

Sixty-Minute Alteplase Protocol: A New Accelerated Recombinant Tissue-Type Plasminogen Activator Regimen for Thrombolysis in Acute Myocardial Infarction

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Objectives. Our aim was to design and evaluate a new and easily administered recombinant tissue-type plasminogen activator (rt-PA) regimen for thrombolysis in acute myocardial infarction (AMI) based on established pharmacokinetic data that improve the reperfusion success rate.

Background. Rapid restoration of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow is a primary predictor of mortality after thrombolysis in AMI. However, TIMI grade 3 patency rates 90 min into thrombolysis of only 50% to 60% indicate an obvious need for improved thrombolytic regimens.

Methods. Pharmacokinetic simulations were performed to design a new rt-PA regimen. We aimed for a plateau tissue-type plasminogen activator (t-PA) plasma level similar to that of the first plateau of the Neuhaus regimen. These aims were achieved with a 20-mg rt-PA intravenous (i.v.) bolus followed by an 80-mg i.v. infusion over 60 min (regimen A). This regimen was tested in a consecutive comparative trial in 80 patients versus 2.25 10⁶ IU of streptokinase/60 min (B), and 70 mg (C) or 100 mg (D) of rt-PA over 90 min. Subsequently, a confirmation trial of regimen A in 254 consecutive patients was performed with angiographic assessment by independent investigators of patency at 90 min.

Results. The comparative phase of the trial yielded, respectively, TIMI grade 3 and total patency (TIMI grades 2 and 3) of 80% and 85% (regimen A), 35% and 50% (B), 50% and 55% (C) and 60% and 70% (D). In the confirmation phase of the trial, regimen A yielded 81.1% TIMI grade 3 and 87.0% total patency. At follow-up angiography 7 (4.1%) of 169 vessels had reoccluded. In-hospital mortality rate was 1.2%. Nadir levels of fibrinogen, plasminogen and alpha₂-antiplasmin were 3.6 ± 0.8 mg/ml, 60 ± 21% and 42 ± 16%, respectively (mean ± SD). Fifty-seven patients (22.4%) suffered from bleeding; 3.5% needed blood transfusions.

Conclusions. The 60-min alteplase thrombolysis in AMI protocol achieved a TIMI grade 3 patency rate of 81.1% at 90 min with no indication of an increased bleeding hazard; it was associated with a 1.2% overall mortality rate. These results are substantially better than those reported from all currently utilized regimens. Head to head comparison with established thrombolytic regimens in a large-scale randomized trial is warranted.

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In the past two decades, thrombolysis has become the mainstay in the treatment of acute myocardial infarction (AMI) (1-3). However, recent trials indicate that only Thrombolysis in Myocardial Infarction (TIMI) grade 3, and not TIMI grade 2 coronary blood flow, if achieved early, substantially lessens infarct mortality (4-6). Thrombolytic therapy today is limited by the fact that even the most aggressive recombinant tissue-

type plasminogen activator (rt-PA) regimens achieve coronary reperfusion at 90 min in only slightly >50% of patients (5). This fact has prompted an intense search for improved thrombolytic protocols, which include rt-PA (7) and its newer derivatives (8-10), as well as conjunctive therapy with direct inhibitors of thrombin activation or platelet aggregation (11,12). Though seemingly very successful in a small single-center pilot trial in 84 patients (7), a double-bolus rt-PA regimen did not result in increased TIMI grade 3 patency rates at 90 min in a larger scale randomized angiographic trial (13) and failed to fulfill expectations in a large cohort of patients with infarction (14). With 40% to 50% of infarct vessels remaining insufficiently reperfused, the need for better thrombolytic regimens persists. We report here a new accelerated rt-PA regimen, the 60-min alteplase protocol, that achieved TIMI grade 3 coronary blood flow in the infarct-related vessel in 80% of patients. We initially performed a small comparative

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
AP	= alpha ₂ -antiplasmin
ECG	= electrocardiographic
Fg	= fibrinogen
i.v.	= intravenous, intravenously
PLG	= plasminogen
PTCA	= percutaneous transluminal coronary angioplasty
rt-PA	= recombinant tissue-type plasminogen activator
TIMI	= Thrombolysis in Myocardial Infarction
t-PA	= tissue-type plasminogen activator

phase of the trial with routinely used thrombolytic regimens. We subsequently performed a large confirmation phase of the trial in 254 consecutive patients with AMI, which corroborated our results. These favorable results were achieved without an increased risk of hemorrhage or stroke.

Methods

Study design. This study in consecutive patients with AMI consisted of two parts. The first part was an open label, nonrandomized, prospective, angiographically controlled comparison with three standard regimens. The second part was an open, prospective angiographically controlled dose-confirmation study in consecutive patients. On enrollment in the study, all patients were given 250 mg of oral aspirin and 5,000 IU of heparin as an intravenous (i.v.) bolus, followed by an i.v. infusion of 1,000 IU/h (starting dose) that was intended to maintain an activated partial thromboplastin time target range between 50 and 80 s and was not interrupted during thrombolysis. Heparin infusion was continued during the first 3 days of therapy.

During the first comparison phase of the study, thrombolysis was performed with one of the following four predefined thrombolytic regimens. Regimen A was derived from the rt-PA pharmacokinetic simulations as outlined later. Regimen B was a continuous infusion of 2.25 MU of streptokinase over 60 min. Regimen C was 10 mg of rt-PA given as an i.v. bolus followed immediately by 50 mg infused i.v. over 60 min and a further 10 mg infused over the next 30 min. This regimen was also used by the investigators of the European Cooperative Study Group (15,16). Regimen D was 15 mg of rt-PA given as an i.v. bolus followed immediately by 50 mg infused i.v. over 30 min and a further 35 mg infused over the next 60 min as described by Neuhaus et al. (17,18). During the second confirmation phase of the study, the newly designed rt-PA dose regimen (A) was given to all consecutive patients.

The first coronary angiogram was recorded at 90 min after the start of therapy. If the infarct-related coronary artery was still occluded (TIMI grade 0 to grade 2 flow) it was left to the discretion of the investigator to perform rescue percutaneous transluminal coronary angioplasty (PTCA). On day 3, heparin infusions were stopped and patients were given 10,000 IU

of subcutaneous heparin twice daily. The maintenance dose of aspirin was 100 to 250 mg once daily. All other medication—including antiarrhythmic drugs, diuretic agents, opiate analgesics or sedatives—was given as clinically required. To avoid interference with any of the additionally given drugs, the thrombolytic agents were given through a separate intravenous line. If the first angiogram revealed TIMI grade 3 flow, the investigators were requested to perform follow-up angiography before the patient's discharge. The study protocol was approved by the local ethics committee.

Patient selection. Patients of either gender, with symptoms characteristic of AMI occurring <6 h before therapy and not responsive to a single dose of sublingual nitrates or nifedipine, were considered for study entry if they met the following electrocardiographic (ECG) criteria: ST segment elevation 1) >0.2 mV in leads I to aVF or V₅ and V₆, or 2) >0.3 mV in leads V₁ through V₄, or 3) >0.1 mV in leads III and aVF plus corresponding ST segment depression >0.2 mV in leads V₁ and V₂. More stringent ECG criteria were applied in this cohort of patients to avoid enrollment of patients whose ECG changes originated from other cardiac diseases. Exclusion criteria were defined as follows: 1) history of recent cerebrovascular accident, 2) active or recent gastric ulcer, 3) overt bleeding, 4) recent major surgery or trauma, 5) known bleeding tendency or coumarin therapy, 6) known renal or hepatic failure, 7) childbearing potential, 8) end-stage malignancies, 9) all other contraindications to either thrombolytic therapy, heparin therapy or cardiac catheterization, and 10) inability to give informed consent. A history of remote AMI was not considered an exclusion criterion if the infarction occurred in a region clearly distinct from the current occlusion site. Patients with left bundle branch block were not entered into this study because of possible difficulties in definition of the localization of the acutely infarcted region. If patients fulfilled the entry criteria, informed consent was obtained before they were enrolled into the study.

Assessment of angiograms. Cineangiograms were recorded on 16-mm cinefilm and assessed for perfusion in the infarct-related coronary artery by two experienced, independent investigators. These investigators did not know the dosage regimen administered to each patient. In the event of discordant patency judgments, a third independent investigator who also did not know the dosage regimen was asked for final judgment. Perfusion was assessed according to the score first introduced by the TIMI investigators (19), with rating grade 0 = no perfusion in the distal coronary bed; grade 1 = penetration of the thrombus with minimal opacification beyond the occlusion; grade 2 = partial perfusion with delayed but complete opacification (>3 cycles) and delayed emptying of the distal vessel; and grade 3 = complete filling and emptying of the vessel at a rate comparable to that of nonseverely stenosed coronary arteries. On the basis of this grading system, thrombolytic therapy was rated successful only when perfusion was rated TIMI grade 3 flow at the first injection of contrast medium into the infarct-related coronary artery.

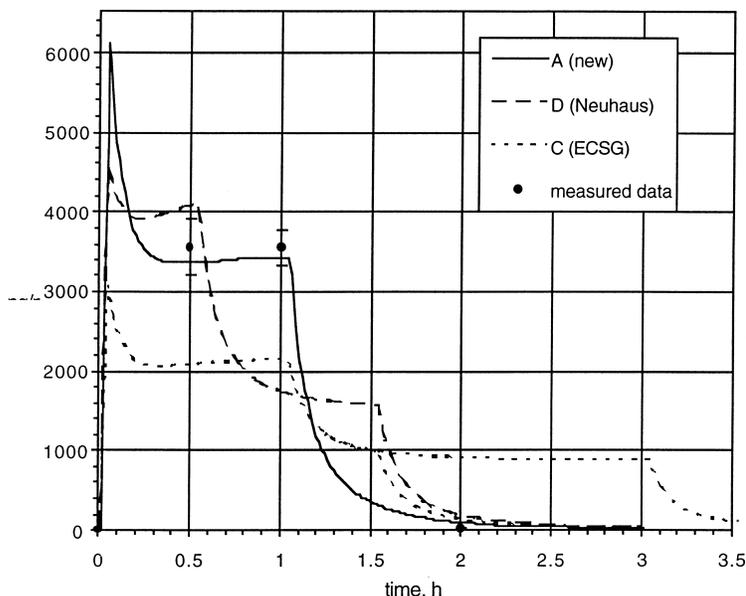


Figure 1. Predicted rt-PA plasma concentration profiles for various dosage regimens based on pharmacokinetic simulation. **Circles** = measured rt-PA plasma concentrations (mean \pm SD) during the new 60-min regimen. ECSCG = European Cooperative Study Group.

Pharmacokinetic simulations. Pharmacokinetic simulations were performed with the program TopFit (20). The data base for simulations comprised model parameters that were derived from fitting of a three-compartment model to rt-PA plasma antigen concentration-time profiles of 12 patients with AMI who underwent rt-PA lysis (21). In that study, the patients were administered the standard dosage regimen of 100 mg of rt-PA over 3 h, that is, an initial 10-mg bolus followed by 50 mg infused over 1 h and 40 mg infused over the next 2 h. Individual fits were performed for each patient data set, and mean pharmacokinetic microconstants were calculated over all patients. Pharmacokinetic simulations were performed on the basis of the following predefined requirements. A brief high peak concentration should be achieved by an initial bolus (the simulated bolus duration was 2 min). To avoid an increase in bleeding hazards, steady state rt-PA levels during infusions should not exceed those that are generated with the regimen of Neuhaus et al. (17,18) during its first plateau. These levels, however, should be maintained for 60 min instead of only 30 min. Finally, the new regimen should offer more simple and convenient handling properties than those of the regimen of Neuhaus et al.

Assays for coagulation variables and tissue plasminogen activator (t-PA). Citrated blood samples were collected (final concentration 0.01 mmol) at baseline and at 120 min into thrombolysis. From these samples plasminogen and α_2 antiplasmin plasma levels were determined. From additional citrated blood samples containing aprotinin (final concentration 200 KIU/ml) fibrinogen levels were assessed. After collection, the blood samples were immediately transferred to the hematology laboratory where they were centrifuged at 3,000 g. The resulting plasma samples were frozen within 2 h and stored at -80°C until analysis.

For fibrinogen determinations, the Clauss method (22) was employed. Plasminogen and α_2 -antiplasmin determina-

tions used the chromogenic peptide substrate H-D-Val-Leu-Lys-pNA (S-2251) according to the method of Friberger et al. (23). To confirm the predicted plasma levels, aliquots of the citrated plasma from 12 randomly selected patients were diluted 1:100 or 1:1 with a 0.9% NaCl dilution buffer containing 1% albumin, 0.5% Tween 20, and 0.5 mmol/liter EDTA. The samples were assayed for t-PA-antigen plasma levels according to the method described by Wojta et al. (24) at baseline (undiluted) and at 30 and 60 min (diluted 1:100) and at 120 min (diluted 1:1) after thrombolysis was begun. These were assumed to be steady state levels, and rt-PA plasma clearance was calculated by dividing them by the infusion rate.

Materials. High molecular weight (unfractionated) heparin (Liquemin) was purchased from Hoffman la Roche AG, Grenzach-Wyhlen, Germany, Streptokinase (Streptase) from Behringwerke, Marburg, Germany and rt-PA (Actilyse) from Dr. Karl Thomae GmbH, Biberach, Germany. For laboratory monitoring the following test kits were used: Clauss fibrinogen assay kit from Boehringer Mannheim GmbH, Mannheim, Germany and the assay kit for t-PA antigen (Actibind t-PA) from Immuno GmbH, Heidelberg, Germany. The chromogenic peptide substrate H-D-Val-Leu-Lys-pNA (S-2251) was purchased from KabiVitrum GmbH, Munich, Germany.

Statistics. Statistical comparisons were performed with the use of the *t* test and Fisher exact test. Only *p* values < 0.05 were considered significant. All reported *p* values are two-sided. Continuous variables are given as mean value \pm SD.

Results

Pharmacokinetic simulations and design of the new regimen. rt-PA plasma concentration-time profiles simulated for the different regimens are shown in Figure 1. The regimen of Neuhaus et al. (17,18) (our regimen D) resulted in an initial peak at 4,600 ng/ml, a first steady state plateau of $\sim 4,000$ ng/ml

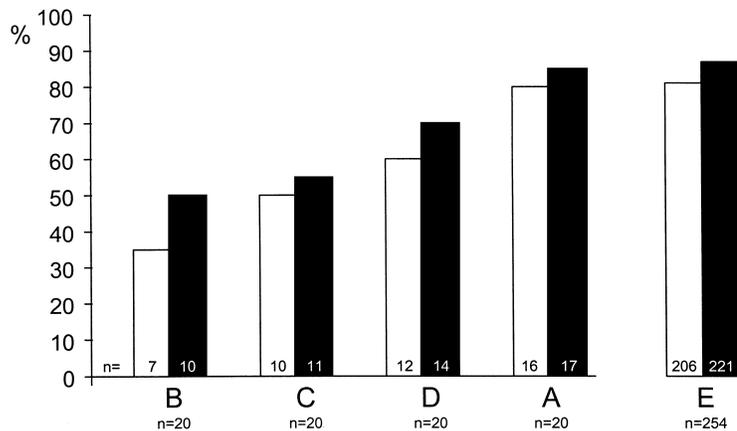


Figure 2. Patency results of the comparative phase (regimens A to D) and confirmation phase (regimen E [identical to A]) of the trial. A = 100 mg of rt-PA/60 min (60-min alteplase protocol); B = 2.25 10⁶ IU of streptokinase; C = 70 mg of rt-PA/90 min; D = 100 mg of rt-PA/90 min (Neuhaus regimen); E = 100 mg of rt-PA/60 min (60-min alteplase protocol). **Open bars** = TIMI grade 3 patency; **solid bars** = total patency (TIMI grades 2 and 3).

during 30 min and a second steady state level of 1,700 ng/ml between 60 and 90 min after the start of infusions. The European Cooperative Study Group regimen of 70 mg over 1.5 h (regimen C) (15,16) produced a lower initial peak of 3,900 ng/ml, a first plateau of only 2,100 ng/ml and a second plateau of 1,000 ng/ml. With the implementation of a single rt-PA bolus injection of 20 mg immediately followed by a constant infusion of additional 80 mg of rt-PA over 60 min (regimen A), the simulation predicted an initial peak of 6,100 ng/ml and a single steady state plateau of 3,500 ng/ml for a duration of 1 h. This latter regimen was selected for further investigation. For practical reasons, we decided to dissolve the lyophilized substance (100 mg of rt-PA) in 50 ml instead of 100 ml of the solvent. The resulting rt-PA solution was then withdrawn into a 50-ml syringe designed for use in a perfusion pump and 10 ml was injected as a bolus. The syringe then was mounted onto a perfusion pump and the remaining 40 ml of the rt-PA solution was infused at a constant speed of 40 ml/h.

Comparison phase of the trial. The comparison phase of the trial was carried out from February 1988 through April 1989 at Hannover Medical School. Four consecutive groups of 20 consecutive patients were enrolled into the study (Table 1).

Table 1. Baseline Characteristics and Results of the Comparative Study

	Regimen			
	B	C	D	A
Patients	20	20	20	20
Female/male ratio	2:18	4:16	3:17	6:14
Age (yr)	59 ± 10	56 ± 10	58 ± 9	55 ± 10
Weight (kg)	86 ± 13	82 ± 10	80 ± 4	83 ± 11
Height (cm)	173 ± 8	172 ± 8	171 ± 9	176 ± 6
Results				
TIMI 0 and 1	10 (50%)	9 (45%)	6 (30%)	3 (15%)
TIMI 2 and 3	10 (50%)	11 (55%)	14 (70%)	17 (85%)
TIMI 2	3 (15%)	1 (5%)	2 (10%)	1 (5%)
TIMI 3	7 (35%)	10 (50%)	12 (60%)	16 (80%)

Data are presented as number (%) of patients or mean value ± SD. TIMI = Thrombolysis in Myocardial Infarction flow grade.

Thrombolysis was performed with one of the four predefined regimens. Patency as assessed in this phase of the study yielded TIMI grade 3 flow in 80% of patients in regimen A and 35%, 50% and 60% in regimens B, C and D, respectively. Total patency (TIMI grade 2 and grade 3 flow combined) was 85% in regimen A and 50%, 55% and 70% in regimens B, C, and D, respectively (Fig. 2). Thrombolysis was accompanied by significant consumption of fibrinogen (Fg), plasminogen (PLG) and alpha₂-antiplasmin (AP) (Table 2). In this part of the trial the overall rate of any hemorrhage was 28.8%, but only three patients required transfusions. Included in the overall bleeding rate are one patient with retroperitoneal hemorrhage treated conservatively (regimen B) and one patient with pseudoaneurysm that required operation (regimen D). All other bleeding events occurred at sites of intravenous or intraarterial access. No strokes were observed in this phase of the trial, but five patients (6.3%) died (one patient each in groups A, B and D and two patients in group C).

Confirmation phase of the trial. The confirmation phase of the trial was carried out from June 1989 through November 1992 at Hannover Medical School in 161 patients, and it was continued in 93 additional patients at the Franz Volhard Clinic from July 1993 through May 1995, resulting in a total enrollment of 254 patients (Table 3). The patency assessment in this part of the trial yielded 81.1% TIMI grade 3 flow with a total patency rate (TIMI grade 2 and grade 3 flow) of 87.0% (Fig. 2) with TIMI grade 3 and total patency rates at an interim analysis after enrollment of 161 patients of 79.5% and 88.1%, respectively. These values were not significantly different from the final results. Follow-up angiography was obtained at 19.6 ± 5.4 days in 164 (79.6%) of those patients with TIMI grade 3 flow at initial angiography. In seven patients (4.3%) the initially successfully reperfused coronary artery was found to be reoccluded (2.5% at Hannover, 5.4% at Berlin). During the hospital phase three patients died, resulting in an overall in-hospital mortality rate of 1.2%.

During thrombolysis Fg levels decreased from 4.2 ± 1.0 g/liter to 3.6 ± 0.8 g/liter (p < 0.01). PLG and AP levels decreased from 113 ± 23% and 92 ± 27% to 60 ± 21% (p <

Table 2. Hemostatic Variables of the Comparative Study

	Regimen			
	B	C	D	A
Plasminogen (%)				
Before	98 ± 12	113 ± 33	97 ± 28	104 ± 33
After 120 min	15 ± 6	76 ± 24	83 ± 35	65 ± 26
Alpha ₂ -antiplasmin (%)				
Before	102 ± 25	91 ± 27	92 ± 28	94 ± 24
After 120 min	13 ± 9	41 ± 27	37 ± 25	38 ± 29
Fibrinogen (g/liter)				
Before	3.0 ± 1.5	3.1 ± 1.4	3.7 ± 1.2	3.9 ± 1.3
After 120 min	0.4% ± 0.5	3.1 ± 1.6	3.4 ± 1.3	3.2 ± 1.6

Data are presented as mean value ± SD.

0.01) and 42 ± 16% (p < 0.01) of the standard values. The rt-PA steady state plasma concentrations as assessed in 12 randomly selected patients resulted in 3.45 ± 1.47 ng/ml at baseline, and 3,560 ± 340, 3,550 ± 218 and 19.5 ± 5.5 ng/ml at 30, 60 and 120 min into thrombolysis were in good agreement with the simulated values (Fig. 1). They yielded an rt-PA plasma clearance of 377 ± 28 ml/min.

Bleeding complications developed in 57 patients (22.4%); the majority were located at the catheter access site. Transfusions ≥1 U of packed red blood cells were required by nine patients (3.5%). Among these patients are two patients who needed surgery for pseudoaneurysms and 1 patient with retroperitoneal bleeding. Three patients had a stroke, two of which were ischemic and one was confirmed by computed tomography to be a small intracranial hemorrhage. That patient nevertheless recovered almost completely.

Discussion

In patients with AMI, rapid restoration of unrestricted infarct-related artery blood flow (TIMI grade 3 flow) has been established as the prime mediator of an improved clinical outcome (4-6,25). The goal of rapid and complete coronary reperfusion can be addressed with either primary coronary angioplasty or thrombolytic therapy. With direct angioplasty, >90% of the occluded coronary arteries can be reperfused

within an average of 30 to 40 min. However, for logistic and other reasons, pharmacologic therapy is more often selected. However, a major problem has been that even the most aggressive thrombolytic regimens do not achieve complete restoration of coronary blood flow in >50% to 60% of patients (5,8,10). This state of affairs suggests an obvious need for further improved thrombolytic regimens.

Many new plasminogen activators are under active investigation in the quest for faster and more complete thrombolysis. Staphylokinase, DSPA_{alpha-1} and the TNK-mutant of t-PA are examples (26-28). Efforts continue to explore preferred dosing strategies with these new agents, as well as with established fibrinolytic agents because the quantity and schedule of dose delivery may substantially affect efficacy. Efforts for improvement are particularly directed at rt-PA, a plasminogen activator that offers a linear dose-effect relation in a wide dose range (29-31). For the initial large trials with this agent, doses of 80 or 100 mg were infused within 3 h by some groups (15,32,33), whereas others (16,34) selected doses of 0.75 mg/kg or 70 mg infused within 90 min. In the TIMI II pilot trial (35), the dose of rt-PA was increased to 150 mg given over 6 h. However, this dose caused an unacceptably high rate of intracranial hemorrhage (36). Combining both increased efficacy with an acceptably low hemorrhagic risk (17,18), the accelerated, front-loaded rt-PA regimen of 100 mg over 90 min (Neuhaus regimen) proved to be a substantial improvement. With TIMI grade 3 flow of only 54% at 90 min, even this improved rt-PA dose regimen warrants further improvement (5).

On the basis of findings from animal studies (30,37) indicating that high peak rt-PA plasma concentrations of brief duration are highly effective in lysing clots without provoking bleeding, other innovative strategies (7,37-40) included single- or double-bolus administration of 30 or 50 mg of rt-PA. Though seemingly most promising, the administration of two 50-mg rt-PA boluses 30 min apart failed to demonstrate superiority over the Neuhaus regimen in terms of efficacy or bleeding hazards (13,14). We chose to utilize computer simulation models of the plasma rt-PA levels to design a new dosing regimen that might achieve several apparently important pharmacokinetic goals. These goals included 1) a high rt-PA plasma

Table 3. Baseline Characteristics and Results of the Dose Confirmation Study

Patients	254
Female:male ratio	63:189
Age (yr)	59 ± 8
Weight (kg)	76 ± 12
Height (cm)	174 ± 8
Results	
TIMI 0 and 1	33 (13.0%)
TIMI 2 and 3	221 (87.0%)
TIMI 2	15 (5.9%)
TIMI 3	206 (81.1%)

Data are presented as mean value ± SD or number (%) of patients. TIMI = Thrombolysis in Myocardial Infarction flow grade.

concentration that is maintained over 60 min, 2) an initially high peak rt-PA plasma level, and 3) maintenance below the rt-PA threshold beyond which the "plasminogen steal" paradoxically reduces the thrombolytic efficacy of the agent (41,42). Because the Neuhaus regimen appears quite safe, we targeted a high initial peak rt-PA plasma level followed by a plateau level similar to the first plateau level of the Neuhaus regimen. We also sought to achieve greater simplicity and ease of administration than those of the current regimens. Current regimens require either changing the infusion rate or the administration of the second bolus precisely 30 min into treatment. The 60-min protocol we subsequently selected for testing consisted of a single 20-mg rt-PA bolus given up front and an 80-mg constant infusion over the next 60 min. This regimen appeared capable of achieving the stated goals.

Our 60-min alteplase regimen produced very encouraging results. In a first comparative trial with 2.25 megaU of SK given over 60 min, 70 mg of rt-PA given over 90 min and the Neuhaus regimen, our alteplase regimen produced 80% TIMI grade 3 patency compared with 35%, 50% and 60%, respectively. The 85% total patency (TIMI grade 2 and 3) of our regimen was also favorable compared with 50%, 55% and 70% for the other treatments, respectively. Furthermore, there was no apparent increase in bleeding hazard. For the nonrandomized design of the study and the small number of patients enrolled, the favorable patency rates of the 60-min alteplase protocol, although consistent with our expectations, may have resulted from chance. We therefore further tested the efficacy and safety of this regimen further in an open, nonrandomized trial in 254 consecutive patients. The TIMI grade 3 and total patency rate assessments by independent investigators were 81.1% and 87.0% with an in-hospital mortality rate as low as 1.2%. Furthermore, only 3.5% of patients required blood transfusions. The new regimen produced nadir PLG and AP levels of $65 \pm 25\%$ and $60 \pm 21\%$ that were within the targeted concentration range. Importantly, the ease of administration of this dosing regimen resulted in excellent acceptance by physicians and nurses in the emergency and intensive care environments.

Study limitations. The major limitation of our study is that it was open label and nonrandomized. However, the principal end point, TIMI grade 3 patency at 90 min, was established by the interpretations of at least two experienced and independent angiographers. Thus, the potential impact of investigator enthusiasm was limited. The large number of patients studied and the consistently high TIMI grade 3 patency rates over the entire 5.5 years of patient enrollment make us confident in our conclusion that our protocol has utility. Nevertheless, we are aware that multicenter studies tend to yield lower patency rates than those of single-center investigations. Our results should be confirmed by a blinded, randomized comparison with an alternative treatment such as reteplase or the t-PA regimen used by the GUSTO I investigators.

Conclusions. In summary, we developed a new accelerated front-loaded rt-PA dosage regimen for thrombolysis in AMI. We designed our regimen on the basis of computer-assisted

pharmacokinetic simulations. This regimen consists of an initial 20 mg i.v. bolus followed immediately by the continuous infusion of an additional 80 mg over the next 60 min. In addition to offering greatly improved handling properties in an emergency setting, this new rt-PA dose regimen produced TIMI grade 3 patency in 80% of patients both in a small comparative phase of the trial and in a larger confirmation phase in 254 consecutive patients. This patency advantage was not achieved at the expense of increased bleeding hazards. We conclude that this protocol warrants further study in a double-blind, multicenter trial in a large cohort of patients with AMI.

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