographic study at 24 h	14	10	
Reoccluded after >10 days (TIMI 0 or 1)	7/72 (9.8%)	8/62 (12.9%)	0.57
No data	30	27	
Patient artery (TIMI 2 or 3) at 90 min angiogram without additional intervention	63	66	0.51
Reoccluded at 24 h (TIMI 0 or 1)	6/57 (10.5%)	1/63 (1.6%)	0.09*
No angiographic study at 24 h	6	3	
Reoccluded after >10 days (TIMI 0 or 1)	5/47 (10.6%)	5/49 (10.2%)	0.94
No data	18	18	

*Chi-square test corrected according to Yates. Abbreviations as in Tables 1 and 2.

Systemic fibrinolysis. Systemic fibrinolytic effects as reflected in fibrinogen levels after infusion were significantly more frequent and pronounced with urokinase treatment. The fibrinogen level (local assessment, Clauss method [8]) before the infusion was 3.2 ± 1 g/liter in both groups; 90 min after the end of the infusion it decreased to 2.9 ± 0.9 g/liter in the rt-PA group and to 0.9 ± 0.9 g/liter in the urokinase group ($p < 0.001$). A decrease below 1 g/liter was found 90 min after the end of the infusion in 12.7 versus 70%, respectively, of the patients receiving rt-PA and urokinase, and it persisted for ≥24 h in 4.5 versus 27.7%, respectively ($p < 0.001$).

Discussion

Several large clinical trials (9–12) have clearly demonstrated the efficacy of intracoronary and intravenous thrombolysis with streptokinase in reducing both infarct size (9,10) and hospital mortality (11,12) from acute myocardial infarction. Therefore, interest has focused on improvement of the risk/benefit ratio of thrombolysis. The development of fibrin-specific fibrinolytic agents, especially rt-PA, is considered a major step forward in this direction. In contrast to strepto-

Table 5. Patency Rate of Infarct-Related Arteries 90 min After Start of Infusion

TIMI Grade	Total		Treatment ≤3 h		Treatment 3 to 6 h After Symptom Onset	
	rt-PA (n=121)	UK (n=117)	rt-PA (n=72)	UK (n=70)	rt-PA (n=49)	UK (n=47)
3	67 (55.4%)	63 (53.8%)	35 (48.6%)	44 (62.9%)	32 (65%)	19 (40%)
	p=0.81		p=0.08		p=0.01	
2	17 (14%)	14 (12%)	11 (15.3%)	5 (7.1%)	6 (12.2%)	9 (19.1%)
	p=0.64		p=0.12		p=0.35	
0 or 1	37 (30.6%)	40 (34.2%)	26 (36.1%)	21 (30%)	11 (22.4%)	19 (40.4%)
	p=0.56		p=0.45		p=0.05	

Abbreviations as in Tables 1 and 2.

kinase, rt-PA has no antigenic or pyrogenic properties and it induces much less systemic fibrinolysis; reperfusion rates after its administration have been found superior to those after administration of streptokinase when both drugs were given intravenously (1,2).

Recent experience (4) has shown, however, that the risk of bleeding with prolonged high dose rt-PA treatment (150 mg over 6 h) may approach that of intravenous streptokinase, and the rate of early reocclusion may be comparable with that after streptokinase treatment. Because urokinase offers the same advantages as rt-PA apart from fibrin specificity and has been shown to be effective in recanalization of infarct-related arteries (5), we tested rt-PA versus urokinase comparing a 90 min intravenous infusion of both agents with respect to patency and reocclusion rate of infarct-related arteries.

Urokinase versus rt-PA dosage. According to available data at the time of study design, a total dose of 70 mg predominantly single-chain rt-PA administered over 90 min starting with a loading dose of 10 mg was chosen. For reasons of comparability, urokinase was also given over 90 min with an initial bolus and a total dose of 3 million units. The dosage was derived from previous experience of one of us (K.L.N., unpublished data) with the use of a loading dose of 1 million units of urokinase followed by another million units over 60 min. This regimen was well tolerated with only minor bleeding complications as was the single 2 million unit bolus of urokinase reported by Mathey et al. (5). Because dose-ranging studies for urokinase and streptokinase are not available to date, the dosage of 3 million units may appear arbitrary.

Coronary patency rates. Because pretreatment angiograms were not obtained in this study, only patency of infarct-related arteries at the end of fibrinolytic therapy can be compared. A major imbalance in the incidence of total occlusions, however, is unlikely because of the large sample size and the balanced baseline characteristics at entry into the study. In contrast to our assumptions, the patency rate at the end of infusion was very similar (69.4 versus 65.8%, TIMI grade 2 or 3) after treatment with rt-PA and urokinase, and almost identical with regard to prompt distal filling (TIMI grade 3) (55.4 versus 53.8%).

These results are close to the patency rates reported for double-chain rt-PA in a dosage of 0.75 mg/kg over 90 min (1,13) and in a dosage of 80 mg over 3 h (2). With single-chain rt-PA a patency rate of 69%, which is identical to our result, was achieved by a similar cumulative dose of up to 70 mg at 90 min in a subset of 71 patients studied by Topol et al. (14). The incidence of patent infarct-related arteries was greater after treatment with urokinase in the dosage used in this study than after a single bolus injection of 2 million units of urokinase in an uncontrolled study by Mathey et al. (5). This difference occurred even though the time from onset of symptoms to infusion, considered to be important for successful thrombolysis (9,10), was shorter in the patients studied by Mathey et al. This finding is in agreement with the concept of a direct dose-related fibrinolytic effect of urokinase.

When the data are stratified for early (≦3 h) and late treatment (3 to 6 h from symptom onset), urokinase seems to be more effective than rt-PA in achieving complete reperfusion (TIMI grade 3) in the early treatment group, whereas in the late treatment group the patency rate was lower after urokinase (Table 5). This retrospective analysis, however, does not prove a time-related difference in thrombolytic efficacy despite its statistical significance because this subgroup analysis had not been anticipated in the study protocol.

Early coronary reocclusion. The problem of early reocclusion after successful thrombolysis in this study was addressed by angiographic restudy of the infarct-related artery 24 h after fibrinolytic therapy. A 24 h coronary angiogram was available in 105 patients in each group (86.8% of the rt-PA and 89.7% of the urokinase group). Because there were more successful additional recanalization procedures in the rt-PA group (28 versus 17), the total number of reocclusions during the first 24 h may be biased. The difference in favor of urokinase treatment (6.6 versus 14.8%)

is further confounded by the fact that >10% of the patients did not have a 24 h angiogram. In those patients who did have a patent artery and no additional intervention, the difference in an early reocclusion rate of 1.6 versus 10.5% with urokinase and rt-PA treatment, respectively, gives rise to the hypothesis that the prolonged systemic lytic state after urokinase treatment may prevent early rethrombosis. The rate of early reocclusion in the rt-PA group, however, might well be adversely affected by the lower total dose and the shorter duration of treatment in our study as compared with others (2,3,14).

Late coronary reocclusion. The data of this study suggest that reocclusion after the first 24 h is less affected than early reocclusion by the type of fibrinolytic agent, being about 10% in both treatment groups. These angiographic findings are somewhat inconsistent with the total number of reinfarctions, which was slightly larger (13.2 versus 8.9%) in the urokinase group. This seeming discrepancy may occur in part because the fact on the one hand, very early reocclusion may not appear clinically as a reinfarction and, on the other hand, prevention of early reocclusion will increase the potential for later reinfarction. The validity of these explanations, however, cannot be assessed from the data of this trial for the reasons mentioned previously.

Side effects. As expected, for both fibrinolytic agents occurring as natural human proteins, no significant side effects were observed. Despite the stronger fibrinogenolytic activity of urokinase, bleeding complications in the rt-PA and urokinase groups were similar apart from bleeding at puncture sites (14.5 versus 22.3%, NS).

Conclusions. From the data of this study, we conclude that the risk-benefit ratio in the treatment of acute myocardial infarction is similar for rt-PA and urokinase at least in the dosages that were used in this trial. The differences in coronary patency rate with early and late treatment and in the rate of early reocclusion have to be confirmed by further studies before definite conclusions may be reached.

Appendix

Steering Committee. Karl-Ludwig Neuhaus, MD, Goettingen (Chairman); Kurt Bachmann, MD, Erlangen; Martin Gottwik, MD, Nuernberg; Berthold Schneider, MD, Hannover; Wolfram Theiss, MD, Munich; Michael A.J. Weber, MD, Munich.

Advisory Board. Wolfgang Kuebler, MD, Heidelberg; Paul Schoelmerich, MD, Mainz; Rolf Schroeder, MD, Berlin.

Coordinating Center, Goettingen. Karl-Ludwig Neuhaus, MD (Chairman); Susanne Jeep-Tebbe; Ulrich Tebbe, MD.

Data Center, Biberach. Werner Feuerer, MD (Chairman); Andrea Maucher.

Data Center, Goettingen. Karl-Ludwig Neuhaus, MD (Chairman); Susanne Jeep-Tebbe; Ulrich Tebbe, MD; Sieglinde Kellner.

Statistic Board, Biberach. Till Mey, MD; Franz Szottka, MD; Andrea Maucher.

Statistic Board, Hannover. Berthold Schneider, MD.

Central Angiographic Study Analysis, Erlangen. Kurt Bachmann, MD (Chairman); Bernhard Kunkel, MD; Andreas Weikl, MD; Rolf Gansser, MD, Silvia Paucke; Susanne Meier.

Central Angiographic Study Analysis, Goettingen. Karl-Ludwig Neuhaus, MD (Chairman); Susanne Jeep-Tebbe; Ulrich Tebbe, MD.

Electrocardiogram analyzing center. Michael A.J. Weber, MD.

Central Coagulation Laboratories. Wolfram Theiss, MD, Munich; Erhard Hiller, MD, Munich-Grosshadern; Wolfgang Brockhaus, MD, Nuernberg; Erhard Seifried, MD, Ulm; Wolfgang Schramm, MD, Munich; Heinz Koestering, MD, Goettingen.

Clinical Centers

Klinikum der Stadt Nuernberg. Martin Gottwik, MD, Wolfgang Reiser, MD.

Kliniken der Universitaet Ulm. Martin Stauch, MD, Winfried Haerer, MD.

Klinikum Muenchen-Grosshadern. Gernot Autenrieth, MD, Thomas von Arnim, MD.

Klinikum Muenchen-Innenstadt. Michael A.J. Weber, MD, Jochen Kotzur, MD, Mathias C. Haufe, MD.

Universitaetsklinik Goettingen. Karl-Ludwig Neuhaus, MD, Ulrich Tebbe, MD.

Stadtkrankenhaus Traunstein. Guenter Alber, MD.

Staedtische Krankenanstalten Krefeld. Klaus-Dieter Grosser, MD, Klaus Knoch, MD.

Medizinische Universitaetsklinik III Koeln. Hans Hermann Hilger, MD, Hans-Wilhelm Hoepp, MD.

Medizinische Hochschule Luebeck. Abdohlhamid Sheikhzadeh, MD, Hasib Djonlagic, MD.

Katharinen-Hospital Stuttgart. Anton Both, MD, Jochen Balbach, MD.

Medizinische Universitaet Bonn. Berndt Luederitz, MD, Jobst Nitsch, MD.

Medizinische Universitaet Duesseldorf. Franz Loogen, MD, Joachim Jehle, MD.

Krankenhaus Regensburg. Walter Niederer, MD, Udo Reisp, MD.

Stadtkrankenhaus Offenbach. Frank Praetorius, MD, Ernst Girth, MD.

Medizinische Klinik I Fulda. Wolfgang Huhmann, MD, Rainer Hoffmann, MD.

St. Elisabeth Krankenhaus Essen. Georg Sabin, MD, Guenther Szurawitzki, MD.

References

1. Verstraete M, Bernard R, Bory M, et al. Randomized trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Lancet 1985;1:842–7.
2. TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial: Phase I findings. N Engl J Med 1985;312:932–6.
3. Gold HK, Leibach RC, Garabedian HD, et al. Acute coronary reocclusion after thrombolysis with recombinant human tissue-type plasminogen activator: prevention by a maintenance infusion. Circulation 1986;73:347–52.
4. TIMI-Operations Committee. Announcement of protocol change in TIMI trial. Letter to the editor. J Am Coll Cardiol 1987;9:467.
5. Mathey DG, Schofer H, Sheehan FH, et al. Intravenous urokinase in acute myocardial infarction. Am J Cardiol 1985;55:878–82.
6. Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volumen in man. Am Heart J 1968;75:325–34.
7. Reiber JHC, Kooijman CJ, Slager CJ, et al. Coronary artery dimensions from cineangiograms: methodology and validation of a computer-assisted analysis procedure. IEEE Trans Med Imag 1984;MI-3:131–41.
8. Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. Acta Haematol 1957;17:237–46.
9. Schröder R, Neuhaus KL, Leizorovicz A, Linderer T, Tebbe U for the ISAM Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.). N Engl J Med 1986;314:1465–71.
10. Kennedy JW, Ritchie JL, Davis KB, et al. The Western Washington

randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1985;312:1073–8.

11. Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–402.
12. ISIS Steering Committee. Intravenous streptokinase given within 0–4 hours of onset of myocardial infarction reduced mortality in ISIS-2. Lancet 1987;1:502.
13. Verstraete M, Bleifeld W, Brower RW, et al. Double-blind trial of intravenous tissue-type plasminogen activator versus placebo in acute myocardial infarction. Lancet 1985;2:965–9.
14. Topol EJ, Douglas CM, Smalling RW, et al. A multicenter, randomized, placebo-controlled trial of a new form of intravenous recombinant tissue-type plasminogen activator (Activase) in acute myocardial infarction. J Am Coll Cardiol 1987;9:1205–13.