BENEFITS AND RISKS OF THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION

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BENEFITS AND RISKS OF THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION

Trombolyse voor het acute hartinfarkt

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
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Cover: Acute coronary angiography of the right coronary artery in a patient admitted to the rt-PA/PTCA trial. The intraluminal defect is strongly suggestive for thrombus.

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aan Reneé
aan mijn ouders

CONTENTS

PREFACE

In chapter 1 a concise overview of thrombolytic therapy for acute myocardial infarction is given. Many questions remain unanswered and research looking at various aspects of this treatment modality continues. Although thrombolytic therapy for acute myocardial infarction is not at all new and was used already more than 25 years ago, progress in this field has been rapid during the last years. Reports of new trials are being published shortly after each other. In the review only randomized trials have been referred to and unpublished data or results of very small trials have been ignored. The main clinical trial results are summarized in tables. For more detailed information on each trial the reader is referred to the abstract booklet [1].

In chapters 2 to 6 the clinical effects of rt-PA are described. Unlike other thrombolytic agents as streptokinase and urokinase, tissue plasminogen activator was found to be mainly active at the site of the thrombus (fibrin-specific), thereby saving circulating fibrinogen and other clotting factors. In chapter 2, the fibrin-specificity, earlier studied with in vitro and animal experiments or in healthy volunteers, was studied in the clinical setting. In chapter 3 the efficacy of rt-PA in terms of enzymatic infarct size reduction and improvement of left ventricular ejection fraction was studied. Chapters 4 and 5 deal with the value of immediate percutaneous transluminal coronary angioplasty (PTCA) in addition to thrombolytic therapy.

In chapter 7 patient selection for thrombolytic therapy is addressed. Since mortality after acute myocardial infarction is low in certain subsets of patients and thrombolytic therapy may result in intracerebral bleeding and since benefits of thrombolytic therapy are related to treatment delay, patients should be carefully selected for thrombolytic therapy. In chapter 8 the value of coronary angiography for risk stratification of patients with and without thrombolytic therapy for acute myocardial infarction before hospital discharge is assessed.

Reference

1. Arnold AER, Ferdinand RF, Soward AL, Schmidt WG, Lubsen J. Thrombolysis in suspected acute myocardial infarction - a summary. Universimed, Frankfurt (Main), 1990.

CHAPTER 1

TREATMENT STRATEGIES FOR ACUTE MYOCARDIAL INFARCTION A REVIEW

Introduction

Acute myocardial infarction remains one of the most common causes of death in the western world. With the development of coronary care units allowing prompt recognition and treatment of potentially lethal cardiac arrhythmias, the extent of myocardial damage remains an important determinant of morbidity and mortality. Accordingly much interest and research in recent years has focused on limitation of infarct size. In most patients with acute myocardial infarction, the coronary artery supplying the infarct region is occluded by thrombus at a site of atherosclerotic plaque. Early restoration of coronary blood flow by thrombolytic therapy results in smaller infarct size, improved left ventricular function and reduced mortality. Recanalization can occur spontaneously but prompt intervention with thrombolytic therapy has had dramatic results, particular when given within the first few hours after onset of coronary occlusion.

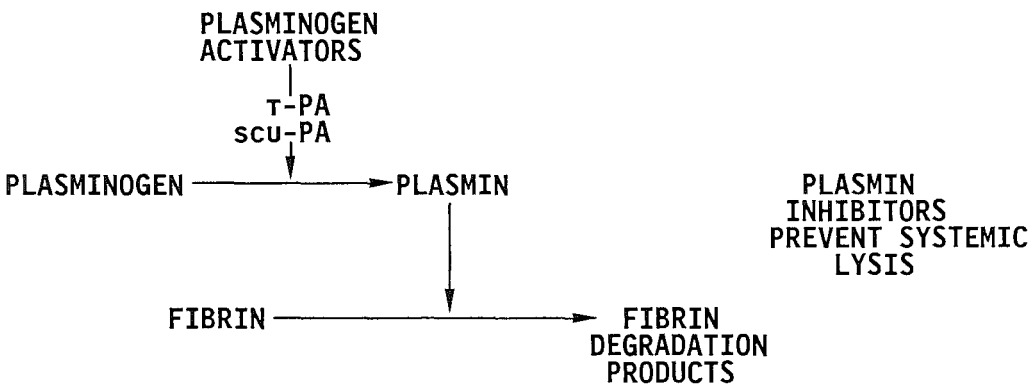
Thrombolytic agents

Physiologic clot lysis occurs by conversion of plasminogen to the proteolytic enzyme plasmin at the site of the thrombus. Plasmin breaks down fibrin in the thrombus and produces lysis. Any circulating plasmin is inactivated by alpha-2-antiplasmin and a systemic thrombolytic effect does not occur under normal circumstances [1]. Thrombolytic agents also result in clot dissolution through activation of native plasmin (figure 1). Circulating as well as clot-bound plasminogen may be converted to plasmin and act not only on fibrin within the thrombus, but also on circulating fibrinogen and clotting factors such as factors V and VIII producing a systemic fibrinolytic effect, increasing the risk of hemorrhagic complications. Streptokinase is inactive until it has formed a complex with plasminogen. It is this complex which splits another molecule of plasminogen to plasmin [1]. Urokinase, recombinant tissue plasminogen activator (rt-PA or alteplase), pro-urokinase (scu-PA or saruplase) and anisoylated plasminogen streptokinase activator complex (APSAC or anistreplase) activate plasminogen directly.

FIGURE 1. THE FIBRINOLYTIC SYSTEM

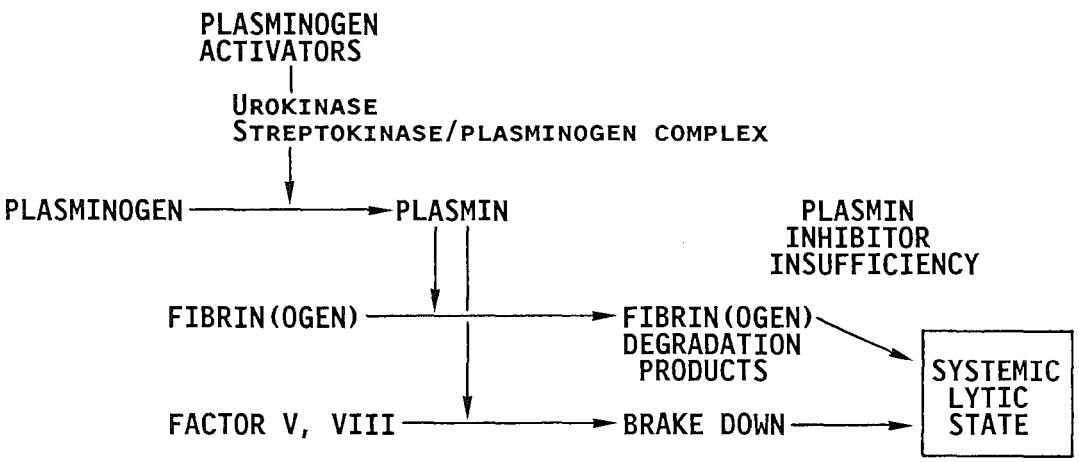
- FIBRIN-SPECIFIC AGENTS (t-PA, scu-PA)

AT THE SITE OF THE THROMBUS:



- NON-SPECIFIC AGENTS (STREPTOKINASE, UROKINASE)

IN FREE CIRCULATION:



The action of streptokinase, urokinase and APSAC is non-specific and results in systemic conversion of plasminogen to plasmin and depletion of circulating fibrinogen for 12 to 36 hours. Rt-PA and scu-PA on the other hand, are relatively fibrin-specific with little effect on circulating fibrinogen and other clotting factors. Rt-PA acts predominantly upon fibrin-bound plasminogen within the thrombus and has little effect on circulating plasminogen, unless high doses are given [1]. Scu-PA is probably protected against circulating plasminogen by an unknown substance in human plasma that is inactivated by fibrin [1]. Streptokinase is produced by beta-hemolytic streptococci (Lancefield C) which also commonly cause throat infections. Therefore antibodies are frequently present,especially after repeated use, and may limit the efficacy of streptokinase therapy. Side effects include hypotension and allergic reactions varying from rash to anaphylactic shock and autoimmune vasculitis. APSAC is a complex of streptokinase and plasminogen isolated from donor blood, inactivated by the addition of an anisoyl group. In the circulation APSAC is gradually activated by deacylation, giving it a plasma half time of 90 minutes which is much longer than that of the parent streptokinase. APSAC can be administered as a bolus in 4 to 6 minutes whereas 1.5 million units streptokinase requires an infusion time of 30 to 60 minutes. Side effects are similar to those of streptokinase. Urokinase, originally isolated from human urine, and the other naturally occurring plasminogen activators have no antigenic properties and thus lack many of the side effects of streptokinase and APSAC. Scu-PA is the inactive precursor of urokinase. Scu-PA can be activated into urokinase by plasminogen. As is the case for rt-PA, scu-PA can be produced by genetic engineering. Tissue-type plasminogen activator is a naturally occurring plasminogen activator. The initial genetically engineered rt-PA was predominantly in the double chain form, but most rt-PA in current use is single chain. The latter has a shorter plasma half life and higher doses are needed to yield similar coronary patency rates [2].

Clinical trials

Clinical trials of thrombolytic therapy have investigated effects on coronary patency (without pre-treatment coronary angiography), recanalization (trials with pre-treatment coronary angiography), enzymatic infarct size, left ventricular function (contrast or radionuclide angiography) and early and late mortality. The benefit of thrombolytic therapy must be finally evaluated in terms of clinical outcome (functional status and mortality). Intermediate endpoints related to clinical outcome (patency, enzymatic infarct size and left ventricular ejection fraction) have the advantage that smaller trial sizes suffice, while for mortality trials more patients are needed to demonstrate a treatment effect. Furthermore, intermediate endpoint assessment helps to elucidate pathophysiologic mechanisms. The pathophysiologic model for thrombolytic therapy in acute myocardial infarction (coronary artery recanalization results in limitation of infarct size, preservation of left ventricular function and mortality reduction would not exist without trials in which intermediate endpoints were assessed together with mortality.

Coronary patency and recanalization

In about 80 to 85% of patients with symptoms of acute myocardial infarction an occluded infarct-related coronary artery is found when coronary angiography is performed within 4 hours after onset of symptoms [3]. Without thrombolytic treatment recanalization occurs in some patients probably due to physiologic fibrinolysis, and at 12 to 24 hours after onset of symptoms only approximately 65% have an occluded infarct related vessel. Studies directly comparing all thrombolytic agents have not been performed. Comparative conclusions regarding individual agents from existing trials are weakened by the limitations imposed by comparing different trials. The impact of physiologic thrombolysis in different patient groups, variations in the timing and number of angiographic contrast injections (which may induce recanalization mechanically), and lack of uniformity in the definition of coronary patency are examples of factors which interfere with direct comparison. Trials with coronary angiography performed approximately 90 minutes after start of treatment are documented in tables I and II. Initial trials dealt with recanalization rather than with coronary patency. Later on, investigators considered treatment delay, caused by baseline coronary angiography, not justifiable. Coronary patency and recanalization at 90 minutes are interrelated. The former can be derived from the latter on the assumption that 15 to 20% of patients have a patent vessel before thrombolysis. After intracoronary streptokinase about 85% of patients have a patent infarct related artery at 90 minutes after start of the infusion. Intravenous rt-PA and scu-PA produce coronary patency in approximately 75%, and intravenous streptokinase in 50% of cases. Data on APSAC are not always consistent since APSAC was reported to be similarly effective in terms of coronary patency at 90 minutes as intravenous streptokinase (see table I) and somewhat less efficacious in inducing coronary recanalization as intracoronary streptokinase (see table II).

Angiographic reocclusion

Reliable assessment of reocclusion is difficult for two reasons. Firstly, a thrombus is the result of a dynamic process of clot formation and lysis. This may result in opening, closure and reopening of the coronary vessel [4]. Even with repeated coronary angiography reocclusion may be missed. Secondly, repeated catheterization carries significant risks and may not be possible in some of the patients due to refusal, cardiac contraindications, or intercurrent revascularization procedures. Reocclusion could predispose to such an unstable clinical state, thereby distorting the estimation of the reocclusion rate. In a pooled analysis of trials with intracoronary streptokinase reocclusion within two weeks occurred in 17% of patients [4]. Initially, reocclusion after rt-PA was reported to occur in about one third of the patients shortly after cessation of rt-PA infusion, especially if a severe stenosis remained in the infarct related vessel [5,6]. In subsequent larger trials reocclusion after 1 to 24 hours was found in 7 to 10% of patients and after 1 to 2 weeks in 12 to 18% of patients (see table III), when full heparinization was given. The need for concomitant heparin administration was recently reported by Bleich et al [7]. They found considerably higher 48 to 72 hours coronary

patency when rt-PA was combined with heparin than after rt-PA alone (72% versus 43%). Similar results were found in the Heparin Aspirin Reperfusion Trial [8]. The European Cooperative Study Group reported recently on the superior patency at 48 to 120 hours after the combination of rt-PA and heparin (83.4%) than rt-PA alone (74.7%) in a larger trial with 652 patients. Since there was no effect of heparin on initial coronary patency in TAMI V (table I), reocclusion has most likely played an important role. The effect of prolonged rt-PA infusion on reocclusion was assessed in two trials with very similar protocols (table III). In the first trial using double chain rt-PA there was no benefit from long term rt-PA infusion. In the other trial prolonged infusion of single chain rt-PA prevented most reocclusions. For APSAC similar reocclusion rates were published (5% and 8%). The latter trial must be interpreted with caution since 34% of patients with successful recanalization after 90 min were excluded because of other revascularization procedures or additional thrombolytic therapy (table III).

Enzymatic infarct size

Infarct size can be estimated by cumulative release of cardiac enzymes. Peak plasma levels may give an unreliable estimate of infarct size: because of a more rapid enzyme release after thrombolysis, peak levels are reached earlier and the peak may be higher despite of a lower cumulative release compared to conventional therapy. Enzymatic infarct size from cumulative release is assessed in a limited number of studies listed in table IV. Intracoronary streptokinase reduces enzymatic infarct size by 30% whereas intravenous rt-PA, APSAC and intravenous streptokinase produce 20%, 19% and 9% reduction respectively. The relative efficacy of these thrombolytic agents in terms of enzymatic infarct size seems to correlate with the relative efficacy in restoration of coronary patency. Benefit was most pronounced when treatment was started early. In patients treated with intravenous streptokinase within 3 hours after onset of symptoms, infarct size was 16% smaller [9]. After treatment with intracoronary streptokinase within 2 hours reduction was even 51% [10].

Left ventricular function

Global left ventricular ejection fraction as determined by contrast or radionuclide ventriculography is a rather insensitive parameter for assessing efficacy of thrombolytic therapy. Left ventricular ejection fraction measurement is subject to considerable error due to compensatory hyperkinesia in the noninfarcted myocardium, which may be blunted in some patients by previous myocardial infarction. An assessment of regional left ventricular wall motion would seem a more accurate measure of determining effect on left ventricular function. In addition, a systematic error may occur in the determination of left ventricular function due to the fact that in each trial ventriculography is lacking in up to 30% of patients. Inability to assess left ventricular function is more likely to occur in patients with larger infarctions. Since these patients are more common in the group receiving the least effective thrombolytic drug, exclusion of these patients could result in underestimation of the difference in thrombolytic

efficacy between the treatment strategies in a trial. In addition, patients with larger infarctions are more likely to be studied at a later stage than patients with smaller, uncomplicated infarctions. As a consequence, infarct "healing" in patients with large infarctions is more complete, which also may result in underestimation of the true difference in efficacy of thrombolytic strategies. Despite these limitations, benefit has been demonstrated for nearly all thrombolytic agents (table V). The wide variance of left ventricular ejection fraction among placebo groups of the various trials dictate that one trial may not be compared directly with another.

Mortality

In table VI and VII trials reporting mortality are recorded. For intravenous and intracoronary streptokinase, APSAC and rt-PA, sufficient evidence is available to conclude that all reduce mortality. Mortality in the placebo groups varies substantially principally due to differences in entry criteria (age, previous myocardial infarction, etc.) and concomitant therapy again making direct comparisons of thrombolytic agents unreliable. Intravenous streptokinase and rt-PA have been compared in the large, multicenter trial of the International Study Group (including GISSI-2) [11]. No additional benefit could be ascribed to either agent. Heparin was administered subcutaneously 12 hours after start of thrombolytic therapy to half of the patients. Since the anticoagulant effect of subcutaneous heparin is delayed 12 to 24 hours after administration, most patients would have experienced little effect from heparin during the first 24 hours when reocclusion and reinfarction are most likely to occur. The importance of full heparinization to prevent reocclusion after rt-PA is outlined above. The question remains whether a strategy of rt-PA together with immediate and full intravenous heparinization produces a greater mortality reduction than a strategy of intravenous streptokinase.

Benefit of thrombolytic therapy in relation to treatment delay

In nearly every thrombolytic trial mortality reduction is greatest when treatment is given soon after the onset of symptoms. In GISSI-1 mortality reduction at 3 weeks in patients treated 3 hours or less after onset of symptoms was 3 per hundred patients, from 3 to 6 hours 2 per hundred and from 6 to 9 hours only 1 per hundred. In patients with 9 to 12 hours treatment delay mortality was adversely affected with 3 weeks mortality increased from 14% to 16% [12]. Hemorrhage in the infarct territory, occurring more frequently after thrombolytic therapy than without [13] and especially in patients treated after 3 hours delay [14], might play a role. In ISIS-2 some benefit was still present when treatment started after a delay of 12 to 24 hours [15]. However this trial has been criticized for having studied a heterogenous group of patients, resulting from loose entry criteria. In order to include a patient in the trial it sufficed that the investigator considered myocardial infarction likely. It might be that the 6 to 24 hours subgroup partly consisted of patients in whom the time of onset of symptoms was not exactly known, but well within 6 hours before start of treatment, e.g. because the actual

myocardial infarction was preceded by a period of unstable angina. These patients were excluded in other trials. Because thrombolytic therapy may result in serious side effects, treatment after a delay of 6 hours cannot be recommended until other clinical trials provide further evidence.

Concomitant therapy

In the first 6 to 12 hours of the acute phase of myocardial infarction, when ischemic myocardium is converted into necrotic tissue, limitation of oxygen demand may improve clinical outcome. Indeed, in the acute phase undue tachycardia and hypertension on one hand and raised ventricular diastolic pressure on the other hand may further deteriorate the balance of oxygen demand and supply. Early hemodynamic optimalization by beta-blockade, nitrates, inotropics or intra-aortic balloon pumping (in case of heart failure) may limit infarct size, but proof from randomized clinical trials is lacking. Although the pathophysiologic mechanism remains unclear, in-hospital mortality was reduced by immediate (intravenous) beta-blockade [16,17]. In ISIS-2 aspirin reduced 5 week mortality by 2 patients per hundred, when given immediately on admission and continued for 1 month [15]. Benefit of aspirin was additive to that of intravenous streptokinase and, interestingly, not related to the treatment delay. This suggests a different pathophysiologic mechanism than for thrombolytic agents, e.g. prevention of reocclusion. Heparin may not only reduce coronary reocclusion after rt-PA, but also reduces stroke after myocardial infarction by 50% [18]. Although a subcutaneous regimen have been successful for the latter [19,20], intravenous and full heparinization seems necessary to prevent reocclusion after rt-PA [7,8]. Long term coumarins may contribute to improved survival and less frequent reinfarction [21]. Prevention of late recurrent ischemic events and death with beta-blockade for at least one year is sufficiently proven [22-24].

Risks of thrombolytic therapy

Thrombolytic agents do not discriminate clots at a potential bleeding site from a clot in an occluded coronary artery. Indeed, hemorrhages are a feared complication after thrombolytic therapy for acute myocardial infarction. Patients with increased bleeding risk, e.g. extensive cardio-pulmonary resuscitation or trauma (especially head), recent gastrointestinal bleeding, cerebrovascular accident, major surgery or hemostatic disorders, were excluded in nearly all trials. Bleeding complications, depending on definitions and treatment protocol used (immediate catheterization) were reported in 20% to 40% of patients, most frequently being hematoma formation and prolonged bleeding at puncture sites. The most serious complication is intracerebral hemorrhage. The risk of intracerebral bleeding is probably underestimated in mortality trials due to their nature (simple protocols and collection of few clinical data) and because computerized tomography or obduction was not performed in all patients with stroke. For example, in ISIS-2 only 17% of cases with stroke on day 0 and 1 were proven to be hemorraghic by CT-scanning or necropsy, while data from the pre-thrombolysis era suggest that non-

hemorraghic strokes tend to become manifest later on [25]. The most accurate estimate is that intracerebral bleeding occurs in about 0.5% of patients [9,11,26,27]. The International Study Group found that the risk of stroke was 1.3% with rt-PA as compared to 1.0% with streptokinase. However, in 30% of cases the cause of stroke was not established. If these were ischemic, they might be prevented by adequate intravenous heparinization. For rt-PA a dose-dependence is reported; after 150 mg single chain rt-PA an intracerebral bleeding occurred in 5 out of 311 patients (1.6%), after 100 mg in 15 out of 3768 patients (0.4%) [28]. Furthermore, bleeding was reported to be less frequent in a weight adjusted dosage scheme than after a fixed dose [29] and in patients with less serum levels of fibrinogen degradation products [30].
Life threatening arrhythmias during myocardial reperfusion, often encountered in animal experiments, were not frequently encountered in clinical trials. Periods of accelerated idioventricular rhythm without hemodynamic consequence are often seen at the time of coronary recanalization. Ventricular tachycardia and fibrillation are most frequently secondary to poor left ventricular function and more common in patients not treated with thrombolytic treatment [9,26].

Thrombolytic therapy for all patients with suspected acute myocardial infarction?

In most thrombolysis trials 75% of patients presenting with acute myocardial infarction were excluded, predominantly due to delayed admission and advanced age. Thrombolytic therapy is associated with intracerebral bleeding in approximately 0.5% of patients, irrespective of which thrombolytic agent is used. Half of these are lethal [9,15,26,27]. Clinicians thus need to balance the risks and expected benefits of thrombolytic therapy. Overall results of clinical trials cannot be automatically extrapolated to individual patient care and the decision to treat patients with thrombolytic therapy is not as simple as suggested in some publications. Reliable determination of patients' "baseline risk" (defined as the predicted outcome in the absence of thrombolytic therapy), of expected benefit of thrombolytic therapy and identification of predictors of intracerebral bleeding after thrombolytic therapy are prerequisites for good clinical decision making and need the full attention of present and future investigators. In the mean time the adage "in dubio abstine" still holds.

Role of routine coronary angioplasty

Recovery of left ventricular function [31] and the incidence of reocclusion [32,33] were reported to be related to the degree of residual stenosis after thrombolysis and small randomized trials, assessing immediate angioplasty with and without intracoronary streptokinase, suggested that recovery of left ventricular function might be improved by angioplasty [34,35]. However, large randomized trials have failed to confirm this. There was no additional benefit in terms of enzymatic infarct size or left ventricular function of immediate [36-38] or delayed (18-48 hours) angioplasty [39] in patients treated with rt-PA (table VIII), probably due to reocclusion or reinfarction following further destabilization of the infarct related atherosclerotic lesion, caused by

the balloon dilatation [40].

Conclusion

Most data are consistent with the hypothesis that early coronary recanalization results in limitation of infarct size, preserves left ventricular function and reduces mortality. Earlier administration of a thrombolytic agent improves the clinical outcome. Rt-PA, scu-PA and possibly APSAC are more efficacious in restoring coronary patency than intravenous streptokinase. However, in terms of clinical benefit, it remains unclear which is best, also after the report of The International Study Group (GISSI-2). The latter trial learned us that we should not discuss differences in efficacy of different thrombolytic drugs, but rather of different thrombolytic strategies.

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TABLES

If no comments on treatment regimens are made in the tables, standard treatment schedules were used:

- intravenous streptokinase 1.5 million U over one hour;
- recombinant tisue-type plasminogen activator (rt-PA or alteplase) 100 mg over three hours (unless indicated otherwise rt-PA refers to the single chain form).
- anisoylated plasminogen streptokinase activator complex (APSAC or anistreplase) 30 mg bolus over 4-6 min.

The abstract numbers in the tables refer to the list of main clinical trial publications on page 27 to 29, to provide quick reference. For more detailed information on each trial the reader is referred to the abstract booklet:

Arnold AER, Ferdinand RF, Soward AL, Schmidt WG, Lubsen J. Thrombolysis in suspected acute myocardial infarction - a summary. Universimed, Frankfurt (Main), 1990.

Table I. Studies in which patency within 2 hrs was assessed.

Patency: SK IC vs standard therapy

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK IC dose	Patency SK vs control	95% CI
Anderson (1)	50	<4 hrs	<100 min	<300,000 U	79% vs *%[1]	63 to 95%
ICIN[2] (13)	533	<4 hrs	60–90 min	<250,000 U	85% vs *%[1]	80 to 90%

Patency: rt-PA (double chain) vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Patency rt-PA vs plac	Difference (95% CI)
European Cooperative-1 (11)	129	<6 hrs	90 min	0.75 mg/kg	61 vs 21%	+40% (22 to 56%)

Patency: rt-PA (double chain) vs SK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Patency rt-PA vs plac	Difference (95% CI)
European Cooperative-2 (12)	129	<6 hrs	90 min	0.75 mg/kg	70 vs 55%	+15% (-3 to 32%)

Patency: rt-PA with vs without heparin IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Heparin dose	Patency with vs without heparin	Difference (95% CI)
TAMI-3 (50)	134	<4–6 hrs	90 min	<90 mg	10,000 U	79 vs 79%	+ 1% (- 13 to + 15%)

Patency: rt-PA vs UK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	UK dose	Patency rt-PA vs UK	Difference (95% CI)
GAUS (45)	246	<6 hrs	90 min	3,000,000 U	69 vs 66%	+ 3% (- 9 to + 14%)

Patency: Dose finding study of a combination of UK and rt-PA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	UK	rt-PA dose	Patency	95% CI
TAMI-2[3] (49)	146	<4–6 hrs	90 min	0.5 million U	25 mg	36%	11 to 61%
				1.0 million U	25 mg	42%	19 to 61%
				0.5 or 1.0 or 2.0 million U	1.0 mg/kg	73%[4]	66 to 83%

Patency: APSAC IV vs SK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Patency APSAC vs SK	Difference (95% CI)
IRS-2 (26)	116	< 6 hrs	1.75 hrs	70 vs 51%	+ 19% (+ 1 to + 38%)
Hogg (66)	128	< 6 hrs	90 min	55 vs 53%	+ 3% (- 14 to + 20%)

Patency: scu-PA vs SK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	scu-PA dose	Patency scu-PA vs SK	Difference (95% CI)
PRIMI (61)	401	< 4 hrs	90 min	80 mg	71 vs 64%	+ 7% (- 2 to + 17%)

1 * not measured.

2 SK IC was preceded by 500,000 U SK IV in 117 cases.

3 Difference for 25 mg rt-PA vs 1.0 mg/kg: 36% (95% CI: 18 to 55%).

4 Only overall outcome given.

Table II. Studies in which recanalization was assessed.

Recanalization: SK IC vs control

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	Recanalization SK IC vs control	Difference (95% CI)
Western Washington (4)	250	<12 hrs	during therapy	<350,000 U	68 vs *% [1]	59 to 76%

Recanalization: SK IC vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	Recanalization SK IC vs placebo	Difference (95% CI)
Khaja (2)	40	≤6 hrs	55 min	250,000 U	60 vs 10%	+50% (+20 to +80%)

Recanalization: SK IC vs NTG IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	NTG IC dose	Recanalization SK vs NTG	Diff. (95% CI)
Leiboff (6)	55	<4 hrs	90 min	<300,000 U	<1 mg [2]	69% vs 17%	+52% (20 to 83%)

Recanalization: SK-IC vs SK-IC + NTG-IC vs NTG-IC

Acronym (abstr nr)	Time to therapy	Evaluation	Treatment	Nr of patients	Recanalization	95% CI
Mount Sinai-2 (59)	<12 hrs	during therapy	SK-IC 240,000 U [3]	67	60%	40 to 72%
			SK-IC 240,000 U [3] + NTG-IC 0.01 mg/min	62	63%	51 to 75%
			NTG-IC 0.01 mg/min [3]	65	8%	1 to 14%

Recanalization: SK IV vs standard therapy[4]

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IV dose	Recanalization SK vs NTG	Difference (95% CI)
Cribier (16)	28	<4 hrs	2 hrs	1,500,000 U	50 vs 61%	-11% (-50 to +28%)

Recanalization: SK IV vs SK IC[5]

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IV dose	SK IC dose	Recanalization SK IV vs IC	Diff. (95% CI)
Rogers (3)	51	<12 hrs	75 min	1,000,000 U	240,000 U	31 vs 76%	-45% (-73 to -18%)

Recanalization: SK IV vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IV dose	SK IC dose	Recanalization SK IV vs SK IC	Diff. (95% CI)
Alderman (5)	28	3 hrs	90 min	725,205 U	343,375 U	62 vs 73%	+11% (-24 to +47%)

Recanalization: UK IV vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	UK IV dose	Recanalization UK vs placebo	Difference (95% CI)
UK Double Blind (38)	210	<6 hrs	45 min	<960,000 U	74 vs 14%	+60% (+47 to +74%)

Recanalization: rt-PA vs SK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	rt-PA dose	Recanalization rt-PA vs SK	Difference (95% CI)
TIMI-1 (33)	316	<7 hrs	45 min	80 mg[6]	62 vs 31%	+31% (+19 to +42%)

Recanalization: APSAC IV vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	Recanalization APSAC vs SK IC	Difference (95% CI)
Bonnier (23)	85	<4 hrs	90 min	250,000 U	64 vs 68%	-4% (-26 to +18%)
Kaspar (29)	16	<6 hrs	90 min	250,000 U	83 vs 63%	+20% (-29 to +71%)
APSAC (41)	258	<4 hrs	APSAC 90 min SK 60 min	180,000 U	51 vs 60%	-9% (-21 to +4%)

Recanalization: UK IV vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	UK IC dose	Recanalization SK vs UK	Diff. (95% CI)
Tennant (9)	143	<12 hrs	<2 hrs	240,000 U	720,000 U	57 vs 60%	-3% (-25 to +19%)

Recanalization: pro-UK IC vs UK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	Treatment	Recanalization	95% CI
Kambara (47)	148	<6 hrs	45 min	pro UK[7] 6,000 U	90%	82 to 98%
				pro UK 3,000 U	59%	45 to 74%
				UK IC[7] 960,000 U	61%	48 to 74%

Recanalization: Immediate PTCA vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	Recanalization PTCA vs SK IC	Diff. (95% CI)
O'Neill (21)	56	<12 hrs	after therapy	250,000-350,000 U	83 vs 85%	-2% (-22 to +17%)

1 not measured

2 5 boluses of 100-200 microgram IC in 75 min.

3 SK-IC was given until recanalization was achieved, up to a maximal dose of 240,000 U over 2 hrs. Difference between SK-IC or SK-IC + NTG-IC treated patients and patients treated with NTG-IC only: 54% (95% CI: 39% to 68%)

4 Standard therapy included heparin at 0.35 U/kg/min for at least 1 hour. After 1 hour patency was assessed in both treatment groups. In case of occlusion SK IC was administerd at 4,000 U/min for 1 hour, after which recanalization was assessed.

5 If no thrombolysis was noted angiographically, 120,000 U of SKIC were administered.

6 Double chain rt-PA.

7 Difference between pro-UK IC (6,000 U) and UK IC (960,000 U): +29% (95% CI: +12 to +46%).

Table III. Studies in which reocclusion was assessed.

Reocclusion: double chain rt-PA followed by heparin with or without rt-PA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Reocclusion rt-PA vs placebo	Difference (95% CI)
European Cooperative-3[1] (24)	122	<4 hrs	6–24 hrs	6 vs 5%	0% (- 11 to - 11%)

Reocclusion: single chain rt-PA followed by heparin with or without rt-PA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Reocclusion rt-PA vs control	Difference (95% CI)
Johns[2] (46)	68	<6 hrs	150 min	0 vs 19%	- 19% (- 5 to - 32%)

Reocclusion: APSAC IV vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK IC dose	Reocclusion APSAC IV vs SK IC	Difference (95% CI)
Bonnier (23)	85	<4 hrs	24 hrs	250,000 U	5 vs 17%	- 13% (- 31 to + 6%)
APSAC (41)	258	<4 hrs	24 hrs	180,000 U	8 vs 3%	+ 5% (- 5.2 to + 14.8%)

Reocclusion: UK dose finding study

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	UK dose	rt-PA dose	Reocclusion	95% CI
TAMI-2 (49)	146	<4–6 hrs	7 days	0.5 million U	25 mg	0%	
				1.0 million U	25 mg	20%	2 to 38%
				0.5 million U	1.0 mg/kg	11%	0 to 26%
				1.0 million U	1.0 mg/kg	6%	0 to 14%
				2.0 million U	1.0 mg/kg	11%	3 to 19%

Reocclusion: SK IV+IC with and without PTCA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK IV	SK IC	Reocclusion PTCA vs control	Diff. (95% CI)
Erbel (17)	162	<6 hrs	in-hospital	250,000 U	200,000 U	14 vs 20%	- 6% (- 18 to + 7%)

Reocclusion: rt-PA + immediate PTCA vs delayed PTCA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Reocclusion Immediate vs delayed PTCA	Difference (95% CI)
TAMI-1 (32)	386	<4–6 hrs	24 hrs	11 vs 13%	- 2% (- 13 to + 10%)

[1] The initial dose of rt-PA was 40 mg in 90 min. Patients with a patent infarct related vessel were randomized to receive either 30 mg rt-PA or placebo in 6 hrs in addition to 1,000 IU/hr heparin.

[2] The initial dose of single chain rt-PA was 1.0 mg/kg in 90 min. Patients with a patent vessel were randomized to receive either 0.8 mg rt-PA in 4 hrs with heparin 1,000 IU/hr or heparin only.

Table IV. Studies in which enzymatic infarct size was assessed.

Acronym (abstr nr)	Nr of pts	Time to therapy	Therapy	Enzymatic Infarct size	Relative difference
ISAM (20)	1741	<6 hrs	SK IV vs placebo	CK-MB 1701 vs 1869 U/l/h	-9%
ICIN (13)	533	<4 hrs	SK IC or IC+IV[1] vs standard therapy	Median HBDH-Q72 770 vs 1100 U/l	-30%
European Cooperative-4 (43)	721	<5 hrs	rt-PA IV vs placebo	Median HBDH-Q72 694 vs 867 U/l	-20%
Ikram (19)	149	<4 hrs	APSAC IV vs standard therapy	CK-Q48 1588 vs 1951 U	-19%
European Cooperative-5 (44)	367	<5 hrs	PTCA vs standard therapy after rt-PA IV	Median HBDH-Q72 703 vs 665 U/l	+6%

[1] SK IC up to 250,000 U, preceded by 500,000 U SK IV in 117 pts.

Table V. Studies in which left ventricular ejection fraction was measured.

LVEF: SK IC vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK dose	LVEF SK IC vs plac.	Difference (95% CI)
Khaja (2)	40	<6 hrs	1 hr	250,000 U	51 vs 49%	+2.0 (-6.2 to +10.2)
			2 days	250,000 U	45 vs 36%	+9.0 (+0.5 to + 17.5)

LVEF: SK IC vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK dose	LVEF SK IC vs control	Difference (95% CI)
IC Western Washington (4)	250	<12 hrs	8–9 weeks	<350,000 U	46 vs 46%	0,0 (-3.7 to +3.7)
Anderson (1)	50	<4 hrs	10 days	<300,000 U	47 vs 39%	+8.0 (+1.7 to + 14.3)
Leiboff[1] (6)	55	<4 hrs	2 weeks	<300.00 U	43 vs 42%	(no SD given)
ICIN[2] (13)	533	<4 hrs	2 weeks	<250,000 U	50 vs 43%	+6.0 +3.1 to +9.1)

LVEF: SK IV vs placebo

Acronym (abstr nr)	Nr of pts	Time of therapy	Evaluation after	LVEF SK IV vs placebo	Difference (95% CI)
ISAM (20)	1741	<6 hrs	1 month	57 vs 54%	+2.9 (+2.8 to +3.0)
White[3] (39)	219	<4 hrs	3 weeks	59 vs 53%	+6.0 (+2.8 to +9.3)

LVEF: SK IV vs standard therapy

Acronym (abstr nr)	Nr of pts randomized	Time to therapy	Evaluation after	LVEF SK IV vs control	Difference (95% CI)
IV Western Washington (54)	368	<6 hrs	2 weeks	54 vs 51%	+ 3.0 (- 0.1 to + 6.1)

LVEF: rt-PA vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	LVEF rt-PA vs placebo	Difference (95% CI)
TPAT[4] (62)	118	<3.75 hrs	4 hrs	49 vs 45%	+4.2 (+0.6 to +7.8)
			9 days	54 vs 48%	+ 6.0 (+ 5.3 to + 6.8)
National Heart Foundation of Australia (48)	144	<4 hrs	1 week	58 vs 52%	+6.0 (-0.1 to +12.1)
European Cooperative-4 (43)	721	<5 hrs	10-22 days	51 vs 49%	+2.2 (+0.3 to +3.7)
TICO (51)	147	<2.5 hrs	3 weeks	61 vs 54%	+7.0 (+2.2 to +11.8)
			3 weeks	52 vs 48%[5]	+4.0 (-0.6 to +8.6)

[1] SK IC versus Nitroglycerin IC. Data of 40 pts with occluded infarct-related artery at base-line.
[2] SK IC was preceded by 500,000 U SK IV in 117 cases.
[3] Patients with first infarction.

LVEF: rt-PA vs SK IV

Acronym (abstr nr)	Nr of pts	Time of therapy	Evaluation after	rt-PA dose	LVEF rt-PA vs SK IV	Difference (95% CI)
PAIMS (60)	171	<3 hrs	4 days	100 mg	55 vs 53%	+2.0 (-1.4 to +5.4)
TIMI-1[6] (33)	316	<7 hrs	before discharge	80 mg	46 vs 45%	+1.0 (-2.3 to +4.3)

LVEF: rt-PA vs UK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	UK dose	LVEF rt-PA vs UK	Difference (95% CI)
GAUS (45)	246	<6 hrs	10 days	70 mg	3,000,000 U	53 vs 52%	+1.0 (-2.9 to 4.9)

LVEF: rt-PA with vs without heparin

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	heparin dose	LVEF with vs without heparin	Difference (95% CI)
TAMI-3 (50)	134	<4-6 hrs	1 week	max 90 mg	10,000 U	49 vs 50%	-1.0 (-4.6 to +2.6)

LVEF: APSAC IV vs heparin

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	heparin dose	LVEF APSAC vs heparin	Difference (95% CI)
APSIM (55)	231	< 6 hrs	2-7 days	5,000 U (bolus)	53 vs 47%	+6.0 (+2.6 to +9.4)
			2-3 weeks		43 vs 39%	+4.0 (+0.9 to +7.1)

LVEF: PTCA (immediate) vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	LVEF PTCA vs SK IC	Difference (95% CI)
O'Neill (21)	56	< 12 hrs	pre-discharge	250,000-350,000 U	50 vs 53%	-3.0 (-10.6 to +4.6)

LVEF: PTCA + SK-IC vs SK-IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK dose	LVEF PTCA + SK vs SK	Difference (95% CI)
Erbel (17)	162	<6 hrs	3-4 weeks	SK-IV 250,000 U SK-IC 250,000 U	55 vs 55%	0.0 (-5.2 to +5.2)

LVEF: PTCA + rt-PA vs rt-PA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	LVEF PTCA vs control	Difference (95% CI)
TAMI-1 (32)	386	<4-6 hrs	1 week	150 mg	53 vs 56%	-3.0 (-6.4 to +0.4)
European Cooperative-5 (44)	367	<5 hrs	2 weeks	100 mg	51 vs 51%	(no SD given)
TIMI-2A (52)	389	<4 hrs	pre-discharge	150 or 100 mg	50 vs 49%	(no SD given)
TIMI-2B (35)	3262	<4 hrs	6 weeks	150 or 100 mg	50 vs 50%	(no SD given)

[4] 39 pts received 0.4 MU/kg intravenous double-chain rt-PA in the first hr, 0.14 MU/kg in the second hr and 0.03 MU/kg/hr in the subsequent 8 hrs. 79 pts received 0.4 MU/kg in the first hr, 0.08 MU/kg in the second hr and 0.03 MU/kg/hr in the subsequent 4 hrs.

[5] Measured by radionuclide angiography.

[6] Double chain rt-PA.

Table VI. Mortality Studies (mortality within 3 months).

Mortality: Aspirin[1] vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Aspirin dose	Mortality Aspirin vs plac.	Difference (95% CI)
ISIS-2 (27)	17187	<24 hrs	5 weeks	162.5 mg/day[2]	9 vs 12%	-3% (-4 to -2%)

Mortality: SK IC vs standard therapy

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK IC dose	Mortality SK IC vs control	Difference (95% CI)
IC Western Washington (4)	250	<12 hrs	1 month	<350,000 U	4 vs 11%	-7% (-14% to -1%)
ICIN (13)	533	<4 hrs	1 month	250,000 U	6 vs 12%	-6% (-11 to -1%)

Mortality: SK IV vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality SK IV vs placebo	Difference (95% CI)
ISIS-2 (27)	17187	<24 hrs	5 weeks	9 vs 12%	-3% (-4 to -2%)
	8592		5 weeks	8 vs 13%[3]	-5% (-6 to -4%)
White (39)	219	<4 hrs	3 weeks	3 vs 13%	-11% (-3 to -18%)
ISAM (20)	1741	<6 hrs	3 weeks	6 vs 7%	-1% (-3 to +1%)

Mortality: SK IV vs standard therapy

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality SK IV vs control	Difference (95% CI)
GISSI-1 (18)	11806	<12 hrs	3 weeks	11 vs 13%	-2% (-3 to -1%)

Mortality: rt-PA vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality rt-PA vs placebo	Difference (95% CI)
European Cooperative-4 (43)	721	<5 hrs	2 weeks	3 vs 6%	-3% (-6 to 0%)
			3 months	5 vs 8%	-3% (-7 to -1%)
ASSET (42)	5011	<5 hrs	1 month	7 vs 10%	-3% (-5 to -2%)

Mortality: APSAC IV vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality APSAC vs placebo	Difference (95% CI)
AIMS (22)	1258	<6 hrs	1 month	6 vs 12%	-6% (-9 to -3%)

Mortality: rt-PA vs SK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Heparin dose	Mortality rt-PA vs SK IV	Difference (95% CI)
TIMI-1[4] (33)	316	<7 hrs	3 weeks	80 mg		4 vs 5%	-1% (-6 to +3%)
GISSI-2 (65)	20749		in-hospital	100 mg	0 U	8.7% vs 9.2%	-1% (-5 to +2%)
					12,500 U 2 times daily	9.2% vs 7.9%	+1% (0 to +2%)

Mortality: APSAC IV vs SK IC

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation	SK IC dose	Mortality APSAC IV vs SK IC	Difference (95% CI)
APSAC (41)	258	<4 hrs	in-hospital	180,000 U	4 vs 8%	-4% (-10 to +2%)

Mortality: APSAC IV vs heparin

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Heparin dose	Mortality APSAC vs heparin	Difference (95% CI)
APSAC Multicenter (40)	313	<4 hrs	1 month	5,000 U bolus	6 vs 13%	-7% (-14 to -1%)

(40)

Mortality: PTCA (immediate) + rt-PA vs rt-PA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Mortality PTCA vs control	Difference (95% CI)
TAMI-1 (32)	386	<4-6 hrs	in-hospital	150 mg	4 vs 1%	+3% (-1 to +7%)
European Cooperative-5 (44)	367	<5 hrs	2 weeks	150 or 100 mg	7 vs 3%	+3% (-1 to +8%)
			3 months		8 vs 3%	+5% (0 to +10%)
TIMI-2A (52)	389	<4 hrs	3 weeks	100 or 150 mg	7 vs 6%	+1% (-4 to +6%)

Mortality: PTCA within 2 hrs + rt-PA vs PTCA within 18-48 hrs + rt-PA

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Mortality immediate vs delayed	Difference (95% CI)
TIMI-2B (35)	3262	<4 hrs	6 weeks	100 mg	5 vs 5%	0% (-2 to +2%)

1 with or without randomly assigned streptokinase.

2 During 1 month.

3 SK IV + Aspirin vs placebo.

4 Double chain rt-PA.

Table VII. Mortality Studies (mortality > 6 months).

Mortality: SK IC vs standard therapy

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	SK IC dose	Mortality SK IC vs control	Difference (95% CI)
IC Western Washington (4)	250	<12 hrs	1 year	<350,000 U	8 vs 14%	-6% (-13 to +2%)
ICIN (13)	533	<4 hrs	3 years	250,000 U	13 vs 21%	-8% (-14 to -2%)

Mortality: SK IV vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality SK IV vs placebo	Difference (95% CI)
ISAM (20)	1741	<6 hrs	7 months	11 vs 11%	0% (-3 to +3%)
			21 months	14 vs 16%	-2% (-5 to +1%)

Mortality: SK IV vs standard therapy

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality	Difference (95% CI)
GISSI-1 (18)	11806	<12 hrs	1 year	17 vs 19%	-2% (-3 to -1%)
IV Western Washington (54)	368	<6 hrs	2 years	19 vs 35%	-17% (-28 to -6%)

Mortality: rt-PA vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality	Difference (95% CI)
ASSET (42)	5011	<5 hrs	1 year	13 vs 15%	-2% (-4 to 0%)

Mortality: APSAC IV vs placebo

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	Mortality APSAC vs placebo	Difference (95% CI)
AIMS (22)	1258	<6 hrs	1 year	11 vs 18%	-7% (-11 to -3%)

Mortality: rt-PA vs SK IV

Acronym (abstr nr)	Nr of pts	Time to therapy	Evaluation after	rt-PA dose	Mortality rt-PA vs SK IV	Difference (95% CI)
White (64)	270	<3 hrs	9 months	100 mg	6 vs 9%	-2% (-8 to +4%)
TIMI-[1] (33)	316	<7 hrs	1 year	80 mg	11 vs 12%	-1% (-8 to +6%)

[1] Double chain rt-PA.

Table VIII. PTCA trials.

Trial (abstr nr)	Nr of pts	Therapy	Outcome measures
O'Neill (21)	56	Immediate PTCA vs SK-IC	recanalization after therapy: 83 vs 85%. charge in LVEF 8 vs 1%
Erbel (17)	162	SK-IV + IC with or without PTCA	Patency after therapy: 90 vs 86% in hospital reocclusion 14 vs 20% Predischarge LVEF 55 vs 55%
TAMI-1 (32)	386	Immediate vs delayed (7 days) PTCA with rt-PA[1]	24 hrs reocclusion 11 vs 13% in hospital mortality: 4 vs 1% 1 wk LVEF 53 vs 56%
TIMI-2A (52)	389	Immediate (<2 hrs) vs delayed (18-48 hrs) PTCA with rt-PA[2]	predischarge patency 78 vs 80% predischarge LVEF 50 vs 49% 3 wks mortality 7 vs 6%
European Cooperative-5 (44)	367	PTCA + rt-PA vs rt-PA	enz. infarct size 694 vs 867 U/l[3] 2 wks LVEF 51 vs 51% 2 wks mortality 7 vs 3%
TIMI-2B (35)	3262	PTCA (18-48 hrs) + rt-PA vs rt-PA only[4]	6 wks LVEF 50 vs 50% 6 wks mortality 5 vs 5%

1 150 mg rt-PA.

2 100 mg in 83% of pts, 150 mg in 17%.

3 Median HBDH-Q72.

4 520 pts received 150 mg rt-PA, 2742 pts received 100 mg.

LIST OF MAIN CLINICAL TRIALS

ordered by year of publication

Year	Number	Acronym or first author	Main publication
1983	1	Anderson JL	N Engl J Med 1983;308: 1312-8
	2	Khaja F	N Engl J Med 1983;308: 1305-11
	3	Rogers WJ	Circulation 1983;68:1051-61
	4	Western Washington Intracoronary Streptokinase Trial	N Engl J Med 1983;309:1477-82
1984	5	Alderman EL	Am J Cardiol 1984;54:14-9
	6	Leiboff RH	Am J Cardiol 1984;53:404-7
	7	Mount Sinai - New York University Reperfusion Trial-1	N Engl J Med 1984;311:1457-63
	8	Sutton JM, Taylor GJ	Am J Cardiol 1986;57:1227-31
	9	Tennant SN	Circulation 1984;69:756-60
	10	Van de Werf F	N Engl J Med 1984;310:609-13
1985	11	European Cooperative Study for rt-PA in AMI-1	Lancet 1985;965-9
	12	European Cooperative Study for rt-PA in AMI-2	Lancet 1985;1:842-7
	13	ICIN	Lancet 1985;ii:578-82
	14	Society for Cardiac Angiography	Am J Cardiol 1985;55:871-7
	15	Tendera MP	Circulation 1985;71:124-8
1986	16	Cribier	Haemostasis 1986;16: suppl.3:122-9
	17	Erbel	JACC 1986;8:485-95
	18	GISSI-1	Lancet;1986:1:397-402
	19	Ikram S	Brit Med J 1986;293:786-9
	20	ISAM	New Engl J Med 1986;314: 1465-71
	21	O'Neill W	New Engl J Med 1986; 314:812-8
1987	22	AIMS	Lancet 1988;545-9
	23	Bonnier JJRM	Am J Cardiol 1988;62:25-30
	24	European Cooperative Study for rt-PA in AMI-3	Am J Cardiol 1987;60:231-7

	25	European Multicenter Study, Belgian Group	Drugs 1987;33 (Suppl.3):287-92
	26	IRS-2	Drugs 1987;33 (Suppl3):140-5
	27	ISIS-2	Lancet 1988;2:349-60
	28	Julian DG	Drugs 1987;33 (Suppl.3): 261-7
	29	Kaspar L	Drugs 1987;33 (Suppl.3): 179-82
	30	SWIFT	Drugs 1987;33 (Suppl.3): 229-30
	31	TAMI Pilot Study	New Engl J Med 1987;1613-8
	32	TAMI-1	New Engl J Med 1987; 317:581-8
	33	TIMI-1	Circulation 1987;76:142-54
	34	TIMI-1B	N Engl J Med 1985;312:932-6
	35	TIMI-2B	JACC 1987;10:51B-64B
	36	TIMI-2 Subtrial	JACC 1987;10:51B-64B
	37	Treese N	Int J Cardiol 1987;15:19-31
	38	Urokinase Double Blind Study Group	Japan Cir J 1987;51:1072-6
	39	White HD	N Engl J Med 1987;317:850-5
1988	40	APSAC Multicenter Trial	Am J Cardiol 1988;62:347-51
	41	APSAC Study	JACC 1988;11:1153-63
	42	ASSET	Lancet 1988;525-30
	43	European Cooperative Study for rt-PA in AMI-4	Brit Med J 1988;297:1374-9
	44	European Cooperative Study for rt-PA in AMI-5	Lancet 1988;197-203
	45	GAUS	JACC 1988;12:581-7
	46	Johns JA	Circulation 1988;78:546-56
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	49	TAMI-2	Circulation 1988;77:1100-7
	50	TAMI-3	Circulation 1989;79:281-6
	51	TICO	Circulation 1988;77:1311-5
	52	TIMI-2A	JAMA 1988;260:2849-58
	53	Wisenberg G	Am J Cardiol 1988;62:1011-6
	54	Western Washington Intravenous Streptokinase Trial	Circulation 1988;78:258-66
1989	55	APSIM	JACC 1989;13:988-97
	56	Cortadellas J	JACC 1989;14:1566-9
	57	EMIP	Am J Cardiol 1989;64:30A-33A

	58	KAMIT	JACC 1989;14:573-80
	59	Mount Sinai - New York University Reperfusion Trial-2	Circulation 1989;80:1166-75
	60	PAIMS	JACC 1989;13:19-26
	61	PRIMI	Lancet 1989;863-7
	62	TPAT	JACC 1989;13:1469-76
	63	Tranchesi B	Am J Cardiol 1989;64:229-32
	64	White HD	New Engl J Med 1989; 320:817-21
1990	65	GISSI-2 / International Study Group	Lancet 1990;336:65-75
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	67	Six AJ	Am J Cardiol 1990;65:119-23

CHAPTER 2

INCREASED SERUM LEVELS OF FIBRINOGEN DEGRADATION PRODUCTS DUE TO TREATMENT WITH RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR FOR ACUTE MYOCARDIAL INFARCTION ARE RELATED TO BLEEDING COMPLICATIONS, BUT NOT TO CORONARY PATENCY

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Increased Serum Levels of Fibrinogen Degradation Products Due to Treatment With Recombinant Tissue-Type Plasminogen Activator for Acute Myocardial Infarction Are Related to Bleeding Complications, But Not to Coronary Patency

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The association of increasing serum levels of fibrinogen degradation products after recombinant tissue-type plasminogen activator (rt-PA) therapy with bleeding and early coronary patency was assessed in 242 patients with acute myocardial infarction. After administration of 5,000 IU heparin, a median of 40 mg (range 35 to 60) of double chain rt-PA was given intravenously in 90 min. Bleeding occurred in 62 patients; in 73% of patients it was observed within the 1st 24 h and 84% of events consisted of hematoma or prolonged bleeding, or both, at puncture sites. Bleeding events occurred 2.12 times as often in patients with serum levels of fibrinogen degradation products >85 mg/liter as in patients with serum levels <22 mg/liter (95% confidence interval 1.01 to 4.43).

The infarct-related coronary vessel was patent in 65% of patients at 90 min after the start of rt-PA infusion. In patients with high serum levels of fibrin(ogen) degradation products, coronary patency at 90 min after the start of rt-PA infusion was not better (13% less, 95% confidence interval −33%, 13%) than in patients with low serum levels. This uncoupling of thrombolytic effect in terms of coronary patency and systemic fibrinogenolysis confirms the experimentally demonstrated fibrin specificity of double chain rt-PA in human subjects. Because fibrin specificity of single chain rt-PA is at least similar to that of double chain rt-PA, the observations in this analysis most likely hold also for single chain rt-PA.

These findings suggest that a dose of rt-PA just below the threshold that causes systemic fibrinogenolysis might be optimal in terms of bleeding and coronary patency. Measurements of fibrinogen degradation products during rt-PA infusion might help to titrate rt-PA dosing in individual patients.

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Recombinant human tissue-type plasminogen activator (rt-PA) has been shown in the Thrombolysis in Myocardial Infarction (TIMI I) trial (1) to be twice as effective as intravenous administration of streptokinase to recanalize occluded infarct-related coronary arteries in patients with acute myocardial infarction and to yield more frequently patent coronary arteries 90 min after the start of treatment (2). Furthermore, rt-PA preserves left ventricular function (3,4) and reduces both enzymatic infarct size and mortality after myocardial infarction (3,5).

It is a fibrin-specific thrombolytic agent: plasminogen is converted to plasmin primarily at the site of the thrombus. However, at high dosages used for treatment of acute myocardial infarction, this fibrin specificity is partly lost and fibrinogen breakdown in the circulation occurs in part of the patients (2,6). In patients treated with intracoronary streptokinase or urokinase, increasing systemic fibrinogenolysis is associated with more frequent recanalization (7,8). It is unknown whether this sequence is similar for patients treated with rt-PA. Furthermore, it is unknown to which degree fibrinogen degradation products developing after

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administration of rt-PA contribute to the occurrence of bleeding complications.

In this analysis, the association of increasing serum levels of fibrinogen degradation products with bleeding and early coronary patency after rt-PA therapy in 242 patients with acute myocardial infarction is assessed. The influence of other known determinants of bleeding or coronary patency on this association (confounding) is eliminated by multivariate logistic regression analysis.

Methods

Patients and management. The present investigation is based on data from patients treated with rt-PA in the first three trials of the European Co-operative Study Group for rt-PA (2,9,10) in which the protocols and methods for data collection were similar. All protocols were approved by institutional committees on human research and for all three trials only patients who gave informed consent were eligible for participation. The first trial (9) was a double-blind and randomized comparison of coronary patency after rt-PA (0.75 mg rt-PA/kg body weight intravenously over 90 min) with coronary patency after placebo in 129 patients from six centers. In the second trial (2), coronary patency after 0.75 mg rt-PA/kg body weight given intravenously over 90 min was compared with coronary patency after 1.5 million IU streptokinase given intravenously over 60 min in 129 patients from seven centers. In the third trial (10), coronary patency and the influence of a second infusion of 30 mg rt-PA over 6 h on subsequent reocclusion at 6 to 24 h was assessed in 123 patients from 11 centers treated with 40 mg rt-PA over 90 min.

Patients between 21 and 70 years of age with ≥30 min of chest pain and ST segment elevation of ≥0.3 mV in two or more electrocardiographic (ECG) precordial leads or ≥0.2 mV in two or more limb leads were eligible for inclusion, provided that rt-PA infusion could be started within 6 h from onset of symptoms in the first two trials and within 4 h in the third trial. In the first two trials, patients with a previous infarction were excluded, whereas a previous myocardial infarction in another territory did not disqualify the patient for the third study. Otherwise, exclusion criteria were identical.

All consenting patients were immediately registered at an independent telephone service and received treatment allocation from that service. After blood sampling for coagulation assays, an intravenous bolus of 5,000 IU heparin was given. Thereafter, an intravenous infusion of rt-PA was given over 90 min. The same batch of primarily double chain rt-PA was used in all three studies (G-11021, manufactured by Genentech Inc. and supplied by Boehringer Ingelheim International GmbH).

Coronary angiography. The first coronary angiogram of the infarct-related vessel was performed between 75 and 90 min after the start of rt-PA infusion. In the patients of the third study, coronary angiography was repeated at 6 to 24 h. All coronary angiograms were centrally assessed by teams of three assessors, of whom two were always present to maintain consistency. The infarct-related segment was identified on the basis of ECG and angiographic evidence. Patency was defined as complete distal filling of the infarct-related coronary artery, not through collateral vessels, within three cardiac cycles at the first adequate contrast injection.

Bleeding events. The protocol required a detailed description of all bleeding complications at the end of the rt-PA infusion, after the first coronary angiogram and at discharge, including hematoma >5 cm in diameter and prolonged bleeding of >30 min duration.

Hemostasis variables. Blood samples were collected before and at 60 and 90 min after the start of rt-PA infusion. Tubes for blood collection were provided containing 0.5 ml sodium citrate (final concentration 0.01 mol/liter) and aprotinin to counteract proteolysis by in vitro plasmin formation (final concentration 150 KIU/ml) for the determination of levels of fibrinogen, fibrinogen degradation products and activated partial thromboplastin time. Blood samples were centrifuged within 1 h and stored at −20°C. All hemostasis tests were performed centrally in the Central Coagulation Laboratory (Leuven). Methods of assessment have been described previously (11). The normal value for the plasma level of fibrinogen is 2 to 4 g/liter and for serum level of fibrin(ogen) degradation products is <8 mg/liter.

Data analysis. Of the 251 patients allocated to rt-PA in the three European trials, 9 were excluded from this analysis: 2 did not receive the full dose of rt-PA, 6 had unassessable 90 min angiograms, and 1 had bleeding that was noticed during rt-PA infusion and therefore could not be related to the serum level of fibrinogen degradation products after rt-PA administration. The remaining 242 patients received the full dose of rt-PA and had assessable 90 min angiograms.

Because the exact start of bleeding complications is often difficult to assess, all bleeding events throughout the hospital phase were included in this analysis. Bleeding rate was defined as the percent of patients with at least one bleeding event. When more than one bleeding event was reported for a patient, the time of the first noticed event was used. Patency rate was defined as the percent of patients with a patent infarct-related artery on the angiogram at the end of the 90 min rt-PA infusion.

Patients were grouped in three equally sized subgroups according to the serum level of fibrinogen degradation products after rt-PA infusion. The chosen levels of fibrin(ogen) degradation products of 22 and 85 mg/liter are therefore arbitrary. Three groups were selected to enable assessment of trends in bleeding and coronary patency and because more groups would weaken strength of associations. Subse-

Table 1. Effect of rt-PA Infusion on Hemostasis Variables in 242 Patients

	1st Trial (n = 61)	2nd Trial (n = 62)	3rd Trial (n = 119)	Total (n = 242)*
rt-PA dosage (mg)	60 (40,60)	55 (35,60)	40 (40,40)	40 (35,60)
Fibrinogen (g/liter)				
Before infusion	2.7 (2.3 to 3.5)	2.4 (2.0 to 2.8)	2.6 (2.3 to 2.9)	2.6 (2.2 to 2.9)
At 60 min	2.0 (1.7 to 2.5)	1.8 (1.3 to 2.2)	2.3 (1.9 to 2.7)	2.1 (1.7 to 2.6)
At 90 min	1.4 (0.9 to 2.3)	1.3 (0.9 to 1.7)	1.8 (1.2 to 2.2)	1.5 (1.0 to 2.2)
Fibrin(ogen) degradation products (mg/liter)				
Before infusion	5 (5 to 7)	6 (5 to 12)	3 (2 to 3)	5 (3 to 5)
At 60 min	15 (8 to 34)	20 (12 to 35)	14 (9 to 27)	17 (9 to 31)
At 90 min	38 (14 to 155)	40 (20 to 120)	36 (15 to 90)	38 (17 to 110)
Activated partial thromboplastin time (s)				
Before infusion	60 (51 to 75)	61 (50 to 73)	58 (51 to 86)	60 (51 to 75)
At 60 min	102 (81 to 141)	99 (73 to 152)	158 (105 to 180)	125 (85 to 180)
At 90 min	112 (72 to 165)	126 (96 to 180)	180 (145 to 180)	163 (98 to 180)

*For fibrinogen and fibrin(ogen) degradation products, the number of patients with assessable blood samples before infusion, at 60 min and at 90 min, respectively, was 198, 212 and 210; for activated partial thromboplastin time, 199, 212, 208. Continuous variables are given as median with the 1st and 3rd quartile in parentheses. rt-PA = recombinant tissue-type plasminogen activator.

quently, bleeding and patency rates were determined in each subgroup. The subgroup with low serum levels of fibrin(ogen) degradation products was chosen as the reference group. The second and third subgroups were compared with the reference group with use of rate ratios (that is, the rate in the second or third group divided by the rate in reference group); 95% confidence intervals for rate ratios were determined according to the method of Katz et al. (12).

Distortion in the relation between serum levels of fibrin or fibrinogen degradation products and bleeding or patency (confounding) caused by unequal distributions of other known determinants of bleeding or patency among these subgroups was simultaneously eliminated by multivariate logistic regression analysis. The following determinants of bleeding were considered: 1) trial in which the patient participated, 2) age, 3) gender, 4) pulmonary rales before allocation, 5) thrombocyte count before rt-PA infusion, 6) fibrinogen after rt-PA, 7) activated partial thromboplastin time after rt-PA, reflecting mainly the degree of heparinization, 8) streptokinase given after rt-PA, and 9) second infusion of rt-PA in the third trial (10). Similarly, for coronary patency, the determinants considered were: 1) trial in which the patient participated, 2) age, 3) gender, 4) use of intravenous nitrates, which has been reported to be beneficial for coronary patency in the setting of thrombolytic therapy (13,14), and 5) activated partial thromboplastin time, prolonged mainly by heparinization, which possibly improves thrombolytic efficacy (15,16). A detailed description of the design of the multivariate logistic regression models and methodology to obtain adjusted rate ratios and 95% confidence intervals is given in the Appendix.

Results

Clinical features. The median age of the 242 patients was 56 years (range 31 to 70); 223 were male (84%). The median delay from the onset of symptoms to the start of rt-PA infusion was 2.8 h (range 0.9 to 5.8). A median dose of 40 mg (range 35 to 60) of rt-PA was administered over 90 min. Ten patients (4.1%) died during the hospital stay, 2 on the 1st day and 8 after the 4th day. No death was related to a bleeding complication. Cardiogenic shock was the cause of death in five patients, thromboembolism in 2, cardiac tamponade in 2 and electromechanical dissociation during late angiography in 1.

Hemostasis variables before, during and after rt-PA (Table 1). A moderate decrease in fibrinogen and a moderate increase in serum level of fibrin or fibrinogen degradation products were observed during rt-PA infusion. Before treatment, 1% of the patients (2 of 198 with analyzable blood samples) had a fibrinogen level <1 g/liter and at 90 min 22% (46 of 210 with analyzable blood samples). At 90 min, a serum level of fibrin(ogen) degradation products ≥22 mg/liter was found in 67% of the patients (141 of 210 with assessable blood samples). The activated partial thromboplastin time was increasingly prolonged during rt-PA infusion, a finding that reflects the heparin administration and to a minute extent the formation of fibrin(ogen) degradation products.

In the first two trials, the rt-PA dosage was higher than that in the third trial (Table 1). This is reflected in a trend toward a lesser decrease in fibrinogen and lower serum levels of fibrin(ogen) degradation products at 90 min after start of rt-PA infusion in the third trial (10). Nevertheless,

Table 2. Survey of the 62 Bleeding Events in All 242 Patients and the Time That the Bleeding Was First Noticed

No. of Patients With	Within 24 h	24 to 48 h	After 48 h	Total
Retroperitoneal bleeding	—	1	—	1
Hematemesis	2	—	—	2
Hematuria	1	—	1	2
Hematuria + gum bleeding	1	—	—	1
Gum bleeding	2	—	—	2
Hematuria + prolonged bleeding	—	—	1	1
Hematoma and/or prolonged bleeding				
Blood transfusion given	6	2	1	9
No blood transfusion given	33	7	3	43
Unexplained anemia	—	—	1	1
Total	45	10	7	62
No. of patients with blood transfusion	—	6	4	10

the activated partial thromboplastin time was more prolonged than that in the other trials, probably by more rigid heparinization in the third trial.

Bleeding events (Table 2). In seven patients, two bleeding events were reported; the bleeding rate was 26% (62 of 242 patients). Most bleeding complications occurred within the 1st 24 h (73%) and consisted of hematoma or prolonged bleeding, or both, at a puncture site (84%). Two patients had hematemesis; one was treated with cimetidine, the other did not receive special therapy. Retroperitoneal bleeding was suspected in another patient with epigastric pain and decrease in hemoglobin from 14.7 to 10.2 g/dl; no special treatment was given and the patient was discharged on the 11th day. No intracranial bleeding occurred. Blood transfusion was given to 10 (16%) of 62 patients with a bleeding event: for hematoma in 7 patients, a combination of hematoma and prolonged bleeding in 2 and unexplained anemia in 1 patient. No patient classified as a nonbleeder received blood transfusion.

Table 3. Increasing Serum Levels of Fibrin(ogen) Degradation Products (mg/liter at 90 min) in Relation to Bleeding and Coronary Patency Rate

Fibrin(ogen) Degradation Products at 90 min (mg/liter)		Crude Rate Ratio	Adjusted Rate Ratio
	Bleeding Rate		
<22	16% (11/69)	Reference	Reference
22 to 85	29% (20/69)	1.82 (0.94 to 3.50)	1.40 (0.73 to 2.65)
≥85	38% (27/72)	2.35 (1.27 to 4.37)	2.12 (1.01 to 4.43)
Missing	13% (4/32)	0.78 (0.27 to 2.28)	0.83 (0.27 to 2.55)
	Patency Rate		
<22	70% (48/69)	Reference	Reference
22 to 85	58% (40/69)	0.83 (0.65 to 1.08)	0.75 (0.57 to 0.99)
≥85	64% (46/72)	0.92 (0.73 to 1.16)	0.87 (0.67 to 1.13)
Missing	75% (24/32)	1.08 (0.84 to 1.39)	1.13 (0.82 to 1.56)

Crude and adjusted rate ratio, respectively, before and after elimination of distortion of the relation between serum levels of fibrin(ogen) degradation products and bleeding or coronary patency caused by unequal distribution of other determinants of bleeding or coronary patency over the various categories of serum levels of fibrin(ogen) degradation product (see Methods); 95% confidence intervals are presented in parentheses.

Fibrinogen degradation products and bleeding (Table 3). The bleeding rate was higher among patients with higher serum levels of fibrin(ogen) degradation products. Patients with a serum level of >85 mg/liter had a bleeding complication approximately twice as often as did those with a serum level <22 mg/liter. This relation was maintained after adjustment by multivariate logistic regression analysis. The variables that were used for this adjustment are listed in the Appendix. The other variables mentioned in the Methods section did not influence the relation between serum levels of fibrin(ogen) degradation products and bleeding. Figure 1 depicts the relation between serum levels of fibrinogen degradation products and bleeding, adjusted for the variables listed in the Appendix, together with its 95% confidence range.

Coronary patency. At 90 min after the start of rt-PA infusion, the infarct-related vessel was found patent in 159 of the 242 patients (patency rate 65%, 95% confidence interval 59 to 71). The patency rate was similar in the three trials: 61% (95% confidence interval 48 to 73) in the first trial, 69% (95% confidence interval 56 to 80) in the second trial and 66% (95% confidence interval 56 to 74) in the third trial.

Fibrin or fibrinogen degradation products and patency (Table 3). A trend of decreasing coronary patency was observed with increasing serum levels of fibrinogen degradation products before and after correction by logistic analysis. The variables used in the logistic regression model are given in the Appendix. The other determinants of coronary patency mentioned in the Methods section did not distort the relation between fibrin(ogen) degradation products and coronary patency. Figure 2 illustrates the absence of higher patency rates with increasing serum levels of fibrinogen degradation products.

Discussion

Recombinant tissue-type plasminogen activator (rt-PA) is an effective thrombolytic agent with limited systemic fibrinogenolysis in the vast majority of patients, when compared with intravenous streptokinase. However, bleeding has remained a frequent side effect in the clinical trials so far (1,2,3,6). This analysis reveals that increasing serum levels of fibrinogen degradation products are related to more frequent bleeding complications, but not to greater coronary patency at 90 min after the start of rt-PA infusion.

Fibrinogen degradation products and bleeding. The relation between fibrin(ogen) degradation products and bleeding might be explained by the fact that fibrinogen degradation

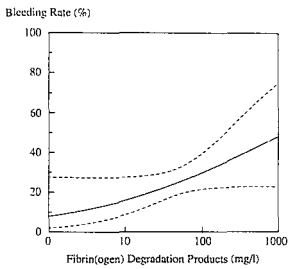
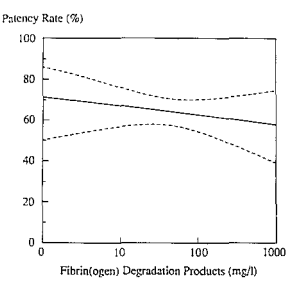


Figure 1. Bleeding rate as a function of increasing serum levels of fibrin(ogen) degradation products (as continuous variable, logarithmic scale) at 90 min after start of rt-PA infusion. Confounding by other determinants of bleeding was eliminated by multiple logistic regression analysis. The dotted lines represent 95% confidence limits. rt-PA = recombinant tissue-type plasminogen activator.

products act as antithrombins, fragment Y being the most active (18). There is evidence that fibrinogen degradation after rt-PA results in relatively large amounts of early degradation products belonging to the fragment X and Y groups (11). In addition, fibrinogen degradation products inhibit fibrin polymerization, resulting in a defective fibrin structure, and impair platelet function (18). Also, the TIMI study group reported a relation between serum levels of fibrinogen degradation products and bleeding after administration of double and single chain rt-PA (6). However, in that report no adjustment for confounding variables was made by multivariate regression analysis.

The adjusted rate ratios of 1.40 and 2.12 for bleeding at increasing levels of fibrinogen degradation products are probably an underestimation of the strength of the relation

Figure 2. Coronary patency rate as a function of increasing serum levels of fibrinogen degradation products (as continuous variable, logarithmic scale) at 90 min after infusion of rt-PA. Confounding by other determinants of coronary patency was eliminated by multiple logistic regression analysis. The **dotted lines** represent 95% confidence limits. rt-PA = recombinant tissue-type plasminogen activator.



because they are conditional on the prolongation of activated partial thromboplastin time, which is partly caused by fibrinogen degradation products.

Fibrinogen degradation products and patency. Increasing serum levels of fibrin(ogen) degradation products were not related to better coronary patency at 90 min, but tended to be inversely related to coronary patency. The TIMI study group (19) also reported an inverse relation between systemic fibrinogenolysis and recanalization at 90 min for double chain rt-PA; patients with recanalization had 31% decline in fibrinogen versus 41% in those patients without recanalization (95% confidence interval for this 10% difference: 8% to 12%). The possibility of an inverse relation is worth further investigation, both in vitro and in animal and clinical studies. An explanation could be that systemic fibrinogenolysis counteracts the fibrinolytic efficacy of rt-PA through negative feedback (inactivation of t-PA by fibrinogen degradation products?).

In patients treated with streptokinase or urokinase, recanalization occurs more frequently with increasing serum levels of fibrinogen degradation products (7,8). This finding is in agreement with the fact that streptokinase and urokinase are not fibrin specific and result in conversion of plasminogen to plasmin in the free circulation, producing breakdown of fibrinogen and clotting factors V and VIII (18).

It could be argued that prolongation of activated partial thromplastin time might not be a determinant of coronary patency, because the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group (20) recently reported that patients given heparin concomitant with rt-PA did not have a higher coronary patency rate than did patients given rt-PA alone. Also, it has been suggested (21) that heparin might reduce plasmin formation by t-PA at the site of the thrombus. Therefore, the multivariate logistic regression analysis in this analysis was repeated without activated partial thromboplastin time. The same trend was found for the relation between serum levels of fibrinogen degradation products and coronary patency, although less pronounced (rate ratio and 95% confidence interval for serum level of fibrinogen degradation products from 22 to 85 mg/liter, 0.82; 0.63 to 1.06; for serum level of fibrinogen degradation products ≥85 mg/liter, 0.92, 0.72 to 1.18).

Limitations of the analysis. The test developed by Merskey that we used in these studies does not differentiate between fibrin degradation and fibrinogen degradation products. However, this lack does not invalidate our analysis because the degradation products after thrombolysis with rt-PA for acute myocardial infarction consist primarily of fibrinogen degradation products (22). Similarly, in pulmonary embolism where fibrin mass is much larger than that in coronary thrombosis, predominantly fibrinogen degradation products were found (23). Therefore, in the present analysis the degradation products observed most likely reflect fibrinogen degradation and not fibrin degradation.

Another concern could be that in vitro degradation of fibrinogen might have occurred between blood collection and deep-freezing, which is not completely eliminated by aprotinin. If indeed fibrinogen degradation products in the present analysis originated mainly from in vitro degradation, the serum level of such products reflects lytic activity in serum rather than in vivo fibrinogen breakdown. Greater lytic activity in serum would then be associated with increased bleeding rate, but not with higher coronary patency.

One should be cautious in extrapolating the relation between fibrinogen degradation products and bleeding events that was observed in the present analysis to other forms of bleeding (e.g., intracranial bleeding). In this investigation, the incidence of serious bleeding events was too low to allow separate analyses of various types of bleeding. Finally, it should be appreciated that in all patients in these trials acute angiography was performed to assess coronary patency. One would expect less frequent bleeding if acute catheterization is not performed. However, in patients treated with rt-PA without acute angiography, similar incidence rates ranging from 23% to 29% and similar types of bleeding have been reported (3,24).

Implications of the present analysis. Increasing serum levels or fibrinogen degradation products were related to more frequent bleeding, but not to better coronary patency. The observation that thrombolytic effect and systemic fibrinogenolysis were completely uncoupled confirms the fibrin specificity of double chain rt-PA in patients. These findings probably hold also for single chain rt-PA because fibrin specificity of single chain rt-PA is at least similar to fibrin specificity of double chain rt-PA. Although single chain rt-PA needs to be administered at higher doses than does double chain rt-PA, because of its shorter plasma half-life, it resulted in less fibrinogen breakdown at equipotent doses in terms of coronary recanalization (6).

These considerations suggest that there may be an optimal dose of rt-PA for every individual with maximal thrombolytic effect and without fibrinogen breakdown, whereas at higher doses, systemic fibrinogenolysis is induced with an increased risk for bleeding but without better thrombolytic effect. Determination of fibrinogen degradation product levels during rt-PA infusion might help to identify this optimal dose for an individual patient. Rapid tests for quantitative or semiquantitative determination of levels of fibrinogen degradation products, preferrably in whole blood and specifically measuring fibrinogen degradation products, should be developed. These tests might enable the clinician to titrate the rt-PA dosage, in a manner similarly to the titration of insulin dosage on the basis of blood sugar levels. This approach, which is restricted to fibrin-specific thrombolytic agents, might be even more relevant for possible indications as pulmonary lung embolism, artificial heart valve thrombosis and venous thrombosis, where time is less crucial than that in acute myocardial infarction. In addition, prolonged rt-PA infusion for prevention of coronary reocclusion after thrombolysis for acute myocardial infarction might be individualized in this manner.

Appendix

Multivariate logistic regression analysis. Multiple logistic regression analysis was performed with the BMDP statistical package (program LR). The relation between serum levels of fibrinogen degradation products and bleeding or patency was expressed in a multivariate logistic regression model. A set of reported variables that were known to be predictors of bleeding or patency was selected. These variables were forced in a model, one at a time, together with the various categories of serum levels of fibrin(ogen) degradation products. Only those variables affecting the relation

Table 4. Multivariate Logistic Regression Model for the Assessment of the Relation Between Serum Levels of Fibrin(ogen) Degradation Products and Bleeding

Variable ($X_{i,j}$)	Bleeding Rate	Coefficient ($b_{i,j}$)	Standard Error
Fibrin(ogen) Degradation Products (mg/liter) at 90 min			
<22	16% (11/69)	Reference	—
22 to 85	29% (20/69)	0.47	0.46
≥85	38% (27/72)	1.10	0.55
Missing	13% (4/32)	−0.25	0.77
Pulmonary Rales Before Allocation			
No	22% (43/194)	Reference	—
Yes	40% (19/48)	0.90	0.39
Thrombocytes Before Infusion (10^9/liter)			
<220	39% (26/74)	1.13	0.45
220 to 280	23% (15/71)	0.31	0.47
≥280	19% (11/71)	Reference	—
Missing	39% (10/26)	1.35	0.57
Fibrinogen at 90 min (g/liter)			
<1.21	31% (22/70)	−0.40	0.56
1.21 to 1.91	24% (18/74)	−0.35	0.44
≥1.91	27% (18/66)	Reference	—
Missing	13% (4/32)	−0.25	0.77
aPTT at 90 min (s)			
<95	16% (8/49)	Reference	—
95 to 180	24% (15/63)	0.41	0.52
≥180	37% (35/96)	0.77	0.49
Missing	12% (4/34)	−0.25	0.77
Second Infusion of 30 mg rt-PA (3rd trial)			
No	24% (47/200)	Reference	—
Yes	36% (15/42)	0.54	0.42
Intercept	—	−2.74	0.61

aPTT = activated partial thromboplastin time (s); rt-PA = recombinant tissue-type plasminogen activator.

Table 5. Multivariate Logistic Regression Model for Assessment of the Relation Between Serum Levels of Fibrin(ogen) Degradation Products and Coronary Patency

Variable ($X_{i,j}$)	Patency Rate	Coefficient ($b_{i,j}$)	Standard Error
Fibrin(ogen) Degradation Products (mg/liter) at 90 min			
<22	70% (48/69)	Reference	—
22 to 85	58% (40/69)	−0.76	0.38
≥85	64% (46/72)	−0.39	0.37
Missing	75% (24/32)	0.39	0.54
Nitroglycerin iv			
No	62% (106/170)	Reference	—
Yes	72% (52/72)	0.58	0.32
aPTT at 90 min (s)			
<95	59% (29/49)	Reference	—
95 to 180	56% (35/63)	−0.24	0.39
≥180	71% (68/96)	0.62	0.38
Missing	77% (26/34)	0.39	0.54
Intercept	—	0.59	0.35

iv = intravenous; other abbreviations as in Table 4.

between the various categories of these serum levels and bleeding or patency were combined in a final model. Adjusted rate ratios and 95% confidence intervals for the various categories of serum levels of fibrinogen degradation products were obtained according to the method of Miettinen (17) by the following formula, in which the mean was entered for all variables (X_i) other than the category of serum levels of fibrinogen degradation products for which the adjusted rate ratio was determined; one for the category of serum level of fibrinogen degradation products under study (variable X_j) in the numerator and 0 in the denominator:

$$\text{Rate ratio} = \frac{[1+\exp(-(\text{intercept}+\Sigma_i b_i X_i + b_j * 1))]^{-1}}{[1+\exp(-(\text{intercept}+\Sigma_i b_i X_i + b_j * 0))]^{-1}}$$

95% confidence interval: rate ratio$^{(1-1.96/\text{chi-0})}$, rate ratio$^{(1+1.96/\text{chi-0})}$;

where chi-0 is the ratio of the fitted coefficient for the category of serum level of fibrinogen degradation products of which the confidence interval has to be determined, to the standard error (SE) of this coefficient. Coefficients (b_i, b_j) and standard errors for all variables in the final model are listed in Tables 4 and 5.

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CHAPTER 3

INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR AND SIZE OF INFARCT, LEFT VENTRICULAR FUNCTION, AND SURVIVAL IN ACUTE MYOCARDIAL INFARCTION

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Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction

Frans Van de Werf, Alfred E R Arnold

For the European Cooperative Study Group for recombinant tissue type plasminogen activator

Abstract

***Study objective*—To assess effect of intravenous recombinant tissue type plasminogen activator on size of infarct, left ventricular function, and survival in acute myocardial infarction.**

***Design*—Double blind, randomised, placebo controlled prospective trial of patients with acute myocardial infarction within five hours after onset of symptoms.**

***Setting*—Twenty six referral centres participating in European cooperative study for recombinant tissue type plasminogen activator.**

***Patients*—Treatment group of 355 patients with acute myocardial infarction allocated to receive intravenous recombinant plasminogen activator. Controls comprised 366 similar patients allocated to receive placebo.**

***Intervention*—All patients were given aspirin 250 mg and bolus injection of 5000 IU heparin immediately before start of trial. Patients in treatment group were given 100 mg recombinant tissue plasminogen activator over three hours (10 mg intravenous bolus, 50 mg during one hour, and 40 mg during next two hours) by infusion. Controls were given placebo by same method. Full anticoagulation treatment and aspirin were given to both groups until angiography (10-22 days after admission). β Blockers were given at discharge.**

***End point*—Left ventricular function at 10-22 days, enzymatic infarct size, clinical course, and survival to three month follow up.**

***Measurements and main results*—Mortality was reduced by 51% (95% confidence interval −76 to 1) in treated patients at 14 days after start of treatment and by 36% (−63 to 13) at three months. For treatment within three hours after myocardial infarction mortality was reduced by 82% (−95 to −31) at 14 days and by 59% (−83 to −2) at three months. During 14 days in hospital incidence of cardiac complications was lower in treated patients than controls (cardiogenic shock, 2·5% *v* 6·0%; ventricular fibrillation, 3·4% *v* 6·3%; and pericarditis, 6·2% *v* 11·0% respectively), but that of angioplasty or artery bypass, or both was higher (15·8% *v* 9·6%) during the first three months. Bleeding complications were commoner in treated than untreated patients. Most were minor, but 1·4% of treated patients had intracranial haemorrhage within three days after start of infusion.**

Enzymatic size of infarct, determined by α hydroxybutyrate dehydrogenase concentrations, was less (20%, 2p=0·0018) in treated patients than in controls. Left ventricular ejection fraction was 2·2% higher (0·3 to 4·0) and end diastolic and end systolic volumes smaller by 6·0 ml (−0·2 to −11·9) and 5·8 ml (−0·9 to −10·6), respectively, in treated patients.

***Conclusion*—Recombinant tissue type plasminogen activator with heparin and aspirin reduces size of infarct, preserves left ventricular function, and reduces complications and death from cardiac causes but at increased risk of bleeding complications.**

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Introduction

Intravenous thrombolysis is becoming widely accepted as a standard treatment for acute myocardial infarction. Nevertheless, the effects on early and late survival, site of infarct, and left ventricular function are variable and not always consistent.[1-15] Furthermore, in most trials thrombolytic treatment has been associated with an increased risk of bleeding.

Newer thrombolytic agents are being evaluated for intravenous use in the acute stage of myocardial infarction.[16-18] Among these, recombinant tissue plasminogen activator has a considerably higher specificity for fibrin and a greater thrombolytic efficacy than streptokinase.[17 18] To study the effect of intravenous recombinant tissue plasminogen activator on size of infarct, left ventricular function, and follow up a large prospective, placebo controlled, double blind, multicentre trial was launched by the European Co-operative Study Group for recombinant tissue plasminogen activator in May 1986; the main results are presented here.

Patients and methods

Patients between 21 and 71 years old who had chest pain typical of myocardial ischaemia for at least 30 minutes were eligible for the trial, provided that experimental treatment could be started within five hours after the onset of symptoms. ST segment elevation of at least 2 mm (measured 60 milliseconds after the J point) in two or more limb leads or leads V5 and V6 had to be present or an elevation of 3 mm in two or more precordial leads. Patients with ST segment depression of 2 mm or more in two precordial leads together with ST segment elevation of a least 1 mm in two limb leads or leads V5 and V6, indicating infarction of the posterior wall, were also included.

Exclusion criteria were: oral anticoagulation treatment, recent major trauma, prolonged or traumatic heart massage, artificial respiration, transmural myocardial infarction during the preceding two weeks, previous myocardial infarction at the same site or previous coronary artery bypass surgery, history of cerebrovascular accident or gastrointestinal bleeding during the previous three months, major hepatic or renal disease, known proliferative diabetic retinopathy, bleeding disorders and other diseases with an expected survival of less than two years, and expected problems with catheterisation of the heart or with follow up.

Consenting patients were registered with a central telephone allocation service. Allocation to receive either recombinant tissue plasminogen activator or placebo was made double blind during the same telephone call by opening a sealed envelope containing the treatment number corresponding to a treatment package at the clinic. Randomisation was in blocks of four patients and was balanced for each of the 26 participating hospitals (see appendix).

TREATMENT

All patients received 250 mg aspirin and a bolus injection of 5000 IU heparin immediately before the start of the trial treatment. Patients in the treatment group were given 10 mg intravenous bolus of predominantly single chain recombinant tissue plasminogen acuivator (G-11044, Genentech supplied by Boehringer Ingelheim International) followed by 50 mg during one hour and 40 mg during the next two hours given with an infusion pump; in the other group

(controls) placebo was given in exactly the same way. After the start of infusion all patients were treated with intravenous heparin 1000 IU/hour and aspirin 75-125 mg orally every other day until angiography. After three days heparin could be replaced by oral anticoagulants. Any other treatment was given only if clinically indicated. At discharge patients were given a β blocker, unless this was contraindicated.

LABORATORY ANALYSES

Samples of blood for assessment of the activities of cardiac enzymes locally and of plasma α hydroxybutyrate dehydrogenase centrally were collected before the start of the trial treatment and after 12, 24, 36, 48, 72, and 96 hours. Cumulative release of plasma α hydroxybutyrate dehydrogenase was calculated in the core laboratory for enzyme determinations as described before[19,20] and expressed in U/l of plasma. The value at 72 hours was used as an estimate of the size of infarct. In patients in whom data was incomplete this value was estimated by extrapolation of the data at 48 or 36 hours, or from a single value of the activity determined after at least 24 hours, or from serum aspartate aminotransferase activity, which was determined locally. In a predetermined subset of patients samples of blood for assays of coagulation and fibrinolysis were obtained before the start of infusion and at two and 24 hours afterwards. The concentrations of fibrinogen and fibrin(ogen) degradation products were estimated centrally.[18]

CARDIAC CATHETERISATION

Coronary arteriography and left ventriculography were done 10-22 days after the acute event with either the Sones or the Judkins technique and recorded on 35 mm x ray film. Each hospital chose a time interval of 4 days in which angiography had to be performed, at 10-14, 12-16, 14-18, 16-20, or 18-22 days after the allocation of patients. All films were examined centrally by the angiography assessment group, which identified the infarcted vessel with the help of the electrocardiogram, assessed its patency according to the thrombolysis in myocardial infarction study,[17] and confirmed that the technical quality of the left ventricular angiograms was adequate for quantitative measurements. Left ventricular end systolic and end diastolic volumes and ejection fraction were measured by the central core laboratory from the 30° right anterior oblique projection of the angiogram by the area-length method. Internal calibration was provided by a cast of known volume filmed at the time of the angiogram.

STATISTICAL ANALYSES

Calculation of the size of the trial was based on the left ventricular ejection fraction at 10-22 days: to detect a relative 5% difference in ejection fraction between the two treatment groups with 80% power at a 0·05 level of significance 300 patients whose angiograms were analysable were needed in each group. Assuming that missing and non-analysable angiograms might be predicted in 15% of the patients, we calculated that 700 patients would be needed.

Collection and analysis of data were performed by an autonomous data centre, which was independent of the investigators and the sponsor. All registered patients were included in the analysis even if the experimental treatment had not been started. All assessments were performed without knowledge of the treatment allocation. Continuous variables are reported as median and 90% range values. When the distribution of a variable permitted, the difference between means and 95% confidence intervals were calculated.[21] Results for release of myocardial α hydroxybutyrate dehydrogenase at 72 hours were analysed by the Mann-Whitney rank sum test. The ratio of proportions (rate ratio) and its 95% confidence interval were calculated according to Miettinen and Nurminen,[22] in addition to the χ^2 test.

Results

Between May 1986 and November 1987, 721 patients were randomised in the 26 participating hospitals: 366 were allocated to receive placebo and 355 to receive plasminogen activator. In eight patients the trial treatment was not given. Three patients violated the protocol: one in each group refused consent after being allocated and one control was given streptokinase instead of the trial treatment. In five patients the trial treatment was not given for clinical reasons: normalisation of ST-T changes in two controls and cardiac arrest and death, diabetic retinopathy, and a severe haematoma due to arterial puncture in three patients allocated to receive plasminogen activator. The eight patients were included in the analysis according to their allocation to treatment. Two patients in the placebo group were allocated, although coronary artery bypass had been performed previously. Baseline characteristics on admission were similar in the two groups (table I).

TABLE I—*Baseline characteristics at admission*

	Placebo (n=366)	Recombinant plasminogen activator (n=355)
Median (range)* age (years)	58 (43-69)	58 (41-69)
No (%) men	304 (83)	313 (88)
No (%) with:		
History of angina	176 (48)	168 (47)
History of previous infarction	26 (7)	27 (8)
Anterior infarction	130 (36)	145 (41)
Electrocardiogram missing	12 (3)	13 (4)
Median (range)*:		
Heart rate (beats/min)	72 (49-102)	72 (50-104)
Systolic blood pressure (mm Hg)	130 (90-170)	130 (90-180)
Diastolic blood pressure (mm Hg)	80 (60-110)	80 (60-109)
No (%) with:		
Mild heart failure (Killip class II)	78 (21)	71 (20)
Overt heart failure or shock (Killip class III, IV)	17 (5)	11 (3)
Ventricular fibrillation	12 (3)	8 (2)
Third degree atrioventricular block	11 (3)	11 (3)
Median (range)* delay from onset of symptoms to treatment (hours)	2·8 (1·3-4·5)	2·9 (1·4-4·6)

*90% Range.

CLINICAL COURSE

Tables II and III summarise the clinical course during the stay in hospital and the three month follow up. During the first 14 days after allocation 21 out of the 366 controls (5·7%) died. The cause of death was cardiogenic shock (12), documented tamponade (six), sudden death (two), refractory ventricular fibrillation (one). After three months' follow up eight additional patients had died. Among the 355 patients allocated to receive plasminogen activator 10 (2·8%) died during the first two weeks, of whom one developed a third degree atrioventricular block and asystole and died before the infusion could be started. Another patient had intracranial bleeding and died in cardiogenic shock a few hours after the interruption of the heparin infusion and administration of tranexamic acid and plasma. Further causes of death were: cardiogenic shock (five patients) and ventricular fibrillation, electromechanical dissociation, and asystole (three). Eight additional patients died during the three month follow up, one of whom died from intracranial bleeding 12 hours after angioplasty and intravenous streptokinase. The reduction in mortality in the patients treated with plasminogen activator was 51% (95% confidence interval −76 to 1) at 14 days and 36% (−63 to 13) at three months (figure). In patients in whom the

TABLE II—*Clinical events during hospital stay in patients allocated to receive placebo or recombinant plasminogen activator. Figures are numbers (percentages) of patients*

	Placebo (n=366)	Recombinant plasminogen activator (n=355)	Rate ratio	95% Confidence interval
Bleeding complications and stroke	27 (7·4)	104 (29·3)	3·97	(2·69 to 5·91)
Documented haemorrhagic stroke		6 (1·7)		
Documented non-haemorrhagic stroke		1 (0·3)		
Non-documented stroke	2 (0·6)			
Gastrointestinal bleeding	4 (1·1)	5 (1·4)		
Retroperitoneal bleeding	1 (0·3)	2 (0·6)		
Macroscopic haematuria	4 (1·1)	16 (4·5)		
Haemoptysis	2 (0·6)	4 (1·1)		
Epistaxis	1 (0·3)	4 (1·1)		
Oropharyngeal bleeding		7 (2·0)		
Pericardial bleeding	6 (1·6)			
Genital bleeding		2 (0·6)		
Local haematoma	9 (2·5)	68 (19)		
Prolonged bleeding	2 (0·6)	15 (4·2)		
Unexplained anaemia	3 (0·8)			
Blood transfusion	7 (1·9)	13 (3·7)	1·92	(0·80 to 4·62)
Cardiac complications:				
Shock	22 (6·0)	9 (2·5)	0·37	(0·17 to 0·83)
Pulmonary oedema	24 (6·6)	22 (6·3)	0·95	(0·54 to 1·64)
Pericarditis	40 (11)	22 (6·2)	0·57	(0·35 to 0·93)
Ventricular fibrillation	23 (6·3)	12 (3·4)	0·54	(0·28 to 1·05)
Third degree atrioventricular 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)
	State at 14 days			
Deaths:				
All patients	21 (5·7)	10 (2·8)	0·49	(0·24 to 1·01)
Patients treated <3 hours after onset of symptoms*	13 (6·3)	2 (1·1)	0·18	(0·05 to 0·69)
Angioplasty	9 (2·5)	9 (2·5)	1·03	(0·43 to 2·50)
Bypass surgery	1 (0·3)	10 (2·8)	7·22	(1·17 to 4·09)
Angioplasty and bypass surgery	1 (0·3)	1 (0·3)	1·03	(0·11 to 9·86)
Reinfarction	15 (4·1)	14 (3·9)	0·96	(0·48 to 1·94)

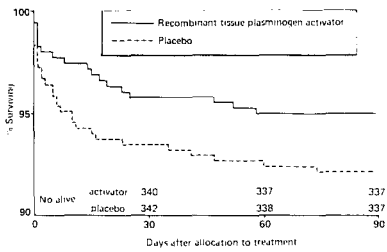
*207 Patients allocated to receive placebo, 179 patients allocated to receive recombinant plasminogen activator.

TABLE III—*Clinical events during three month follow up in patients allocated to receive placebo or plasminogen activators. Figures are cumulative numbers (percentages) of patients*

	Placebo (n=366)	Recombinant plasminogen activator (n=355)*	Rate ratio	95% Confidence interval
Deaths:				
All patients	29 (7·9)	18 (5·1)	0·64	(0·37 to 1·13)
Patients treated <3 hours after onset of symptoms†	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)
Bypass surgery	17 (4·6)	32 (9·0)	1·94	(1·11 to 3·41)
Angioplasty and bypass surgery	2 (0·5)	2 (0·6)	1·03	(0·18 to 5·84)

†207 Patients allocated to receive placebo, 179 patients allocated to receive recombinant plasminogen activator.

experimental infusion was started within three hours after the onset of symptoms (207 controls and 179 allocated to receive plasminogen activator) the reduction in mortality was 82% (−95 to −31) at 14 days and 59% (−83 to −2) at three months.



Survival to 90 days after allocation to receive recombinant tissue plasminogen activator (n=355) or placebo (n=366)

Cardiovascular complications occurred less commonly in the treatment group. In particular the incidence of shock, ventricular fibrillation, and pericarditis was lower in this group than in the controls. Angioplasty or coronary artery bypass, or both, were performed in a higher percentage of patients in the thrombolysis group during the three month follow up.

On the other hand, complications of bleeding were more common with plasminogen activator. Most were of little importance. In five patients (1·4%), however, intracranial bleeding occurred within three days after the infusion of plasminogen activator; one died whereas two recovered without neurological deficit. Table IV summarises all cases of intracranial events. In one patient receiving plasminogen activator (case 6) intracranial haemorrhage and death occurred on the 15th day, 12 hours after treatment of reocclusion with angioplasty and intravenous streptokinase. Three additional strokes occurred, one documented cerebral infarct in the treatment group (case 7) and two in the placebo group (cases 8 and 9), in which computed tomography had not been performed. Gastrointestinal bleeding was fairly uncommon in both groups.

TABLE IV—*Details of clinical course and outcome in cases of cerebrovascular accident during treatment with recombinant plasminogen activator or placebo*

Case No	Age and sex	Time after allocation	Syndrome and diagnosis	Outcome	Risk factors*	Fibrinogen (g/l) Before treatment	After 2 hours	After 24 hours
				Treatment group				
1	56 M	2 Days	Hemiparesis due to subdural bleeding†	Complete recovery after operation		3·7	3·5	3·9
2	55 M	2-3 Days	Hemianopsia due to intracerebral bleeding†	Complete recovery	Hypertension	4·0	4·0	3·9
3	64 M	12 Hours	Diplopia and ataxia due to intracerebral bleeding†	Partial recovery	Hypertension			
4	64 M	2 Days	Hemiplegia due to intracerebral bleeding†	Partial recovery	Hypertension, diabetes	4·4	2·2	2·3
5	67 M	16 Hours	Cerebellar syndrome due to intracerebral bleeding† due to unrecognised syncope and head trauma before allocation	Reocclusion 23 hours later, cardiogenic shock, and death		1·9	1·8	2·0
6	67 F	15 Days	Probable intracerebral bleeding after streptokinase for reocclusion before angiography	Coma and death				
7	53 M	4 Days	Hemiplegia one hour after angioplasty due to cerebral infarct†	Partial recovery	Hypertension			
				Controls				
8	70 M	10 Days	Paresis of left arm after prolonged hypotension, diagnosis uncertain	Partial recovery				
9	65 M	17 Hours	Insult and cerebral deterioration during cardiogenic shock	Death		2·0	2·3	

*Hypertension and diabetes.
†Confirmed by computed tomography.

SIZE OF INFARCT

Cumulative release of α hydroxybutyrate dehydrogenase into plasma up to 72 hours could be determined from complete data in 618 patients. In 37 this value was extrapolated from data at 48 and 36 hours, and in 43 it was estimated from a single measurement of plasma α hydroxybutyrate dehydrogenase activity. The values of aspartate aminotransferase activity were used to estimate release of α hydroxybutyrate dehydrogenase up to 72 hours in four patients. Thus for 702 patients a value for release of the enzyme at 72 hours could be calculated. Median (90% range) values in the controls and treated patients were 867 (123-2143) U/l and 697 (119-1889) U/l respectively. The figures indicate a significant reduction in the size of infarct of 20% (2p= 0·0018) with plasminogen activator.

ANGIOGRAPHIC FINDINGS

Angiography could not be performed in 22 patients (6%) allocated to receive plasminogen activator and in 30 (8%) controls, including 10 treated patients and 20 controls who died before catheterisation. Other reasons for not performing the procedure were: cardiovascular complications (four in treatment group and two controls), patient refusal (six in treatment group and seven controls), non-cardiovascular complications (one in treatment group), or organisational and technical problems (one in both groups). In 14 patients (4%) allocated to receive recombinant tissue plasminogen activator and in 17 controls (5%) angiography was performed outside the chosen time interval because of cardiovascular complications (five patients in treatment group and four controls), non-cardiovascular clinical reasons (three patients in treatment group and one control), or organisational problems (six patients in treatment group and 12 controls).

Table V shows the patency of the affected vessel 10-22 days after the experimental treatment. A high

TABLE V—*Angiographic findings in patients allocated to receive placebo or plasminogen activator 10-22 days after admission*

	Placebo (n=366)	Recombinant plasminogen activator (n=355)
Patency of affected vessel*	(n=336)	(n=333)
Grade 0	58 (17·3)	37 (11·1)
Grade 1	17 (5·1)	19 (5·7)
Grade 2	38 (11·3)	28 (8·4)
Grade 3	221 (65·8)	247 (74·2)
Undetermined	2 (0·6)	2 (0·6)
Mean (SD) ejection fraction (%)	(n=288) 48·5 (11·3)	(n=289) 50·7 (10·9)
Mean (SD) left ventricular volumes (ml)	(n=283)	(n=282)
End diastolic	124·2 (34·6)	118·2 (35·2)
End systolic	65·6 (29·7)	59·8 (28·1)

*According to grades of perfusion in the thrombolysis in myocardial infarction trial: 0=non-perfusion; 1=penetration with minimal perfusion (contrast fails to opacify entire coronary bed distal to the stenosis for the duration of filming); 2=partial perfusion (contrast opacifies the entire coronary bed distal to the stenosis; the rate of entry or clearance or both, is, however, slower in coronary bed distal to the obstruction than in comparable areas not perfused by the affected vessel); 3=complete perfusion (filling and clearance of contrast as rapid in coronary bed distal to stenosis as in other coronary beds).

percentage of patent (grades of perfusion 2 and 3 according to the criteria of the thrombolysis in myocardial infarction trial) coronary arteries was found in both groups: 77% in the controls and 83% in the thrombolysis group. The vessel could not be identified in 26 treated patients and in 11 control patients, in whom angiography was performed.

Left ventricular angiograms that were suitable for quantitative analysis were obtained in 577 (80%) of the recruited patients. The ejection fraction was significantly greater by 2·2% (95% confidence interval 0·3 to 4·0), in the treated group than the controls (50·7% *v* 48·5%). The end diastolic volume was 6·0 ml (−0·2 to −11·9) smaller and the end systolic volume 5·8 ml (−0·9 to −10·6) smaller in the thrombolysis group than in the control (table V).

COAGULATION TESTS

In a subset of 140 patients allocated to receive plasminogen activator the median (90% range) value for circulating fibrinogen at the start of infusion was 2·4 (1·5-4·3) g/l, after 120 minutes 1·9 (0·6-3·3) g/l, and after 24 hours 2·2 (0·9-3·5) g/l. The corresponding values for 143 controls were 2·5 (1·1-4·0) g/l, 2·5 (1·3-3·9) g/l, and 3·1 (1·3-4·6) g/l. Fibrin(ogen) degradation products rose from 1 (1-17) μg/ml before infusion to 16 (2-145) μg/ml after 120 minutes and to 6 (1-64) μg/ml after 24 hours in the treated group and from 2 (1-24) μg/ml to 2 (1-39) μg/ml after 120 minutes and to 2 (1-36) μg/ml after 24 hours in the controls.

Discussion

In this randomised, double blind, placebo controlled trial intravenous administration of recombinant plasminogen activator within five hours after the onset of symptoms was associated with limitation of the size of infarct, preservation of left ventricular function, and lower mortality. The limitation of the size of infarct measured from myocardial release of α hydroxybutyrate dehydrogenase was 20%. Smaller infarcts were also shown after intravenous[2 10] and intracoronary streptokinase.[23] The limitation of enzymatic infarct size in this trial was associated with preserved left ventricular function as measured by a higher angiographic ejection fraction of 2·2% and by smaller left ventricular end diastolic and end systolic volumes. Several studies have reported a 2·9-6% higher ejection fraction after intravenous streptokinase.[2-7] Furthermore, a significant improvement in ejection fraction has also been shown in patients with a first myocardial infarction and in those with anterior infarction in two placebo controlled trials of anisoylated plasminogen streptokinase activator complex.[10 11] Three placebo controlled trials with much smaller numbers of patients have shown a 6-7% higher ejection fraction in patients treated with intravenous plasminogen activator. The exclusion of patients with a previous infarction together with the earlier administration of activator (less than 2½ hours) after the onset of symptoms in one trial,[14] and the possible interaction of reperfusion and angioplasty[13] and a larger proportion of patients with anterior infarction assigned to active treatment[15], in the other, might explain the greater difference in ventricular function in these trials. As in two other studies with streptokinase[5 24] the end diastolic and end systolic volumes were significantly smaller in patients allocated to receive plasminogen activator. These findings suggest that early reperfusion not only improves contractile function but also prevents or at least limits expansion of the infarct and cardiac dilatation. Limitation of expansion of the infarct and cardiac dilatation may be even more important as ventricular volumes have a greater predictive value for survival after infarction than ejection fraction.[25]

Although this trial was not designed as a study of mortality, the administration of plasminogen activator was associated with improved short term survival. Despite low mortality in the controls mortality was reduced in patients treated with plasminogen activator from 5·7% to 2·8% at 14 days and from 7·9% to 5·1% at three month follow up. In patients treated within three hours after the onset of symptoms mortality decreased from 6·3% to 1·1% at 14 days and from 8·2% to 3·4% after three months. Mortality after treatment with plasminogen activator in this trial is close to that recently reported by us for patients similarly selected and treated[2b] and is the lowest reported so far in large

thrombolysis trials. Mortality in the controls was low when compared with other studies of thrombolytic treatment (13·0% at 21 days in the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico trial[1], 12·0% at five weeks in the second international study of infarct survival,[8] and 12·2% at 30 days in the anistreptase intervention mortality study[9]). This is unlikely to have been caused by selection of low risk patients as the electrocardiographic entry criteria were more stringent than in the other studies[1 9] and patients with cardiogenic shock were not excluded. All patients in our study were treated with low dose aspirin and heparin, which may have contributed to the low mortality in the controls.[8] The reduction in mortality despite the low mortality in the controls supports the efficacy of treatment with plasminogen activator.

In addition to reduced mortality, the incidence of cardiovascular complications such as shock, ventricular fibrillation, and pericarditis was considerably lower in the treated patients. The reduced cardiovascular morbidity and mortality in conjunction with the reduction in the size of infarct, the smaller cardiac volumes, and the preservation of contractile function suggest a substantial saving of ischaemic myocardium as a result of the early administration of plasminogen activator.

Despite a moderate decrease in fibrinogen concentration five out of the 355 patients given plasminogen activator had an intracranial haemorrhage after the infusion (table IV). This incidence of intracranial bleeding of 1·4% (95% confidence interval 0·2 to 2·7) in the present study is higher than the 0·3% incidence (one patient out of 367 treated with plasminogen activator) reported in a trial by the European Study Group.[26] In this twin study the entry criteria; treatment regimens with plasminogen activator, heparin, and aspirin; and the registration of events were identical. When the data of these two trials are combined the total incidence of intracranial bleeding is six patients out of 722 (0·8% (0·2 to 1·5)). Out of 3768 patients treated with 80-120 mg single chain recombinant plasminogen activator from the same source as ours up to summer 1987, intracranial bleeding occurred in 0·4% (0·2% to 0·6%).[27] The number of patients with gastrointestinal or other serious bleeding and the number of blood transfusions given were small. Whether the concomitant administration of heparin and aspirin is partly responsible for the bleeding complications in patients treated with plasminogen activator is unknown and will be the subject of a future trial of our study group.

In conclusion, the intravenous infusion of plasminogen activator over three hours in addition to heparin and aspirin, within five hours after the onset of an acute myocardial infarction, has a beneficial effect on the size of infarct, left ventricular function, early survival, and cardiovascular morbidity, but at a cost of an increased risk of bleeding.

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CHAPTER 4

THROMBOLYSIS WITH TISSUE PLASMINOGEN ACTIVATOR IN ACUTE MYOCARDIAL INFARCTION: NO ADDITIONAL BENEFIT FROM IMMEDIATE PERCUTANEOUS CORONARY ANGIOPLASTY

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THROMBOLYSIS WITH TISSUE PLASMINOGEN ACTIVATOR IN ACUTE MYOCARDIAL INFARCTION: NO ADDITIONAL BENEFIT FROM IMMEDIATE PERCUTANEOUS CORONARY ANGIOPLASTY

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Summary A randomised trial of 367 patients with acute myocardial infarction was performed to determine whether an invasive strategy combining thrombolysis with recombinant tissue-type plasminogen activator (rTPA), heparin, and acetylsalicylic acid, and immediate percutaneous transluminal coronary angioplasty (PTCA) would be superior to a noninvasive strategy with the same medical treatment but without immediate angiography and PTCA. Intravenous infusion of 100 mg rTPA was started within 5 h after onset of symptoms (median 156 min). Angiography was performed 6–165 min later in 180 out of 183 patients allocated to the invasive strategy; 184 patients were allocated to the non-invasive strategy. Immediate PTCA reduced the percentage stenosis of the infarct-related segment, but this was offset by a high rate of transient (16%) and sustained (7%) reocclusion during the procedure and recurrent ischaemia during the first 24 h (17%). The clinical course was more favourable after non-invasive therapy, with a lower incidence of recurrent ischaemia within 24 h (3%), bleeding complications, hypotension, and ventricular fibrillation. Mortality at 14 days was lower in patients allocated to non-invasive treatment (3%) than in the group allocated to invasive treatment (7%). No difference between the treatment groups was observed in infarct size estimated from myocardial release of alpha-hydroxybutyrate dehydrogenase or in left ventricular ejection fraction after 10–22 days. Since immediate PTCA does not provide additional benefit there seems to be no need for immediate angiography and PTCA in patients with acute myocardial infarction treated with rTPA.

Introduction

RANDOMISED trials of thrombolytic therapy with intracoronary streptokinase[1] or intravenous streptokinase[2] have demonstrated improved survival as well as limitation of infarct size[3] and preservation of left ventricular function[4] in patients treated within 4–6 h after onset of symptoms of acute myocardial infarction. Several groups have proposed immediate percutaneous transluminal coronary angioplasty (PTCA) for reperfusion of the ischaemic myocardium in addition to[5] or without[6] thrombolytic therapy. Immediate PTCA may open vessels that remain occluded despite thrombolytic therapy and reduce the residual coronary stenosis after thrombolytic therapy. The improved bloodflow might further reduce infarct size and preserve left ventricular function.[7] Finally, PTCA might reduce the incidence of post-infarction angina, reocclusion, and reinfarction after thrombolytic therapy.[8,9]

The European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator (rTPA) has conducted a randomised trial to determine whether an

invasive strategy, combining thrombolysis with rTPA, heparin, acetylsalicylic acid, and immediate PTCA, would be superior to a non-invasive strategy of treatment with intravenous rTPA, heparin, and acetylsalicylic acid alone. The end-points were enzymatic infarct size, global left ventricular function, and findings on clinical follow-up. Patient enrolment started in May, 1986. The trial was prematurely terminated in June, 1987, on the advice of the data monitoring and ethical committee. This report presents the main results of the trial.

Patients and Methods

Ten hospitals with extensive PTCA experience in six European countries participated in the trial. Patients were admitted with a diagnosis of suspected myocardial infarction, characterised by chest pain of at least 30 min duration and typical changes in the electrocardiogram: ST-segment elevation of 0·3 mV or greater in two or more chest leads (V_1–V_4) and/or greater than 0·2 mV in leads I, II, III, aVL, aVF, V_5, or V_6. In addition, patients were included with at least 0·1 mV ST-segment elevation in two leads (II, III, aVF, V_5, V_6) and at least 0·2 mV ST-segment depression in two chest leads V_1–V_4.

Patients younger than 71 years in whom treatment could be started within 5 h after the onset of symptoms were included. The usual contraindications for thrombolytic therapy were applied.[10] In addition, patients with a previous myocardial infarction at the same site or with previous coronary artery bypass surgery were excluded. Patients with heart failure or shock were not excluded.

When informed consent had been obtained, intravenous administration of rTPA was started without delay. After a 10 mg bolus injection, 50 mg was given in the first hour, followed by 40 mg in the next 2 h. Thus, in total 100 mg was administered in 3 h. Single-chain rTPA (Genentech Inc, G-11044) was supplied by Boehringer Ingelheim International GmbH. In addition to rTPA, 250 mg acetylsalicylic acid was given intravenously, plus heparin 5000 IU followed by a continuous infusion of 1000 IU/h. Patients were allocated by telephone to either the non-invasive strategy of treatment with intravenous rTPA, acetylsalicylic acid, and heparin or to the invasive strategy with the same medical treatment combined with immediate PTCA. At first a lower dose of 75–125 mg acetylsalicylic acid was given as initial treatment. As the PTCA procedure was complicated by reocclusion in about 5 out of 7 patients allocated to invasive strategy, the initial dose of acetylsalicylic acid was increased to 250 mg.

The protocol specified that coronary angiography was to be performed as soon as the catheterisation laboratory was available. Mechanical recanalisation should be attempted if the infarct-related segment of the coronary artery appeared occluded. PTCA should be attempted in all patients, unless the diameter stenosis of the lesion was judged to be less than 60%. Until hospital discharge all patients were anticoagulated with heparin, which could be replaced by warfarin after 3 days, provided that full anticoagulation was maintained. In addition, 75–125 mg acetylsalicylic acid was given every other day. Beta-blockers, calcium antagonists, and nitrates could be prescribed when indicated but were to be withdrawn the night before late angiography.

Infarct size was estimated from serial alpha-hydroxybutyrate dehydrogenase (HBDH) determinations by the core laboratory for enzyme determination.[11,12] Blood samples were taken at admission and at 12, 24, 36, 48, 72, and 96 h. Enzymatic infarct size was estimated by the cumulative quantity of HBDH released by the heart per litre plasma in 72 h (Q72).

Coronary arteriography and ventriculography were performed before hospital discharge. To ensure comparability, each hospital chose a time window in which late angiography was scheduled: 10–14, 12–16, 14–18, 16–20, or 18–22 days after admission. Left ventricular ejection fraction was computed by the core laboratory for quantitative angiography. In addition to local assessment of the coronary angiograms, both acute and late angiograms were centrally assessed by members of the angiography assessment group. In patients who underwent immediate PTCA, all intracoronary manipulations, including further dilatations with a larger size balloon in case of reocclusion, were considered to be part of the same PTCA procedure until the guiding catheter was withdrawn. Further procedures that were performed after withdrawal of the guiding catheter are reported as new interventions (re-PTCA). Two methods of grading of coronary angiograms were applied—the grades of diameter stenosis as previously used by the European Cooperative Study Group[10] and the TIMI perfusion score:[13]

Grades of Stenosis

5 = 100% diameter stenosis
4 = 91–99% diameter stenosis, no complete filling within 3 cycles
3 = 91–99% diameter stenosis, complete filling within 3 cycles
2 = 50–90% diameter stenosis
1 = less than 50% diameter stenosis
0 = normal

Grades of Perfusion

0 = non-perfusion
1 = penetration with minimal perfusion (contrast fails to opacify entire coronary bed distal to the stenosis for the duration of the cine run)
2 = partial perfusion (contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in coronary bed distal to the obstruction than in comparable areas not perfused by the infarct related vessel)
3 = complete perfusion (filling *and* clearance of contrast as rapid in coronary bed distal to stenosis as in other coronary beds)

Both the core laboratory for enzyme determination and the core laboratory for quantitative angiography were unaware of the treatment allocation.

Results

367 patients were evaluated. The median number of patients per hospital was 34, ranging from 13 to 78 patients. 184 patients were allocated to non-invasive treatment and 183 to rTPA followed by immediate angiography and PTCA. 1 additional patient had been allocated to non-invasive therapy but has been excluded from analysis because treatment allocation as given by telephone was not

correctly interpreted by the local investigator and immediate PTCA was performed. This patient had an uneventful follow-up. Baseline characteristics were similar in the two treatment groups, except that the non-invasive group had 1 patient with severe cardiac failure on admission and the invasive group 7 patients, and mild heart failure on admission was more frequent in the non-invasive group (table I). Immediate angiography was performed in 180 patients (fig 1). Angiography was not performed in 1 patient who died from shock, in 1 patient because of withdrawal of consent, and in 1 patient for technical reasons. The delay between onset of symptoms and rTPA infusion ranged from 30 to 294 min, median 156 min, and the delay between

TABLE I—BASELINE CHARACTERISTICS

	Non-invasive strategy	Invasive strategy
No of patients	184	183
Age (yr)	54 (37–67)	58 (38–68)
Male	164 (89)	161 (88)
History of angina	133 (72)	136 (74)
Previous infarction	12 (7)	13 (7)
Anterior infarction	82 (45)	83 (45)
Heart rate (/min)	76 (52–100)	76 (55–100)
Systolic blood pressure (mm Hg)	130 (100–160)	130 (95–160)
Diastolic blood pressure (mm Hg)	80 (60–100)	80 (60–100)
Mild heart failure	46 (25)	36 (20)
Overt heart failure/shock	1 (1)	7 (4)
Immediate angiography	—	180 (98)
Infarct-related vessel		
Left main stem	—	1
Anterior descending artery	—	80
Left circumflex artery	—	28
Right coronary artery	—	69
Normal coronary arteries	—	2

Actual number of patients are shown. Continuous variables are presented as median and 90% range. Percentages of patients in each treatment group or ranges are shown in parentheses.

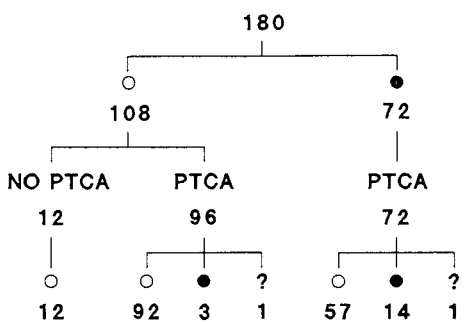

Fig 1—Results of angiography and PTCA in 180 patients allocated to invasive treatment who underwent immediate angiography.

Vessels were classified as patent (○ = stenosis grades 0–3) or occluded (● = stenosis grades 4–5). In 2 patients no angiogram was available after attempted PTCA.

infusion and angiography ranged from 6 to 165 min, median 42 min.

Immediate Angiography

In patients allocated to invasive therapy, patency (defined as stenosis grades 0–3) was related to the delay between onset of rTPA infusion and angiography as shown in fig 2. Complete occlusion (grade 5) was observed in 42 patients and subtotal occlusion without complete filling of the distal vessel (grade 4) in 30 patients (fig 3a). PTCA was attempted in 168 patients. No immediate PTCA was done in 8 patients who did not have significant lumen narrowing, in 3 patients in whom the anatomy was judged unsuitable for PTCA (1 left main equivalent, 1 severe 3-vessel disease, and 1 old occlusion in the anterior descending artery with retrograde filling by the right coronary artery), and in 1 patient in whom the infarct-related vessel could not be identified (fig 1).

Immediate PTCA in this study appeared to be more troublesome than elective PTCA. The number of balloon inflations ranged from 1 to 15, median 4, with a total inflation time between 30 and 885 s, median 180. In 5 patients the lesion could not be crossed with guidewire or balloon. In 32 patients more than one stenosis was dilated. At the end of intervention, central angiographic assessment revealed an occluded vessel (grades 4 and 5) in 17 patients and less than 50% stenosis (grades 0 and 1) of the infarct-related segment in 103 patients (fig 3). Before the initial acetylsalicylic acid dose was increased to 250 mg

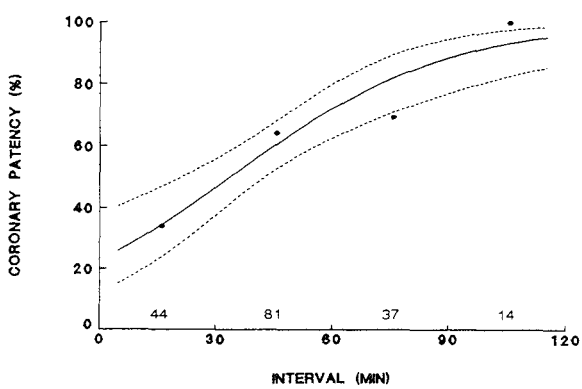

Fig 2—Patency of infarct related vessel (stenosis grades 0–3) in relation to interval between start of rTPA infusion and angiography.

The four large dots indicate percentage of patients with a patent vessel when angiography was performed within 30, 30–60, 60–90, and later than 90 min after start of infusion. A logistic regression model was used to estimate the relation between the duration of rTPA infusion and patency. The result of this analysis is presented by the closed line, and its 95% confidence intervals by the dotted lines. Estimated patency at 90 min was 89%. In 4 patients the exact delay was uncertain. In the four groups patency was 15/44, 51/81, 25/37, and 14/14.

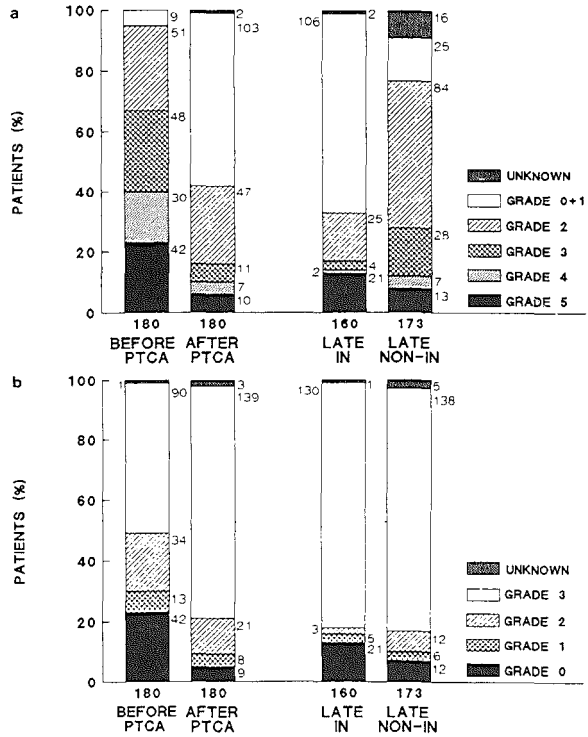

Fig 3—Grades of stenosis (a) and perfusion (b) of infarct-related vessel before and after PTCA and after 10–22 days in patients allocated to invasive (IN) and non-invasive (non-IN) therapy.

Unknown = patients in whom the infarct-related segment (a) or artery (b) could not be identified in the angiogram. The number of patients with angiography is given under each bar: numbers next to the bars represent the number of patients in that particular subgroup.

intravenously, transient reocclusion during intervention occurred in 4 out of 7 patients and permanent reocclusion in 1. After increasing the acetylsalicylic acid dose, transient reocclusion during intervention occurred in 22 and permanent reocclusion in 12 patients in whom PTCA was attempted. Additional intracoronary streptokinase was given in 2 patients with transient reocclusion and in 1 patient because of recurrent stenosis. In 2 patients an initially patent infarct-related segment was found to be occluded after completion of the PTCA procedure. In 1 other patient reocclusion occurred during coronary angiography before PTCA. Subsequent PTCA was not successful.

Clinical Course

The clinical course is summarised in table II. Overall, the outcome was more favourable in patients with non-invasive therapy. Differences between the treatment groups were equally distributed over the participating clinics, and not

TABLE II—CLINICAL COURSE AND FOLLOW UP

—	Non-invasive strategy (n = 184)	Invasive strategy (n = 183)
Recurrent ischaemia within 24 h	6 (3)	31 (17)
Hypotension (less than 90 mm Hg)	17 (9)	57 (31)
Shock	6 (3)	11 (6)
Pulmonary oedema	8 (4)	9 (5)
3rd degree A-V block	7 (4)	11 (6)
Ventricular fibrillation	6 (3)	21 (11)
Ventricular tachycardia	51 (28)	54 (30)
Pericarditis	12 (7)	11 (6)
Bleeding complications:	43 (23)	75 (41)
Local haematoma	30	55
Prolonged bleeding	11	22
Intracranial bleeding/CVA	1*	1
Haemoptysis	1	1
Epistaxis	1	1
Gingival bleeding	3	9
Haematemesis	—	5
Melaena	1	1
Rectal bleeding	2	—
Macroscopic haematuria	4	5
Retroperitoneal haematoma	1	3
Haemopericardium	1	2
Blood transfusion	7 (4)	18 (10)
Surgical correction at bleeding site	1 (1)	2 (1)
Status at 14 days		
Mortality	5 (3)	12 (7)
Recurrent ischaemia after 24 h	21 (11)	23 (13)
Reinfarction	12 (7)	8 (4)
(re-)PTCA	11 (6)	8 (3)
CABG	—	3 (2)
(re-)PTCA + CABG	1 (1)	—
Status at 3-month follow-up:		
Mortality	6 (3)	15 (8)
Recurrent ischaemia after 24 h	55 (30)	52 (28)
Reinfarction	18 (10)	12 (7)
(re-)PTCA	23 (13)	11 (6)
CABG	7 (4)	9 (5)
(re-)PCTA + CABG	3 (2)	—

Actual number of patients with an event after allocation are presented; percentages of patients in each treatment group are shown in parentheses. Recurrent ischaemia after 24 h represents patients without reinfarction. Numbers given for status at 3-month follow-up are cumulative. *CT scan: no bleeding.

dependent on infarct location at admission. Mortality at 14 days and at three months was low (3%) in patients allocated to non-invasive strategy. 1 patient in this group was resuscitated during rTPA infusion (table III). He had intraperitoneal bleeding from a liver haematoma on day 2 and died on day 3 after reinfarction and shock. In patients allocated to invasive therapy, 14 day mortality was 7%. 4 of the 7 patients in this group admitted with severe heart failure or shock died. Two deaths after immediate PTCA were associated with bleeding complications, one of them in a patient who died from intraperitoneal bleeding, probably caused by trauma before hospital admission.

TABLE III—EARLY AND LATE MORTALITY

Sex	Age	Site	IRV	Stenosis grades/ intervention	Time	Cause of death and details of intervention
Non-invasive strategy						
M	59	I	—	—	8 h	Shock, cardiac arrest
M	55	I	—	—	3 d	Intraperitoneal bleeding after resuscitation, reinfarction
M	58	A	—	—	3 d	Shock
M	59	A	LAD	—	7 d	Shock after reinfarction PTCA not successful
M	62	A	—	—	13 d	At LV-angio possibly dissection aorta, shock
M	67	A	—	—	22 d	Low output after aneurysmectomy
Invasive strategy						
M	64	I	RCA	2-PTCA-2	2 h	Shock after PTCA, VF
M	58	I*	—	—	2 h	Shock, no angiography
F	64	I	RCA	5-PTCA-5	4 h	Cardiac arrest, VF
M	62	A	LAD	2-PTCA-1	15 h	Cerebral bleeding
F	67	I	RCA	4-PTCA-1	15 h	Intraperitoneal bleeding
M	61	A*	LAD	5-PTCA-1	17 h	Mainstem lesion, shock, death during CAGB
M	45	I	LCX	3-5	2 d	Occlusion during angio, PTCA attempt failed, shock
F	69	I	RCA	3-PTCA-3	3 d	Reinfarction
F	62	I	LCX	2	3 d	No PTCA (3 vessel), asystole after delayed PTCA for angina
M	53	A	LAD	5-PTCA-2	3 d	Reinfarction, shock
F	66	A*	LAD	3-PTCA-2	7 d	Reocclusion, shock
M	67	A*	LAD	3-PTCA-2	14 d	Shock
M	56	I	RCA	3-PTCA-1	47 d	Late VF, coma
M	60	I	RCA	3-3	48 d	Failure to cross lesion, old anterior MI, sudden death
M	47	A	LAD	3-PTCA-4	66 d	Sudden death

Baseline data, results of angiography and PTCA, when performed, as well as time and cause of death are given. Stenosis grades before and after PTCA as centrally assessed are presented. IRV = infarct-related vessel; A = anterior, I = inferior; * = shock at admission; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery; VF = ventricular fibrillation; CABG = coronary artery bypass grafting; h = hours after allocation; d = days after allocation.

Recurrent ischaemia within 24 h was observed in 17% of patients with immediate PTCA and in 3% of patients allocated to non-invasive therapy. In the latter group exacerbation or recurrence of chest pain was recorded in 1 patient, chest pain with ST-segment elevation in 4 patients, and ST-elevation without chest pain in 1 patient. After PTCA these figures were 4, 19, and 8, respectively. Episodes of hypotension and ventricular fibrillation were more frequent after PTCA.

Bleeding complications were more prominent after immediate PTCA, mostly as a result of arterial puncture and the catheterisation procedure. 1 patient in the PTCA group underwent surgery for a retroperitoneal haematoma after angiography, and 2 patients survived after pericardiocentesis for cardiac tamponade. In 1 patient this was related to perforation by a pacemaker electrode, in the other there was no apparent trauma. In the group allocated to non-invasive treatment, 1 patient survived after pericardiocentesis for cardiac tamponade. The greater incidence of bleeding complications after attempted PTCA is also apparent from the greater drop in haematocrit in these patients (44 SD 4% at admission and 37 SD 5% after 72 h) in comparison with those treated non-invasively (44 SD 4% and 40 SD 5%, respectively), and from the greater need for blood transfusions.

Enzymatic Infarct Size

Complete blood sample series for determination of enzymatic infarct size by the core laboratory were obtained in 309 patients (84%). HBDH-Q72 could be estimated from series of HBDH measurements obtained up to 36 or 48 h in 18 patients, and from a single HBDH plasma level between 24 and 96 h after onset of symptoms in 25 patients. Local determinations of aspartate aminotransferase (ASAT) or HBDH could be employed to estimate HBDH-Q72 in 7 patients. Thus, enzymatic infarct size could be assessed in 359 patients (98%). In 7 patients HBDH data were not available because of early death and in 1 patient because of early bypass surgery. Enzymatic infarct size did not differ between the non-invasive group (median 665 U/l, 90% range 32-2022 U/l) and the invasive group (median 706 U/l, 90% range 115-1914 U/l). Similar results were obtained when only complete sample series from 309 patients were used.

Late Angiography

The effect of immediate PTCA on the status of the infarct-related segment after 10–22 days is best described by the grade of residual stenosis (fig 3a). An occluded vessel (grades 4 and 5) was observed in 20 patients without PTCA and in 23 patients with immediate PTCA. On the other hand, stenoses of less than 50% diameter were observed more frequently in patients allocated to invasive therapy

(n = 106) than in the other group (n = 25). These differences were not apparent if the TIMI perfusion score was applied, as shown in fig 3b. Complete perfusion (TIMI grade 3) was observed in 138 patients after non-invasive initial therapy and in 130 patients after immediate PTCA.

Left ventricular angiography was performed in 333 patients between days 10 and 22. Missing angiograms were due to patient death (n = 17), patient refusal (n = 6), coronary bypass surgery (n = 3), very poor ventricular function (n = 2), ventricular tachycardia (n = 1), and re-infarction (n = 1), and in 4 cases to clinical, non-cardiac reasons. Quantitative analysis was performed in 291 angiograms of adequate quality. There were no differences in left ventricular ejection fraction between patients allocated to non-invasive therapy and those allocated to invasive therapy (median 51%, 90% range 29–65%, versus median 51%, 90% range 31–66%).

Discussion

Contrary to what was expected when the study was designed, thrombolytic therapy combined with immediate PTCA did not appear to be superior to early non-invasive treatment with intravenous rTPA, heparin, and acetyl-salicylic acid in acute myocardial infarction. Immediate PTCA was effective in increasing the number of patients with a patent infarct-related vessel and improved perfusion as visualised during angiography (fig 3). However, in the setting in which it was studied, PTCA was associated with a high rate of early reocclusion and/or early recurrent ischaemia. Also, immediate PTCA did not further reduce enzymatic infarct size or improve global left ventricular function when compared with non-invasive treatment. Finally, a complicated clinical course occurred more frequently after PTCA and 3-month mortality was higher than after non-invasive therapy.

The present study was planned to include a total of 400 patients. However, when the data monitoring and ethical committee reviewed the data in June 1987, it became apparent that immediate PTCA in this setting was not beneficial and might even be detrimental in some cases. At that time mortality was 6 out of 171 patients allocated to non-invasive therapy and 11 out of 173 patients allocated to invasive therapy, while cardiovascular and bleeding complications were also more frequent in the latter group. Enzymatic infarct size had been determined in 165 patients and left ventricular ejection fraction in 110 patients. Median values in the non-invasive and invasive group were 730 U/l versus 911 U/l for HBDH-Q72 and 53% versus 47% for left ventricular ejection fraction. Therefore, patient intake was terminated by the steering committee as of June 27, 1987.

In patients allocated to invasive strategy who underwent angiography 42 min after the start of rTPA infusion

(median), the infarct-related segment was patent (stenosis grades 0–3) in 59%. It should be appreciated that in most other studies[8,10,13,14] patency rates were reported after 90 minutes' infusion of rTPA. Fig 2 shows that patency is achieved gradually during rTPA administration and ranges from 34% in patients studied within 30 min to 100% in patients studied between 90 and 165 min from the start of infusion. Patency at 90 min, estimated by a logistic regression model, was 89%.

Recurrent ischaemia and/or reinfarction within 14 days was observed in 15% of patients after non-invasive therapy. Similar results were obtained in the TAMI Study, where recurrent ischaemia and/or reinfarction was observed in 17% of patients with a patent vessel without immediate PTCA.[14] It should be appreciated that the clinical observation of recurrent ischaemia or reinfarction does not necessarily coincide with angiographic reocclusion. For example, in the TAMI study reocclusion was observed in only 6 out of 17 patients who underwent angiography for recurrent ischaemia.[14] These observations confirm the results from an earlier study by the European Cooperative Study Group in which reocclusion occurred in 7% of 73 patients 6–24 h after double-chain rTPA.[15] Thus reocclusion after thrombolysis with rTPA occurs less frequently than indicated by earlier studies in a small number of patients treated with a relatively low dose of double-chain rTPA.[16]

Immediate PTCA in patients with acute myocardial infarction was introduced as an extension of intracoronary thrombolytic therapy with streptokinase.[5] In selected patients, PTCA after intracoronary streptokinase has been reported to reduce the risk of reocclusion and mortality.[5,6] In a randomised trial, Erbel et al[17] compared treatment with intracoronary streptokinase with and without immediate PTCA in 162 patients. These workers report that PTCA reduced the reocclusion rate at 4 weeks from 14 out of 71 patients with a patent vessel without PTCA (20%) to 10 out of 71 patients (14%) after PTCA, while a trend towards lower mortality in patients with immediate PTCA was also observed.[17-19] Thus, the question arises whether the response to angioplasty in patients treated with streptokinase differs from that in patients treated with rTPA. The higher tendency to reocclude in the latter group might be related in part to the "thrombus specificity" of rTPA. Remnants of thrombus material, together with the endothelial trauma caused by PTCA and subintimal bleeding,[20,21] can then be held responsible for the tendency to thrombosis in patients treated with rTPA, despite concomitant treatment with acetylsalicylic acid and heparin, while early rethrombosis after PTCA in patients treated with streptokinase may be prevented by the depletion of fibrinogen and other coagulation factors due to streptokinase. On the other hand, it is possible that differences between studies of PTCA in combination with

streptokinase or rTPA are merely due to patient selection and small sample sizes.

The clinical course in the present study was less favourable in patients allocated to immediate PTCA. The higher mortality in the invasive group may be due in part to the greater number of patients with severe heart failure or shock at admission, of whom 4 died, and to the high incidence of reocclusion during or after immediate PTCA. The latter factor can also explain the higher incidence of hypotension and ventricular fibrillation. The higher incidence of bleeding complications was related to arterial puncture for angiography and PTCA. The observations in the present trial are similar to those reported from the TAMI[14] trial which likewise showed a trend towards higher mortality without improvement in global or regional ejection fraction. It should be noted, however, that the design of these two studies was different. In TAMI all patients underwent acute angiography and only those with a patent vessel, suitable for PTCA, were randomised (197 out of 386 patients). In the present study acute angiography was performed only in patients randomised to invasive strategy and PTCA was attempted in 92% of these. TAMI answered the question whether PTCA would be beneficial in a selected subgroup of patients who underwent angiography during thrombolytic therapy with intravenous rTPA. The European Cooperative Study Group investigated whether an invasive strategy, including angiography and immediate PTCA, would be superior to non-invasive intravenous thrombolytic therapy with rTPA. These differences notwithstanding, both studies indicate that immediate PTCA after intravenous rTPA in combination with acetylsalicylic acid and heparin should be avoided.

The present study was not designed to demonstrate the effect of thrombolysis with intravenous rTPA per se. The value of thrombolytic therapy in selected patients with acute myocardial infarction has been shown by randomised trials with intracoronary and/or intravenous streptokinase.[1-4] Patient selection criteria in the present trial were similar to those of the trial conducted by the Interuniversity Cardiology Institute in the Netherlands.[1] Hospital mortality in conventionally treated patients in that study was 10%, and 6% in patients allocated to intracoronary streptokinase. In the present trial 14-day mortality in patients treated non-invasively was even lower—3%. Were these findings to be confirmed by ongoing trials comparing the effect of intravenous rTPA and placebo on enzymatic infarct size, left ventricular function, and mortality, treatment with rTPA should certainly be recommended in selected patients. An invasive strategy of treatment with rTPA, acetylsalicylic acid, and heparin, in combination with immediate angiography and PTCA has no additional benefit. Delayed angiography, PTCA, or bypass surgery

might be offered to patients with new episodes of myocardial ischaemia.

Participating Clinics

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CHAPTER 5

IMMEDIATE PERCUTANEOUS CORONARY ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION MIGHT BE BENEFICIAL IF REOCCLUSION AND REINFARCTION ARE PREVENTED

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[1]A listing of investigators and participating centers has been published previously [1].

ABSTRACT

Regional ventricular wall motion analysis utilizing three different methods was performed on pre-discharge left ventriculograms from 291 of 367 patients enroled in a randomized trial of single chain recombinant tissue type plasminogen activator (rt-PA), aspirin and heparin with and without immediate angioplasty in patients with acute myocardial infarction.

With univariate analysis no difference in parameters of regional wall motion between the 2 treatment groups was observed. However, with individual baseline risk assessment by multivariate linear regression analysis using baseline characteristics known to be related to left ventricular function after thrombolytic therapy and/or outcome of coronary angioplasty, an excess of high risk patients in the invasive treatment group was detected. To adjust for this unequal distribution of baseline risk, multivariate linear regression analysis was performed. No benefit of immediate coronary angioplasty was observed after adjustment.

Reocclusion and/or reinfarction occurred more frequent in the invasive than in the non-invasive group (18% versus 13%). Among patients with a patent infarct related vessel at 10-22 days angiography and without reinfarction prior to angiography, there was a trend towards benefit of the invasive strategy, indicating that reocclusion and reinfarction might be responsible for the lack of benefit of the invasive strategy. This implies that immediate coronary angioplasty may be beneficial in selected patients, provided that these complications can be prevented.

INTRODUCTION

In 1988 the European Cooperative Study Group published the results of a trial comparing an invasive strategy, combining thrombolysis with recombinant tissue-type plasminogen activator (rt-PA), heparin, aspirin and immediate coronary angioplasty, to a non-invasive strategy of intravenous rt-PA, heparin and aspirin in patients with acute myocardial infarction [1]. Contrary to the expectations when the trial was initiated, the invasive treatment strategy did not result in smaller enzymatic infarct size, better global left ventricular function, and lower mortality. In fact, complications were more frequent and mortality was higher after the invasive strategy [1].

Additional analyses were performed to evaluate whether: (1) a true benefit of immediate angioplasty was not detected because of an excess of high risk patients in the invasive treatment group, despite randomization; (2) a true benefit in one subgroup was obscured by an adverse effect in another. This would have important implications if these subgroups could be identified on admission or if they would be characterized by an untoward effect like reocclusion or reinfarction, which may be prevented by new treatment strategies; (3) preservation of function in the infarct territory was missed by using global function because of compensatory hyperkinesia of the contralateral wall [2].

The results of these investigations are presented in this report. Multivariate

analysis was used to adjust for unequal baseline risk and to assess treatment effects in subgroups. Regional left ventricular wall motion analysis in the infarct territory was performed to evaluate the role of compensatory hyperkinesia of the non-infarcted area.

PATIENTS AND METHODS

Of 367 patients less than 71 years of age with at least 30 minutes of chest pain and electrocardiographic evidence of extensive transmural myocardial ischaemia, 184 were allocated to non-invasive treatment and 183 to immediate angiography and coronary angioplasty, provided that thrombolytic therapy could be started within 5 hours after onset of symptoms. Patients with a previous myocardial infarction at the same site or with previous coronary artery bypass surgery were excluded, but patients with heart failure or shock were not. Further details of patient selection have been published elsewhere [1].

Left ventricular angiography of adequate quality for analysis was available in 291 patients (table I). These patients form the study population of the present analysis.

TABLE I - Reasons for missing 10-22 days regional wall motion.

10 to 22 days angiography	**Non-I N=184**		**Invasive N=183**	
not performed due to:				
death	5		12	
cardiac reason	1		3	
non-cardiac reason	1		2	
refused	3		4	
other	1		2	
performed		173		160
not analyzable due to:				
extrasystole	15		15	
inadequate filling	4		1	
ventricle outside screen	2		1	
other	2		1	
available and analyzable		149		142

Non-I: non-invasive treatment strategy.

Patient management

After informed consent, patients were treated with 5000 IU heparin bolus followed by 1000 IU/hour intravenously, 250 mg aspirin and 100 mg single chain rt-PA (alteplase) over 3 hours. Coronary angiography was performed as soon as possible in all patients who had been randomized to the invasive strategy. Angioplasty was to be attempted, provided that there was a luminal diameter stenosis of 60% or more in the infarct related coronary artery. In case of complete occlusion mechanical perforation had to be performed.

Aspirin (75-125 mg) was continued on alternate days until hospital discharge. Heparin could be replaced by oral anticoagulants after three days, provided that full anticoagulation was maintained until cardiac catheterization.

Electrocardiographic analysis

Infarct localization was determined from the admission electrocardiogram by the Core Laboratory. It was judged anterior if ST-segment elevation was present in leads V_1 -V_4 and inferior if ST-segment elevation occurred in leads II, III and aVF. In case of ST-segment elevation in leads I, aVL, V_5 and V_6, infarct localization was deemed anterior unless ST-segment elevation was also present in II, III or aVF, or ST-depression was present in leads V_1 to V_4, in which cases the localization was inferior. ST-segment shift was measured at J-point.

Coronary angiography and ventriculography

Coronary angiography and left ventriculography were performed 10 to 22 days after treatment allocation. In order to enhance comparability between the 2 groups, each clinic was required to perform angiography within a preselected time window of 10-14, 12-16, 14-18, 16-20, or 18-22 days after allocation. Beta-blockers, calcium antagonists and nitrates were stopped the night before angiography. All angiograms were assessed by members of the Angiography Assessment Group. Perfusion of the infarct related vessel was assessed using the TIMI perfusion score [3-5].

Left ventriculography was performed with a 0.5-1 ml/kg non-ionic contrast injection at a flow of 6-20 ml/sec in the 30 degrees right anterior oblique projection. End-systolic and end-diastolic contours were digitized. Left ventricular volumes in right anterior oblique projection were calculated according to Simpson's rule after calibration with a phantom of known volume filmed after ventriculography, and were indexed for body surface area. No corrections for trabeculae and papillary muscles were applied. All analyzes were performed at the Core Laboratory for Quantitative Angiography without knowledge of treatment allocation.

Regional left ventricular wall motion analysis

Regional wall motion was analyzed according to the "Regional contribution to ejection fraction"-method, which assesses wall motion along experimentally determined and validated vectors [2,6], and can detect small differences in regional wall motion [2], the "Centerline-method" [7-9], which assesses fractional shortening in 100 chords perpendicular to a centerline between the end-diastolic and end-systolic contours, and the "Radial-axes-method" which assesses fractional shortening in 300 radii from the center of mass of the end-diastolic contour [10]. In none of the methods translational or rotational corrections were made. A description of each model is given in figure 1.

The extent of hypokinesia (wall motion in the infarct territory) can be assessed by quantitative regional wall motion with all three models. In the "Regional contribution to ejection fraction"-method as the number of segments with abnormal regional contribution to ejection fraction (below 10th percentile of a population of 31 normal individuals) per patient. In the "Centerline-method" as the number of contiguous chords of which the shortening fraction differed more than 1 standard deviations from the mean shortening fraction in a group of normals (so called circumferential extent of wall motion abnormality). In the "Radial-axes-method" as percentage of radii of which the shortening fraction differed more than 2 SD from the mean normal shortening fraction in a group of normal individuals (so called hypokinetic circumference).

The severity of hypokinesia was assessed with the "Regional contribution to ejection fraction"-method as the mean regional contribution to ejection fraction per abnormal segment (%) and was calculated by dividing the sum of regional contributions below 10th percentile of normal by the number of abnormal regions [11].
In the "Centerline-method" the severity of the hypokinesia was defined as maximally abnormally contracting 50% (expressed in standard deviation/chord) and is computed as follows. The difference between shortening fraction of each chord and mean shortening fraction of the corresponding chord in a group of normals was divided by 1 standard deviation of normal for each chord in the hypokinetic area. This difference divided by 1 standard deviation of normal is called "standardized motion" of a chord. The hypokinetic area was defined as a set of contiguous chords, chosen in such way that half the number of chords in the infarct territory are included and that the mean "standardized motion" in that set of chords is most abnormal. This mean "standardized motion" in the hypokinetic area is called maximally abnormally contracting 50% [7-9].

In the "Radial-axes-method" the severity of hypokinesia was given by the contribution to the global ejection fraction by the sector of radii with wall motion abnormality exceeding 2 SD of normal wall motion (called regional ejection fraction in the infarct territory.

Similarly, the extent and severity of hyperkinesia (wall motion abnormality in the contralateral area) were determined with the "Regional contribution to ejection fraction"-method as the number of segments with abnormal regional contribution to ejection fraction and the mean regional contribution to ejection fraction per abnormal segment (%). Abnormal segments were defined as regional contributions exceeding the 90th percentile of normal. For the Centerline-method only the severity of hyperkinesia was calculated [7] as maximally abnormally contracting 50% (standard deviation/chord).

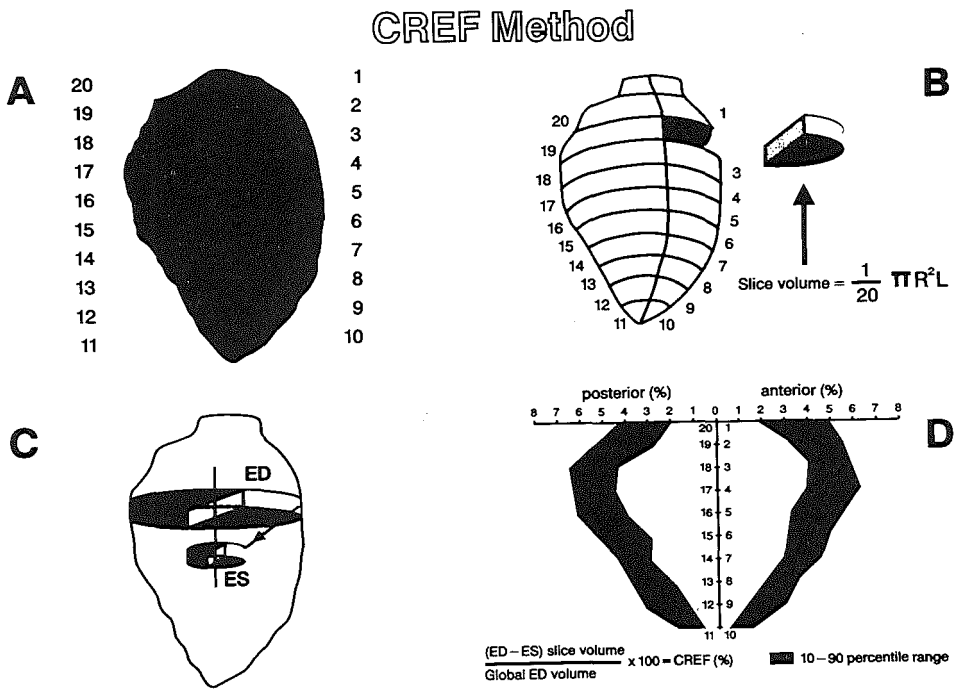

Figure 1a. "Regional contribution to ejection fraction"-method of regional wall motion analysis. A. End-diastolic left ventricular endocardial contour in 30 degree right anterior oblique left ventriculogram. The 20 coordinates along which left ventricular wall motion occurs are superimposed. B. The volume of each slice in the end-diastolic volume is calculated from the radius of the slice (R) and 1/20th of the left ventricular long axis length (L): $Vi = 1/20 \times \pi \times Ri2 \times L$.
The slices or segments are numbered from 1 to 10 for the anterior wall and from 11 to 20 for the infero-posterior wall. C. Similarly, the volume of each slice in the end-diastolic volume is calculated. The regional contribution to global ejection fraction is determined as:

$$\frac{\text{(end-diastolic - end-systolic) slice volume}}{\text{global end-diastolic volume}} \times 100\%$$

D. An example of a plot of regional contribution to ejection fraction, in which the values for regional contribution to ejection fraction (x-axis) for all 20 segments (y-axis) are given. The shaded zones represent the 10th and 90th percentiles of the regional contribution to ejection fraction for each segment in 31 normal individuals. (Reproduced from reference 2 with permission of the author and the Journal of the American College of Cardiology).

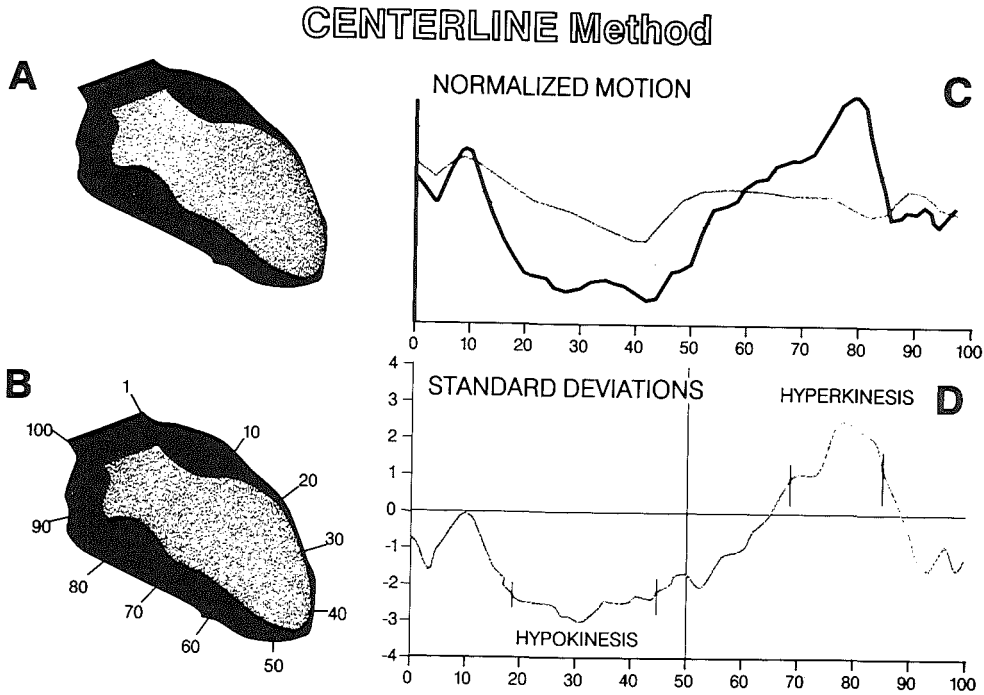

Figure 1b. "Centerline"-method of regional wall motion analysis. A. End-diastolic and end-systolic left ventricular endocardial contours with the computer-constructed centerline in between. B. Motion is measured along 100 chords constructed perpendicular to the centerline. C. Motion at each chord divided by the end-diastolic perimeter yields a shortening fraction. Motion along each chord is plotted for the patient. In addition, the mean motion (+ 1 standard deviation) in the group of normal individuals (for RAO projection 31) is plotted for comparison. D. Standardized motion. The difference between the shortening fraction of a chord and the mean shortening fraction of that chord number in a group of normal individuals was divided by the standard deviation of the mean shortening fraction of that chord number in the group of normal individuals. (Reproduced from reference 9 with permission of the author and Circulation).

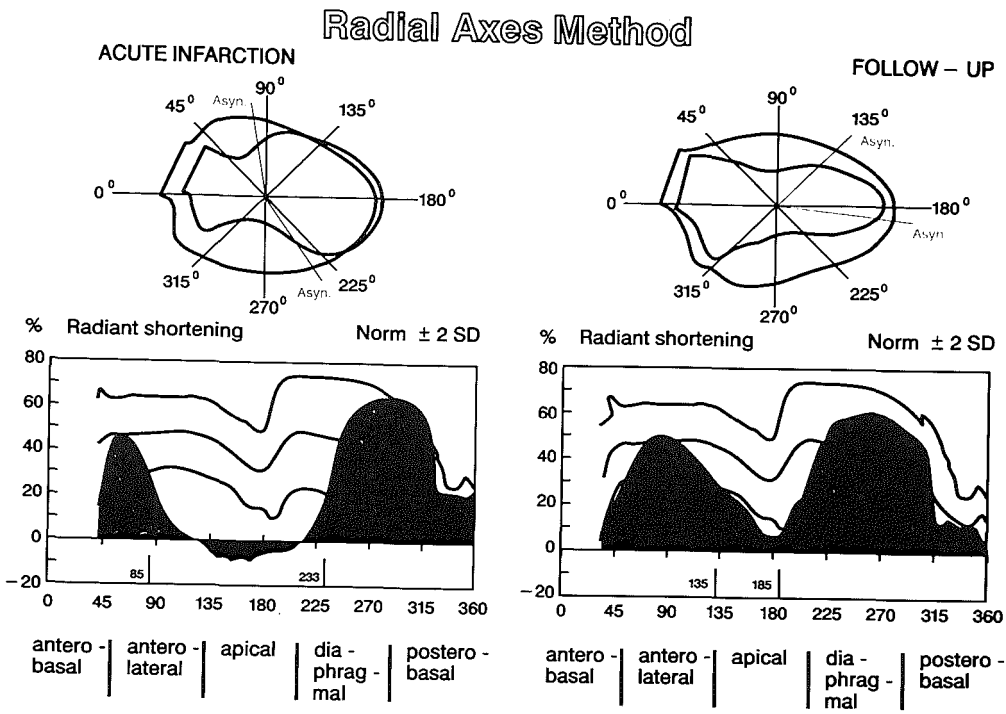

Figure 1c. "Radial axes"-method. The central axis (0-180 degrees) are determined by the center of mass of the end-diastolic contour and the junction of the mitral and aortic valve. The percentage radiant shortening of approximately 300 radii is calculated as:

$$\frac{\text{(end-diastolic radius - end-systolic radius)}}{\text{end-diastolic radius}},$$

and plotted together with the mean (+ 2 standard deviations) of a group of 31 normals. The sector in which radiant shortening was less than the mean normal radiant shortening minus 2 standard deviations is called the hypokinetic region (in this example from 85 to 233 degrees).

Localization of infarct- and non-infarct territories in the "Centerline-method", are defined by the angiographically assessed infarct related vessel and the number of diseased coronary arteries [7-9]. In the "Regional contribution to ejection fraction"-method and the "Radial-axes-method" regions of hypokinesia are not defined by coronary anatomy, but considered in all segments, except for the latter method if 2 hypokinetic regions separated by at least 25 radii were found. In that case selection of the appropriate region was made on the basis of infarct localization on the qualifying electrocardiogram.

Enzymatic infarct size

Cumulative release of plasma α-hydroxybutyrate dehydrogenase was determined centrally in the core laboratory for enzyme determinations from serial plasma samples at 12, 24, 36, 48 and 72 hours after start of treatment onset. Details have been published elsewhere [1,12].

DATA ANALYSIS

Baseline risk assessment

Since more patients in the invasive treatment group did not undergo cardiac catheterization because of death or cardiac contraindications than in the non-invasive group (see table I), unequal distribution of high risk patients over the 2 treatment groups in the present analysis was likely to influence the measured treatment effect of the invasive strategy. Therefore individual baseline risk was assessed.

Baseline risk assessment consisted of three steps. Firstly, the relation between baseline characteristics and the number of segments with regional contribution to ejection fraction below the 10th percentile of normal was assessed with multivariate linear regression analysis. Only baseline characteristics known to be related to left ventricular function [13] and/or outcome of coronary angioplasty [14] were considered: (1) age, (2) gender, (3) history of previous infarction, (4) history of angina exceeding 4 weeks, (5) sum of ST-segment elevation on electrocardiogram, (6) infarct localization, (7) hemodynamic status before thrombolytic treatment and (8) delay from symptom onset to start of rt-PA. Details of the multivariate linear regression analysis are given in the Appendix. Secondly, the number of segments with regional contribution to ejection fraction below the 10th percentile of normal was calculated from this multivariate model in each individual patient by setting the indicator variable for treatment allocation to values indicating non-invasive treatment. Finally, patients were subdivided in three equally sized groups of low, medium and high baseline risk.

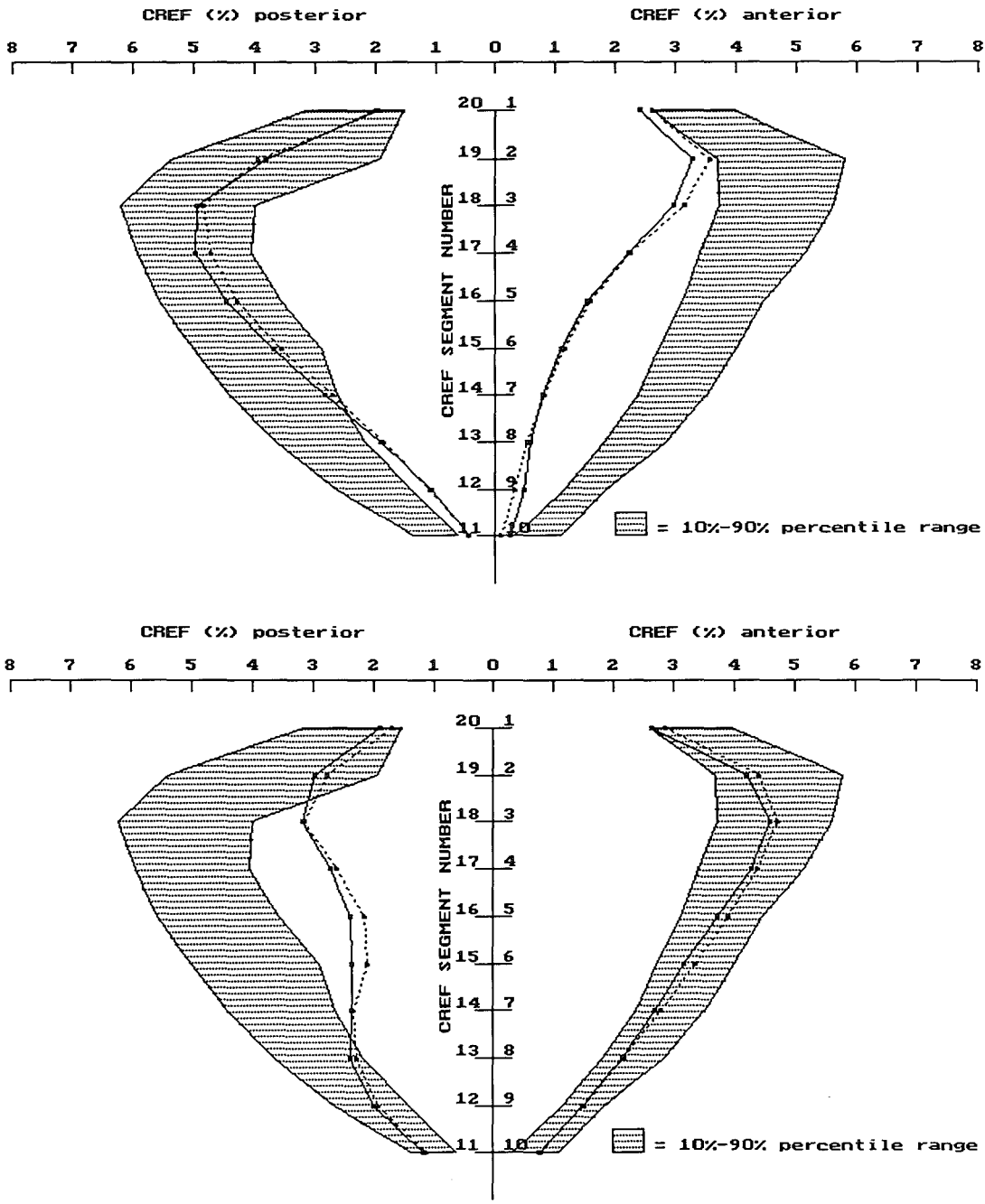

Figure 2. Mean regional contribution to global ejection fraction in 20 segments of the left ventriculography in patients with anterior (upper plot) and diaphragmatic (lower plot) infarct localization. The hatched area represents the normal 10 to 90 percent range. Patients allocated to the non-invasive strategy are represented by the dotted line; patients allocated to invasive treatment by the solid line.

Subgroup analysis

The number of segments with regional contribution to ejection fraction below the 10th percentile of normal was assessed in both treatment groups stratified according variables available before treatment allocation.
The "Regional contribution to ejection fraction"-method was chosen a priori for the baseline risk assessment and subgroup analysis, because this method has the advantage that it is applicable without knowledge of the infarct related vessel. The method is therefore available in a higher proportion of patients. Furthermore, the method is validated in both animal experimental and patient studies [2,6]. The multivariate methodology is described in the Appendix.

Adjustment for imbalances of baseline risk

Differences between both treatment groups for all parameters of regional wall motion were adjusted for imbalances in baseline risk by multivariate linear regression analysis. With this technique the treatment effect of immediate coronary angioplasty, adjusted for other determinants of the outcome parameter is provided by the coefficient of the indicator variable for treatment allocation (see Appendix) [15].

RESULTS

The "Regional contribution to ejection fraction"-model could be assessed in all 291 patients with analyzable left ventriculography at 10 to 22 days. Determination of the maximally abnormally contracting 50% ("Centerline-method") was not possible in 28 patients in the non-invasive and 9 patients in the invasive treatment group, due to uncertainty about which vessel was infarct related.

Baseline characteristics

Baseline characteristics related to regional left ventricular wall motion are presented in table II. Anterior infarct localization and previous myocardial infarction were strong predictors of regional left ventricular function. Other contributors to reduced wall motion were the sum of ST-segment elevation and delay to start of rt-PA. Linear regression coefficients, listed in table III, indicate the independent contribution of each determinant of baseline risk. Intercept and coefficients as observed in this trial were very similar to those in 577 other patients entered in the rt-PA/placebo trial, which is conducted by the same study group using similar methodology in 23 other hospitals

[12]. This supports the validity of the baseline risk model used in the present analysis.

Baseline risk assessment successfully separated high risk patients from low risk patients. The number of segments with abnormal regional contribution to ejection fraction in the non-invasive treatment group was twice as high in the high risk group than in the low risk group (table II). There was an excess of high risk patients with assessable left ventriculography in the invasive treatment group (40.8% versus 34.2%) (table II). As a consequence, any true difference in regional wall motion between treatment groups cannot be assessed without adjustment for this unequal distribution of baseline risk.

Left ventricular function

Left ventricular function after adjustment for unbalanced distribution of baseline risk was similar in the 2 treatment groups, both for global and regional wall motion (table IV). Confidence intervals for the differences were nearly symmetrically around zero, indicating that no real difference in treatment effect between the two treatment strategies was present. In figure 2 the CREF-plots are shown for bot treatment groups.

Subgroup analysis

None of the patient subsets defined by the baseline characteristics mentioned in the Methods section benefited from immediate angioplasty, neither with univariate (table II), nor with multivariate analysis.

Occlusion of infarct related vessel and reinfarction

Patency of the infarct related vessel could not be assessed in 4 out of 149 patients in the non-invasive group and in 1 out of 142 patients in the invasive group with analyzable left ventriculography. An occluded infarct related vessel at 10 to 22 days angiography and/or reinfarction occurred more often in the invasive group (25 out of 141 patients) than in the non-invasive group (19 out of 145 patients).

In patients with a patent infarct related vessel at 10-22 days angiography and without reinfarction, global left ventricular ejection fraction was 1.9 points better in the invasive strategy group (table V). This was merely due to a smaller area of hypokinesia (see figure 3). Severity of hypokinesia and hyperkinesia were similar in both treatment groups. Findings for all three models of regional wall motion analysis were consistent. In this subset of patients, enzymatic infarct size was similar in both treatment groups (median α-hydroxybutyrate dehydrogenase plasma activity 615 U/l with 90% range 46 to 1882 U/l in 126 patients in the non-invasive group and 660 U/l with 90% range 115 to 1576 U/l in 116 patients in the invasive group). The same was found after adjustment for unequal baseline risk (infarct localization, time to rt-PA, and ST-segment elevation) with linear regression analysis.

TABLE II - Baseline characteristics related to left ventricular ejection function at hospital discharge. The simultaneous impact of all baseline characteristics in an individual patient is summarized in the baseline risk score.

	Patients with characteristic		Number of abnormal CREF's (mean and SD)	
	Non-I N=149	Invasive N=142	Non-I N=149	Invasive N=142
History of infarction				
no	138	134	8.6(4.2)	8.6(3.7)
yes	11	8	10.3(5.7)	12.1(5.1)
Sum ST (mV)				
<2	115	105	8.3(4.4)	8.3(3.7)
≥2	34	36	9.9(4.1)	10.6(3.7)
mis	-	1		
Anterior infarct localization				
no	86	78	7.0(3.2)	7.2(2.9)
yes	63	64	11.0(4.6)	10.8(4.0)
Delay to rt-PA (hrs)				
<2	42	30	7.4(3.7)	8.3(3.8)
2-3	53	46	8.5(4.4)	8.4(3.8)
≥3	54	66	9.8(4.5)	9.4(3.9)
Allocation to invasive strategy				
no	149	-	8.7(4.3)	-
yes	-	142	-	8.8(3.9)
Baseline risk score				
low	43	35	6.2(2.8)	6.6(2.3)
medium	55	49	7.7(3.7)	7.8(3.2)
high	51	58	11.8(4.3)	11.1(4.0)

Number of abnormal CREF's: number of segments with regional contribution to ejection fraction below 10th percentile of normal. Baseline risk score: predicted number of abnormal CREF's with linear regression analysis from above baseline characteristics (see methods).

TABLE III - Prediction of the number of segments with abnormal regional contribution to ejection fraction. A similar multivariate model was developed in an independent group of 577 patients with left ventriculograms from the rt-PA/placebo trial [12].

Model	All patients N=291	Patent IRV/ no reinfarction N=242	rt-PA/placebo trial N=577
Intercept	5.6	5.8	6.5
History of infarction			
no	--	--	--
yes	2.5(0.8)	2.6(0.9)	2.4(0.6)
Sum ST (mV)			
<2	--	--	--
≥2	1.8(0.5)	1.7(0.5)	1.6(0.3)
Anterior infarct localisation			
no	--	--	--
yes	3.7(0.4)	3.6(0.4)	3.1(0.3)
Delay to rt-PA (hrs)			
<2	--	--	--
2-3	1.0(0.5)	1.1(0.6)	0.6(0.4)
≥3	1.5(0.5)	1.3(0.6)	1.1(0.4)
Allocation to invasive strategy			
no	--	--	
yes	-0.1(0.4)	-0.4(0.4)	
Allocation to rt-PA			
no			--
yes			-0.5(0.3)

IRV:infarct related vessel. The number of abnormal segments in an individual patient may be determined by adding up intercept and all relevant coefficients. For example, a patient without previous infarction, more than 2mV ST elevation, inferior infarction, Killip 1, treated with rt-PA within two hours and allocated to invasive strategy has 5.6 + 1.8 - 0.1 = 7.3 segments with abnormal contribution to ejection fraction. The same patient after non-invasive therapy has 7.4 abnormal segments.

TABLE IV - Treatment effect of immediate PTCA before and after adjustment for unequal baseline risk in all 291 patients.

	Mean (SD)		Difference (Invasive - Non-invasive)		
	Non-I N=149	Invasive N=142	Crude	Adjusted	95% Confidence
Global left ventricular function					
LVEF (%)	49.7(11.4)	49.7(10.8)	0.0	0.7	-1.6 to 2.9
Extent of hypokinesia					
CREF	8.7(4.3)	8.8(3.9)	0.2	-0.1	-0.8 to 0.7
Centerline	32.4(21.4)	33.2(20.9)	0.8	-0.1	-4.3 to 4.1
Radial axes	44.7(21.0)	43.8(20.1)	-0.9	-1.5	-6.1 to 3.0
Severity of hypokinesia					
CREF	1.4(0.7)	1.5(0.7)	0.1	0.1	-0.1 to 0.2
Centerline	-2.8(1.6)	-2.7(1.6)	0.1	0.1	-0.3 to 0.5
Radial-axes	0.6(0.8)	0.7(0.9)	0.1	0.1	-0.0 to 0.3
Extent of hyperkinesia					
CREF	2.1(2.3)	2.0(2.2)	-0.1	0.0	-0.5 to 0.5
Severity of hyperkinesia					
CREF	4.3(2.2)	4.2(2.1)	-0.1	-0.3	-0.8 to 0.3
Centerline	0.2(1.2)	0.1(1.3)	-0.0	-0.1	-0.4 to 0.2

LVEF: left ventricular ejection fraction (%) (N=291). CREF: "Regional contribution to ejection fraction"-method. The definitions of the measurements have been presented in the methods section. **Extent of hypokinesia** was assessed with the CREF, Centerline and Radial-axes method in respectively 291, 289 and 291 patients. **Severity of hypokinesia** in 289, 255 and 285 patients respectively. **Extent of hyperkinesia** was assessed in 291 patients. **Severity of hyperkinesia** in 189 patients (in 102 patients no hyperkinesia was present according to the CREF-method) and in 255 patients with the "Centerline"-method.

DISCUSSION

In spite of thrombolytic therapy with rt-PA, the infarct related vessel remains occluded in approximately 25% of patients [1,4,16]. Furthermore part of the patients have a hemodynamically significant stenosis after thrombolysis. Immediate coronary angioplasty has been proposed to recanalize the remaining occluded vessels and to improve blood flow in patients with a severe residual stenosis.

Recovery of left ventricular function and the incidence of reocclusion were reported to be related to the degree of residual stenosis after thrombolysis [17-19] and small randomized trials, assessing immediate angioplasty with and without intracoronary streptokinase, suggested that recovery of left ventricular function might be improved by angioplasty [20,21]. However, the present larger randomized trial of the European Cooperative Study Group failed to confirm this. Other investigators also reported lack of benefit of immediate [4,16] or delayed (18-48 hours) angioplasty [5] in patients treated with rt-PA.

Baseline comparability

There was an excess in baseline risk in the invasive treatment group in the present analysis. This could not be explained by the fact
that patients without predischarge left ventriculography were excluded for the present analysis, since missing left ventriculography was related to poor left ventricular function and more patients in the invasive treatment group had no left ventriculography (table 1). The explanation is that randomization did not yield groups of identical baseline risk. Although randomization is the best way of achieving patient groups with identical baseline risk, it is not always successful, especially in small and medium sized trials [22].

Multivariate linear regression analysis provides an estimation of relative efficacy of treatment strategies, independent of imbalances in baseline risk. After adjustment, no benefit of immediate angioplasty was found.

Occlusion of infarct related vessel and reinfarction

In the present trial, immediate angioplasty was associated with more frequently an occluded infarct related vessel and reinfarction during stay in the hospital, which might have abolished a benefit of immediate angioplasty. In fact, a trend towards improved regional wall motion, was observed in those patients with a patent infarct related vessel and without recurrent infarction at the time of hospital discharge. The magnitude of treatment effect of immediate angioplasty in these patients was of the same order of magnitude as found for thrombolytic therapy with rt-PA in comparison to placebo (table III). This suggests that immediate angioplasty may be beneficial if the complications of angioplasty, i.e. reocclusion and reinfarction can be prevented.

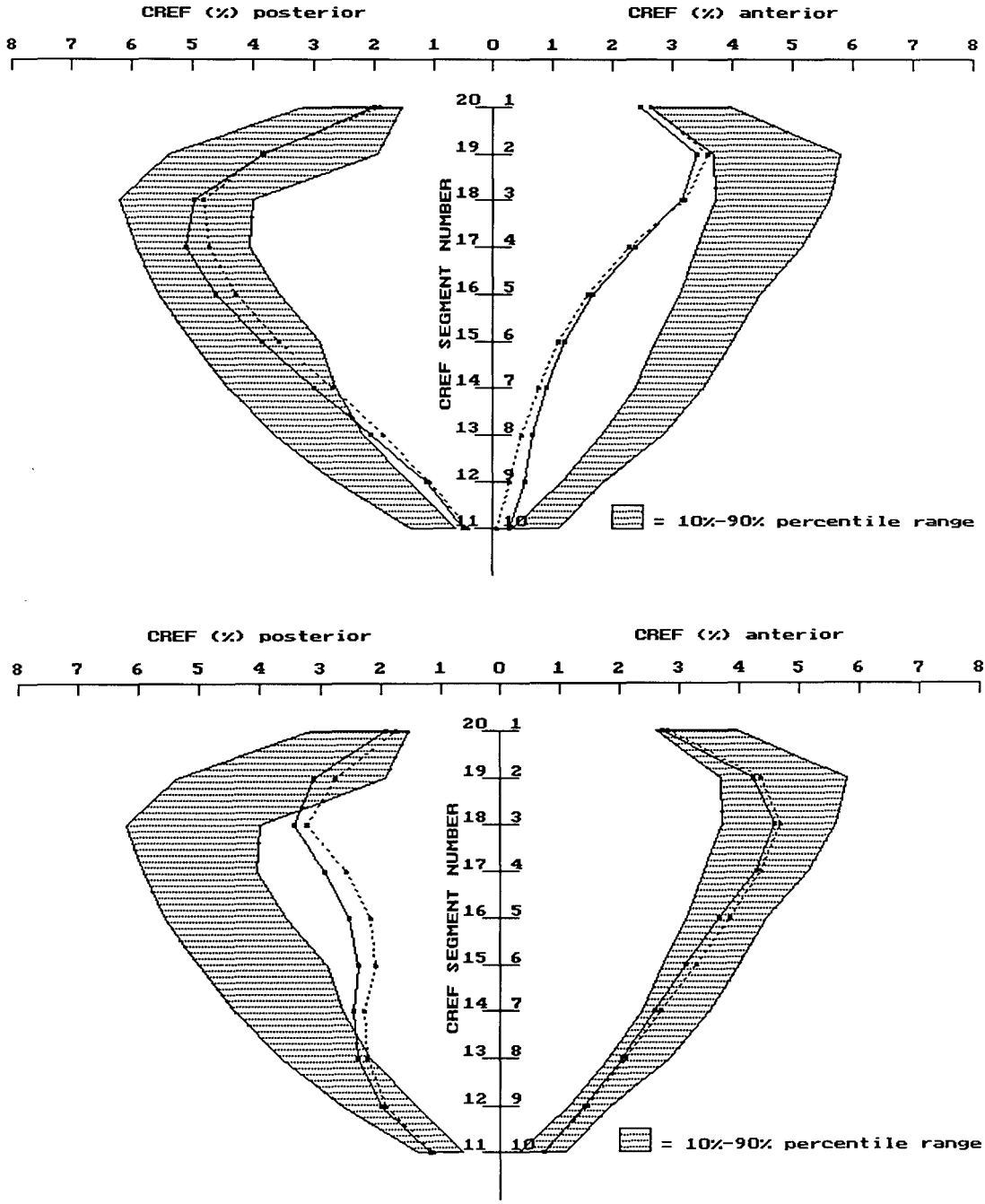

Figure 3. Mean regional contribution to global ejection fraction in 20 segments of the left ventriculography in patients with a patent infarct related vessel at 10-22 days angiography (TIMI perfusion grade 2 or 3) and without reinfarction prior to angiography for anterior (upper plot) and diaphragmatic infarct localization (lower plot). The hatched area represents the normal 10 to 90 percent range. Patients allocated to the non-invasive strategy are represented by the dotted line; patients allocated to invasive treatment by the solid line.

TABLE V - Treatment effect of immediate PTCA before and after adjustment for unequal baseline risk in 242 patients with a patent infarct related vessel at 10-22 days angiography (TIMI perfusion grade 2 or 3) and without reinfarction prior to angiography only.

	Mean (SD)		Difference (Invasive - Non-invasive)		
	Non-I N=126	Invasive N=116	Crude	Adjusted	95% Confidence
Global left ventricular function					
LVEF (%)	49.0(11.5)	50.8(9.9)	1.9	1.9	-0.5 to 4.4
Extent of hypokinesia					
CREF	9.1(4.3)	8.6(3.7)	-0.5	-0.5	-1.3 to 0.4
Centerline	34.5(22.1)	32.1(19.5)	-2.4	-2.1	-6.7 to 2.5
Radial-axes	46.3(20.5)	42.4(19.3)	-3.9	-3.9	-8.7 to 0.9
Severity of hypokinesia					
CREF	1.4(0.6)	1.6(0.7)	0.1	0.1	-0.0 to 0.3
Centerline	-2.9(1.6)	-2.6(1.5)	0.3	0.2	-0.2 to 0.6
Radial-axes	0.6(0.7)	0.8(0.9)	0.2	0.2	-0.0 to 0.4
Extent of hyperkinesia					
CREF	1.9(2.1)	1.8(2.0)	-0.1	-0.1	-0.6 to 0.4
Severity of hyperkinesia					
CREF	4.3(2.3)	4.2(2.2)	-0.1	-0.3	-0.9 to 0.3
Centerline	0.1(1.2)	0.2(1.3)	0.1	0.1	-0.3 to 0.4

See legend of table IV. **Extent of hypokinesia** was assessed with the CREF, Centerline and Radial-axes method in respectively in 242, 239 and 242 patients. **Severity of hypokinesia** in 242, 215 and 237 patients respectively. **Extent of hyperkinesia** in 242 patients. **Severity of hyperkinesia** was assessed with the CREF-method in 152 pts, in the remaining 90 patients no hyperkinesia was present; with the "Centerline"-method in 214 patients.

Better left ventricular function after immediate coronary angioplasty in patients without reocclusion and/or reinfarction may be explained by further limitation of infarct size, and by enhancement or acceleration of left ventricular recovery. The fact that enzymatic infarct size was not reduced, favours the latter explanation. In addition, this is in agreement with the observation that recovery of left ventricular function is related to residual stenosis after thrombolytic therapy [17].

One might argue that excluding the patients in whom infarct related vessel patency could not be assessed might have influenced the effect of immediate angioplasty in patients with a patent infarct related vessel and without reinfarction. However, the same results were obtained if these patients were included in the analysis.

The lack of benefit of the invasive strategy in the present trial may also be due in part to sudden and complete reperfusion during angioplasty. There is evidence from animal experiments that recovery of left ventricular function is accelerated after gradual (in 2 hours time) in comparison to recovery after sudden reperfusion. The underlying mechanism is unknown, but the no-reflow phenomenon and increased calcium influx with contraction band necrosis may contribute [23]. Thus a certain degree of residual stenosis after thrombolysis may help protect myocardium against reperfusion damage. This would favour an approach of immediate thrombolytic recanalization or mechanical recanalization with a guidewire, followed by coronary angioplasty after a few hours. This regimen requires further study.

Patient selection

In the present trial no patient subset benefited from coronary angioplasty. In the present trial angioplasty was attempted in most patients (92%), including patients with an occluded infarct related vessel. Initial experience with immediate coronary angioplasty in patients with an occluded infarct related vessel at 90 min after start of thrombolysis with rt-PA ("rescue angioplasty") was not favourable [16], but promising results were obtained when rt-PA was combined with urokinase [24]. The concept of "rescue" angioplasty deserves further study in connection with treatment regimen for the prevention of reocclusion or reinfarction, especially if patients with persistent occlusion (failed thrombolysis) can be recognized non-invasively. In the mean time, angioplasty and coronary bypass surgery should be reserved for treatment of recurrent ischemia not responding to medical treatment. The role of thallium myocardial perfusion scintigraphy in the selection of patients for revascularization procedures is unknown sofar.

Conclusion

No benefit of an invasive strategy of immediate coronary angioplasty in addition to rt-PA, heparin and aspirin, could be documented when compared to a non-invasive strategy with rt-PA, heparin and aspirin alone. Nevertheless, a trend towards benefit of immediate angioplasty was found in selected patients with a patent predischarge infarct related vessel and without reinfarction. This suggest that reocclusion and reinfarction are responsible for the lack of benefit of immediate coronary angioplasty after thrombolytic

therapy for acute myocardial infarction. At present, an invasive strategy with immediate angiography and angioplasty cannot be recommended, but angioplasty in selected patients (e.g. with failed thrombolysis) warrants further investigation, provided that reocclusion and reinfarction can be prevented.

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APPENDIX

Linear regression analysis

Linear regression analysis was performed (BMDP statistical package, program 1R and 2R) to assess the relation between the variables mentioned in the "Methods" section (independent variables = X_i) and each parameter of left ventricular function (dependent variable = Y): $Y = A + \Sigma_i B_i X_i$

Independent and dependent variables

Indicator variables were defined by assigning zero to patients in whom an event or characteristic was absent and one in case of presence. Continuous variables were not used directly. For these variables patients were categorized in three equally sized subgroups according to patients value for that variable. The category with the lowest value for the parameter of wall motion under study was chosen as reference group. For the second and third subgroups indicator variables were designed: one in case a patient belonged to that subgroup, zero if not. Thus, patients in the reference group were characterized by zero's for the design variable for the second and third subgroup.

Design of the linear regression models

For the baseline risk model, all indicator variables representing the baseline

characteristics mentioned in the "Methods-section" were simultaneously entered in the model. Only indicator variables with coefficients with $P \leq 0.10$ were retained in subsequent models, unless a product term of that term with another term had to be included in the model. In that case, the indicator variable was forced into the model. The same applied for the indicator variable of treatment allocation.

For each parameter of regional wall motion, the same independent variables as used for the baseline risk assessment, were entered in a model in order to adjust for unbalanced baseline risk of regional wall motion.

To assess the contributions of the various determinants in both treatment groups separately, "product terms" (indicator variable for determinant under study multiplied by the indicator variable of treatment allocation) were tested in the model [25].

Interpretation of results of linear regression model

Since all independent variables are zero/one variables, the coefficients (B_i) reflect the difference (DIF) in the number of segments with regional contribution to ejection fraction below 10th percentile of normal between a patient with characteristic X_i and a patient without that characteristic, all other determinants of regional wall motion being equal. 95% confidence limits for this difference may be calculated from the standard error (SE_i) of the coefficient [26]: $DIF_i \pm 1.96 \times (SE_i)$.

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CHAPTER 6

RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR AND IMMEDIATE ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION, ONE YEAR FOLLOW-UP

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[1]A listing of investigators and participating centers has been published previously [1,2].

ABSTRACT

The European Cooperative Study Group conducted 2 randomized trials in patients with suspected myocardial infarction to assess the effect of single chain recombinant tissue plasminogen activator (rt-PA, alteplase) on enzymatic infarct size, left ventricular function, morbidity and mortality relative to placebo (rt-PA/placebo trial) and to assess the effect of immediate coronary angioplasty in addition to rt-PA (rt-PA/PTCA trial). In the rt-PA/placebo trial 721 patients with chest pain of less than 5 hours and extensive ST-segment elevation were entered and in the rt-PA/PTCA trial 367 similar patients. In the former trial patients were allocated at random to 100 mg rt-PA or placebo (double blind) over 3 hours. In the rt-PA/PTCA trial all patients received rt-PA and were subsequently allocated at random to immediate coronary angiography and angioplasty of the infarct related vessel or control. All patients in both trials received aspirin and intravenous heparin, started with a 5000 U bolus and followed by 1000 U per hour.

In the rt-PA/placebo trial, mortality during the first year was reduced by 36% with rt-PA, from 9.3% to 5.6%. Late revascularization was performed more frequently after rt-PA (in 66 versus 57 patients) and more patients were in New-York Heart Classification class I or II (86.7% versus 81.4%) in the rt-PA group. Non-fatal reinfarction was more common after rt-PA than after placebo (6.8% versus 4.4%). In the rt-PA/PTCA trial, after immediate coronary angioplasty, non-fatal reinfarction was less common (4.9% versus 9.3%) and revascularization procedures less frequent (16.4% versus 25.0%). However, this was offset by a high rate of immediate reocclusion and early recurrent ischaemia and higher mortality at 1 year (9.3% versus 5.5%) in the invasive group, also after adjustment for unequal baseline risk. Benefit of rt-PA tended to be greater in patients treated early. In a multivariate analysis of 1043 hospital survivors, late mortality was related to coronary anatomy, left ventricular function, age and previous infarction, but not to initial treatment allocation. Reinfarction after hospital discharge was more common after rt-PA and tended to be related to coronary anatomy.

INTRODUCTION

In 1988 the European Cooperative Study Group reported two randomized clinical trials with single chain recombinant tissue type plasminogen activator (rt-PA, alteplase). In the rt-PA/placebo trial, 721 patients were allocated at random to rt-PA or placebo [1]. All patients received intravenous heparin and aspirin. Mean left ventricular ejection fraction was higher and enzymatic infarct size was 20% smaller after treatment with rt-PA. Mortality was reduced by 51% at 2 weeks and by 36% at 3 months. In the rt-PA/PTCA trial, 367 patients were allocated at random to a non-invasive strategy of rt-PA, heparin and aspirin or to an invasive strategy of rt-PA, heparin and aspirin followed be immediate coronary angiography and PTCA [2]. No additional benefit of immediate coronary angioplasty was found; left ventricular function and enzymatic infarct size were similar in both treatment groups and mortality at 3 months was higher in the invasive

treatment group.

All patients in both trials were followed during one year in order to answer the following questions: (1) Is the reduction of mortality by rt-PA maintained during follow-up; (2) are clinical course and functional class influenced by rt-PA and immediate angioplasty; (3) which are the predictors of mortality and reinfarction after hospital discharge.

PATIENTS AND METHODS

Patients with electrocardiographic evidence of extensive myocardial infarction were enroled in two different trials, provided that thrombolytic therapy could be started within 5 hours after the onset of symptoms. Details of trial size determination, patient selection and baseline characteristics have been previously published [1,2]. All patients entered in both trials had given their informed consent and the committee on human research in every participating center had approved the study protocol. In the rt-PA/placebo trial, patients were randomized to either rt-PA or placebo. All patients received a bolus of 5000 IU heparin followed by an infusion of 1000 IU/hour and 250 mg aspirin intravenously. Rt-PA was given as a 10 mg bolus injection followed by 50 mg in one hour and 40 mg in the subsequent 2 hours. In the rt-PA/PTCA trial patients were allocated to a non-invasive strategy of rt-PA, heparin and aspirin, or to an invasive strategy of rt-PA, heparin, and aspirin followed by immediate angiography and PTCA. In both trials aspirin (75 to 120 mg on alternating days) as well as anticoagulation with heparin and/or coumarin were continued until pre-discharge angiography which was required in all patients between 10 and 22 days after admission. After discharge long term treatment with beta blockers was recommended (metropolol 100 mg twice a day). In case of recurrent ischaemia resistant to medical treatment, coronary angioplasty or coronary bypass surgery should be performed. In the rt-PA/placebo trial, investigators remained unaware of the treatment allocation. Left ventricular ejection fraction and coronary anatomy were assessed centrally by the Core Laboratory and the Angiographic Assessment Group. Residual stenosis in the infarct related vessel at 10 to 22 days was assessed visually. Left ventricular ejection fraction was determined from contrast left ventricular angiography in left anterior oblique projection [1].

Follow-up information was obtained by the investigators at each participating center, during a visit of the patient to the outpatient clinic some weeks later than 3 months and 1 year after myocardial infarction. Data on survival, date and cause of death, dates and duration of any hospital admission, reinfarction, coronary angioplasty and bypass surgery, functional class (New-York Heart Association classification) and use of medication were obtained. If a patient could not visit the outpatient clinic, information was gathered by telephone contact or via the general physician.

Data analysis

Survival and survival without reinfarction were determined according to Kaplan-Meier [3]. Relative risk in one patient group compared to a reference group is reported as hazard ratio, obtained with Cox regression analysis [4]. Baseline risk was assessed in each individual patient by calculating a baseline risk score based on the independent contribution of multiple determinants of mortality available before treatment allocation. The independent contribution was assessed by Cox multivariate regression analysis (see Appendix) in the rt-PA/placebo trial. The obtained risk prediction model was subsequently applied in the rt-PA/PTCA trial. Similarly, determinants of death after hospital discharge were identified with Cox multivariate regression analysis [4] (see Appendix).

To assess the relation between residual stenosis in the infarct related vessel and reinfarction during the first year after hospital discharge, a multivariate logistic regression model was designed. Adjusted rate ratios were calculated from this logistic model according to Miettinen [5].

RESULTS

Mortality

Mortality at one year follow-up was 9.3% in the placebo group and 5.6% in the rt-PA group (table I and figure 1). Mortality reduction was 36% (Cox regression analysis, 95% confidence interval from -62% to +8%). Most benefit was found for patients treated within 3 hours after onset of symptoms; mortality was 9.7% (20/207 patients) in the placebo group and 3.9% (7/180) in the rt-PA group. In the rt-PA/PTCA trial mortality appeared higher after invasive therapy, both at 14 days and at one year follow-up. In both trials, heart failure was the most common cause of death (36 patients). Other common causes of death were ventricular arrhythmia (9 patients), sudden death (8 patients), tamponade (7 placebo treated patients) and bleeding (in 6 patients).

Reinfarction

Reinfarction within one year was reported for 8% of patients, of which more than half occurred within 14 days (table I and figure 2). Reinfarction was diagnosed on the basis of a combination of enzyme elevation and electrocardiographic pattern (in 57% of cases) or on the basis of one of these criteria (31%). In the remaining patients, diagnosis was made on clinical pattern or at autopsy. Reinfarction occurred in 78% of

TABLE I - Mortality, reinfarction and revascularization procedures within first year.

		rt-PA/placebo trial		rt-PA/PTCA trial	
		Placebo N=366	rt-PA N=355	rt-PA N=184	Invasive N=183
Events: (%) patients with@:					
Death	14 days	5.7	2.8	2.7	6.6
	1 year	9.3	5.6	5.4	9.3
Reinfarction	14 days	4.1	3.9	6.0	4.4
	1 year	6.8	8.2	11.4	6.6
PTCA	14 days	2.5	2.5	6.0	4.9
	1 year	7.7	7.3	16.3	7.7
CABG	14 days	0.3	2.3	0.0	2.2
	1 year	7.4	10.1	7.6	8.2
PTCA+CABG	14 days	0.3	0.3	0.5	0.0
	1 year	0.5	1.1	1.6	0.5
Patient status at 14 days (%)#:					
Survival		94.3	97.2	97.3	93.4
Survival without reinfarct		91.3	93.8	92.9	90.7
Survival without reinfarct, PTCA or CABG		89.3	90.4	90.2	86.9
Patient status at 1 year (%)#:					
Survival		90.7	94.4	94.5	90.7
Survival without reinfarct		86.3	87.6	85.2	85.8
Survival without reinfarct PTCA or CABG		72.7	72.4	67.1	73.1

@: Number of patients with event divided by total number of patients allocated in each treatment group. In the rt-PA/placebo trial 1.4% of patients in the placebo group and 1.1% in the rt-PA group could not be followed until 365 days. In the rt-PA/PTCA trial this occurred in 2.7 and 3.8% of patients in the rt-PA and invasive treatment group respectively. However, 3 month follow up was available for all but 1 patient and most events occurred within 3 months. #: Patient status at 14 days and one year were determined by Kaplan-Meier survival analysis. PTCA: percutaneous transluminal coronary angioplasty. CABG: coronary artery bypass grafting.

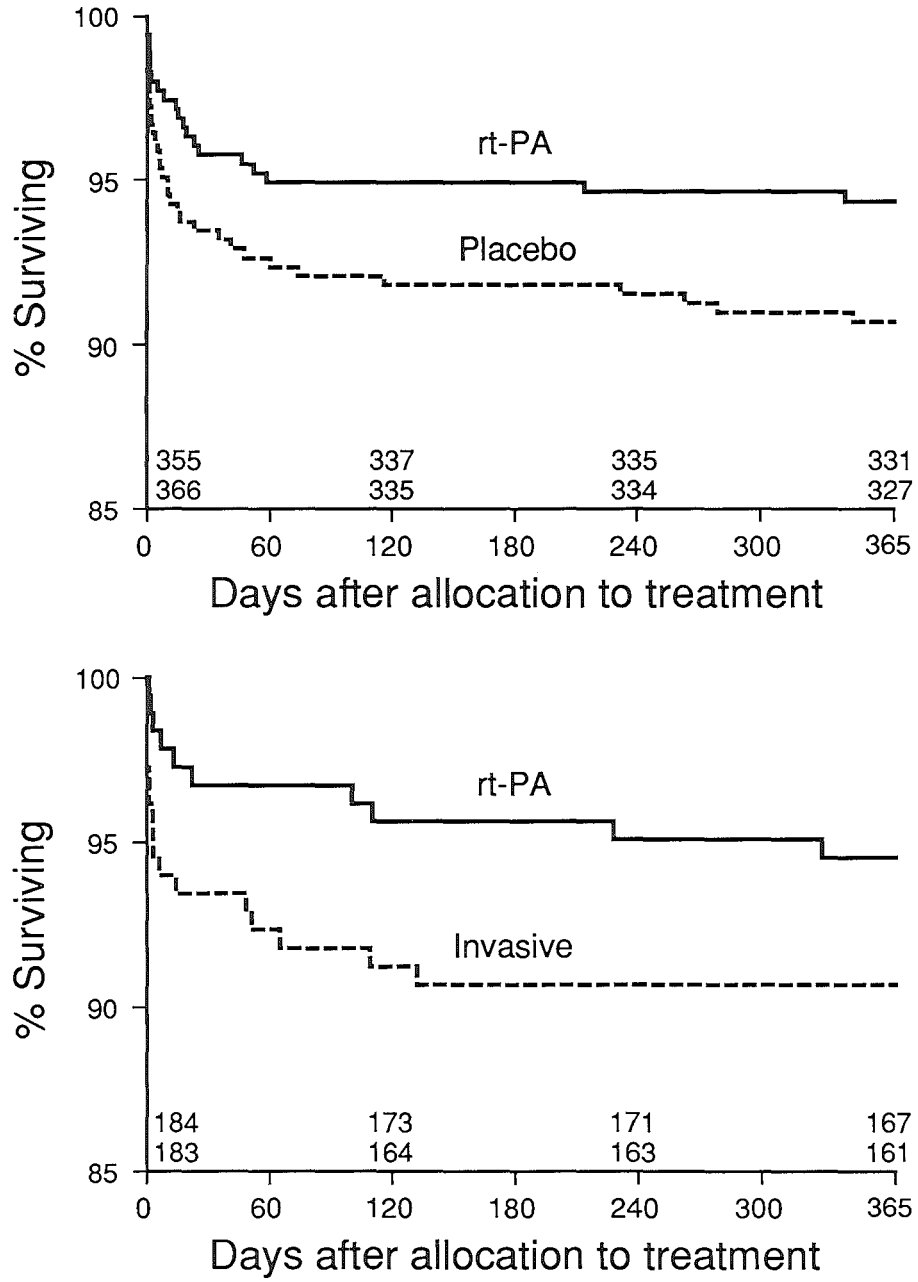

Figure 1. Survival until 1 year after initial treatment allocation in the rt-PA/placebo trial and the rt-PA/PTCA trial of the European Cooperative Study Group.

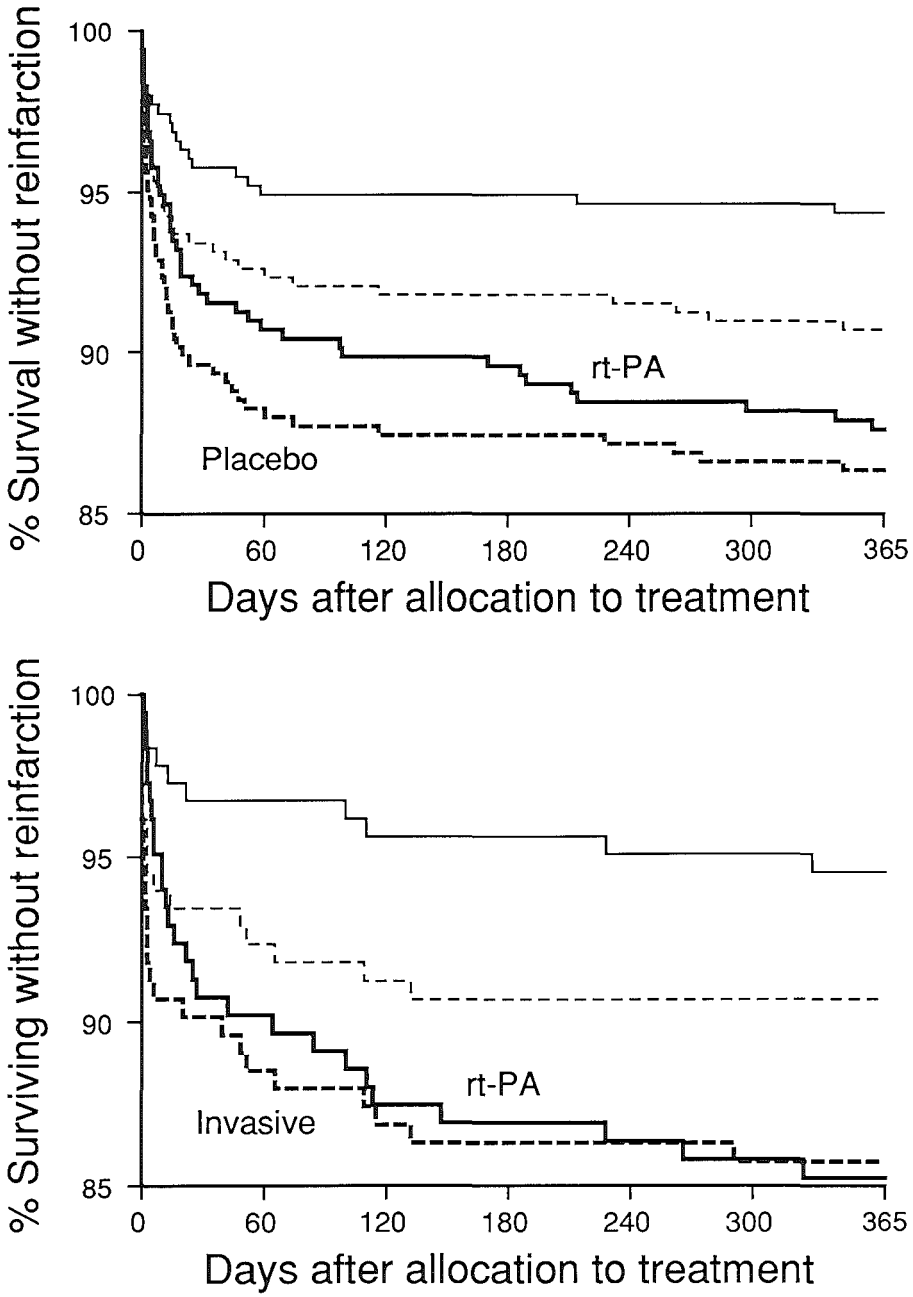

Figure 2. Survival without reinfarction in first year after initial treatment allocation in both trials. The thin solid and dotted lines in the top of the figures represent survival without reinfarction.

cases at the same site as the index infarct, but in 10 patients at a distant site. In 6 cases the localization of reinfarction could not be determined and for 2 patients data were missing. Reinfarction was slightly more common among rt-PA allocated patients with 8.2% versus 6.8% among controls (table I). In the invasive group reinfarction was less frequent than in the non-invasive group: 6.6% versus 11.4%. However, recurrent ischaemia during the first 24 hours after allocation was more frequent in the invasive group, 17% versus 3% [2].

Revascularization and medication

As reported in table I, surgical revascularization was performed more frequently after rt-PA than in the placebo group (table I and II). Most interventions were done after the first two weeks. Overall, interventions were more frequent in the rt-PA/PTCA trial than in the rt-PA/placebo trial. In the invasive group, coronary angioplasty was less frequently performed than in the non-invasive group, while the number of patients undergoing bypass operations was similar in both groups. At one year approximately 72% of patients in both studies were alive, without reinfarction or additional revascularization procedures. About two third of patients were treated with anticoagulant or antiplatelet drugs. In the rt-PA/placebo trial, the most commonly prescribed antithrombotic medication at hospital discharge were coumarins, while antiplatelet drugs were more commonly used in the rt-PA/PTCA trial. This difference disappeared at one year follow-up, when antiplatelet drugs were used by half of the patients in both trials. Betablockade was more commonly used in the rt-PA/placebo trial than in the rt-PA/PTCA trial. Calcium antagonists and nitrates were more frequently prescribed in the rt-PA/PTCA trial than in the rt-PA/placebo trial. Medications such as digitalis, diuretics or anti-arrhythmics were scarcely used in both trials.

Functional class

In the rt-PA/placebo trial, more patients were in functional class I or II in patients treated with rt-PA than among those allocated to placebo (table III). Functional impairment at 1 year was primarily due to angina pectoris (in 44% of cases in the rt-PA group and in 49% among controls) symptoms of congestive heart failure (18% versus 17%) or both (2% and 1% respectively). Other reasons included lung disease (8 patients in rt-PA group and 7 control cases), undetermined dyspnea (8 versus 6), fatigue or psychological reasons (7 versus 9) and arthropathy (3 rt-PA cases versus 2 controls). Among patients allocated to invasive strategy functional class seemed worse compared to the non-invasive strategy throughout the follow-up period. Reasons for functional impairment were angina pectoris and/or congestive heart failure in 88% and 81% in the non-invasive and invasive group respectively. In both trials functional class tended to worsen during follow-up. Functional class at 3 month follow-up was intermediate between hospital discharge and one year follow-up for all treatment groups.

TABLE II - Proportion of patients (%) with medication at hospital discharge, three month and 1 year follow-up for patients alive and with information available.

	rt-PA/placebo trial		rt-PA/PTCA trial	
	Placebo N=366	**rt-PA N=355**	**rt-PA N=184**	**Invasive N=183**
Coumarins				
discharge	59	55	20	17
3 month	55	54	27	20
1 year	21	24	14	15
Antiplatelet				
discharge	35	35	59	50
3 month	41	43	55	52
1 year	50	43	54	54
None of these				
discharge	22	24	25	36
3 month	16	13	22	30
1 year	30	35	33	33
Betablockers				
discharge	56	51	39	37
3 month	59	59	42	48
1 year	59	54	45	42
Calcium antagonists				
discharge	16	17	39	38
3 month	20	20	44	38
1 year	26	25	42	42
Nitrates				
discharge	12	8	35	31
3 month	16	13	57	54
1 year	18	17	45	44

Patients using combinations of medication are counted in each group.

Hospital stay

In the rt-PA/placebo trial duration of the initial hospitalization was 14 days in both treatment groups (median, 90% range 9 to 28 in the placebo; 9 to 23 among controls). Readmissions contributed only 3 days to the total duration of hospitalization during the first year. Thus, the total duration of hospitalization during the first year was 17 days in both treatment groups (median, 90% range 10 to 47 in the rt-PA group and 10 to 43 among controls). In the rt-PA/PTCA trial initial hospitalization was longer, 20 days in each treatment group (median, 90% range 11 to 36 in the invasive group; 11 to 37 among controls). Including readmissions, patients of both treatment groups remained 22 days in the hospital during the first year (90% range 12 to 65 in the invasive, 12 to 58 in the non-invasive group).

Determinants of death and reinfarction after discharge

In order to identify determinants of mortality and reinfarction after hospital discharge, data were analyzed from 1043 hospital survivors. Mortality in the first year after discharge was low (3.4%) and appeared related to coronary anatomy, left ventricular function and to a lesser extent to age and a history of previous infarction (table IV and V). It should be noted that the initial treatment allocation did not affect mortality after hospital discharge. Similarly, for the combined endpoint death or reinfarction left ventricular function and extent of coronary artery disease were predictors. Reinfarction within the first year after hospital discharge occurred in only 39 out of 1043 patients (3.7%). Reinfarction tended to occur 2.4 times more frequently among patients with a patent infarct related vessel with a diameter stenosis between 50 to 99%. This could not be explained by different revascularization approach in this categories of residual stenosis, since entry of indicator variables for bypass surgery and angioplasty in the logistic regression model did not affect this relation. Reinfarction after discharge occurred twice as common in patients treated with rt-PA than among patients allocated to placebo. No other parameters available before hospital discharge appeared related to reinfarction.

DISCUSSION

The reduction in mortality by rt-PA noted during the first 3 months [1] was still present at one year. Other investigators have also reported that the initial benefits of thrombolytic therapy are maintained at 7 months [6], 1 year [7-9] and even at 5 years [10]. In both the rt-PA/placebo and rt-PA/PTCA trial patients with extensive ST-segment elevation were entered. Cardiogenic shock was not an exclusion criterion. Nevertheless, mortality was very low in both trials and among the lowest published to date in any trial with similar inclusion criteria. This is probably due to the combination of effective early thrombolytic therapy and antithrombotic therapy with aspirin [11] and heparin [12].

TABLE III - Functional class according to New-York Heart Association classification at hospital discharge and 1 year follow-up.

	rt-PA/placebo trial		rt-PA/PTCA trial	
	Placebo N=366	**rt-PA N=355**	**rt-PA N=184**	**Invasive N=183**
At hospital discharge				
Median number of days to follow up (90% range)	14(10-29)	14(10-23)	20(11-40)	20(11-39)
Dead	6.6	3.1	3.3	7.1
Alive				
Canadian Functional Class				
I	73.2	78.6	77.2	69.9
II	14.5	12.4	13.0	16.4
III	4.1	3.9	6.5	5.5
IV	1.4	0.8	-	-
Unknown	0.3	1.1	-	1.1
At 1 year follow-up				
Median number of days to follow up (90% range)	399(365-643)	399(365-615)	404(366-599)	412(365-663)
No follow up	0.5	0.6	1.6	1.6
Dead	9.8	6.5	6.0	9.3
Alive				
Canadian Functional Class				
I	60.1	63.9	60.9	51.9
II	21.3	22.8	22.3	25.1
III	7.4	4.5	7.6	9.8
IV	0.5	1.1	1.1	1.6
Unknown	0.3	0.6	0.5	0.5

Proportions of patients are given as percentages.

TABLE IV - Determinants of mortality within first year after hospital discharge in 1043 hospital survivors in order of decreasing importance.

Determinant	N=	Mortality within first year (%)	Relative risk	
			Crude	Adjusted (95% CI)
Nr of coronary vessels with ≥50% diameter stenosis				
<2	623	1.6	-	-
≥2	378	5.8	4.55	3.17 (1.49 to 6.75)
missing	42	11.9		
Left ventricular ejection fraction (%)				
≥40	710	1.8	-	-
<40	158	8.2	4.14	3.13 (1.49 to 6.57)
missing	175	5.7		
Residual diameter stenosis in infarct related vessel (%)				
<90	635	2.2	-	-
≥90	331	5.2	2.31	1.94 (0.99 to 3.79)
missing	77	6.5		
Age (y)				
<60	652	2.3	-	-
≥60	391	5.4	2.23	1.78 (0.95 to 3.33)
Previous infarction				
no	972	2.9	-	-
yes	71	11.3	3.92	2.03 (0.94 to 4.40)
Treatment allocation				
no	345	3.8	-	-
rt-PA	346	3.2	0.92	0.97 (0.47 to 2.02)
rt-PA	180	3.4	0.88	1.13 (0.45 to 2.85)
invasive	172	3.5	0.80	0.98 (0.36 to 2.69)

Proportions of patients are given as percentages and were obtained by Kaplan Meier survival analysis. The crude relative risk is determined by univariate Cox regression analysis; adjusted relative risk by multivariate Cox regression analysis. CI: confidence interval. Indicator variables for treatment allocation were forced into the model.

TABLE V - Reinfarction within the first year after hospital discharge in various categories of residual stenosis in the infarct related coronary artery in 1043 hospital survivors.

Determinant	N=	Reinfarction within first year (%)	Relative risk	
			Crude	Adjusted (95% CI)
Diameter stenosis in infarct related vessel (%)				
≤50	193	2.1	-	-
50 to 99	585	5.0	2.39	2.38 (0.76 to 7.59)
(sub)total	188	2.7	1.28	1.30 (0.39 to 4.32)
missing	77	1.3		
Treatment allocation				
placebo	345	2.6	-	-
rt-PA	346	4.9	1.88	1.95 (0.88 to 4.34)
rt-PA	180	5.0	1.92	2.06 (0.82 to 5.17)
invasive	172	2.3	0.89	1.43 (0.39 to 5.23)

Patients with reinfarction within the first year after hospital discharge divided by total number of patients in that category of residual stenosis at the time of hospital discharge, given as percentage. The crude relative risk in this table is a rate ratio. Adjusted rate ratio is obtained by multivariate logistic regression analysis according to Miettinen (see Appendix). CI: confidence interval.

As in other studies [6,10] revascularization procedures were more common after thrombolytic therapy. This may be explained by a smaller infarct size and thus more myocardium susceptible for ischaemia in the territory of the infarct related vessel.

Patient selection criteria, thrombolytic therapy regimen, therapy with aspirin and heparin and guidelines for further therapy were identical in both trials. Indeed, one year survival was strikingly similar in patients treated with rt-PA but without coronary angioplasty in both trials (94%). Some differences were apparent in patient management between both trials. In the non-invasive group of the rt-PA/PTCA trial PTCA was performed more often than in the corresponding group in the rt-PA/placebo trial. This might be related to an excess of patients with a history of angina before the myocardial infarction in the rt-PA/PTCA trial (70% versus 48% in the rt-PA/placebo trial).

Furthermore the initial hospital stay was longer, coumarins and beta-blockers were prescribed less frequently and calcium antagonists more frequently in the rt-PA/PTCA trial. These differences may reflect differences in medical culture between university hospitals in Germany, France, Belgium, the Netherlands and Spain participating in the rt-PA/PTCA trial on one hand and large district hospitals in Belgium, United Kingdom, the Netherlands, Spain and Switzerland co-operating in the rt-PA/placebo trial [2] on the other hand. However, these differences in medical culture had no major impact on patient outcome at one year, since mortality and functional state at one year were similar in patients treated with rt-PA in the rt-PA/placebo trial and patients in the non-invasive group of the rt-PA/PTCA trial.

Reinfarction

Reinfarction was slightly more common after treatment with rt-PA. Again, a smaller infarct size after thrombolytic therapy and thus more viable myocardium in the territory of the infarct related vessel after thrombolysis is the most likely explanation. In most other trials a higher incidence of reinfarction was reported after thrombolytic therapy than among controls [6,10,13,14], except in one trial [15]. In another trial [16] reinfarction rate after rt-PA was higher than in the present trials. In that trial aspirin was started after 8 to 10 days after myocardial infarction, while reinfarctions tend to occur earlier (figure 2). The low incidence of reinfarction after invasive treatment in the rt-PA/PTCA trial is probably misleading, since recurrent ischaemia during the first 24 hours was much more common in the invasive group [2]. Reinfarctions among patients with early recurrent ischaemia are difficult to diagnose, because the electrocardiographic and enzymatic patterns of the evolving initial myocardial infarction are blurring the diagnosis of reinfarction.

Functional class

Functional class in patients initially treated with rt-PA, heparin and aspirin, was superior to that among patients treated with heparin, aspirin and placebo. Thus, thrombolytic therapy improves survival after myocardial infarction, without negatively influencing quality of life. More than half of the patients treated with rt-PA were asymptomatic at one year follow-up. This is similar to earlier observations after intracoronary streptokinase [13]. Only a few patients were treated for heart failure (vasodilators, digitalis and diuretics), which corresponds with the small number class III and IV patients during follow-up.

Immediate angioplasty

Immediate angioplasty was not beneficial, neither in the early phase, nor in the first year after infarction. Similar conclusions were drawn by other investigators [17,18]. Since routine coronary angioplasty later during hospitalization also proved to be not

beneficial [19], we recommend that coronary angioplasty should be restricted to patients with recurrent ischaemia during follow-up. It has been suggested that the lack of benefit of immediate angioplasty was due to the difference in baseline characteristics since overt heart failure and shock were observed more often in the invasive group (7 patients) than in the non-invasive group (1 patient). However correction for difference in baseline risk did not alter the trial outcome. Mortality was 1.6 times higher after invasive therapy. This increased risk remained 1.46 after adjustment for unequal baseline risk by Cox regression analysis (see Appendix).

Mortality after hospital discharge

Mortality after hospital discharge was mainly determined by left ventricular function and coronary anatomy. Predictors of mortality were identical as reported in an intracoronary streptokinase trial with similar patient selection [10]. Many studies have stressed the predictive value of left ventricular function, determined on admission [20] or before hospital discharge [21-23]. In addition, the importance of coronary patency for mortality have been described [20,23]. Initial treatment, although an important determinant of mortality during hospital stay (table I), did not influence mortality after hospital discharge, independently from coronary anatomy and left ventricular function. Sophisticated analyses in other trials suggested that the same is true for intracoronary streptokinase [10,20]. To evaluate whether the relation between residual stenosis in the infarct related vessel and mortality after discharge was different after angioplasty than after non-invasive treatment, the multivariate analysis was repeated after exclusion of patients in the invasive treatment group. Results were similar to those in the combined group.
The prognostic implication of the extent of coronary artery disease and the degree of residual stenosis of the infarct related vessel after myocardial infarction have received little attention sofar. The rt-PA/PTCA trial was designed because earlier reports suggested that reduction in residual stenosis would be beneficial [24,25]. Therefore, the impact of the degree of residual stenosis in the infarct related vessel was assessed separately in this analysis. Severity of residual stenosis in the infarct related vessel appeared related to mortality and reinfarction. This suggest that routine revascularization may turn out to be beneficial, provided that patients are properly selected and reocclusion and restenosis are sufficiently prevented.

Conclusion

Treatment with rt-PA, heparin and aspirin results in limitation of mortality and better functional class during the first year after myocardial infarction. Reinfarction is not frequent and only slightly more common than after heparin and aspirin without thrombolytic therapy. Immediate coronary angioplasty does not result in a further benefit. Prognosis after hospital discharge is determined by coronary anatomy and left ventricular function but not by the initial treatment.

APPENDIX

Baseline risk was assessed in three steps. First, a Cox multivariate prediction model describing the relation between baseline characteristics and mortality was assessed in the rt-PA/placebo trial. Only baseline characteristics known to be related to mortality after myocardial infarction were considered: (1) age, (2) gender, (3) history of previous infarction, (5) sum of ST-segment elevation (6) infarct localization, (7) haemodynamic status before thrombolytic treatment and (8) delay from symptom onset to start of treatment [26]. In a stepwise manner (BMDP statistical software, program 2L - MPLR), determinants of which the coefficient had a P-value of less than 0.10 for entry in the model were included. Indicator variables for treatment allocation were forced into the model, as was the case with indicator variables for missing values. Determinants included in the final model are listed in table VI. Second, the probability of dying within the first year was calculated from this multivariate model for each individual patient as:

$$1 - 0.979^{\exp(a \times X_1 + b \times X_2 + \ldots)}$$

The number 0.979 is the estimated survival at one year for a patient without any risk factor X_i; a, b, ... represent the Cox regression coefficients of the indicator variables listed in table V and X_1, X_2, ... zero/one depending on absence or presence of each risk factor for each patient. For this calculation, the indicator variable for treatment allocation was set to zero (indicating placebo treatment). Finally, patients were subdivided in a low, medium and high baseline risk group, according to their predicted probability of death within the first year, using arbitrary cutoff values of 0.96 and 0.91 to obtain similarly sized subgroups. In the rt-PA/placebo trial proportions of patients in each baseline risk category were similar in both treatment groups. In the rt-PA/PTCA trial 30.1% of invasively treated patients were in the high risk group, versus 22.3% in the non-invasive group. Mortality (Kaplan-Meier) of high risk patients was 7.4% and 20.0% in the non-invasive and invasive treatment group respectively, and 4.9% and 4.7% in the other categories combined in the non-invasive and invasive treatment group respectively.

Relative risk for mortality in the rt-PA/PTCA trial, adjusted for imbalanced baseline risk in the two treatment groups, was obtained by designing a Cox model in which indicator variables for treatment allocation and high baseline risk were forced.

Similarly as for baseline risk assessment, multivariate Cox models were designed for prediction of mortality and reinfarction after discharge. The Cox assumption of proportionality was checked in the data as described previously [27]. Ninety five percent confidence intervals for the relative risk of an indicator variable X_i was calculated as the natural antilogarithm of the Cox regression coefficient of $X_i \pm 1.96$ x standard error of X_i.

TABLE VI - Determinants of one year mortality in the rt-PA/placebo trial, that were used in the baseline risk assessment of both trials (see methods section and Appendix).

Determinant	N=	Mortality within first year (%)	Relative risk	
			Crude	Adjusted (95% CI)
History of previous myocardial infarction				
no	668	6.3	-	-
yes	53	22.6	3.87	4.03 (2.16 to 7.52)
Age (y)				
<60	412	3.9	-	-
≥60	309	12.3	3.18	3.26 (1.86 to 5.73)
Sum ST				
<2.0 mV	500	5.8	-	-
≥2.0 mV	189	12.2	1.97	2.20 (1.28 to 3.78)
missing	32	6.3		
Anterior infarct localization				
no	446	5.8	-	-
yes	275	10.2	1.73	1.87 (1.11 to 3.15)
Gender				
male	617	6.5	-	-
female	104	13.5	2.10	1.78 (0.98 to 3.23)
Treatment allocation				
placebo	366	9.3	-	-
rt-PA	355	5.6	0.64	0.64 (0.37 to 1.08)

See legend of table IV.

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CHAPTER 7

EXPECTED INFARCT SIZE WITHOUT THROMBOLYSIS A CONCEPT THAT HELPS TO SELECT PATIENTS WITH EVOLVING MYOCARDIAL INFARCTION FOR THROMBOLYTIC THERAPY

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SUMMARY

Benefits and risks of thrombolytic therapy should be carefully considered in each patient. Benefits of thrombolysis differ from patient to patient. Risk factors for intracranial bleeding were recently reported. Benefits of thrombolysis might be best predicted by an estimate of infarct size if no thrombolytic therapy would have been given. This was studied in the present analysis. Enzymatic infarct size was predicted from the clinical state and the admission electrocardiogram in 1088 patients of the European Cooperative Study Group by multivariate regression analysis. This multivariate prediction function was used to predict the "expected infarct size without thrombolytic treatment" in 2274 patients of the ISAM study and the Intracoronary Streptokinase trial of the Interuniversity Cardiology Institute of The Netherlands. This parameter was found to correlate well with the measured infarct size in these trials. Infarct size limitation by thrombolytic therapy was greater in patients with a large "expected infarct size without thrombolysis" and if treated early. Mortality in untreated patients with a small "expected infarct size without thrombolysis" was low (4.0%) at one year. Patients with a small "expected infarct size without thrombolysis" and with increased risk of intracranial bleeding such as patients using coumarins and with low body weight will not benefit of thrombolytic therapy.

INTRODUCTION

Limitation of infarct size, preservation of left ventricular function and reduction of mortality have been demonstrated for all currently available thrombolytic agents [1-6]. Benefits of thrombolytic therapy are greater in patients with extensive ST-segment elevation on admission and in patients with anterior infarction, if treated early after onset of symptoms [1,2,7]. On the other hand, risk of intracranial bleeding was reported to be related to advanced age, use of coumarin, and low body weight [8]. For each individual patient benefits and risks of thrombolytic therapy should be carefully considered. Most patients with evolving myocardial infarction will benefit from thrombolytic therapy, but in some subsets of patients with good infarct related prognosis, an increased risk of intracranial bleeding may exceed the benefits from thrombolytic therapy. It is therefore crucial to identify patient characteristics which determine the infarct related prognosis for an individual patient, the benefit of thrombolytic therapy and the risk of intracranial bleeding.

In this analysis the concept of predicted infarct size in patients not treated with thrombolytic therapy (labelled "expected infarct size without thrombolysis") was used as a determinant of risk. Theoretically, this concept has the advantage to be directly related to the way by which thrombolysis improves clinical outcome, i.e. infarct size limitation.

The following questions were addressed:

1. Is it possible to predict infarct size on hospital admission using simple demographic, historical, hemodynamic and electrocardiographic criteria?
2. Is "expected infarct size without thrombolysis" a useful composite determinant of the risk profile in individual patients with acute myocardial infarction?
3. Does the concept "expected infarct size without thrombolysis" integrates those determinants of prognosis that can be modified by thrombolytic therapy?
4. Does "expected infarct size without thrombolysis" help to identify patients in whom the risk of intracranial bleeding outweigh the benefits of thrombolysis?

DESIGN AND METHODS

Data were analyzed of 3362 patients entered in the four major clinical trials which assessed enzymatic infarct size: the rt-PA/placebo and rt-PA/PTCA trial of the European Cooperative Study Group (ECSG) [6,9], the Intracoronary Streptokinase Trial of the Interuniversity Cardiology Institute of the Netherlands (ICIN) [5,7,10] and the Intravenous Streptokinase in Acute Myocardial Infarction Trial (ISAM) [11,12].

Study design

The essentials of trial design, patient selection, setting and main results are summarized in table I. Patients with chest pain suggesting myocardial ischemia were considered for inclusion when electrocardiographic ST-segment elevation was present on admission. Atrial fibrillation was an exclusion criterium in the ISAM trial, but not in the others. Previous infarction was no reason for exclusion in either trial, although in the trials of the European Cooperative Study Group patients with a previous myocardial infarction at the same site and patients with previous coronary artery bypass surgery were excluded. Patients with heart failure or shock were not excluded. In addition to thrombolytic therapy with streptokinase or rt-PA, patients received aspirin as well as heparin intravenously and/or coumarins until hospital discharge. The controls in the ICIN trial did not receive aspirin. More detailed descriptions of each trial have been published previously [5,6,7,9-12].

Electrocardiographic analysis

Electrocardiograms obtained before start of trial medication were assessed. Infarct location was determined on the basis of the admission ECG by core laboratories for Central ECG reading. ST-segment was measured at J-point. QRS width was measured in all trials except in the ICIN trial. Further details of ECG readings are published elsewhere [7,13].

TABLE I - Study design and main results of the various trials.

	rt-PA/Placebo		rt-PA/PTCA		ICIN		ISAM	
	Plac N=366	rt-PA N=355	rt-PA N=184	PTCA N=183	Control N=264	SK-IC N=269	Plac N=882	SK-IV N=859
Entry criteria:								
age (yrs)	<71		<71		<71		≤75	
ST-segment elevation	60msec after J-point ≥2 x 0.2 mV in limb leads or V5-V6 ≥2 x 0.3 mV in V1-V4		idem idem		at J-point ≥1 x 0.1 mV in limb ≥1 x 0.2 mV in V1-V6		at J-point ≥0.1 mV in limb leads ≥0.2 mV in V1-V6	
depression	≥2 x 0.2 mV in V-V4 + ≥2 x 0.1 mV ST-elevation in II, III, aVF, V5-V6				≥1 x 0.2 mV in V1-V4 compatible with posterior infarction			
treatment delay	start of treatment <5 hrs after onset		start of treatment <5 hrs after onset		admitted to CCU <4 hrs after onset		start of treatment <6 hrs after onset	
Setting:	26 European centers		10 European centers		5 centers in The Netherlands		38 West-German, Swiss, and Canadian centers	
Initial treatment:								
heparin bolus	5000 U	5000 U	5000 U	5000 U	5000 U	5000 U	5000 U	5000 U
infusion	1000 U/hr	1000 U/hr	1000 U/hr	1000 U/hr	aPTT 2x	aPTT 2x	aPTT 2-3x	aPTT 2-3x
aspirin	250 mg	250 mg	250 mg	250 mg	-	250 mg	500 mg	500 mg
thrombolytic agent (dosage)	placebo -	alteplase (100 mg)	alteplase (100 mg)	alteplase (100 mg) + PTCA	-	SK-IV# ($0.5x10^6$IU) + SK-IC ($0.25x10^6$IU)	placebo	SK-IV ($1.5x10^6$ IU)
Late treatment:								
coumarins	until discharge unless indicated		until discharge unless indicated		until discharge unless indicated		until 3 weeks unless indicated	
aspirin	until discharge 75 to 125 mg/2days		until discharge 75 to 125 mg/2days		-		-	
Outcome:								
infarct size	-	-20%	-	0%	-	-30%	-	-9%
LVEF	49%	51%	51%	51%	47%	53%	54%	57%
mortality at 1 year	9.3%	5.6%	5.4%	9.3%	16.3%	9.7%	11.2%	11.1%

#: in the last 117 patients. Plac: placebo. SK-IC: intracoronary streptokinase LVEF: left ventricular ejection fraction. SK-IV:intravenous streptokinase.

Infarct size assessment

Cumulative myocardial enzyme release served as a measure for infarct size. In the European Cooperative trials and the ICIN trial the cumulative release of alpha hydroxy butyric acid (HBDH) was assessed. In the ISAM trial enzymatic infarct size was assessed as cumulative release of creatine kinase (CK-MB fraction). Blood samples, taken at regular intervals (12 hours for HBDH, 4 hours for CK-MB), were sent to the core laboratories. Details of the methodology have been reported previously [5,6,14]. In patients for whom no infarct size determination was available (e.g. due to early death) the enzymatic infarct size was estimated by linear regression analysis as described below. HBDH plasma levels in the ICIN trial were divided by 1.34 in order to compensate for different assay conditions, compared with the European Cooperative trials [14].

DATA ANALYSIS

Prediction of enzymatic infarct size

For each trial separately, enzymatic infarct size was predicted by linear regression analysis using parameters available immediately after onset of symptoms and known to be related to infarct size or limitation of infarct size by thrombolytic therapy. The following parameters were considered: sum of ST-segment elevation and depression on the admission ECG [15], QRS width exceeding 0.12 sec [2], anterior infarct localization [1-4], clinical state before treatment [16,17], history of previous infarction [1-4], age [1-4], female gender [2] and delay from onset symptoms to treatment allocation [1-4]. Medians and 50% ranges of enzymatic infarct size were determined in various categories of above variables. Continuous variables were subdivided into three or four subgroups of approximately equal size. Subsequently, variables associated with enzymatic infarct size were entered in a multivariate linear regression model. For each category, except for the reference category, an indicator variable was used with value one in case the patient belonged to that category and zero if not. To assess the treatment effect in certain subsets of patients, interaction terms were constructed of the indicator variable for a certain characteristic and treatment strategy. Variables were entered in a stepwise regression model if the F statistic to enter was more than 4 and removed if the F to remove was less than 4. In the final model, optimized on the basis of medical plausibility, indicator variables for treatment strategy and missing data were forced to enter the model. Also, indicator variables for characteristics were forced into the model in case their interaction terms with treatment strategy was entered.

Calculation of "expected infarct size without thrombolysis" in individual patients

The multivariate linear regression model for enzymatic infarct size developed in the trials of the European Cooperative Study Group (table II) was used to calculate "expected infarct size without thrombolysis" for every individual patient in all trials, by setting the indicator variables for treatment to values indicative for placebo infusion. For example the expected infarct size without thrombolysis for a patient with anterior infarct location, 12 mm ST-segment elevation (1.2 mV), narrow QRS complex, no signs of heart failure and 1 hour treatment delay is: 495 + 233 + 308 = 1036 U/l (table II). Because QRS-complex width measurement was not available in the ICIN trial, the calculation of the "expected infarct size without thrombolysis" was performed using a slightly different model derived from the European Cooperative Studies, in which that measurement was omitted.

Prognostic implications of "expected infarct size without thrombolysis"

The value of this risk estimate to separate patients with small and large infarctions was assessed in the patient populations of the ICIN and ISAM trial by plotting the median and 50% range of measured enzymatic infarct size for various categories of "expected infarct size without thrombolysis" (figure 1). In addition, the prognostic implications of "expected infarct size without thrombolysis" for one year mortality were evaluated. Cumulative one year mortality is reported for patients with small and extensive "expected infarct size without thrombolysis". To exclude confounding by treatment delay, patient subsets with early and late treatment are reported separately. Subsequently, a multivariate logistic regression model for the prediction of one year mortality was developed using similar methods as described for the prediction of enzymatic infarct size. Determinants of mortality were identified univariately by assessing one year mortality in subgroups of patients and subsequently by multivariate logistic regression analysis. In the stepwise regression analysis variables were entered when the p-value associated with entry of that variable was less than 0.10 and removed if the p-value associated with removal was greater than 0.15. Adjusted rate ratios and 95% confidence intervals in table VI were obtained from the logistic regression equation according to Miettinen [18].
Probabilities of death during the first year for a range of values of "expected infarct size without thrombolysis" for a patient given a certain combination of other risk factors (X_i) were calculated from a logistic regression function, in which "expected infarct size without thrombolysis" was entered as continuous variable (figure 4):

$$P=1/[1+\exp-(a+b_1 \times X_1 + b_2 \times X_2 .....)].$$

The characters b_i represent the logistic regression coefficients. In addition, 95% confidence intervals were calculated [19].

TABLE II - Determinants of enzymatic infarct size in 1088 patients of the rt-PA/placebo and rt-PA/PTCA trial.

	Number of pts				Enzymatic infarct size (median, 50% range HBDH U/l)&				Linear regression analysis@		
	Plac N=	rt-PA N=	rt-PA N=	PTCA N=	rt-PA/Placebo trial		rt-PA/PTCA trial			All pts N=1061	Additional for: rt-PA	PTCA
	366	355	184	183	Plac	rt-PA	rt-PA	PTCA				
									Intercept	495	-207 (84)	1 (50)
Sum ST (mV)												
<0.6	32	31	19	21	569(244,1031)	527(272,801)	370(105,565)	413(305,654)		-		
0.6-1.2	110	105	62	56	727(458,968)	581(406,859)	451(205,784)	537(256,777)		140 (63)		
1.2-2.0	104	118	58	57	913(563,1229)	800(514,1164)	697(389,1005)	867(474,1256)		308 (63)		
≥2.0	107	82	45	48	1215(845,1502)	940(685,1328)	1113(716,1690)	1132(753,1651)		618 (68)	-126 (78)*	
missing	13	19	-	1								
QRS exceeding 0.12 sec												
no	334	329	183	176	894(521,1243)	694(455,1077)	670(355,1062)	721(384,1145)		-		
yes	19	9	1	7	1312(627,2084)	1546(653,1849)	482	1126(620,2101)		273 (97)		
missing	13	17	-	-								
Anterior infarct localization												
no	236	210	101	98	841(503,1195)	664(439,948)	572(304,899)	591(364,888)		-		
yes	130	145	83	85	946(627,1395)	839(491,1343)	818(373,1393)	1007(503,1450)		233 (35)		
Killip 3 or 4												
no	349	344	183	176	867(531,1262)	687(447,1074)	670(358,1062)	697(384,1134)		-		
yes	17	11	1	7	1262(765,1632)	1287(989,1598)	304	1374(1137,1891)		334 (103)		
Treatment delay (hrs)#												
<2	69	61	51	43	966(511,1318)	661(367,1019)	451(161,677)	692(377,1137)		-		
2-3	139	121	68	56	790(499,1294)	751(468,1196)	801(381,1206)	621(444,1057)		47 (76)	115 (91)*	
≥3	158	173	65	84	900(583,1242)	705(512,1017)	716(475,1149)	842(372,1333)				

#: for 8 patients in the rt-PA/Placebo trial, who received no treatment, time of treatment was substituted by time to allocation. &: missing values were imputed by estimates obtained by linear regression analysis without product terms for treatment to avoid induction of differences in treatment effect in various strata; @: coefficients (standard error in parentheses) represent difference in enzymatic infarct size between patients with the characteristic and patients without, conditional on the other vriables in the model. Enzymatic infarct size for each patient is determined by adding up intercept and coefficients of all relevant indicator variables. *: additional treatment effect for patients with ≥2.0 mV ST-elevation and/or 2 hrs treatment delay

TABLE III - Determinants of enzymatic infarct size in 533 patients of the ICIN trial.

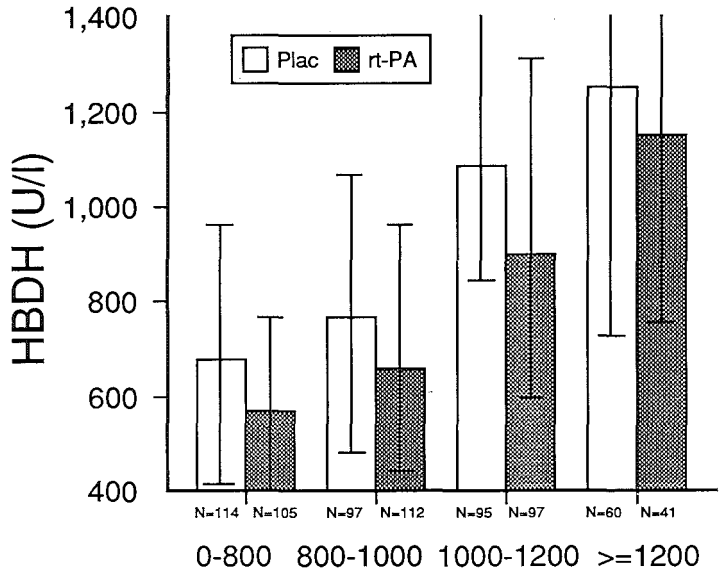
	Number of pts		Enzymatic infarct size (median, 50% range HBDH U/l)		Linear regression analysis		
	Control N=264	SK-IC N=269	Control	SK-IC		All pts N=448	Additonal for SK-IC
					Intercept	552	-348 (102)
Sum ST (mV)							
<0.6	28	23	567 (413, 831)	380 (187, 512)		-	
0.6-1.2	68	93	647 (378, 959)	455 (290, 724)		91 (85)	
1.2-2.0	84	79	891 (643,1237)	654 (390, 813)		300 (85)	
≥2.0	63	50	1264 (870,1501)	910 (540,1271)		627 (105)	-190 (116)
missing	21	24					
Anterior infarct localization							
no	148	139	724 (432,1170)	497 (334,791)		-	
yes	116	130	954 (641,1271)	617 (466,993)		158 (49)	
Killip 3 or 4							
no	253	257	806 (497,1202)	590 (372, 861)		-	
yes	11	12	1287 (1129,1745)	1075 (577,1318)		511 (142)	
Treatment delay (hrs)&							
<2	73	64	853 (584,1199)	445 (207,660)		-	
2-3	110	99	804 (476,1202)	599 (369,907)		-24 (77)	240 (113)
≥3	81	106	815 (522,1279)	690 (456,962)			

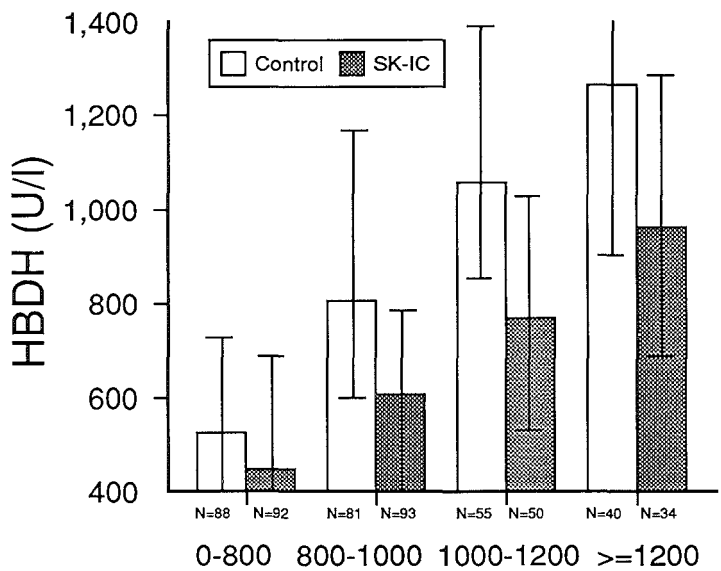
See legend of table II. &: Treatment delay is time to admission on the coronary care unit (zero for in-hospital patients) plus 1 hour, since intracoronary streptokinase started 60 minutes later.

TABLE IV - Determinants of enzymatic infarct size in 1741 patients of the ISAM trial.

	Number of patients		Enzymatic infarct size (median, 50% range CK-MB U/l)		Linear regression analysis		
	Placebo N=882	SK-IV N=859	Placebo	SK-IV		All pts N=1434	Additonal for SK-IV
					Intercept	1222	-484 (150)
Sum ST (mV)							
<0.6	222	194	990 (452,1416)	1033 (492,1343)		-	
0.6-1.2	277	285	1543 (996,2104)	1394 (700,1948)		505 (83)	-
1.2-2.0	179	190	2014 (1238,2749)	1842 (1213,2481)		1045 (116)	-118 (135)
≥2.0	119	117	2199 (1612,2732)	2062 (1242,2793)		1230 (126)	
BBB	47	42	2920 (1859,3230)	2701 (1330,4334)		1673 (159)	
missing	38	31					
Anterior infarct localization							
no	448	465	1337 (785,2052)	1316 (715,2018)			
yes	434	394	1917 (1029,2560)	1664 (855,2370)			
Heart failure							
no	692	676	1495 (843,2204)	1390 (745,2117)		-	
yes	190	183	2023 (1300,2972)	1673 (840,2514)		307 (79)	
Treatment delay (hrs)							
<2	166	163	1967 (831,2714)	1242 (434,1957)		-	
2-3	245	260	1619 (891,2402)	1400 (770,2297)		-214 (131)	357 (182)
≥3	458	419	1495 (870,2145)	1538 (897,2238)		-249 (120)	563 (168)
missing	13	17					

See legend of table II. BBB: Bundle branch block.


1,400
1,200
1,000
800
600
400
HBDH (U/l)
Plac
rt-PA
N=114 N=105 N=97 N=112 N=95 N=97 N=60 N=41
0-800 800-1000 1000-1200 >=1200
Expected infarct size without thrombolysis (U/l)


1,400
1,200
1,000
800
600
400
HBDH (U/l)
Control
SK-IC
N=88 N=92 N=81 N=93 N=55 N=50 N=40 N=34
0-800 800-1000 1000-1200 >=1200
Expected infarct size without thrombolysis (U/l)

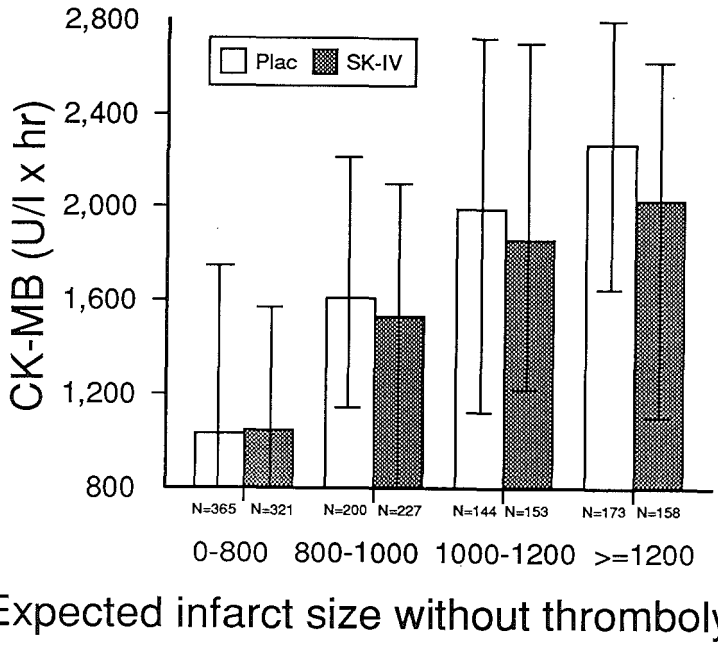


Figure 1. Median and 50% range of enzymatic infarct size in various categories of "expected infarct size without thrombolysis" in the rt-PA/placebo trial of the European Cooperative Study Group, in the ICIN and in the ISAM trial, for the thrombolysis and control groups separately.

"Expected infarct size without thrombolysis" and limitation of infarct size by thrombolytic therapy

Benefit of thrombolytic therapy was assessed in terms of enzymatic infarct size in various categories of "expected infarct size without thrombolysis". Median and 50% range of actually measured enzymatic enzyme release were compared in patients treated with thrombolysis and controls in various categories of "expected infarct size without thrombolysis" (figure 1).

"Expected infarct size without thrombolysis" and limitation of mortality by thrombolytic therapy

One year mortality in patient subsets in the control groups was plotted in a scattergram against one year mortality of patients treated with thrombolytic therapy, stratified for the "expected infarct size without thrombolysis" and treatment delay (figure

2). A linear regression line, weighed for subgroup size [20], was drawn to relate "expected infarct size without thrombolysis" to the limitation of mortality with thrombolytic therapy within 3 hours and after 3 hours after onset of symptoms. Kaplan Meier survival plots were used to study survival of patients in different categories of "expected infarct size without thrombolysis" in time [21] (figure 3).

RESULTS

Prediction of enzymatic infarct size in each trial

The sum of ST-segment elevation, Killip class and QRS width were strongly related to enzymatic infarct size in all trials (tables II to IV). In the European Cooperative trials and the ICIN study anterior infarct location was associated with larger enzymatic infarct size than inferior infarct location, irrespective of the amount of ST-segment elevation. The contributions of each determinant of enzymatic infarct size were very similar in the trials assessing enzymatic infarct size with HBDH (table II and III). In the ISAM trial the contributions of the predictors of enzymatic infarct size cannot be compared directly to those in the other trials since enzymatic infarct size was assessed with cumulative CK-MB release. Nevertheless, the relative contribution of each determinant of infarct size was similar to those in the other trials.

Calculation of "expected infarct size without thrombolysis" in individual patients

In figure 1 the medians and 50% ranges of the actually measured enzymatic infarct size are depicted for various categories of "expected infarct size without thrombolysis". The enzymatic infarct size prediction model developed in the trials of the European Cooperative Study Group was successful in separating patients with small infarctions from those with large infarctions in the ICIN and ISAM trials.

Prognostic value of "expected infarct size without thrombolysis"

"Expected infarct size without thrombolysis" as predicted with the linear regression model obtained in the European Cooperative trials from the admission electrocardiogram and clinical status was highly predictive for mortality (table V). As is apparent from figure 2, patients with a small "expected infarct size without thrombolysis" (open symbols) are in the low mortality range and had about 5% one year mortality without thrombolytic therapy in the rt-PA/placebo trial and ISAM trial and approximately 10% in the ICIN trial. Patients with a large "expected infarct without thrombolysis" (closed symbols) had high mortality without thrombolytic therapy. In figure 3 survival during the first 2 years of follow up is depicted for patients below 60

years and 60 years and older, stratified for "expected infarct size without thrombolysis". In the elderly group overall mortality was higher than in among young patients. Thrombolytic therapy yielded little benefit, if any, in patients with small "expected infarct size without thrombolysis".
The results of the multivariate analysis are presented in table VI. As expected, age and previous infarction were important other determinants of mortality. Female gender was also associated with higher risk. Infarct localization was not predictive for one year mortality, when "expected infarct size without thrombolysis" was included in the model. In figure 4 the probabilities of one year mortality are given for a range of values of "expected infarct size without thrombolysis" for a young male patient without risk any other risk factor, for an similar elderly male and for an elderly male patient with all risk factors.
The observed mortality among patients with a "expected infarct size without thrombolytic therapy" below 800 U/l and without any risk factor (table VI) and not treated with thrombolytic therapy was 6 out 247 at 5 weeks (2.4%, 95% confidence interval 0.5 to 4.3) and 4.0% (95% confidence interval 1.6 to 6.5) at one year.

"Expected infarct size without thrombolysis" and limitation of infarct size by thrombolytic therapy

Limitation of infarct size was greatest in patients with extensive ST-segment elevation in all trials (table II to IV). Limitation of infarct size by thrombolytic therapy was clearly related to treatment delay in the ISAM study (table IV), but was only marginally related to treatment delay in the European Cooperative study and the ICIN study (table II and III). Limitation of infarct size was proportional to the expected infarct size without thrombolysis (figure 1).

"Expected infarct size without thrombolysis" and limitation of mortality by thrombolytic therapy

Limitation of mortality by thrombolytic therapy is depicted in figure 2. The thick dashed line represents the line of identity or "no treatment effect". Patient subsets below the line of "no treatment effect" benefited from the treatment. Patient subsets with a small "expected infarct size without thrombolysis" were scattered around the line of "no treatment effect" and thus had little or no benefit of thrombolytic effect. Patient subsets with large "expected infarct size without thrombolysis" benefitted clearly from thrombolysis in the European Cooperative and the ICIN studies. The thin dotted lines in figure 2 represent linear regression lines, weighed for subgroup size, for early (within hours) or late (3 hours or later) treatment. Treatment effect is greatest if thrombolysis is started early and gain is largest in high risk patients. Since the regression lines cross the line of "no treatment effect", it is suggested by the model that patients at very low risk may be harmed by thrombolysis.
According to figure 3, in both age categories, patients with a small "expected infarct size without thrombolysis" had little or no benefit of thrombolytic therapy, although in the

TABLE V - One year mortality (%) in various categories of "expected infarct size without thrombolysis" stratified for treatment delay.

		rt-PA/Placebo		rt-PA/PTCA		ICIN		ISAM	
		Plac N=366	rt-PA N=355	rt-PA N=184	PTCA N=183	Control N=264	SK-IC N=269	Plac N=882	SK-IV N=859
Expected infarct size (U/l)	**Treatment delay**								
<1000	**<3 hrs**	5 (6/111)	3 (3/ 97)	4 (3/81)	7 (4/57)	10 (11/114)	6 (7/111)	6 (15/246)	6 (16/259)
	≥3 hrs	4 (4/100)	6 (7/120)	5 (2/37)	6 (3/50)	13 (7/ 55)	10 (7/ 74)	8 (25/311)	7 (20/279)
	missing							(1/ 8)	(2/ 10)
	all	5 (10/211)	5 (10/217)	4 (5/118)	7 (7/107)	11 (18/169)	8 (14/185)	7 (41/565)	7 (38/548)
≥1000	**<3 hrs**	14 (14/ 97)	5 (4/ 85)	5 (2/38)	17 (7/42)	26 (18/ 69)	12 (6/ 52)	18 (30/165)	17 (28/164)
	≥3 hrs	17 (10/ 58)	11 (6/ 53)	11 (3/28)	9 (3/34)	27 (7/ 26)	19 (6/ 32)	18 (26/147)	19 (26/140)
	missing							(2/ 5)	(3/ 7)
	all	16 (24/155)	7 (10/138)	8 (5/66)	13 (10/76)	26 (25/95)	14 (12/84)	18 (58/317)	18 (57/311)

elderly group, mortality in the second year tended to be lower in patients treated with thrombolysis. In patients with extensive "expected infarct size without thrombolysis" the benefit of thrombolytic therapy was evident in both age groups, but more pronounced in the elderly. The same results were obtained when the analysis was repeated in each trial separately. Even in the ISAM trial, without overall mortality reduction, the subset of elderly patients with large "expected infarction without thrombolysis" benefited from thrombolytic therapy.

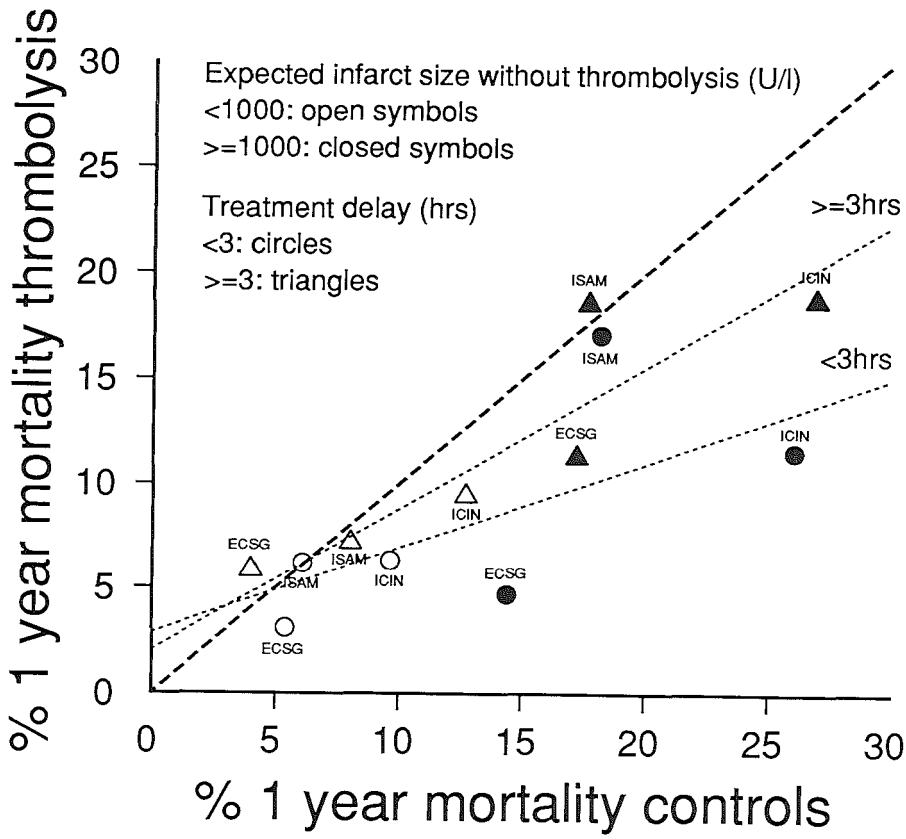


Figure 2. One year mortality for two categories of "expected infarct size without thrombolysis" stratified for treatment delay for the trial of the European Cooperative Study Group, ICIN and ISAM trials. The thick dashed line represent the line of "no treatment effect"; the thin lines are the weighed regression lines for early and late treatment.

TABLE VI - Determinants of one year mortality in all trials combined#.

	% One year mortality		Logistic regression analysis	
	N=3179	Risk ratio	Adjusted risk ratio# (95% CI)	Coefficient (SE)
Expected infarct size without thrombolysis (U/l)				
<800	6 (63/1131)	-	-	-
800-1000	8 (73/ 882)	1.49 (1.08,2.05)	1.33 (0.93,1.89)	0.30 (0.19)
1000-1200	14 (90/ 641)	2.52 (1.87,3.39)	2.30 (1.64,3.21)	0.90 (0.19)
≥1200	19 (101/ 525)	3.45 (2.61,4.57)	2.45 (1.71,3.51)	0.98 (0.20)
Killip 3 or 4				
no	8 (224/2754)	-	-	-
yes	24 (103/ 425)	2.98 (2.41,3.68)	2.02 (1.50,2.72)	0.78 (0.17)
Age (yrs)				
<60	7 (117/1795)	-	-	-
≥60	15 (210/1384)	2.33 (1.89,2.87)	2.10 (1.65,2.65)	0.80 (0.13)
Previous infarction				
no	9 (237/2790)	-	-	-
yes	23 (90/ 389)	2.72 (2.19,3.40)	2.68 (2.06,3.49)	1.11 (0.15)
QRS >0.12 sec				
no	9 (217/2498)	-	-	-
yes	33 (39/ 118)	3.81 (2.82,5.14)	2.83 (1.92,4.17)	1.19 (0.23)
missing	13 (71(563)			
Female				
no	10 (252/2640)	-	-	-
yes	14 (75/ 539)	1.46 (1.14,1.86)	1.33 (1.01,1.76)	0.31 (0.15)
Constant				-3.58 (0.29)

#: Patients allocated to immediate PTCA were excluded because of an excess of, PTCA related, mortality). Indicator variables for treatment delay and their interaction terms with treatment delay are ommitted from the table. The reference categories refer to a patient treated with aspirin and heparin, but without thrombolytic therapy in the rt-PA/placebo trial. CI: confidence interval; #: adjusted risk ratio calculated according to Miettinen [18].

DISCUSSION

Subgroup analyses have been reported for nearly all major thrombolysis trials. This illustrates the interest of investigators to identify subsets of patients who benefit most of thrombolytic therapy. Nevertheless, precise indications of thrombolytic therapy, especially regarding the required ST-segment elevation on admission, infarct location, advanced age and maximal treatment delay and indicators of increased risk of thrombolytic therapy remain uncertain [22]. "Expected infarct size without thrombolysis", which may seem a complicated parameter on first sight, provides an estimate of infarct size for a patient who is treated with aspirin and heparin but without thrombolytic therapy (assessment of "expected infarct size without thrombolysis" is based on the trials of the European Cooperative Study Group in which all patients were treated with aspirin and heparin). It was found to be an important determinant of prognosis and it predicts the benefit of thrombolysis in terms of infarct size limitation and mortality reduction.

Prediction of enzymatic infarct size in each trial

The sum of ST-segment elevation contributed most to the prediction of enzymatic infarct size (table II to IV). Furthermore, QRS widening was an important determinant of infarct size, independent of ST-segment elevation. This was mainly due to right bundle branch block since patients with complete left bundle branch block were excluded. The contribution of QRS widening to enzymatic infarct size in the ISAM trial was larger than in the trials of the European Cooperative Study Group, mainly because ST-segment elevation was not assessed in ISAM, when QRS-widening was present.

Prognostic value of "expected infarct size without thrombolysis"

In the present analysis survival after myocardial infarction was found to be the resultant of patients' pre-existent condition (determined by age, gender and history of previous infarction), "expected infarct size without thrombolysis" and treatment effect of thrombolytic therapy.
In a recent article the GISSI investigators related the low mortality and the lack of benefit from thrombolytic therapy among patients with inferior infarction to the infarct size in terms of the number of electrocardiographic leads with ST-segment elevation. Patients with anterior infarction and small area at risk had a similar low mortality [23]. This is in agreement with earlier reports [13,24] and with the present study in which infarct site did not contribute to the prediction of mortality when the "expected infarct size without thrombolysis" was entered in the model. Heart failure was predictive for

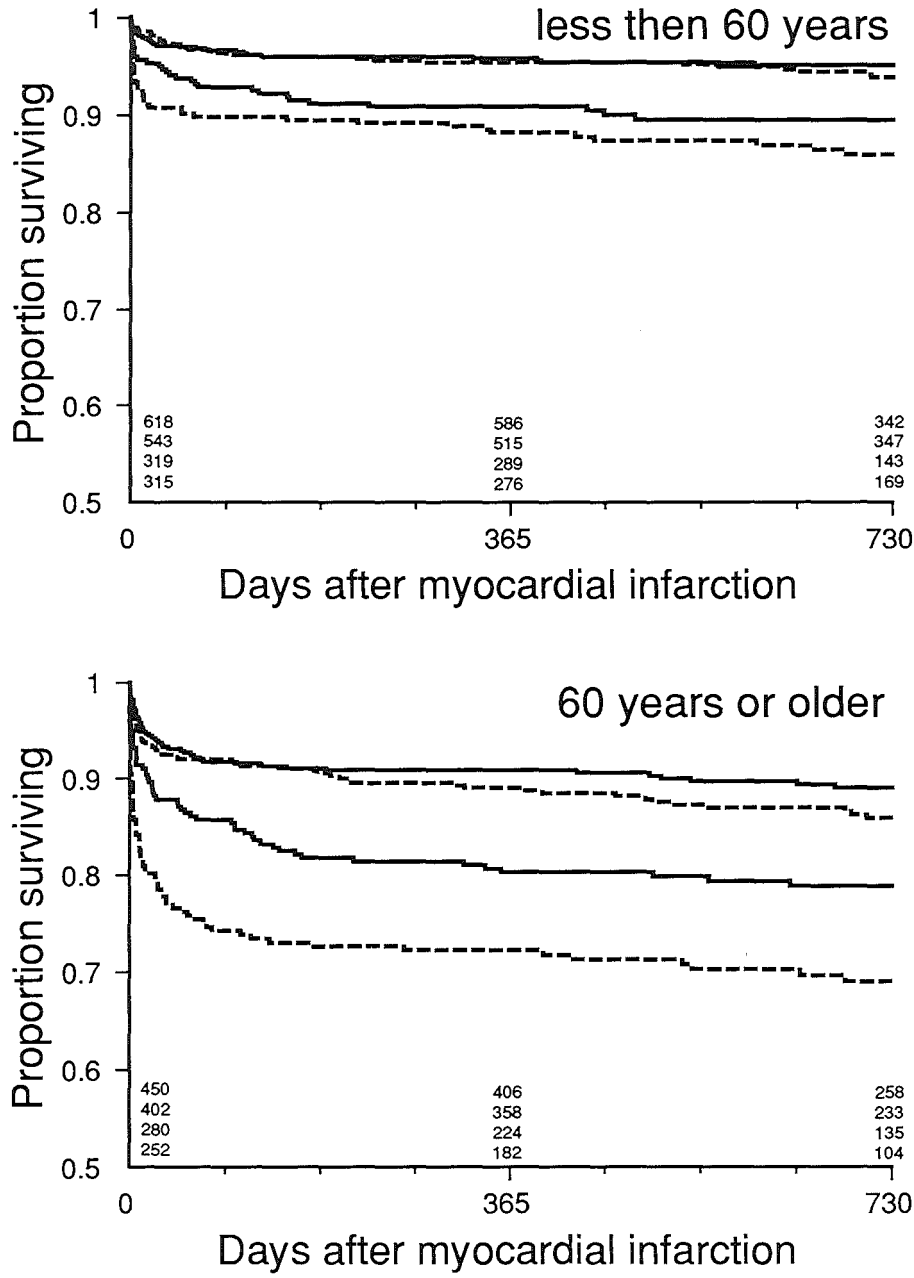


Figure 3. Survival up to 2 years after myocardial infarction for two age categories, stratified for "expected infarct size without thrombolysis". The upper two curves in each plot represent patients with "expected infarct size of less than 1000 U/l; solid lines represent patients who received thrombolytic therapy, the dashed lines the controls.

one year mortality, apart from its effect on "expected infarct size without thrombolysis". QRS-complex widening appeared related to mortality after myocardial infarction in addition to its contribution to infarct size (table VI). This might be related to life threatening arrhythmias, which may occur in patients with acute myocardial infarction and bifascicular block [25]. Mortality at 5 weeks among low risk patients in the present trial was identical to mortality in control patients with a normal ECG in ISIS-2 [2], similar to the 3.0% mortality at 4 weeks among control patients with normal admission ECG in the ASSET trial [3] and corresponded well with the 1.5% mortality in a low risk group treated with plasminogen activator in TIMI-II [26].

"Expected infarct size without thrombolysis" and limitation of infarct size by thrombolysis

Limitation of infarct size tended to be greater in patients with a large "expected infarct size without thrombolysis", especially in the ICIN and ISAM trial (figure 1). Differences in infarct size between the two treatment groups of the European Cooperative study Group in the various categories of "expected infarct size without thrombolysis" must be interpreted with caution, since they are imposed by the linear regression model for calculation of "expected infarct size without thrombolysis" developed in the same patient population.

"Expected infarct size without thrombolysis" and limitation of mortality by thrombolytic therapy

In figure 2, the regression lines crossed the line of "no treatment effect", suggesting the possibility that thrombolysis might harm patients in the low risk region. Myocardial infarction extension [27], especially in patients treated later than 3 hours after symptoms onset [28], lethal bleeding and complications related to acute catheterization in case of intracoronary streptokinase, may contribute.
No improvement of survival by thrombolytic therapy was observed in patients with a small "expected infarct size without thrombolysis" (figure 3). This supports the hypothesis that thrombolysis improves outcome by preserving myocardium. This implies that strategies which will assist in myocardial salvage, for example by reducing reperfusion injury, are likely to confer additional benefits. In elderly patients, there was a tendency for better survival in treated patients in the second year of follow up. This may be related to better late patency of the infarct related vessel, which was shown to result in better survival [10,29,30].

Clinical implications of this analysis

Thrombolytic therapy improves survival in most patients with evolving myocardial infarction. However, it is not rational to give thrombolytic therapy to patients with suspected acute myocardial infarction in whom mortality reduction by thrombolytic

therapy is expected to be less than the excess mortality associated to intracranial bleeding. This is likely to be the case in patients with good prognosis without thrombolytic therapy and with increased risk of intracranial bleeding. Patients with good infarct related prognosis have been identified earlier. In the next paragraph, the identification of patients with increased risk for intracranial bleeding is described.

Estimation of risk of intracranial bleeding in individual patients

The cumulative incidence of intracranial bleeding after thrombolytic therapy was derived from the literature [31] and from a recent registry in The Netherlands [8]. Determinants of intracranial bleeding were assessed in a case-referent analysis with 29 patients with intracranial bleeding in the registry (predominantly intravenous streptokinase) and in the trials of the European Cooperative Study Group compared with 58 controls (table VII). The following patient characteristics were found to be related to the occurrence of intracranial bleeding after thrombolytic therapy: body weight under 70 kg, use of coumarins and age of 65 years or more. The first risk factor may imply that the occurrence of intracranial bleeding is dose-related. A relation between dose per kg body weight and bleeding was reported for rt-PA and resulted in the recommendation of a body weight adjusted rt-PA dose [32]. Similarly a reduced dose of streptokinase migh be recommended in patients with a ow body weight, if these observations are confirmed by careful analysis of other data bases, e.g. ISIS-2. As long as we stick to a fixed streptokinase dose and as long as we don't know whether decreasing the dose will prevent intracranial bleeding in these patients, we have to consider body weight as a risk factor in the selection of patients for thrombolytic therapy.

The risk of intracranial bleeding for each combination of risk factors was calculated from the overall bleeding incidence and likelihood ratio according to Bayes rule [31]. The likelihood ratio (probability of a certain risk profile among patients with intracranial bleeding divided by the probability of that risk profile in patients without intracranial bleeding) for each combination of risk factors was calculated from the logistic regression function [31].

The trade-off between death due to infarction and due to intracranial bleeding

Intracranial bleeding after thrombolytic therapy is fatal in about 50% of cases [2,3,8]. Most deaths occur in the first weeks after thrombolytic therapy. Although part of the surviving patients continue to have neurologic deficits, complete recovery after intracranial bleeding due to thrombolytic therapy is possible [6]. For reasons of simplicity, we will assume that patients surviving the intracranial bleeding recover completely and that, on the other hand, there is no benefit of thrombolytic therapy apart from mortality reduction. Thus, both the reduced quality of life after intracranial bleeding and the improvement of quality of life in most patients after thrombolytic therapy [29,33] are disregarded.

TABLE VII - Determinants of intracerebral bleeding after thrombolytic therapy for acute myocardial infarction. Main results of a case-referent analysis of patients with intracerebral bleeding in the trials of the European Co-operative Study Group and a registry The Netherlands in 1988-1990 [8].

	% of pts with characteristic			Logistic regression analysis	
	Bleeders N=29	**Non-bleeders N=58**	**Odds ratio# (95% CI)**	**Adjusted odds ratio# (95% CI)**	**Coefficient (SE)**
Body weight (kg)					
<70	55 (16/29)	78 (13/58)	4.26 (1.67,10.85)	4.69 (1.68,13.13)	1.55 (0.53)
≥70	45 (13/29)	22 (45/58)	-	-	-
Use of coumarins					
no	83 (24/29)	95 (55/58)	-	-	-
yes	17 (5/29)	5 (3/58)	3.82 (0.91,16.10)	5.93 (1.12,31.29)	1.78 (0.85)
Age (yrs)					
<65	59 (17/29)	81 (47/58)	-	-	-
≥65	41 (12/29)	19 (11/58)	3.03 (1.14,7.99)	2.98 (1.01,8.82)	1.09 (0.55)
Constant					-1.78 (0.41)

CI: confidence interval. #: odds ratio can be interpreted as risk ratio due to the low incidence of intracerebral bleeding.

For a 50% mortality reduction by thrombolytic therapy, the net result of thrombolytic therapy for a patient is zero if the probability of dying in the first year due the myocardial infarction therapy without thrombolytic therapy equals the risk of intracranial bleeding (table VIII). For a 25% mortality reduction the net effect of thrombolytic therapy is zero if the probability of infarct related dying in the first year equals twice the probability ofintracranial bleeding in table VIII. With this simplified trade-off it is possible to determine whether a given patient should receive thrombolytic therapy, or whether he should not receive thrombolysis and for which patients the decision is not clear.

For example, let us consider a male, less than 60 years old, without previous ainfarction, in good clinical condition, with a narrow QRS complex and with 3 mm ST-segment elevation in leads III and aVF. According to table II the "expected infarct size without thrombolysis" is 595 U/l. In figure 4, the probability of death in the first year without thrombolytic therapy, but with aspirin and heparin, is 2.5% for a patient with an "expected infarct size without thrombolytic therapy" of 600 U/l. If the risk of intracranial bleeding would be also 2.5%, e.g. because he uses coumarins and his body weight is less than 70 kg (table VIII), this patient would not benefit from thrombolytic therapy, if the mortality reduction is expected to be 50%.

TABLE VIII - Probablity of intracranial bleeding for various combinations of risk factors for an overall cumulative incidence of intracranial bleeding of 0.5% and 0.9%.

Risk profile			**Likeli-hood ratio#**	**Probability@ of intracranial bleeding**	
age ≥65 yrs	**weight <70 kg**	**cou-marin**		**for an overall incidence of: 0.5%**	**0.9%**
-	-	-	0.17	0.1%	0.2%
+	-	-	0.50	0.3%	0.5%
-	+	-	0.79	0.4%	0.7%
-	-	+	1.00	0.5%	0.9%
+	+	-	2.35	1.2%	2.1%
+	-	+	2.97	1.5%	2.6%
-	+	+	4.67	2.3%	4.1%
+	+	+	13.94	6.5%	11.2%

#: likelihood ratio is the probability of finding the risk profile among patients with intracebral bleeding divided by the probability to find the same risk profile among patients without intracerebral bleeding. @: calculated from the overall incidence and likelihood ratio with Bayes rule [22].

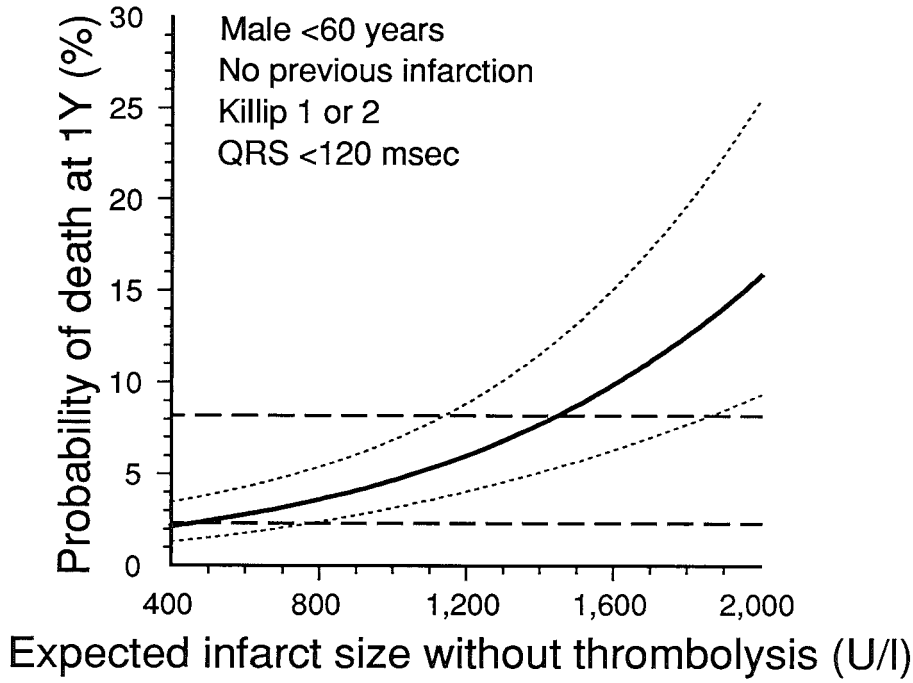


Figure 4a. Probability of death within the first year as a function of "expected infarct size without thrombolysis" according to logistic regression analysis for a patient without risk factors for infaract related death and below 60 years old. The dotted lines represent the 95% confidence limits. The dashed horizontal lines mark the probability of death within the first year without thrombolytic therapy for which the net benefit of thrombolytic therapy is zero in patients using coumarins and with low body weight. For the lower dashed line, 0.5% incidence of intracranial bleeding and 50% mortality reduction by thrombolytic therapy is assumed; for the upper dashed line 0.9% incidence of intracranial bleeding and 25% mortality reduction. Patients without or with one risk factor for bleeding benefited from thrombolysis.

The dashed horizontal lines in figure 4 represent the infarct related probability of death in the first year for which the net result of thrombolytic therapy is zero in a patient using coumarins and with low body weight. The upper dashed line represents the threshold probability for the assumption that the overall incidence of intracranial

bleeding is 0.9% and that the mortality reduction by thrombolytic therapy is 25%, the lower dashed line for a intracranial bleeding rate of 0.5 and a mortality reduction by thrombolytic therapy of 50%. This patient will not benefit from thrombolytic therapy if his "expected infarct size without thrombolytic therapy is smaller than the value corresponding to the crossing of the lower dashed and the solid line (450 U/l). For patients with an "expected infarct size without thrombolytic therapy" corresponding to values between the lower and the upper dashed line benefits are questionable. Patients with large "expected infarct size without thrombolysis" (>1400 U/l, fgure 4a) should be treated .

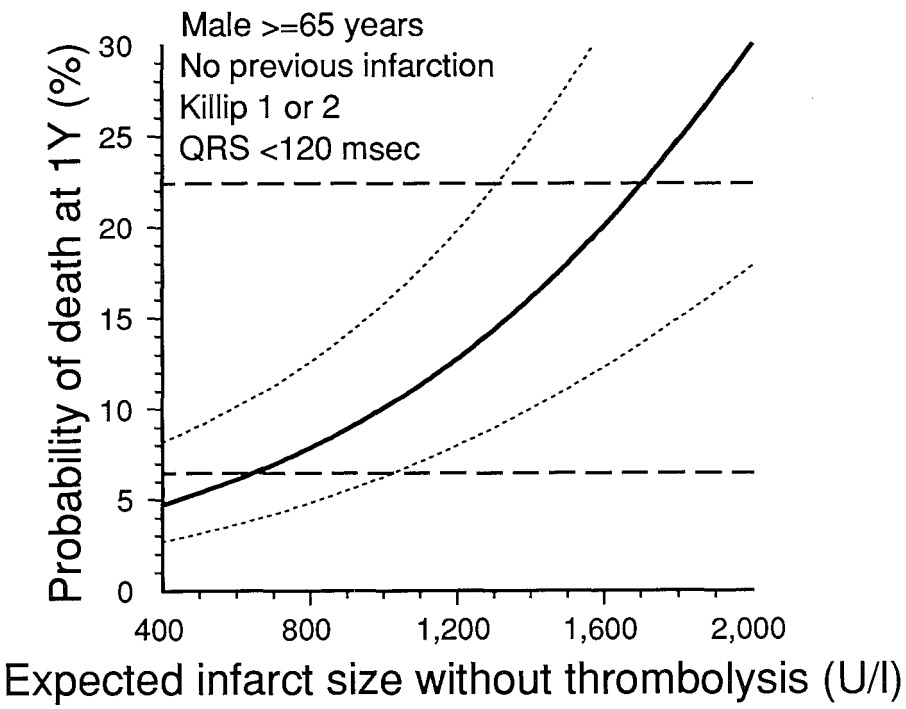


Figure 4b. Similar to figure 4a, for a patient of 65 years or older.

Conclusion

"Expected infarct size without thrombolysis" is a concept that has the advantage of being directly related to the pathophysiologic mechanism by which thrombolysis exerts its beneficial effect, i.e. limitation of infarct size. It can be assessed on hospital admission using readily available criteria. It helps to separate high risk from low risk patients, it predicts who will benefit most of thrombolytic therapy and it is useful to identify a group of patients with increased risk of bleeding who do not benefit from thrombolytic therapy.

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CHAPTER 8

PREDICTION OF MORTALITY AFTER HOSPITAL DISCHARGE IN PATIENTS TREATED WITH AND WITHOUT RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR FOR MYOCARDIAL INFARCTION: IS THERE A NEED FOR CORONARY ANGIOGRAPHY?

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[1]A listing of investigators and participating centers has been published previously [6].

SUMMARY

To assess the role of coronary angiography before hospital discharge in patients with myocardial infarction, a risk function describing the relationship between clinical characteristics, results of exercise test and radionuclide ventriculography and mortality after hospital discharge was compared to a similar risk function including parameters obtained from coronary angiography. The study population consisted of 1043 hospital survivors of the rt-PA/placebo and the rt-PA/PTCA trial of the European Cooperative Study Group. Forty two of 1043 patients (4.0%) died during follow-up ranging from 300 to 1100 days after 10 to 22 days angiography.

With univariate analysis the following determinants of mortality were identified: age, use of diuretics and/or digitalis, history of previous infarction, enzymatic infarct size, inadequate systolic blood pressure increase during exercise testing, contraindications for an exercise test, radionuclide ejection fraction and multivessel disease. In a stepwise multivariate regression model (Cox), use of diuretics and/or digitalis, a history previous infarction and age exceeding 60 years were clinical risk factors. Of the exercise test results inability to perform the test and less than 30 mmHg systolic blood pressure increase were predictive for late mortality. Large enzymatic infarct size, radionuclide left ventricular ejection fraction below 40%, and multivessel disease were also determinants of mortality after hospital discharge.

The risk function including coronary angiography was not better than the risk functions based on clinical data and the results of non-invasive testing. Patients without a history of previous infarction, not treated with diuretics and/or digitalis and with a systolic blood pressure increase of 30 mmHg or more during exercise had an excellent survival (98.6%) in the first year after hospital discharge, irrespective of whether symptoms of recurrent ischemia occurred. This low risk group formed 47% of the total patient population and does not benefit from coronary angiography. Predischarge exercise testing provides useful information for risk stratification before hospital discharge in patients.

INTRODUCTION

Mortality after acute myocardial infarction has decreased substantially in the last 25 years. Early detection and treatment of life threatening arrhythmias in coronary care units and more recently the widespread use of thrombolytic therapy in combination with aspirin have reduced in hospital mortality [1-7]. Nevertheless, mortality in the first year after acute myocardial infarction remains an important problem with an incidence ranging from 6% to 19% [1,2].

Identification of patients at increased risk of dying after hospital discharge has been attempted by many investigators [8-16]. In the guidelines, published by the American College of Cardiology and American Heart Association Task Force [17], coronary angiography is only recommended in patients with completed myocardial infarction "if

prognosis is judged to be poor on the basis of non-invasively obtained parameters (clinical, electrocardiographic, radionuclide ventriculography and exercise test) and if clinical outcome is expected to be improved by urgent coronary bypass surgery or PTCA". It was recommended that low risk patients should not undergo coronary angiography. This recommendation seems reasonable, but the additional prognostic value of coronary angiography in low risk patients has not been tested in clinical studies and in many hospitals predischarge coronary angiography remains a routine procedure, especially in younger patients. Since the procedure is related to some morbidity and has a mortality rate of 0.2% [17], selection of patients who will benefit from knowledge of the coronary anatomy is an important issue.

In the present analysis of 1043 hospital survivors of the rt-PA/placebo and the rt-PA/PTCA trials by the European Cooperative Study Group [6,18], the question is addressed whether the criteria for assessment of risk after myocardial infarction, established in the pre-thrombolysis era [8-16] remain valid in patients after thrombolytic therapy. Particular attention is given to the role of coronary angiography in risk assessment before hospital discharge.

PATIENTS AND METHODS

The patient population of the present analysis comprises individuals enroled in the rt-PA/placebo and rt-PA/PTCA trials by the European Cooperative Study Group [6,18]. In the former trial patients were randomized to receive recombinant tissue plasminogen activator (rt-PA or alteplase) or placebo in addition to aspirin and intravenous heparin, while in the latter all patients received rt-PA, aspirin and intravenous heparin and were randomized to a non-invasive strategy without angiography or an invasive strategy of immediate coronary angiography and percutaneous transluminal coronary angioplasty (PTCA) of the residual infarct related stenosis, if suitable anatomy was found.

Patients

Patients less then 71 years with more than 30 minutes of chest pain suggesting myocardial ischemia and ST-segment elevation (60 msec after J-point) of 0.3 mV or greater in two or more of chest leads V_1 to V_4 and/or greater than 0.2 mV in two or more of leads I, II, III, aVL, aVF, V_5, or V_6, were eligible. Patients were also included with at least 0.1 mV ST-segment elevation in two of leads II, III, aVF, V_5, V_6 and at least 0.2 mV ST-segment depression in two or more of the chest leads V_1 to V_4. The usual contraindications for thrombolytic therapy were applied [6,18]. In addition, patients with a previous myocardial infarction at the same site or who had undergone coronary artery bypass surgery were excluded. Patients with heart failure or shock were not. Treatment should be started within 5 hours after the onset of symptoms.

Protocol

After informed consent, patients were given an intravenous infusion of either 100 mg rt-PA or placebo (in the rt-PA/placebo trial) in 3 hours; all patients received 250 mg of acetyl salicylic acid and 5000 IU of heparin intravenously, followed by a continuous infusion of heparin 1000 IU/hour. The treatment strategies in the rt-PA group of the rt-PA/placebo trial and the non-invasive group of the rt-PA/PTCA trial were identical. In the rt-PA/PTCA trial, those patients allocated to the invasive strategy underwent immediate coronary angiography and subsequently angioplasty if a residual stenosis exceeding 60% was present. Until hospital discharge, all patients were anticoagulated with heparin, which could be replaced by coumarins after three days, provided that full anticoagulation was maintained. In addition, 75-125 mg acetyl salicylic acid was given every other day until hospital discharge.

Exercise testing, radionuclide ventriculography, coronary angiography, and left ventriculography were performed before hospital discharge. Prior to the beginning of the trial, each clinic participating in the study was assigned a specific time window for the performance of these studies (10-14, 12-16, 14-18, 16-20 or 18-22 days). Beta adrenergic blocking agents were to be prescribed unless contraindications were present.

Enzymatic infarct size

Infarct size was determined by assessment of cumulative alpha-hydroxybutyrate dehydrogenase (HBDH) release by the heart during the first 72 hrs (HBDH-Q72). The methodology has been published previously [6,18,19].

Exercise testing

Cardiovascular medication was not stopped before the test. A symptom-limited submaximal exercise protocol was used with either a bicycle ergometer (stepwise increments of 10 watts/min) or treadmill (Weld protocol). Twelve ECG leads were recorded every 60 sec or continuously. In 3 centers Frank orthogonal leads were used. Systolic blood pressure was measured with a cuff at rest, during peak exercise and at rest. The test was terminated when severe symptoms or one of the following occurred: significant arrhythmias, fall in systolic blood pressure >15 mmHg or heart rate exceeding 200 minus age. The latter occurred in 24% of patients. The workload obtained during tread mill testing was translated into watts according to the following algorithm: number of watts = (duration of treadmill testing in min) x 10 [20].

Radionuclide ventriculography

Radionuclide ventriculography was performed prior to exercise testing on the same day. Technetium-99m (15 mCI) was given 20 min after an intravenous injection

of stannous pyrophosphate. R-wave gated or gated list mode data collection was used with at least 20 frames per cycle and 5 min per view. Two regions of interest were used for the calculation of the ejection fraction.

ECG scoring

Electrocardiograms were required by the protocol on admission and between 10 and 22 days after myocardial infarction. QRS and ST-segment measurements were performed centrally. Both the Selvester score and the Cardiac Infarction Injury Score were assessed. Details of the analysis are reported elsewhere [21].

DATA ANALYSIS

The objective of the analysis was to find the combination of clinical patient characteristics, data form the exercise test, radionuclide ventriculography and contrast angiography, which most closely predicted late mortality after 10 to 22 days. The following clinical admission variables considered: age, sex, sum of ST-elevation at J-point, time from symptom onset to treatment allocation, previous myocardial infarction, anterior infarction, Killip class, angina at rest and during effort between 24 hrs and 10 to 22 days, clinical signs of heart failure, atrial fibrillation, pericarditis, use of beta-blockers, digitalis, diuretics or a combination of the latter two between 24 hours and 10 to 22 days angiography and enzymatic infarct size. Exercise test results evaluated were: systolic blood pressure rise from baseline to peak exercise, maximum heart rate during exercise, occurrence of angina, ST-segment depression and elevation during exercise and maximum workload and percentage of predicted workload achieved according to age and height. Finally, global left ventricular ejection fraction from radionuclide ventriculography and contrast left ventriculography, extent and severity of coronary artery disease, end-diastolic and end-systolic volumes, regional wall motion assessed by the "Center-line" model, the "Regional Contribution to ejection fraction" method and the "Radial axes" method were evaluated [22]. Mortality was displayed as the cumulative incidence of death during the follow-up period, beginning the day after coronary angiography was performed or scheduled.

Univariate analysis

For continuous variables patients were categorized into three subgroups of approximately equal size. Subsequently, mortality was assessed in each subgroup. The category with the lowest expected risk was chosen as reference group. The relative risk for the other categories was calculated as the mortality in the subgroup under study, divided by the mortality in the reference group (risk ratio). The 95% confidence interval for the risk ratio was calculated according to Miettinen [23].

Multivariate analysis

Multivariate regression analysis was used to develop a composite risk score based on patient characteristics found to be related to one year mortality in the univariate analysis. The Cox proportional hazard model was applied [24], which provides a conditional probability of death at each moment during follow-up, given a certain combination of risk factors X1, X2, ..., Xi, according to the function:

$$1 - \text{survival at 1 year} = 1 - S_0(1\ \text{year})^{\exp(b1 \times X1 + b2 \times X2 ... bi \times Xi.)}$$

S_0(1 year) is the survival at one year for a patient without any risk factor and B_i represent the Cox regression coefficients, estimated from the data by the maximal likelihood method for indicator variables X_i representing risk factors. The probability of one year survival calculated for each patient individually according to the Cox function was used as a composite risk score.

Besides above absolute risk estimates the Cox proportional hazard function provides relative risk estimates or hazard ratios. If indicator variables are used with value 1 if a patient has the property and 0 if not, a Cox regression coefficient represent the natural logarithm of the hazard ratio. For example, the Cox regression coefficient for use of diuretics and/or digitalis of 1.34 means that patients using diuretics and/or digitalis have a 3.8 fold increased (hazard of) mortality than patients without, conditional on all other risk factors retained in the model. The 95% confidence interval for this relative risk was derived from the standard error (SE_i) of the coefficient by the natural antilogarithm of ($B_i \pm 1.96 \times SE_i$) [25].

Five risk functions were designed, one for clinical data only, one for clinical data with exercise test results, one including enzymatic infarct size, one including data from radionuclide angiography, and one combining all non-invasive variables with findings of coronary angiography. In a stepwise procedure, variables were included in a model if the probability for inclusion was less then 0.10. A variable was removed if the associated probability exceeded 0.15. Clinical data, data of the exercise test, radionuclide angiography and angiographic data were first analyzed in clusters; those retained in the various models were combined in one final model. The Cox assumption of proportionality was checked in the data as described previously [26].

Comparison of the five risk functions

Risk estimates for every individual patient were obtained with each of the five risk functions. Patients were categorized according to each of these five risk estimates in a low and high risk group. The optimal cutoff value between low and high risk in the five risk functions was determined with a receiver operator characteristic (ROC) curve [27]. In this curve the proportion of patients with a high risk score among the deaths ("true positives" or sensitivity) is plotted against the proportion of patients with

TABLE I - Mortality within first year after hospital discharge in various subgroups of patients.

Mortality within first year	rt-PA/placebo trial		rt-PA/PTCA trial			
	Plac	rt-PA	rt-PA	Invas	Overall	Risk ratio (95% CI)
Diuretics and/or digitalis						
no	3/281	5/287	5/138	3/124	16/830	-
yes	10/ 64	6/ 59	1/ 42	3/ 48	20/213	4.9 (2.7 to 8.7)
History of infarction						
no	10/321	8/323	5/168	5/160	28/972	-
yes	3/ 24	3/ 23	1/ 12	1/ 12	8/ 71	3.9 (1.9 to 8.0)
Age (year)						
<60	6/211	3/194	3/135	3/112	15/652	-
≥60	7/134	8/152	3/ 45	3/ 60	21/391	2.3 (1.2 to 4.4)
Enzymatic infarct size (U/l)						
<1100	3/233	7/258	3/141	4/123	17/755	-
≥1100	10/108	4/ 87	3/39	2/ 48	19/282	3.0 (1.6 to 5.5)
mis	0/ 4	0/ 1	-	0/ 1	0/ 6	
Radionuclide ejection fraction (%)						
≥40	4/229	4/232	3/137	1/117	12/715	-
<40	8/104	7/103	3/ 35	3/ 48	21/290	4.3 (2.3 to 8.2)
mis	1/ 12	0/ 11	0/ 8	2/ 7	3/ 38	4.7 (1.5 to 14.7)
Blood pressure increase during exercise (mmHg)						
≥30	4/213	3/233	4/137	2/126	13/709	-
<30	7/113	4/ 91	2/ 27	1/ 31	14/262	2.9 (1.4 to 5.9)
mis	2/ 19	4/ 22	0/ 16	3/ 15	9/ 72	6.8 (3.3 to 14.0)
Nr of coronary vessels with ≥50% diameter stenosis						
<2	4/194	1/192	3/119	1/118	9/623	-
≥2	8/142	8/141	3/ 54	3/ 41	22/378	4.0 (2.0 to 8.2)
mis	1/ 9	2/ 13	0/ 7	2/ 13	5/ 42	8.2 (3.3 to 20.4)
Treatment strategy						
plac	13/345	-	-	-		-
rt-PA	-	11/346	-	-		0.8 (0.4 to 1.9)
rt-PA	-	-	6/180	-		0.9 (0.3 to 2.3)
Invas	-	-	-	6/172		0.9 (0.4 to 2.4)
All					36/1043	

mis: missing; plac: placebo; rt-PA: recombinant tissue-type plasminogen activator. Invas: invasive strategy. Number of deaths divided by total number of patients in each subset.

a high risk score among those remaining alive ("false positives" or 100% minus specificity). Risk functions on the line of identity have no prognostic value, those in the left upper corner are most informative.
The performance of the risk functions regarding the separation of low and high risk patients, as well as the relative efficacy of each of the five risk functions, were assessed by studying patient survival in both risk categories separately with Kaplan-Meier survival plots [28].

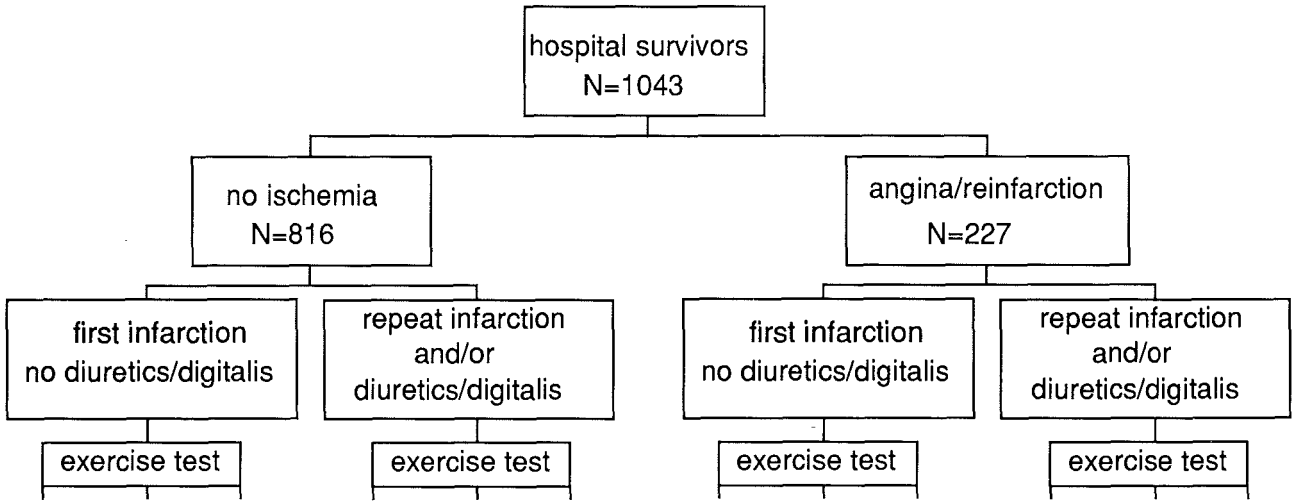
RESULTS

Univariate analysis

Forty two of 1043 patients (4.0%) died during follow-up, ranging from 300 to 1100 days after 10 to 22 days angiography. Mortality rates in the first year were similar in all treatment groups (table I). Determinants of mortality after 10 to 22 days angiography were: use of diuretics and/or digitalis, age, history of previous infarction, enzymatic infarct size, radionuclide left ventriculography, inadequate systolic blood pressure increase during exercise, extent of coronary artery disease. Mortality in various categories of these determinants was similar in all treatment groups (table I). Missing data on systolic blood pressure increase during exercise testing were also predictive of mortality. This occurred in 72 patients of whom in 62 patients the exercise test was not started (in 33 patients for cardiac reasons). In addition, inability to perform coronary angiography was related to mortality.
In figure 1 mortality, reinfarction and revascularization in the first year after hospital discharge are presented for subsets of patients without and with signs of recurrent ischemia during hospital stay (including reinfarction) categorized according to history of previous infarction, use of diuretics and/or digitalis and systolic blood pressure response during exercise test. There was no difference in the occurrence of reinfarction between the patients subsets. Revascularization procedures were more frequent in patients with signs of recurrent ischemia than in patients without, and in patients with a history of previous infarction or use of diuretics and/or digitalis. There was a preference for coronary bypass surgery over angioplasty in patients without adequate systolic blood pressure increase during exercise or missing exercise test data. Revascularization before 10 to 22 days was performed in 4 patients only (these are omitted in figure 1) and therefore is unlikely to influence mortality and reinfarction after hospital discharge.

Multivariate analysis

The probability of mortality within the first year for patients without any risk factor, estimated by Cox regression analysis, is reported in table II as well as the relative risk of each risk factor conditional on the other risk factors in the various risk functions. Coefficients of each risk function can easily be computed by taking the antilogarithm



	mis N=19	<30 N=136	>=30 N=489	mis N=17	<30 N=48	>=30 N=107	mis N=19	<30 N=43	>=30 N=79	mis N=17	<30 N=35	>=30 N=34
mortality	5.3%	2.2%	1.4%	29.4%	6.3%	3.7%	5.3%	2.3%	1.3%	11.8%	20.0%	2.9%
reinfarct	-	2.9%	3.3%	5.9%	-	5.6%	5.3%	4.7%	3.8%	-	17.1%	-
PTCA	-	4.4%	5.7%	-	-	5.6%	21.1%	11.6%	10.1%	5.9%	-	14.7%
CABG	15.8%	4.4%	4.5%	11.8%	10.4%	10.3%	15.8%	20.9%	12.7%	2.4%	11.4%	8.8%
both	-	-	0.6%	-	-	0.9%	-	2.3%	1.3%	-	-	-

Figure 1. Mortality, reinfarction and revascularization procedures within the first year in subsets of patients categorized according to clinical data and exercise test results.

TABLE II - Survival after one year after hospital discharge in patients without any risk factor predicted by various multivariate models and relative risk of each risk factor.

Model including:						
Clinical		+	+	+	+	+
Exercise			+	+	+	+
Enzymes				+	+	+
LVEF					+	+
Angio						+
		Survival in patients without any risk factor at 365 days				
		0.983	0.988	0.991	0.991	0.995
		Relative risk (95% CI)				
Diuretics and/or digitalis used after 24 hours						
no	79.6	-	-	-	-	-
yes	20.4	3.8 (2.0-7.2)	3.2 (1.7-6.0)	2.5 (1.3-4.8)	2.5 (1.3-4.8)	2.4 (1.3-4.6)
History of infarction						
no	93.2	-	-	-	-	
yes	6.8	2.9 (1.4-6.2)	2.6 (1.2-5.5)	2.5 (1.1-5.3)	2.0 (0.9-4.5)	
Age (year)						
<60	62.5	-	-	-	-	-
≥60	37.5	1.7 (0.9-3.2)	1.6 (0.9-3.1)	1.8 (1.0-3.4)	1.6 (0.9-3.0)	1.4 (0.7-2.6)
Enzymatic infarct size (U/l)						
<1100	73.0			-		
≥1100	27.0			2.5 (1.3-4.8)		
Radionuclide ejection fraction (%)						
≥40	68.6				-	-
<40	27.8				2.8 (1.4-5.7)	2.9 (1.4-5.7)
mis	3.6				1.4 (0.4-5.7)	0.9 (0.2-3.9)
Blood pressure increase during exercise test (mmHg)						
<30	68.0		-	-	-	-
>30	25.1		2.2 (1.1-4.5)	2.0 (1.0-4.1)	2.0 (1.0-4.0)	1.9 (1.0-3.9)
no	6.9		3.6 (1.5-8.3)	3.6 (1.5-8.3)	3.9 (1.5-9.7)	3.2 (1.2-8.5)
Nr of coronary vessels with ≥50% diameter stenosis						
<2	59.8					-
≥2	36.2					3.1 (1.5-6.6)
mis	4.0					4.0 (1.1-15)
Treatment strategy						
plac	33.0	-	-	-	-	-
rt-PA	33.2	0.9 (0.4-1.9)	0.9 (0.4-1.9)	1.0 (0.5-2.2)	1.0 (0.5-2.0)	1.0 (0.5-2.1)
rt-PA	17.3	0.9 (0.3-2.1)	0.9 (0.3-2.2)	0.9 (0.4-2.4)	0.9 (0.4-2.4)	1.1 (0.4-2.8)
invas	16.5	0.6 (0.2-1.7)	0.7 (0.3-1.9)	0.8 (0.3-2.1)	0.8 (0.3-2.1)	0.9 (0.3-2.3)

Relative risk for an indicator variable is the exponent of the coefficient of that indicator variable in the Cox regression model and represents a hazard ratio.

of each relative risk. The risk function with clinical data only contains the following parameters (in order of decreasing importance): use of diuretics and/or digitalis after 24 hours, history of previous infarction and age. Prescription of diuretics and/or digitalis at discharge was also highly predictive of mortality, but was likely to be influenced by knowledge of the radionuclide and contrast angiography results. This parameter is therefore disregarded in the present analysis. Clinical signs of heart failure were associated with in-hospital mortality, but to a lesser extent with mortality thereafter. Symptoms of recurrent ischemia after the first 24 hours, at rest and during effort or during the exercise test, did not contribute to mortality prediction. In addition to clinical parameters, exercise test results contributed to the prediction of mortality. Systolic blood pressure rise from rest to peak exercise of less than 30 mmHg was associated with a 2.2 fold increased mortality. ST-segment elevation or depression during or after exercise testing did not contribute to risk assessment. Inability to perform predischarge exercise testing was highly predictive of late mortality (relative risk 3.6, 95% CI 1.5 to 8.3). When enzymatic infarct size or radionuclide left ventricular ejection fraction were entered in the model low systolic blood pressure response to exercise and inability to perform exercise testing remained important determinants of late mortality (table II). When left ventricular ejection fraction below 40% and enzymatic infarct size were simultaneously considered in the stepwise regression, the former was entered as second parameter immediately after use of diuretics and/or digitalis; if left ventricular ejection fraction was not considered, enzymatic infarct size was entered instead. In the risk function with parameters of coronary angiography, multivessel coronary artery disease was a strong predictor of mortality after 10 to 22 days (relative risk 3.1) and was additive to the clinical determinants, the exercise test results and left ventricular ejection fraction. Residual stenosis and patency of the infarct related vessel were related to late mortality but were overshadowed by the other parameters.

Comparison of the five risk functions

In figure 2 the ROC curves are shown for each of the five risk functions. The function containing only clinical data was nearest to the line of "no prognostic value". Performance of the other risk functions was very similar. The best prognostic value of the risk function including angiographic data was obtained for a cutoff value of 0.032. This cutoff value was therefore chosen between the low and high risk category in figure 3. Survival in the low risk category was better than in the high risk category for all five risk functions. The risk functions including non-invasive testing performed better in separation of patients with low and high mortality than the risk function containing clinical data only. The risk function including coronary angiographic data was not better than the risk functions without coronary angiography but including the exercise test results.

Left main stem stenosis

Left main stem diameter stenosis exceeding 50% was found in 9 patients out of

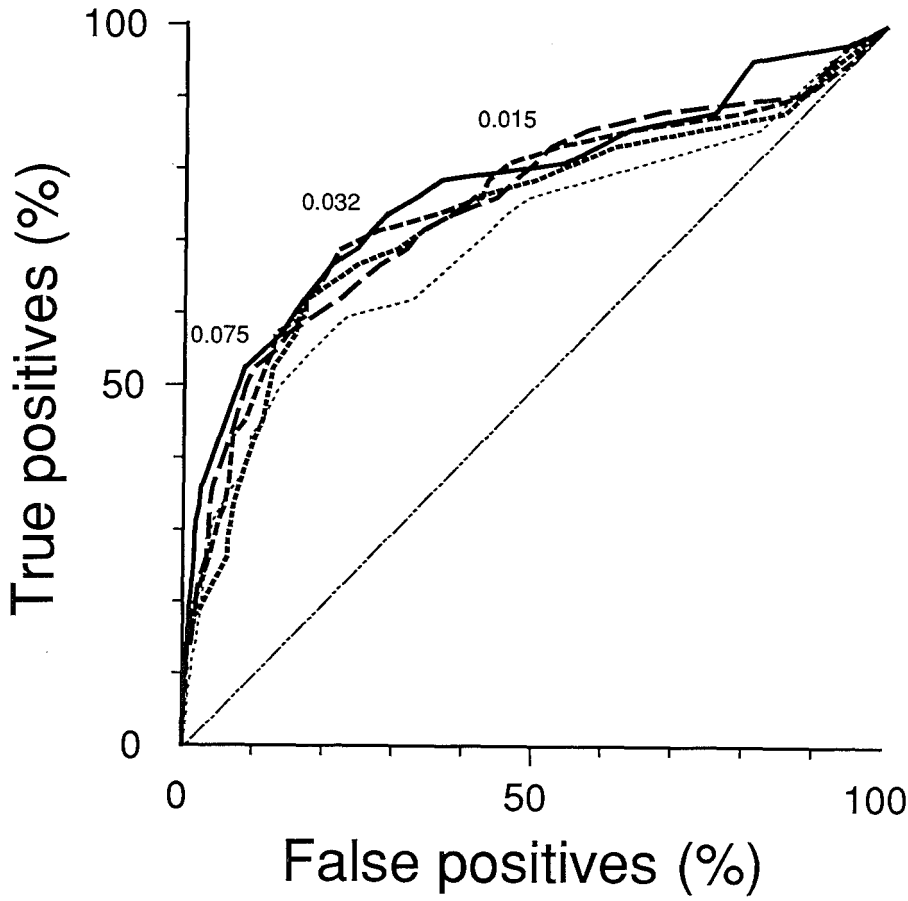


Figure 2. Receiver-operator characteristic curve for comparison of the risk function containing clinical data only (small dots), the risk function containing exercise test data (thick dots), the risk function with enzymatic infarct size (small dash), the risk function including radionuclide ventriculography (large dash) and the risk function with all parameters including those of the contrast angiography (solid line). The value 0.032 represent the cutoff point for which the performance of the risk function including coronary angiography was best.

1043 (0.9%). In none of these patients was the left main stem infarct related. Two suffered from recurrent ischemia and underwent coronary bypass surgery. Of the remaining 7 patients without symptoms of recurrent ischemia, 3 patients were in the low risk group without history of previous infarction, treatment with diuretics or digitalis and with an systolic adequate blood pressure response during exercise. None of these underwent a revascularization procedure and none died. One patient with left main stem

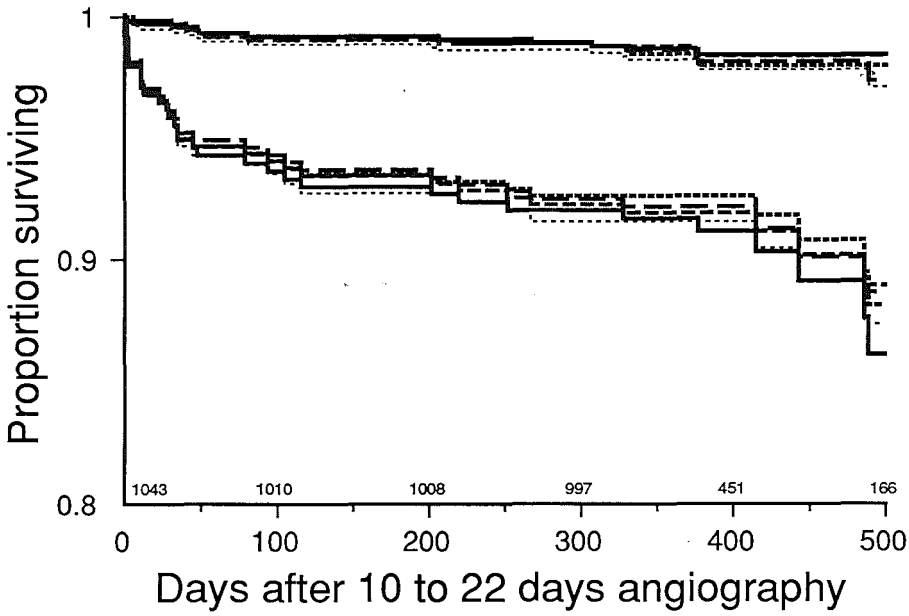


Figure 3. Survival in patients categorized in a low and high risk group by the five risk functions (cutoff value of 0.032 for the probability of death within the first year). Symbols are identical to those in figure 2.

stenosis and a history of previous infarction died 11 days after 10 to 22 days angiography without intervention, the remaining 8 patients survived during a follow-up ranging from 353 to 495 days after hospital discharge.

Multivessel disease with poor left ventricular function

Eighty six patients in the low risk group had a radionuclide left ventricular ejection fraction below 40%. Twenty eight of these 86 patients had also multivessel disease. Three of 28 patients underwent a revascularization procedure and only two of them died during follow up.

DISCUSSION

The importance to identify patients at risk of dying after hospital discharge has been underscored by many investigators [8,9-11,15]. Patients at low risk can be reassured without additional diagnostic investigations or therapy; high risk patients might benefit from further treatment and closer follow-up. The present analysis indicates that the risk for mortality after hospital discharge can be determined using simple clinical data and parameters obtained by exercise testing before hospital discharge. Five hundred sixty eight patients without a history of previous infarction, not treated with diuretics and/or digitalis and with a systolic blood pressure increase of 30 mmHg or more with cuff measurement during exercise had an excellent survival (98.6%) in the first year after hospital discharge, irrespective of symptoms of recurrent ischemia (figure 1).

Overall mortality after hospital discharge was less than half of the 10 to 15% that was reported in earlier studies [8]. This is explained in part by patient selection with an upper age limit of 71 years and allowing entry of patients with previous infarctions only if in a distant area. However, the risk associated with previous infarction in this study is similar to the risk associated with previous infarction in the study of Fioretti with a rate ratio of 3.9 (table I) and 3.5 [8] respectively, although more patients had a history of previous infarction in the latter study (24.8% versus 6.8%) in the latter trial. In addition, mortality reduction by rt-PA [5,6,34] and probably by aspirin [3] might have contributed to the difference in mortality within in the first year. The principle determinants of late mortality are related to impaired left ventricular function and not to residual ischemic myocardium, probably because patients with residual ischemia underwent revascularization procedures. As a consequence, little gain is to be expected from further revascularization procedures, although other treatment modalities like coumarins [32] or ACE-inhibition [33] may improve the prognosis in such patients.

Clinical risk factors

The use of diuretics and/or digitalis after 24 hours was the strongest clinical determinant of mortality after hospital discharge in the present analysis. Fioretti tested the prescription of digitalis at hospital discharge and also found this parameter to be highly predictive of late mortality [8]. Because prescription on hospital discharge may be influenced by the knowledge of non-invasive and invasive test results, in the present analysis only use of diuretics and/or digitalis prior to these tests were used.

Exercise test before hospital discharge

The present analysis confirms the value of a pre-discharge exercise test in patients treated with and without thrombolytic therapy. Previous studies have shown the usefulness of this investigation for patients prior to the widespread use of thrombolytic agents [8,11-15]. As reported by Fioretti et al [8] and recently confirmed by others [16],

parameters suggesting residual ischemic myocardium (chest pain and/or ST-segment changes during exercise testing) were not associated with higher mortality after hospital discharge. This might be explained by the finding that 34% of patients with recurrent ischemia underwent revascularization procedures versus 14% of patients without recurrent ischemia, which possibly has reduced the risk of mortality.

Additional tests

Coronary angiography did not improve the prediction of mortality when clinical data and exercise test results were available (figures 2 and 3). Therefore, low risk patients without symptoms of recurrent ischemia should not undergo routine coronary angiography before hospital discharge. These low risk patients comprised 47% of the study population. This is in agreement with the indications for angiography after acute myocardial infarction as proposed by the Joint Task Force of the American College of Cardiology and the American Heart Association [17]. These recommendations were tested in a large data base of patients with acute myocardial infarction and appeared useful to identify patients at high risk of mortality [30]. However, in that study, the value of coronary angiography in improving risk assessment was not determined and the simultaneous effect of several determinants of risk was not accounted for with multivariate regression analysis as in the present analysis.
A possible benefit of coronary angiography in high risk patients who are using diuretics and/or digitalis, are not able to perform an exercise test or have an inadequate systolic blood pressure response during exercise, may have been missed in the present analysis, since revascularization might have improved survival in these high risk patients [38,39].

Agreement exists that patients with left main coronary artery stenosis should undergo bypass surgery, even if asymptomatic [29]. It should be realized that, in this study, 489 low risk patients underwent coronary angiography to detect 3 patients with a left main stenosis. Since coronary angiography is associated with 0.2% mortality [17], this must be balanced against the expected improvement in prognosis following bypass surgery in a few patients with severe left main stenosis. Therefore, it is unlikely that an invasive strategy for all patients will be superior to a strategy in which coronary angiography is restricted to high risk and symptomatic patients.

Another strategy which has been proposed, with radionuclide ventriculography in the low risk group and subsequent coronary angiography in patients with left ventricular ejection fraction below 40%, would have resulted in coronary angiography in 86 additional patients. The present study does not give much support for the superiority of this strategy (figure 2).

Initial treatment strategy

In contrast to mortality during hospital stay [6,18], mortality after hospital discharge was not related to the initial treatment strategy conditional on enzymatic

infarct size, left ventricular function and coronary anatomy in the multivariate analysis. Similar findings have been reported for thrombolysis with intracoronary streptokinase [31]. To evaluate whether the relation between determinants and mortality was similar for all treatment strategies, the multivariate analysis was repeated for placebo and rt-PA treatment separately with similar results being obtained.

Infarct related residual stenosis

Mortality in patients with an occluded infarct-related vessel is reported to be higher than in patients with a patent infarct-related vessel [31,35-38]. Possible mechanisms are better scar formation in the infarct territory, less ischemia in the infarct territory and better collateral flow to distant myocardial areas especially in case of recurrent infarction due to occlusion of another coronary artery. In the present study population the residual stenosis in the infarct related vessel appeared to be related to late mortality [34], but in the stepwise regression analysis the contribution of the degree of residual stenosis was insufficient for inclusion in the model after prior entry of diuretics and/or digitalis, radionuclide left ventricular ejection fraction and extent of coronary artery disease.

Limitations of the study

Prediction of mortality was hampered by the small number of deaths in the present study. This has made the risk functions less reliable, will have influenced their performance (figure 2 and 3) and made assessment of their performance in more than two risk categories impossible. Secondly, in approximately 40% of patients undergoing revascularization procedures no symptoms of recurrent ischemia were present. In these patients the responsible physician decided to perform a revascularization procedure only because of the coronary anatomy, according to a retrospective questionnaire. This may have influenced the risk functions presented in this report. However, considering the small number of patients with left main stem stenosis and with a combination of multivessel disease with poor left ventricular function in the low risk group not identified by recurrent ischemia and the infrequent revascularization procedures among them (0 of 3 patients with main stem stenosis and 3 of 28 patients with multivessel disease and poor left ventricular function), revascularization procedures are unlikely to be responsible for the excellent survival in the low risk group. Another limitation of the study is that the risk functions were tested in the patient population in which the risk functions were developed. This may have resulted in over-estimation of the efficacy of the risk functions. Application of the findings in the present study to other patient populations with similar patient characteristics is valid only, if similar treatment strategies, including beta-blockade and revascularization strategies in post-infarct angina, are used.

Conclusion

Mortality following hospital discharge may be predicted in patients with acute myocardial infarction, also after thrombolytic therapy. The pre-discharge exercise test retains its usefulness in these patients. Coronary angiography did not improve the prediction of mortality after hospital discharge. Low risk patients, characterized by the absence of symptoms of recurrent ischemia, without prescription of diuretics and/or digitalis and with a normal systolic blood pressure response to exercise, have an excellent prognosis and are unlikely to benefit from predischarge angiography.

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SUMMARY

Thrombolytic therapy is a major step forward in the treatment of acute myocardial infarction and may result in up to 50% mortality reduction, provided that it is administered early (chapter 1). In 80 to 85% of patients with suspected acute myocardial infarction, a coronary artery is blocked by a clot. With thrombolytic therapy the closed coronary artery is desobstructed in may cases, is infarct size limited and left ventricular function preserved. Several thrombolytic agents are available for clinical use: streptokinase, APSAC, urokinase and more recently recombinant tissue-type plasminogen activator (rt-PA or alteplase). The latter is the genetically engineered natural occurring plasminogen activator. Which agent is superior is still a matter of debate. Unlike streptokinase, APSAC and urokinase, rt-PA dissolves blood clots without degradation of circulating fibrinogen during in vitro and in animal experiments, provided that the dose does not exceed a certain threshold. This property of rt-PA is called fibrin-specificity.

In this thesis the effect of rt-PA on coronary patency, infarct size, left ventricular function and clinical outcome is reported, as assessed in the clinical trials of the European Cooperative Study Group. In these trials patients with symptoms of acute myocardial infarction and fulfilling strict criteria for ST-segment change were entered. In addition, more general questions are addressed in this thesis: whether all patients with suspected acute myocardial infarction should receive thrombolytic therapy and whether coronary angiography before hospital discharge is indicated in all patients receiving thrombolytic therapy.

Fibrinogen degradation products, coronary patency and bleeding

In chapter 2 the question is addressed whether rt-PA restores coronary patency in patients without marked degradation of circulating fibrinogen, as is suggested by in vitro and animal experiments. The second question was whether fibrinogen breakdown associated with increased bleeding risk. Coronary patency at 90 minutes after start of rt-PA infusion and bleeding rate are reported for 242 patients entered in the first three trials of the European Cooperative Study Group. All patients were treated with double chain rt-PA. Bleeding occurred more frequently in patients with increased serum levels of fibrin(ogen) degradation products, but coronary patency immediately after rt-PA infusion was not better, indicating that rt-PA, unlike streptokinase and urokinase, is effective in restoring coronary patency without increased serum levels of fibrin(ogen) degradation products. This is in agreement with the fibrin-specificity of rt-PA.

Because the dose that induces fibrinogen degradation may vary considerably from patient to patient, a new way of dosing is proposed. Rt-PA can be administered until fibrinogen degradation products appear. This approach may be compared to the titration of insulin by measuring blood sugar levels. The development of a quick bedside test for measurement of fibrinogen degradation products is a prerequisite for this approach.

Effect of rt-PA on infarct size, left ventricular function and clinical outcome

In chapter 3 the effect of rt-PA, in addition to aspirin and intravenous heparin, on infarct size, left ventricular function and survival in patients with suspected acute myocardial infarction is reported. Seven hundred twenty one patients were enroled in the rt-PA/placebo trial of the European Cooperative Study Group and were allocated at random to treatment with 100 mg rt-PA or placebo. Enzymatic infarct size was limited by 20%, left ventricular function was preserved and mortality was reduced by 51% at 14 days (5.7% versus 2.8%) in comparison to a strategy of aspirin and intravenous heparin alone. Bleeding complications were commoner in patients treated with rt-PA. Intracranial bleeding occurred in 1.4% of patients.

Additional benefit of immediate angioplasty

Does immediate coronary angioplasty provide additional benefit in patients treated with rt-PA, aspirin and intravenous heparin? This question was addressed in the rt-PA/PTCA trial (chapter 4). Three hundred sixty seven patients were at random allocated to an invasive strategy of rt-PA, aspirin, intravenous heparin combined with immediate coronary angiography and balloon dilatation of narrowings in the infarct related vessel or to a non-invasive strategy with rt-PA, aspirin and intravenous heparin alone. The invasive strategy was not superior in terms of infarct size, left ventricular function and clinical outcome to the non-invasive approach of rt-PA, aspirin and intravenous heparin alone and may even be detrimental, since mortality was higher in the invasive group.

The lack of benefit of the invasive treatment strategy was explained by more frequent coronary reocclusion and reinfarction in the invasive treatment group. After exclusion of patients with these events, a small benefit in parameters of regional wall motion was found similar to the benefit in the rt-PA/placebo trial, also after adjustment for other determinants of regional wall motion by multivariate regression analysis (chapter 5). This suggests that an invasive strategy might be beneficial in selected patients, when additional treatment modalities to prevent reocclusion and reinfarction become available.

Long term follow up after rt-PA

Long term results of the rt-PA/placebo and the rt-PA/PTCA trial are reported in chapter 6. The benefit of rt-PA in terms of mortality reduction was still present at one year follow up. Survival after hospital discharge in patients with completed myocardial infarction is determined by the remaining left ventricular function, the extent of coronary artery disease and by the degree of infarct related residual coronary artery narrowing. Differences in survival between patients treated with thrombolytic therapy and controls are explained in differences in these parameters induced by the treatment.

Patient selection

Must all patients with acute myocardial infarction receive thrombolytic treatment? Since some patients have a very good prognosis without thrombolytic therapy and some patients may have an increased risk of intracranial bleeding, this is unlikely. In chapter 7 a model is presented that was developed in the rt-PA/placebo and rt-PA/PTCA trial and tested in patients of two other clinical trials with enzymatic infarct size assessment. This model can be used to predict the expected infarct size and associated prognosis for a patient who is not treated with thrombolytic therapy, based on the admission ECG and Killip class. A second risk function was developed to determine the risk of intracranial bleeding in individual patients. Based on these estimates the decision to administer thrombolytic therapy can be made for an individual patient. Patients with small "expected infarct size without thrombolytic therapy", with a favourable prognosis without thrombolytic therapy should not receive thrombolytic therapy if they have increased risk of intracranial bleeding. Patient selection criteria were proposed based on these findings.

Role of predischarge coronary angiography for risk assessment

Is coronary angiography before hospital discharge needed for the identification of high risk patients after thrombolytic treatment? In chapter 8 this question is addressed in the 1043 patients of the rt-PA/placebo and the rt-PA/PTCA trial, who were alive at the time of the predischarge angiography. Coronary angiography was not useful in patients without symptoms of recurrent ischemia and without risk factors as a previous infarction, use of diuretics and/or digitalis and with a adequate systolic blood pressure response to exercise of at least 30 mmHg. These patients (47% of the study population) have a very good prognosis; 98.6% of these patients are still alive after one year and prediction of mortality is not improved by knowledge of the coronary anatomy. Therefore, coronary angiography should be restricted to high risk patients who may benefit from coronary bypass surgery or balloon dilatation. Thus, after thrombolytic therapy patient management is similar as in patients not treated with thrombolytic therapy.

Conclusion

The fibrin specificity of rt-PA was confirmed in the clinical setting. Tissue plasminogen activator reduces enzymatic infarct size, preserves left ventricular function and reduces mortality. Thrombolytic therapy is life saving for many patients with symptoms of acute myocardial infarction, but in patients with good prognosis without thrombolytic therapy and with increased risk of intracranial bleeding it may be life threatening. Selection of patients for thrombolytic therapy can be made on hospital admission on the basis of clinical state and ECG. Patient management after thrombolytic therapy is not different from that in patients without thrombolytic therapy.

SAMENVATTING

Trombolytische therapie voor het acute hartinfarct blijkt een waardevolle aanvulling van het therapeutisch arsenaal van de cardioloog en resulteert in 50% sterfte vermindering, wanneer de behandeling vroeg na begin van de klachten wordt aangevangen (hoofdstuk 1). Bij 80-85% van de patiënten met symptomen van een acuut hartinfarct kan een door een stolsel afgesloten kransvat worden vastgesteld. Met trombolytische behandeling wordt deze afsluiting in vele gevallen opgeheven, wordt de infarctgrootte beperkt en de linkerhartkamerfunctie gespaard. Meerdere trombolytica zijn beschikbaar voor gebruik in de kliniek: streptokinase, APSAC, urokinase en recombinant weefsel plasminogeen activator (rt-PA of alteplase). Rt-PA is het met recombinant DNA technieken geproduceerde natuurlijke weefsel plasminogeen activator. Over welk trombolyticum het beste is bestaat nog geen overeenstemming. Anders dan streptokinase en urokinase, lost rt-PA stolsels op zonder het circulerende fibrinogeen aan te tasten, tenzij zeer hoge doses worden gebruikt. Deze eigenschap wordt fibrinespecificiteit genoemd.

In dit proefschrift wordt het effect van rt-PA op de kransvatdoorgankelijkheid, de infarctgrootte, de linkerhartkamerfunctie en het klinisch beloop gerapporteerd. Het proefschrift is gebaseerd op de bevindingen in de onderzoekingen van de European Cooperative Study Group. In deze onderzoekingen werden alleen patiënten toegelaten bij wie klachten, suggestief voor een hartinfarct, gecombineerd waren met ECG veranderingen.

Voorts komen in dit proefschrift meer algemene vragen aan de orde: Is behandeling met trombolyse aangewezen bij alle patiënten met een verdenking op een hartinfarct? Is coronairangiografie voor ontslag uit het ziekenhuis aangewezen bij alle patiënten die trombolyse krijgen ter behandeling van een hartinfarct?

Fibrinogeenafbraakprodukten, kransvatdoorgankelijkheid en bloeding

In hoofdstuk 2 wordt de vraag behandeld of rt-PA stolsels kan oplossen bij patiënten met een acuut hartinfarct zonder de circulerende stollingseiwitten af te breken, zoals in vitro en in dierexperimenteel onderzoek werd gesuggereerd. Een tweede vraag was of een verhoogde serumconcentratie van fibrinogeenafbraakproducten geassocieerd is met een verhoogde bloedingsneiging. De kransvatdoorgankelijkheid na 90 minuten na begin van de rt-PA toediening en het vóórkomen van bloedingen worden gerapporteerd voor 242 patiënten die toegelaten zijn tot de eerste drie onderzoekingen van de European Cooperative Study Group. Allen werden behandeld met dubbelketen rt-PA. Bloedingen traden vaker op bij patiënten met hoge serumwaarden van fibrinogeenafbraakprodukten dan bij patiënten met lage waarden, terwijl de kransvatdoorgankelijkheid niet toenam.

Er werd een nieuwe manier van dosering voorgesteld waarbij rt-PA geinfundeerd wordt tot fibrinogeenafbraakprodukten in het bloed optreden. Deze benadering is vergelijkbaar met de titratie van de insulinedosering met bloedsuiker bepalingen. De ontwikkeling van test, waarmee op een eenvoudige manier fibrinogeenafbraakprodukten

bepaald kunnen worden, is een voorwaarde voor deze benadering.

Effect van rt-PA op infarctgrootte, linkerhartkamerfunctie en klinisch beloop

In hoofdstuk 3 wordt verslag gedaan van het rt-PA/placebo onderzoek van de European Cooperative Study Group. Zevenhonderd één en twintig patiënten met het klinische beeld van een acuut hartinfarct, werden gerandomiseerd tussen een behandelingsstrategie van rt-PA, gecombineerd met aspirine en heparine en een behandeling met placebo, aspirine en heparine. De trombolytische behandeling beperkte de infarctgrootte met 20%, spaarde de linkerhartkamerfunctie en verminderde de sterfte na het hartinfarct met 51% na 14 dagen (5.7% versus 2.8%) in vergelijking tot de behandeling met placebo, aspirine en heparine.
Bloedingscomplicaties waren frequenter in patiënten die met rt-PA werden behandeld. Intracraniele bloedingen binnen drie dagen na behandeling kwamen bij 1.4% van de patiënten voor.

Baten van onmiddellijke ballondilatatie

Zijn er baten van een vroegtijdige ballondilatatie van het infarctgerelateerde kransvat bij patienten die behandeld worden met trombolyse voor een acuut hartinfarct? Een strategie van alteplase, heparine en aspirine, gevolgd door onmiddellijke kransvatangiografie en ballondilatatie van vernauwingen in het infarct gerelateerd kransvat, werd vergeleken met een niet-invasieve strategie van alteplase, heparine en aspirine in 367 patiënten met symptomen van een acuut hartinfarct (hoofdstuk 4). De infarctgrootte en de linkerkamerejectiefractie waren eender in beide behandelingsgroepen, terwijl de sterfte hoger was in de invasieve behandelingsgroep, zodat een algemene invoering van deze behandeling moet worden ontraden.

De bevinding dat vroegtijdige ballondilatatie geen gunstig effect heeft, hangt samen met het vaker optreden van een hernieuwde kransvatafsluiting en reinfarcering, mogelijk door verdere beschadiging van de atherosclerotische vaatwand (hoofdstuk 5). In patiënten zonder complicatie na de ballondilatatie werd een trend tot betere wandbeweging in het infarctgebied waargenomen, die qua grootte te vergelijken is met het effect van trombolytische behandeling met rt-PA. Dit suggereert dat deze invasieve benadering een plaats zou kunnen hebben, zodra additieve maatregelen om een hernieuwde afsluiting te voorkomen zijn ontwikkeld. In speciale gevallen blijft de ballondilatatie een belangrijke vorm van therapie, bijvoorbeeld bij patiënten met een contraindicatie voor trombolytische behandeling, zoals uitgebreide hartmassage of een recente bloeding.

Lange termijn overleving na rt-PA

Gegevens betreffende de lange termijn overleving zijn in hoofdstuk 6 gerapporteerd. De baten van rt-PA in termen van sterftevermindering waren na een jaar

nog steeds aanwezig. De overleving na ontslag uit het ziekenhuis wordt bepaald door de linkerhartkamerfunctie en door de uitgebreidheid van de atherosclerotische kransvatafwijkingen, zoals die voor ontslag uit het ziekenhuis kunnen worden vastgesteld. Verschillen in overleving tussen patiënten die alleen met aspirine en heparine zijn behandeld en patiënten die trombolytische behandeling hebben gekregen, zijn terug te voeren op verschillen in linkerhartkamerfunctie en coronair anatomie.

Selectie van patienten

Moeten alle patiënten met een klinisch beeld van een acuut hartinfarct met trombolytica behandeld worden? Deze vraag komt in hoofdstuk 7 aan de orde. Trombolytische therapie, ongeacht welk trombolyticum wordt gebruikt is geassocieerd met het optreden van intracraniele bloedingen in 0.5 tot 0.9% van de patiënten. Patiënten ouder dan 65 jaar, patiënten met een laag lichaamsgewicht en patiënten die coumarines gebruiken, hebben een verhoogd risico op een intracraniele bloeding. Men zal daarom bij iedere patiënt met het klinisch beeld van een acuut hartinfarct de verwachte baten van trombolyse moeten afwegen tegen de risico's. In hoofdstuk 7 wordt een risico functie gepresenteerd om de kans op sterfte na het hartinfarct, gegeven een bepaalde verwachte infarctgrootte bij opname, te voorspellen. Met een tweede risico functie kan het risico op een intracraniele bloeding berekend worden. Op basis van deze kansen kan voor een patiënt een uitspraak gedaan worden of de verwachte baten van trombolyse groter zijn dan de risico's.

Rol van coronairangiografie voor ontslag uit het ziekenhuis

In hoofdstuk 8 wordt een antwoord gegeven op de vraag of een coronair-angiografie voor ontslag uit het ziekenhuis noodzakelijk is voor alle patiënten die behandeld zijn met trombolytica voor een hartinfarct. Coronairangiografie voor ontslag uit het ziekenhuis bleek bij patiënten zonder angina pectoris en zonder risicofactoren zoals een eerder hartinfarct, gebruik van diuretica en/of digitalis en met een bloeddrukstijging van tenminste 30 mmHg tijdens fietsergometrisch onderzoek, niet zinvol. Deze patiënten (47% van de onderzochte populatie) hebben een zeer goede prognose; 98.6% van deze patiënten is na een jaar nog in leven en voorspelling van sterfte bij deze patiënten wordt niet verbeterd door kennis van de coronaire anatomie. Coronairangiografie moet dan ook worden gereserveerd voor patiënten die opnieuw symptomen van ischemie krijgen en voor die patiënten die een verhoogd risico hebben, en dan nog alleen wanneer men mag verwachten dat met een kransvatoperatie of een ballondilatatie dit risico kan worden verkleind.

Conclusie

De fibrinespecificiteit van rt-PA is bevestigd in patientgebonden onderzoek. Rt-PA beperkt de infarctgrootte, spaart de linkerhartkamerfunctie en vermindert de sterfte

na een hartinfarct. Echter, in een aantal patiënten met een verhoogd risico op een intracraniele bloeding, kan trombolyse levensbedreigend zijn. Het is de taak van de clinicus om bij iedere patiënt de verwachte baten en risico's af te wegen. De verwachte infarctgrootte zonder trombolytische behandeling is bij deze afweging van groot belang. Deze verwachte infarctgrootte kan op basis van de klinische toestand van een patient en het ECG bij opname worden voorspeld. De nazorg van patiënten met een acuut hartinfarct die trombolytische behandeling hebben gekregen verschilt niet van de behandeling van patiënten met een acuut hartinfarct die geen trombolyse hebben gekregen.

ACKNOWLEDGEMENTS

First of all, I wish to express my gratitude to Prof. P.G. Hugenholtz, Prof. Dr. J. Lubsen and Prof. Dr. M.L. Simoons. Paul Hugenholtz was my mentor in Cardiology and provided the opportunity to work at the Thoraxcenter. His dynamic personality has been very stimulating and encouraging for so many people, including myself.
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CURRICULUM VITAE

The author was born on February 15, 1954 in Singapore. In 1972 he completed his high school education at the Stedelijk Gymnasium in Haarlem and began his preclinical training in Brussels where he completed his candidature for Medicine in 1975. He continued his training at the Rijks Universiteit in Leiden, where he passed the doctoral examinations in 1978 and the licensing examinations in 1980. During his undergraduate training the author was employed as a clinical assistant in the Department of Thoracic Surgery of the Clinique de Genolier in Switzerland under Professor Ch. Hahn and Doctor H.P. Wijnen. In 1980 he started his residency training in Internal Medicine under Doctor J.P. de Geus in the Onze Lieve Vrouwe Gasthuis in Amsterdam, and in 1983 his training in Cardiology in the Thoraxcenter of the University Hospital Dijkzigt in Rotterdam under Professor P.G. Hugenholtz.

Between 1986 and 1989 the author served as a cardiologist in the Thoraxcenter in Rotterdam. Since 1985 he has been participating in the organization of the clinical trials of the European Cooperative Study Group of rt-PA, chaired by Professor Dr. M. Verstraete. Since 1987 the author is affiliated with the Center of Clinical Decision Analysis, headed by Prof. Dr. J. Lubsen. In 1989 he joined the staff of the Cardiology Department of the Medical Center Alkmaar.

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT
TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

LV-FUNCTION STUDY
CASE RECORD FORM

(rt-PA versus placebo trial)

Inclusion criteria:

1. age 21 - 70 years
2. ECG changes typical for AMI
3. severe chest pain which lasted more than 30 minutes
4. onset of attack less than 5 hours before experimental treatment can be started

TIME-WINDOW FOR YOUR CLINIC:

sticker

Exclusion criteria:

1. age under 21 or over 70 years
2. unable to give informed consent
3. prolonged or traumatic cardiac massage
4. respirator required
5. transmural myocardial infarction less than 14 days ago
6. current treatment with coumarin anticoagulants
7. pregnant or currently menstruating
8. recent major trauma (especially head!)
9. known bleeding disorder
10. previous coronary bypass surgery
11. major non-heart surgery less than 3 months ago
12. cerebrovascular accident less than 3 months ago
13. gastro-intestinal bleeding less than 3 months ago
14. genito-urinary bleeding less than 3 months ago
15. known major hepatic disease (alcoholism)
16. known major renal disease
17. known proliferative diabetic retinopathy
18. any known disease with anticipated survival less than 2 years
19. anticipated problems with follow-up (i.e. no permanent address, living abroad, etc.)
20. persistent hypertension at admission despite treatment (systolic above 200 mmHg)
21. previous myocardial infarction in same localization
22. previous participation in the rt-PA LV Function Study
23. complete left bundle branch block
24. not able to perform 10-22 day exercise test (bicycle or treadmill) for non cardiac reasons
25. any other reason for excluding patient

BLOOD SAMPLE FOR SPECIAL HEMOSTATIC TESTS:

sticker

ID nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

This form consists of THREE TYPES OF ITEMS:
1. Sequentially numbered QUESTIONS,
2. SPECIFIC INSTRUCTIONS,
3. Boxed GENERAL PROCEDURAL INSTRUCTIONS, which appear between numbered items at the moment they must be observed.

How to use this form

WORK THROUGH THIS FORM ITEM BY ITEM AND LINE BY LINE IN SEQUENTIAL ORDER, UNLESS OTHERWISE DIRECTED BY JUMP INSTRUCTIONS (see below). USE CARD PROVIDED TO PREVENT SHOW-THROUGH (NCR PAPER!)

Categorized questions etc.: TICK OFF APPROPRIATE SPACE, I.E. ( ).

(✓) → GO TO ITEM 7, skip all items inbetween
(stop) → PATIENT IS INELIGIBLE, remainder of form need not be filled out. Discard original of form, retain red copy for your own reference and SEND BLUE COPY TO DATA CENTER
(✓) → i.e. neither a number nor a 'stop', GO TO NEXT LINE

Data entry:

A B C _ — TEXT and LOCAL REGISTRATION NUMBERS are entered LEFT-JUSTIFIED, in CAPITALS, ONE CHARACTER PER SPACE
_ 9 0 — NUMERICAL DATA are entered RIGHT-JUSTIFIED, but OBSERVE DECIMAL POINT
3 0/0 1/8 6 (d m y) — Dates: OBSERVE DAY-MONTH-YEAR ORDER
_ _ : _ _ (h : m) — Times: USE 24-HOUR CLOCK, i.e. 9 o'clock p.m. = 21 : 00 (h m)

Correction of mistakes:

draw empty space
tick off space which applies
put your initials in the margin

NO (✓) YES (stop) → NO (✓)( ) YES (stop) β
A A C D _ _ _ → A B C D β

Cross-identification of study material

In some countries, for legal reasons, all study material which is not retained by you must be anonymous as far as the patient is concerned. FOR FUTURE REFERENCE and FOLLOW-UP, OBSERVE THE FOLLOWING:
1. Your own HOSPITAL's patient REGISTRATION NUMBER is essential and MUST BE LEGIBLE ON ALL FORM COPIES.
2. To allow for future linkage between numbers and names; the PATIENT ID PAGES MUST BE FULLY COMPLETED.
3. Forms, tubes for blood sampling, and treatment packages are already numbered and peel-off stickers are provided. THESE MUST BE USED AS DIRECTED.

Notification of serious complications

In case of serious complications telephone in first instance within 24 hours:
Dr. R.J. Lennane: 49 6132 77 2420 (tel. private: 49 6704 2519);
If not available report to:
Dr. W.E. Welbers: 49 6132 77 2152 (tel. private: 49 6121 567169);
Dr. Taylor : 49 6132 77 3141 (tel. private: 49 6132 2894);
Dr. W. Feuerer : 49 7351 54 4292 (tel. private: 49 7351 28165).

For emergency film return and urgent questions

Telephone "TPA - film service" (24 hours a day), tel: 31 20 161771.

Important addresses

1. Dr. W. Feuerer, Dr. K. Thomae GmbH, Postfach 1755, D-7950 Biberach 1, Germany.
2. TPA DATA CENTER, c/o Stichting Cardialysis, Westzeedijk 120, 3016 AH Rotterdam, The Netherlands. In case of questions: call the data center at 31 10 4360511.

FLOW CHART: rt-PA LV-FUNCTION STUDY, rt-PA versus PLACEBO

	Just before To	To	Just after To	2 hrs after To	3 hrs after To	12 hrs after To	24 hrs after To	36 hrs after To	48 hrs after To	72 hrs after To	96 hrs after To	6 days after To	8 days after To	10–22 days after To
Selection procedure	1 – 15													
ECG	11				26		31.1							4 (ETF [1])
Physical examination	13				28+29									
BP + pulse rate	12			23.1	27									
Informed consent	16													
Blood sample central enzyme analysis (ENZ)	17.2					30.1	31.2	43	43	43	43			
Blood sample local hematology and chemistry	17.3					30.2	31.3	65	65	65	65			
Blood sample special hemostatic tests (HEM) (OPTIONAL)	17.4			23.2			31.4							
Heparine bolus + heparine infusion	18													
Acetyl salicylic acid	19								19		19	19	continue every two days	
Patient allocation		20												
START EXPERIMENTAL TREATMENT INFUSION			21	XXXXXXXXXXXX										
Make appointments 10–22 day LV-function tests (TIME-WINDOW on cover)							40+41							
Exercise test														ETF [1]
Radionuclide angiography														RAF [2]
Catheterization														CAF [3]
Blood sample antibody test (ANT)														4 (CAF [3])

[1]ETF : 10–22 day Exercise Test Form
[2]RAF : 10–22 day Radionuclide Angiography Form
[3]CAF : 10–22 day Catheterization Form

Table 1 Classification hemodynamic state

MIRU/KILLIP class	I	II	III	IV
HEMODYNAMIC CLASSIFICATION				
	Hyperdynamic[a]	normal	mild failure	overt failure[b]	shock[b]
Heart rate	> 80	60- 80	80-100	90-110	> 110
MAP[d]	> 100	90-100	80- 90	60- 80	< 60
LVFP[e]	< 12	< 12	12- 16	16- 20	> 20
Cardiac Index	> 4.0	3.0-4.0	2.5-3.0	2.0-2.5	< 2.0
SWI[f]	>4000	3000-4000	1200-3000	1200-2000	<1200
CLINICAL CLASSIFICATION					
	Hyperdynamic	normal	mild failure	overt failure	shock
Mental state	anxiety	normal	tense	anxiety	restless
Skin	dry, warm	dry, warm	warm	cool	clammy
Pulse	normal	normal	normal	weak	very weak
Lungs	clear	clear	basal rhonchi	rhonchi	lung edema
Heart sounds	normal	normal	S_3 ?	$S_3 + S_4$	$S_3 + S_4$
Urine	>50 ml/h	>50 ml/h	40-50 ml/h	20-40 ml/h	<20 ml/h

a. A subset of patients suffers from hypovolemia, LVFP < 5 mmHg
b. Right ventricular infarction may cause hypotension and tachycardia with elevated central venous pressure and low LVFP.
c. MIRU = Myocardial Infarction Research Unit
d. MAP = Mean Arterial Pressure
e. LVFP = Left Ventricular Filling Pressure
f. SWI = Stroke Work Index

Table 2 Guidelines for treatment of patients with myocardial infarction based on hemodynamic classification through combination of heart rate, blood pressure and signs of heart failure. An attempt should be made to achieve the optimal hemodynamic state soon after admission through prompt administration of appropriate short-acting intravenous drugs.

mmHg Systolic pressure	Heart rate 60-90	> 90
A. No signs of left ventricular failure (MIRU I, KILLIP I)		
< 60	atropine nitroprusside (pacemaker)	beta-blocker nitroprusside
> 140	nitroprusside	beta-blocker
100-140	atropine (pacemaker)	optimal hemodynamic state: beta-blocker
< 100	atropine volume exp. (pacemaker)	volume exp. volume exp.
B. Mild left ventricular failure (MIRU II, KILLIP II)		
> 140	atropine nitroprusside (pacemaker)	diuretics nitroprusside diuretics nitroprusside
100-140	atropine (pacemaker)	diuretics diuretics
< 100	atropine dobutamine dopamine	diuretics dobutamine dopamine diuretics dobutamine dopamine
C. Overt left ventricular failure or shock (MIRU III-IV, KILLIP III-IV)		
> 140	atropine pacemaker nitroprusside	diuretics nitroprusside diuretics nitroprusside
100-140	atropine pacemaker (nitroglycerine)	diuretics nitroglycerin diuretics nitroglycerine
< 100	pacemaker dobutamine dopamine IABP	diuretics dobutamine dopamine IABP diuretics dobutamine dopamine IABP

GUIDELINES FOR TREATMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION, PARTICIPATING IN THE TWO RELATED STUDIES OF THE EFFECT OF rt-PA ON INFARCT SIZE, LEFT VENTRICULAR FUNCTION AND CLINICAL FOLLOW-UP.

Treatment of pain and anxiety

For pain at admission: sublingual nitroglycerine and/or nifedipine.
For persistent pain: i.v. morphine or thalamonal.
If the patient was treated with beta-blockers, nitrates or calcium antagonists before admission these should be continued during the first 24 hours, unless contraindicated by the hemodynamic state.

Hemodynamic monitoring with Swan Ganz catheters and intra-arterial line should be performed in patients with overt heart failure (see table 1) or cardiogenic shock. Other patients can be monitored according to local protocol.
Do not introduce catheters via the subclavian vein!

Anticoagulation with i.v. heparine should be undertaken with a dosage of 1000 IU/hour, after an initial bolus of 5000 IU.
Heparin may be followed by oral anticoagulation at the third day, provided that complete anticoagulation is maintained.

Correction of hemodynamic abnormalities

In order to reduce myocardial ischemia, we should aim at prompt correction of hemodynamic abnormalities, when present.
In order to achieve this, the guidelines of tables I and II should be followed.

Treatment of arrhythmias

Ventricular or supraventricular tachyarrhythmias which compromise circulation: cardioversion as treatment of choice.

In case of ventricular tachycardia without hemodynamic impairment, lidocaine bolus 1 mg/kg i.v. (2 injections of 50 mg each) followed by 2-4 mg/min. i.v. infusion.
In cases unresponsive to lidocaine, disopyramide, procaineamide, mexiletine or other drugs should be used according to the local experience. Amiodarone i.v. (1200 mg/24 hours) may be used in patients unresponsive to class I drugs.

THERAPEUTIC GUIDELINES CHART

In case of supraventricular tachyarrhythmias without hemodynamic impairment digoxine or verapamil i.v. should be used.

Pacemakers should be inserted for complete heartblock, Mobitz type II block, sinus bradycardia 60 bpm and hypotension not responsive to atropine, and in case of new right bundle branch block with left anterior or inferior hemiblock.

Recurrent angina or transient ischemia should be treated with beta-blockers (unless heart rate during the episodes of ischemia is less than 60 bpm) and nitrates. Calcium-blockers will be used as third line drugs.

Oral anticoagulants should be used up to angiography and should thereafter be continued in cases of left ventricular aneurysm, mitral insufficiency, or persistent atrial fibrillation, unless the hospital decides to give anticoagulants to all patients.

Long term use of antiarrhythmics should be limited to patients with recurrent symptomatic tachyarrhythmias after the first 48 hours of infarction.

Long term use of digitalis should be limited to patients with persistent signs of heart failure or with paroxysmal supraventricular tachyarrhythmias after the first 48 hours of infarction.

Hypertension should be treated with beta-blockers, if needed with additional diuretics and as a further choice with vasodilators.

Between the 10th and the 22th day an exercise test, cardiac catheterization with left ventriculography and radionuclide angiography should be performed. All clinically prescribed medication should be continued during these procedures.

After completion of the exercise test and cardiac catheterization, all patients should be treated with beta-blockers (recommended dose metoprolol 2x100 mg) since such treatment favourably influences prognosis after myocardial infarction, unless a contraindication is present.

Coronary artery bypass surgery or PTCA will be reconsidered only in patients with recurrent angina despite therapy with beta-blockers. The sole exception is a mainstem lesion (diameter obstruction >50%), which is an indication for bypass surgery (or PTCA) even in the absence of symptoms.

ID nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

THIS PAGE MUST BE COMPLETED FOR EVERY PATIENT CONSIDERED FOR INCLUSION.
HOWEVER, IF YOU CANNOT SUPPLY THE DATA CENTER AND THOMAE WITH THE PATIENT'S NAME AND ADDRESS, YOU ARE ALLOWED TO CUT OFF THE BOTTOM PART OF THE WHITE AND BLUE COPIES OF THE FORM BEFORE SENDING THEM IN.
YOUR OWN RED COPY MUST ALWAYS BE FILLED OUT AND STORED FOR FUTURE REFERENCE, SEPARATELY FROM PATIENT'S HOSPITAL FILE.

P A T I E N T / C L I N I C I D E N T I F I C A T I O N

1. Give clinic identification:

   1.1 Name: _____

   1.2 City: _____

2. Give patient identification:

   2.1 Hospital registration number: '_'_'_'_'_'_'_'_'_'_' (double check!)

   2.2 Date of birth: _'_'_/_'_'_/_'_'_
   d d m m y y

   2.3 Sex: ( ) male
   ( ) female

---

3. Give patient name and address:

   Family name: '_' Initials: '_'_'_'

   Maiden name: '_'
   (if married)

   Street : '_' Nr: '_'_'_'_'

   City : '_'_'_'_'_'_'_'_' '_'
   (postal code)

   Country: '_'_'_'_'_'_'_'_'_'_'_'_'_'_'_'

   Telephone: '_'_'_'_'_'_' '_'_'_'_'_'_'_'

EVALUATE FOR ELIGIBILITY ALL PATIENTS THAT FULFIL THE FOLLOWING CRITERIA:
1. Age 21-70 years.
2. ECG-changes typical for AMI and severe chest pain which lasted more than 30 minutes.
3. Onset of attack less than 5 hours before experimental treatment can be started.

COMPLETE SELECTION PROCEDURE AND PROCEED TO EXPERIMENTAL TREATMENT INFUSION AS SOON AS POSSIBLE!!

THERAPEUTIC GUIDELINES (for more details see "Therapeutic Guidelines Chart"):
- For chest pain at admission: sublingual nitroglycerine and/or nifedipine.
- For persistent chest pain: i.v. morphine or Thalamonal.
- Antiarrhythmics only on indication.
- If the patient was on maintenance treatment with β-blockers, nitrates or calcium antagonists before admission these should be continued during the first 24 hrs, unless contraindicated.
- Other supportive medication may be given as required.
- Prophylactic β-blockers should not be given until after 10-22 days LV function assessments.
- Hemodynamic monitoring may be done according to local routine.

4. Time of admission to CCU: _ _:_ _ (h m) Date: _ _/_ _/_ _ (d m y)

5. Do you consider catheterization (day 10-22) contraindicated or anticipate technical problems?	NO (6)	YES (stop)
If yes, why: _____		
6. Did the patient have at least one major attack of severe chest pain typical for AMI that lasted more than 30 min.?	NO (stop)	YES (7)
7. Is the onset of the major attack that lasted more than 30 min. definable in time?	NO (stop)	YES (8)

8. Time of onset: _ _:_ _ (h m) Date: _ _/_ _/_ _ (d m y)

9. Can infusion of experimental treatment be started within 5 hours from onset of major attack?	NO (stop)	YES (10)
10. Is it likely that the patient has had a previous myocardial infarction IN THE SAME LOCALIZATION?	NO (11)	YES (stop)

CONTINUE NEXT PAGE

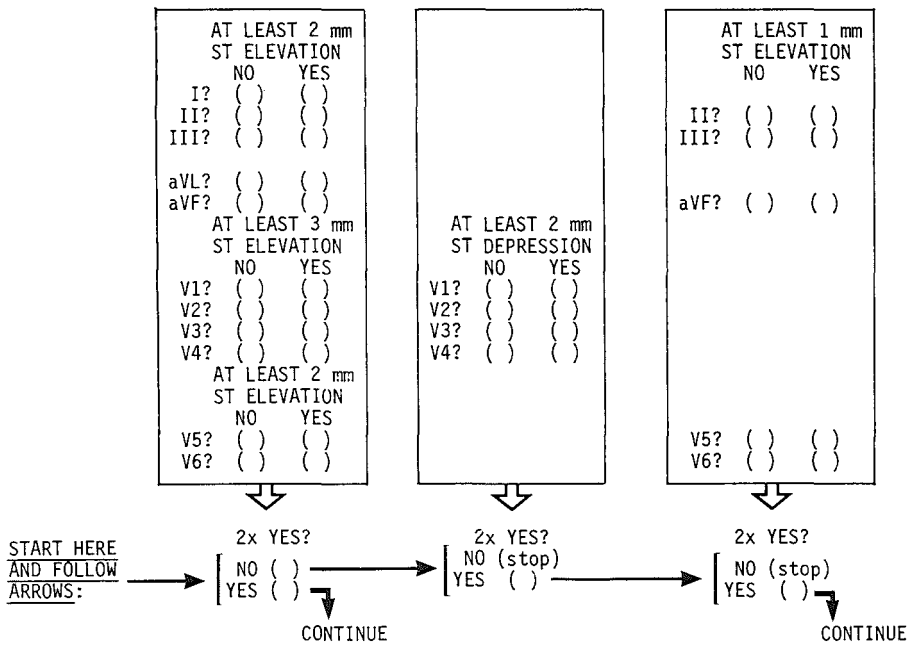
ID nr:

11. Evaluate most recent standard 12-lead ECG made after CCU admission:

11.1 Time made: _'_:_'_ (h m)

	NO	YES
11.2 Complete left bundle branch block?	( )	(stop)

11.3 Evaluation of ST-segment 60 msec after J-point: Complete all 3 columns



- STORE ORIGINAL OF THIS ECG FOR TRANSFERRAL TO DATA CENTER
- MARK WITH DATE, TIME AND ID NR PEEL-OFF STICKER
- IF YOU NEED ECG FOR PATIENT FILE, REPEAT ECG OR MAKE COPY

12. Measure cuff blood pressure (diastolic = disappearance of sound), pulse rate and perform physical examination

12.1 Time: _'_:_'_ (h m) sys: _'_'_' mmHg dia: _'_'_' mmHg pulse rate: _'_'_' bpm

	NO	YES
12.2 Systolic blood pressure over 200 mmHg?	(13)	(12.3)

12.3 If yes, treat blood pressure (see "Therapeutic Guidelines Chart") and reevaluate:

Time: _'_:_'_ (h m) sys: _'_'_' mmHg dia: _'_'_' mmHg pulse rate: _'_'_' bpm

	NO	YES
12.4 Systolic blood pressure now under 200 mmHg?	(stop)	(13)

ID nr:

13. Evaluate clinical hemodynamic state:

13.1 Tick one aspect in each horizontal row:

Mental state:	( ) normal	( ) tense	( ) anxiety	( ) restless
Skin :	( ) dry, warm	( ) warm	( ) cool	( ) clammy
Pulse :	( ) normal		( ) weak	( ) very weak
Heart sounds:	( ) normal	( ) weak S_3	( ) $S_3 + S_4$	
Lungs :	( ) clear	( ) crepitations (≤ 10 cm)	( ) crepitations (> 10 cm)	( ) lung edema

13.2 Give an overall impression of hemodynamic state (tick all that apply):

( ) normal
( ) mild left heart failure
( ) overt left heart failure
( ) shock
( ) right heart failure

IF: - heartrate under 60 or over 90 bpm or
- systolic blood pressure under 100 or over 140 mmHg or
- signs of heart failure:

➡ INITIATE CORRECTION IMMEDIATELY (SEE "Therapeutic Guidelines Chart")

	NO	YES
14. Was correction of hemodynamic state initiated?	(15)	(14.1)

14.1 If yes, specify: _____

15. Verify absence of remaining reason(s) for exclusion (check all):	NO	YES
15.1 age under 21 or over 70 years	( )	( )
15.2 unable to give informed consent	( )	( )
15.3 prolonged or traumatic cardiac massage	( )	( )
15.4 respirator required	( )	( )
15.5 transmural myocardial infarction less than 14 days ago	( )	( )
15.6 current treatment with coumarin anticoagulants	( )	( )
15.7 pregnant or currently menstruating	( )	( )
15.8 recent major trauma (especially head!)	( )	( )
15.9 known bleeding disorder	( )	( )
15.10 previous coronary bypass surgery	( )	( )
15.11 major non-heart surgery less than 3 months ago	( )	( )
15.12 cerebrovascular accident less than 3 months ago	( )	( )
15.13 gastro-intestinal bleeding less than 3 months ago	( )	( )
15.14 genito-urinary bleeding less than 3 months ago	( )	( )
15.15 known major hepatic disease (alcoholism)	( )	( )
15.16 known major renal disease	( )	( )
15.17 known proliferative diabetic retinopathy	( )	( )
15.18 any known disease with anticipated survival less than 2 years	( )	( )
15.19 anticipated problems with follow-up (i.e. no permanent address, living abroad, etc.)	( )	( )
15.20 previous myocardial infarction in same localization	( )	( )
15.21 previous participation in the rt-PA LV Function Study	( )	( )
15.22 not able to perform 10-22 day exercise test (bicycle or treadmill) for non cardiac reasons	( )	( )
15.23 any other reason for excluding patient	( )	( )

Give pertinent details below: ⬅ ANY "YES" STOP

_____

_____

_____

➡ ALL "NO": CONTINUE

ID nr:

16. Obtain consent

16.1 Time attempted: _'_:_'_ h m

By Dr : _'_ Signature: _____

Witness: _'_ Signature: _____

	NO (stop)	YES (16.3)
16.2 Was consent obtained?		

16.3 FILL OUT PATIENT CONSENT FORM (if required in your clinic)

17. Execute the following (give times and measurements as indicated):

	TIME
17.1 Make standard 12-lead ECG IF THE LAST ONE WAS MADE MORE THAN 30 MIN AGO (store original for transferral to data center, mark with date, time, ID nr peel-off sticker).	_'_:_'_ h m
17.2 Obtain blood sample (5 ml) for central enzyme analysis. Use provided tube (marked ENZ). Put peel-off sticker with tube number in box (all 3 copies!). Centrifuge blood immediately (10-20 min, 2500-4000 RPM). Transfer plasma with pipette to tube with same number and store at -20°C.	_'_:_'_ h m
17.3 Obtain blood samples for local hematology and chemistry; at least: hemoglobin, hematocrit, platelet count, serum Na, K, creatinine, SGOT, SGPT, LDH, α-HBDH, CK, CK-MB if available.	_'_:_'_ h m
17.4 OPTIONAL (see STICKER on cover): Obtain blood sample (5 ml) for special hemostatic tests. Use provided tube (marked HEM). Put peel-off sticker with tube number in box (all 3 copies!). Store on ice until centrifugation.	_'_:_'_ h m
17.5 Measure blood pressure and pulse rate: sys: _'_'_' mmHg dia: _'_'_' mmHg pulse rate: _'_'_' bpm	_'_:_'_ h m

sticker

18. Give heparin; i.v. bolus 5.000 IU, start heparin infusion (1000 IU/hour) and continue until catheterization or at least for 4 days until therapeutic effect of oral coumarins has been achieved (see "Therapeutic Guidelines Chart") _'_:_'_ h m

19. Give acetyl salicylic acid; 75-125 mg and continue once every TWO DAYS. _'_:_'_ h m

Indicate dosage used: _'_'_' mg

CONTINUE NEXT PAGE

** ERRATUM CASE RECORD FORM PAGE 5 **

Item 19: Give acetyl salicylic acid:

250 mg INTRAVENOUSLY (Aspisol, Aspegic)

Continue with 75-125 mg orally once every TWO DAYS until discharge.

ID nr:

20. Obtain treatment allocation:

Dial (international access code) 31 20 839601, call will be responded by:
'TPA allocation service'. DO NOT USE THIS TELEPHONE NUMBER FOR ANY OTHER PURPOSE!

Dictate the following information (in the order given):
- Your clinic name and city (allow time at other end to search for appropriate file)
- Your name
- Patient's hospital registration number, sex, date of birth (item 2)
- ID nr (see top of page)

TELEPHONE OPERATOR WILL GIVE YOU THE NUMBER OF THE TREATMENT PACKAGE TO BE USED

➡ WARNING: PATIENTS NOT ALLOCATED THROUGH ALLOCATION SERVICE WILL NOT BE EVALUATED!!

	NO	YES
20.1 Was allocation obtained?:	(stop)	(20.2)

If no, why not? _____

20.2 Note number of treatment package: _'_'_'_'_'

20.3 Time and date allocation obtained: TIME _'_'_:_'_ (h m) DATE _'_'_/_'_'_/_'_ (d m y)

THE PATIENT IS NOW IRREVOCABLY ADMITTED TO THE TRIAL.

IF YOU DECIDE NOT TO ADMINISTER EXPERIMENTAL TREATMENT, ALL OBSERVATIONS AND MEASUREMENTS MUST BE COMPLETED AS MUCH AS POSSIBLE ('INTENTION-TO-TREAT' PRINCIPLE!!)

USE SEPARATE INTRAVENOUS LINE FOR INFUSION OF EXPERIMENTAL TREATMENT.
DO NOT ADMINISTER OTHER DRUGS THROUGH SAME LINE!!

21. Open treatment package which bears number obtained from allocation service (item 20).

Put peel-off sticker in box (all 3 copies!).

MAKE UP INFUSION AND ADMINISTER
EXPERIMENTAL TREATMENT AS DIRECTED
BY TREATMENT PACKAGE INSERT.

sticker

	NO	YES
21.1 Did you start experimental treatment infusion?	(21.2)	(21.3)

21.2 IF NO, reason: _____

_____

➡ COMPLETE MEASUREMENTS AND OBSERVATIONS IF AT ALL POSSIBLE
GO TO ITEM 22

21.3 Indicate time INFUSION STARTED: TIME _'_'_:_'_ (h m) DATE _'_'_/_'_'_/_'_ (d m y)

CONTINUE NEXT PAGE

ID nr:

22. Chest pain present at start of experimental treatment infusion? NO (22.1) YES (22.2)

22.1 If no, indicate time pain disappeared: TIME _:_ h m
GO TO ITEM 23

22.2 If yes, indicate type (tick one):
( ) typical ischemic chest pain
( ) atypical chest pain

IF EXCESSIVE BLEEDING OCCURS, HANDLE AS FOLLOWS:
- INTERRUPT INFUSION
- WHEN ADDITIONAL MEASURES ARE REQUIRED:
  - give fresh whole blood or fresh frozen plasma
  - give tranexamic acid 10 mg/kg slow i.v.; if necessary repeat after 30 min.
  - OR give aprotinin (Trasylol®) 500.000 KIU slow i.v.; if necessary followed by 100.000 KIU every 2 hours.

DO NOT BREAK DOUBLE BLINDING UNLESS ABSOLUTELY NECESSARY
TREAT OTHER COMPLICATIONS ACCORDING TO LOCAL PROTOCOL

23. 120 min. after start of experimental treatment infusion, execute the following: (give actual times)

23.1 Measure blood pressure and pulse rate: TIME _:_ h m

sys: _,_,_ mmHg dia: _,_,_ mmHg pulse rate: _,_,_ bpm

23.2 OPTIONAL (see STICKER on cover): Obtain blood sample (5 ml) for special hemostatic tests. Use provided tube (marked HEM). Put peel-off sticker with tube number in box (all 3 copies!). Store on ice until centrifugation.

sticker

_:_ h m

AS SOON AS EXPERIMENTAL TREATMENT INFUSION HAS BEEN COMPLETED, PROCEED AS FOLLOWS:

24. Indicate time experimental treatment infusion was stopped: TIME _:_ h m

24.1 Was full dose of experimental treatment infusion given? NO (24.2) YES (25)

24.2 If no, why not? _____

_____

Indicate amount given: _,_,_ ml

➡ COMPLETE MEASUREMENTS AND OBSERVATIONS IF AT ALL POSSIBLE

25. Was double-blind code broken? NO (26) YES (25.1)

25.1 If yes, why? _____

ID nr:

26. Make standard 12-lead ECG (store original for transferral to data center, mark with date, time, ID nr peel-off sticker). TIME _'_:_'_ h m

27. Measure cuff blood pressure (diastolic = disappearance of sound) and pulse rate

Time: _'_:_'_ h m sys: _'_'_' mmHg dia: _'_'_' mmHg pulse rate: _'_'_' bpm

28. Evaluate clinical hemodynamic state:

Tick one aspect in each horizontal row:

Mental state :	( ) normal	( ) tense	( ) anxiety	( ) restless
Skin :	( ) dry,warm	( ) warm	( ) cool	( ) clammy
Pulse :	( ) normal		( ) weak	( ) very weak
Heart sounds :	( ) normal	( ) weak S_3	( ) $S_3 + S_4$	
Urine, if known:	( ) >50 ml/h	( ) 40-50 ml/h	( ) 20-40 ml/h	( ) <20 ml/h
Lungs :	( ) clear	( ) crepitations (≤10 cm)	( ) crepitations (>10 cm)	( ) lung edema

29. Give an overall impression of hemodynamic state (tick all that apply):
( ) normal
( ) mild left heart failure
( ) overt left heart failure
( ) shock
( ) right heart failure

12 HOURS AFTER TELEPHONE ALLOCATION, PROCEED AS FOLLOWS:
(It is allowed to take the following blood sample slightly earlier, but not later than 12 hours after allocation)

30. Execute the following (give actual times as indicated):

30.1 Obtain blood sample (5 ml) for central enzyme analysis. Use provided tube (marked ENZ). Put peel-off sticker with tube number in box (all 3 copies!). Centrifuge blood immediately (10-20 min, 2500-4000 RPM). Transfer plasma with pipette to tube with same number and store at -20°C.

sticker

DATE _'_/_'_/_'_ d m y TIME _'_:_'_ h m

30.2 Obtain blood samples for local hematology and chemistry. At least: hemoglobin, hematocrit, platelet count, serum Na, K, creatinine, SGOT, SGPT, LDH, α-HBDH, CK, CK-MB if available.

TIME _'_:_'_ h m

24 HOURS AFTER TELEPHONE ALLOCATION, PROCEED AS FOLLOWS:
(It is allowed to take the 24 hours blood sample slightly earlier or later, provided that the timespan between the previous blood sample (at 12 hours) and the blood sample at 24 hours does not exceed 12 hours).

31. Execute the following (give actual times as indicated):

31.1 Make standard 12-lead ECG (store original for transferral to data center, mark with date, time, ID nr peel-off sticker).

DATE _'_/_'_/_'_ d m y TIME _'_:_'_ h m

ID nr:

(31. continued)

31.2 Obtain blood sample (5 ml) for central enzyme analysis. Use provided tube (marked ENZ). Put peel-off sticker with tube number in box (all 3 copies!). Centrifuge blood immediately (10-20 min, 2500-4000 RPM). Transfer plasma with pipette to tube with same number and store at -20°C.

sticker

TIME _ _ : _ _ h m

31.3 Obtain blood samples for local hematology and chemistry. At least: hemoglobin, hematocrit, platelet count,serum Na, K, creatinine, SGOT, SGPT, LDH, α-HBDH, CK, CK-MB if available.

TIME _ _ : _ _ h m

31.4 OPTIONAL (see STICKER on cover): Obtain blood sample (5 ml) for special hemostatic tests. Use provided tube (marked HEM). Put peel-off sticker with tube number in box (all 3 copies!). Store on ice until centrifugation.

sticker

TIME _ _ : _ _ h m

GIVE BELOW INTERIM CLINICAL HISTORY UP TO 24 HOURS AFTER TELEPHONE ALLOCATION

32. Give details of use of medication up to 24 hours after allocation: (tick appropriate drug/time combination(s)):

	in use 72 h before admission	within 72 h before admission	admission till allocation	allocation till end of infusion	after end of infusion
- antiplatelet drugs	( )	( )	( )	( )	( )
- analgesics (opiates)	( )	( )	( )	( )	( )
- beta-blockers	( )	( )	( )	( )	( )
- calcium antagonists: - oral	( )	( )	( )	( )	( )
- i.v.	( )	( )	( )	( )	( )
- nitrates: - s.l.	( )	( )	( )	( )	( )
- i.v. (continuous)	( )	( )	( )	( )	( )
- other vasodilators	( )	( )	( )	( )	( )
- antiarrhythmics	( )	( )	( )	( )	( )
- digitalis	( )	( )	( )	( )	( )
- dopamine/dobutamine	( )	( )	( )	( )	( )
- other positive inotropics	( )	( )	( )	( )	( )
- diuretics	( )	( )	( )	( )	( )
- thrombolytic agents other than trial medication, specify:					
_____	( )	( )	( )	( )	( )
- any other medication, specify:					
_____	( )	( )	( )	( )	( )
_____	( )	( )	( )	( )	( )
_____	( )	( )	( )	( )	( )
_____	( )	( )	( )	( )	( )

ID nr:

(continued) INTERIM CLINICAL HISTORY UP TO 24 HOURS AFTER TELEPHONE ALLOCATION

33. Indicate total amount of opiates (if any) given up to 24 hours after allocation (tick all that apply). If none were given indicate with zero:

( ) morphine ,_,_,_, mg, number of injections:,_,_,

( ) Thalamonal,_,_,_, ml, number of injections:,_,_,

( ) others ,_,_,_, mg, number of injections:,_,_,

specify:_____

34. Were any bleeding complications observed up to 24 hours after allocation? NO (35) YES (34.1)

34.1 If yes, tick appropriate complication/time combination(s) and give site:

	before allocation	allocation till end of infusion	after end of infusion
- major (more than 5 cm diameter) hematoma e.g. at puncture site. Give site: _____	( )	( )	( )
- prolonged (more than 30 mins) bleeding e.g. at puncture site. Give site: _____	( )	( )	( )
- retroperitoneal hematoma	( )	( )	( )
- cerebral or subarachnoidal hemorrhage Give site: _____	( )	( )	( )
- hematemesis	( )	( )	( )
- melena	( )	( )	( )
- hemoptysis	( )	( )	( )
- hematuria	( )	( )	( )
- other, specify: _____	( )	( )	( )

34.2 Were any special measures taken? NO (35) YES (34.3)

34.3 If yes, tick all that apply and give details:

( ) blood (product) transfusion
Indicate number of units equivalent to 0.5 liter whole blood: ,_,_,

( ) surgery

( ) other, describe: _____

_____

35. Were any clinical signs of reocclusion observed up to 24 hours after allocation? NO (36) YES (35.1)

35.1 If yes, indicate time: _,_:_,_ (h m) and date: _,_/_,_/_,_ (d m y)

35.2 Diagnosis based on (tick all that apply):

( ) reappearance of chest pain
( ) exacerbation of chest pain
( ) reappearance of ST elevation
( ) increase of ST elevation
→ IF YES, STORE ORIGINAL ECG(s), MARK WITH TIME, DATE AND ID NR PEEL-OFF STICKER
( ) other, describe:

_____

ID nr:

(continued) INTERIM CLINICAL HISTORY UP TO 24 HOURS AFTER TELEPHONE ALLOCATION

36. Were any other complications observed up to 24 hours after allocation? NO (37) YES (36.1)

36.1 If yes, tick appropriate complication/time combination(s):

	before allocation	allocation till end of infusion	after end of infusion
- (exacerbation of) chest pain	( )	( )	( )
- systolic blood pressure under 90 mmHg	( )	( )	( )
- cardiogenic shock	( )	( )	( )
- pulmonary edema	( )	( )	( )
- peripheral edema	( )	( )	( )
- hepatomegaly	( )	( )	( )
- elevated CVP	( )	( )	( )
- bradycardia (pulse rate under 50 bpm)	( )	( )	( )
- second degree AV-block	( )	( )	( )
- third degree AV-block	( )	( )	( )
- IV conduction defect	( )	( )	( )
- atrial fibrillation/SVT	( )	( )	( )
- accelerated idioventricular rhythm (100 bpm or less)	( )	( )	( )
- ventricular tachycardia (100 bpm or more)	( )	( )	( )
- ventricular fibrillation	( )	( )	( )
- mitral regurgitation	( )	( )	( )
- papillary muscle rupture	( )	( )	( )
- LV aneurysm	( )	( )	( )
- LV free wall rupture	( )	( )	( )
- ventricular septum rupture	( )	( )	( )
- cerebro vascular accident	( )	( )	( )
- pulmonary embolus	( )	( )	( )
- pericarditis (i.e. at least two of the following three: pain with breathing, friction rub, fever)	( )	( )	( )
- other: _____	( )	( )	( )

37. Were any allergic reactions observed? NO (38) YES (37.1)

37.1 If yes, describe and indicate time period(s) of occurrence by putting tick mark(s) in appropriate column(s):

	before allocation	allocation till end of infusion	after end of infusion
1. _____	( )	( )	( )
2. _____	( )	( )	( )
3. _____	( )	( )	( )
4. _____	( )	( )	( )

37.2 Were any special measures taken? NO (38) YES (37.3)

37.3 If yes, specify: _____

_____

_____

ID nr:

(continued) INTERIM CLINICAL HISTORY UP TO 24 HOURS AFTER TELEPHONE ALLOCATION

38. Were any of the following procedures--allowed only in case of a medical emergency--done between admission and 24 hours after allocation? NO (39) YES (38.1)

38.1 If yes, tick all that apply and give date (first time only) and indication:

	DATE	TIME	INDICATION
( ) catheterization	_ _/_ _/_ _	_ _:_ _	_____
( ) PTCA	_ _/_ _/_ _	_ _:_ _	_____
( ) bypass surgery	_ _/_ _/_ _	_ _:_ _	_____
( ) other cardiac surgery	_ _/_ _/_ _	_ _:_ _	_____
( ) intra-aortic balloon pumping	_ _/_ _/_ _	_ _:_ _	_____
( ) respirator used	_ _/_ _/_ _	_ _:_ _	_____
( ) electrical counter shock	_ _/_ _/_ _	_ _:_ _	_____
( ) temporary pacemaker used	_ _/_ _/_ _	_ _:_ _	_____
( ) permanent pacemaker insertion	_ _/_ _/_ _	_ _:_ _	_____
( ) other, specify:			
_____	_ _/_ _/_ _ (d m y)	_ _:_ _ (h m)	_____

39. Give details on clinical history at admission: (check all)

	NO	YES
39.1 angina pectoris since more than 4 weeks?	( )	( )
39.2 angina pectoris since less than 4 weeks?	( )	( )
39.3 arrhythmias or heart block?	( )	( )
39.4 heart failure?	( )	( )
39.5 heart surgery other than CABG?	( )	( )
39.6 previous myocardial infarction?	( )	( )
if yes, specify (year, etc.): _____		
39.7 other?	( )	( )
if yes, specify: _____		

40. Make an appointment for:

1. Catheterization on day: 10-14, 12-16, 14-18, 16-20, 18-22 (refer to the sticker on the cover of the form for your clinic's prefixed time window). Use biplane equipment if available.
2. Symptom limited exercise test on the day BEFORE catheterization. All tests in patients from one clinic should be performed on the same time of the day. Do not combine exercise test with radionuclide angiography or Thallium scintigraphy.
3. Radionuclide angiography on the day BEFORE catheterization.

41. Indicate time and date of appointments:

	DATE	TIME
- symptom limited exercise test	_ _/_ _/_ _	_ _:_ _
- radionuclide angiography	_ _/_ _/_ _	_ _:_ _
- catheterization	_ _/_ _/_ _ (d m y)	_ _:_ _ (h m)

CONTINUE NEXT PAGE

ID nr:

MAKE SURE THAT THE APPROPRIATE FORMS ACCOMPANY THE PATIENT WHEN HE/SHE GOES TO CENTER WHERE THE ABOVE TESTS ARE PERFORMED, i.e. 10-22 day Exercise Test Form
10-22 day Radionuclide Angiography Form
10-22 day Catheterization Form.

ADD COPY OF ADMISSION ECG (item 11) TO THE CATHETERIZATION FORM.

β-BLOCKERS, CALCIUM ANTAGONISTS AND NITRATES MUST BE STOPPED THE NIGHT BEFORE 10-22 DAY CATHETERIZATION. COUMARINS (ORAL ANTICOAGULANTS) MUST BE REPLACED BY HEPARIN 1000 IU/L.

42. Supply name and signature of responsible physician:

Dr: _'_'_'_'_'_'_'_'_'_'_'_'_ Signature: _____ Date signed: _'_/_'_/_'_ d m y

THANK YOU FOR YOUR CO-OPERATION!

* DO NOT FORGET TO OBTAIN BLOOD SAMPLES FOR CENTRAL ENZYME ANALYSIS 36, 48, 72 and 96 HOURS AFTER ALLOCATION (item 43).

→ DO NOT FORGET TO OBTAIN BLOOD SAMPLES FOR LOCAL HEMATOLOGY AND CHEMISTRY 36, 48, 72 and 96 HOURS AFTER ALLOCATION (item 65).

THIS PART OF THE FORM SHOULD BE COMPLETED AND RETURNED 24 HOURS AFTER ALLOCATION OF THE PATIENT.

STORE RED COPY OF FORM TOGETHER WITH PATIENT CONSENT FORM, READY FOR LATER REFERENCE (NOT IN PATIENT's FILE, USE SPECIAL STUDY BINDER).

SEND ORIGINAL TO THOMAE (USE ENVELOPE PROVIDED).

SEND BLUE COPY TOGETHER WITH ORIGINAL ECGs (item 11, 17.1, 26, 31.1 and 35.2 (if applicable)) TO DATA CENTER (USE ENVELOPE PROVIDED).

ID nr:

BETWEEN 24 AND 4x24 HOURS AFTER ALLOCATION, PROCEED AS FOLLOWS:

43. Obtain blood samples (5 ml each) for central enzyme analysis 36, 48, 72 and 96 hours after allocation. Use provided tubes (marked ENZ). Put peel-off sticker with tube numbers in box (all 3 copies!). Centrifuge blood immediately (10-20 min, 2500-4000 RPM). Tranfer plasma with pipette to tube with same number and store at -20°C.

NOTE: BLOOD SAMPLES AFTER 24 HOURS MAY BE TAKEN AT A FIXED TIME IN THE MORNING AND EVENING, e.g. 8.00 a.m. and 8.00 p.m. RECORD ACTUAL TIMES!!

sticker *36 hours*	*sticker* *48 hours*	*sticker* *72 hours*	*sticker* *96 hours*
Date: __/__/__ d m y	Date: __/__/__ d m y	Date: __/__/__ d m y	Date: __/__/__ d m y
Time: __:__ h m	Time: __:__ h m	Time: __:__ h m	Time: __:__ h m

→ DO NOT FORGET TO OBTAIN BLOOD SAMPLES FOR LOCAL HEMATOLOGY AND CHEMISTRY 36, 48, 72 and 96 HOURS AFTER ALLOCATION (item 65).

STORE RED COPY OF FORM TOGETHER WITH PATIENT CONSENT FORM, READY FOR LATER REFERENCE (NOT IN PATIENT's FILE, USE SPECIAL STUDY BINDER).

SEND ORIGINAL TOGETHER WITH REMAINDER OF THE FORM TO THOMAE (USE ENVELOPE PROVIDED).

SEND BLUE COPY TOGETHER WITH REMAINDER OF THE FORM TO DATA CENTER (USE ENVELOPE PROVIDED).

DO NOT FORGET TO STOP β-BLOCKERS, CALCIUM ANTAGONISTS AND NITRATES THE NIGHT BEFORE 10-22 DAY CATHETERIZATION. COUMARINS (ORAL ANTICOAGULANTS) MUST BE REPLACED BY HEPARIN 1000 IU/H.

REFER TO THERAPEUTIC GUIDELINES CHART FOR RECOMMENDED THERAPY AT DISCHARGE.

** ERRATUM CASE RECORD FORM PAGE 14, 135.10 **

Make standard 12-lead ECG within 10-22 days time-window (see sticker on cover).
Store original, mark with date, time and ID-nr peel-off sticker.

DATE: __/__/__ d m y TIME: __:__ h m

ID nr:

THIS PART OF THE FORM MUST BE COMPLETED FOR ALL PATIENTS AT DISCHARGE
REFER TO THE STICKER ON THE COVER OF THE FORM FOR YOUR CLINIC'S PRE-FIXED TIME WINDOW.

44. Was the symptom limited pre-discharge exercise test performed? NO (44.1) YES (44.2)

44.1 If no, why not (tick all that apply):

( ) persistent angina pectoris

( ) heart failure

( ) other cardiac, specify: _____

( ) non cardiac, specify: _____

( ) other, specify: _____
GO TO ITEM 45

44.2 Date performed: _d_/_m_/_y_

44.3 Clinic where test was done: _____

44.4 Is the above date within your clinic's pre-fixed time window? NO (44.5) YES (45)

44.5 If no, why not: _____

45. Was radionuclide angiography performed? NO (45.1) YES (45.2)

45.1 If no, give reason (tick all that apply):

( ) cardiac, specify: _____

( ) non cardiac, specify: _____

( ) other, specify: _____
GO TO ITEM 46

45.2 Date performed: _d_/_m_/_y_

45.3 Clinic where test was done: _____

45.4 Is the above date within your clinic's pre-fixed time window? NO (45.5) YES (46)

45.5 If no, why not: _____

46. Was pre-discharge cardiac catheterization (coronary angiography and left ventriculography) performed? NO (46.1) YES (46.2)

46.1 If no, give reason (tick all that apply):

( ) cardiac, specify: _____

( ) non cardiac, specify: _____

( ) other, specify: _____
GO TO ITEM 47

46.2 Date performed: _d_/_m_/_y_

46.3 Clinic where test was done: _____

46.4 Is the above date within your clinic's pre-fixed time window? NO (46.5) YES (47)

46.5 If no, why not: _____

ID nr:

The information you are asked to provide below should relate to the PATIENT'S STATUS AT DISCHARGE FROM YOUR HOSPITAL (NOT NECESSARILY YOUR CCU!).
- If the patient was transferred from your CCU to another ward in your hospital, the information given should also cover that part of the hospitalization.
- If the patient was transferred to another hospital, this is considered a new hospitalization and information is only required up to the time the patient left your hospital.

47. Was the patient discharged alive from your hospital? NO ( ) YES ( )

IF YES: COMPLETE ITEMS 48-51 AND 57-66
IF NO : COMPLETE ITEMS 52-56 AND 57-66

PATIENT DISCHARGED ALIVE FROM YOUR HOSPITAL

48. Discharged from CCU on (time): _ _:_ _ (h m) (date): _ _/_ _/_ _ (d m y)

If discharged directly from CCU: fill out same date at 48 and 49

49. Discharged from hospital on (date): _ _/_ _/_ _ (d m y)

50. Destination at discharge (tick one):
( ) home
( ) other hospital
( ) rehabilitation clinic
( ) other institution
( ) destination unknown

51. Functional state at discharge (tick one):
(57) no limitations of physical activity
(51.1) slight limitations of physical activity but comfortable at rest
(51.1) marked limitation of physical activity but comfortable at rest
(51.1) inability to carry on any physical activity, with or without symptoms at rest
(57) unknown

51.1 Limitation due to (tick one):
( ) angina pectoris
( ) congestive heart failure
( ) both
( ) other : _____

➔ GO TO ITEM 57

PATIENT DIED IN YOUR HOSPITAL

52. Patient died on (time): _ _:_ _ (h m) (date): _ _/_ _/_ _ (d m y)

53. Place of death (tick one): (53.1) other ward
(54) CCU

53.1 Patient discharged from CCU on (time): _ _:_ _ (h m) (date): _ _/_ _/_ _ (d m y)

54. Describe briefly the circumstances of death:

_____

_____

_____

ID nr:

55. Was an autopsy performed? NO ( ) YES (55.1)

55.1 IF YES, ATTACH COPY OF REPORT

56. Which factors contributed to death (tick all that apply)

( ) reinfarction
( ) congestive heart failure
( ) cardiogenic shock
( ) ventricular septum rupture
( ) papillary muscle rupture
( ) tamponade
( ) ventricular fibrillation
( ) electro-mechanical dissociation
( ) electrical standstill
( ) thromboembolism
( ) cardiac surgery
( ) PTCA
( ) other cardiac, describe: _____
( ) non-cardiac, describe: _____
( ) unknown

ALL PATIENTS

THIS PART MUST BE COMPLETED FOR ALL PATIENTS IRRESPECTIVE WHETHER DISCHARGED ALIVE OR DIED IN-HOSPITAL.
Unless otherwise stated, information is required for the time span between 24 hours after telephone allocation and eventual hospital discharge or death.

Indicate eventual (discharge or pre-death) diagnosis:

57. MYOCARDIAL INFARCTION AT ADMISSION? NO (58) YES (57.1)

57.1 If yes, site (tick one):
( ) anterior
( ) infero-posterior
( ) lateral
( ) impossible to determine

57.2 If yes, diagnosis based on (tick one):
( ) both ECG and enzymes typical
( ) typical ECG pattern only
( ) typical enzyme pattern only
( ) other grounds, describe: _____

58. MYOCARDIAL (RE)INFARCTION LATER DURING HOSPITALIZATION? NO (59) YES (58.1)

58.1 If yes, site (tick one):
( ) anterior
( ) infero-posterior
( ) lateral
( ) impossible to determine

58.2 If yes, diagnosis based on (tick one):
( ) both ECG and enzymes typical
( ) typical ECG pattern only
( ) typical enzyme pattern only
( ) other grounds, describe: _____

58.3 If yes, send copy of your laboratory data sheet for CPK, CPK-MB (if available), SGOT, SGPT, LDH and α-HBDH together with this form to the Data Center.

59. OTHER CARDIAC DIAGNOSIS? NO (60) YES (59.1)

59.1 If yes, describe: _____

60. NON-CARDIAC DIAGNOSIS? (61) (60.1)

60.1 If yes, describe: _____

ID nr:

61. Were any bleeding complications observed between 24 hours after allocation and discharge (or death)? NO (62) YES (61.1)

61.1 If yes, indicate date first noticed and site (tick all that apply):

	DATE	SITE
( ) major (more than 5 cm diameter) hematoma e.g. at puncture site	__/__/__	_____
( ) prolonged (more than 30 mins) bleeding e.g at puncture site	__/__/__	_____
( ) retroperitoneal hematoma	__/__/__	
( ) cerebral or subarachnoidal hemorrhage	__/__/__	_____
( ) hematemesis	__/__/__	
( ) melena	__/__/__	
( ) hemoptysis	__/__/__	
( ) hematuria	__/__/__	
( ) other: _____	__/__/__ (d m y)	_____

61.2 Were any special measures taken? NO (62) YES (61.3)

61.3 If yes, tick all that apply and give details:

( ) blood (product) transfusion
Indicate number of units equivalent to 0.5 liter whole blood: ___
( ) surgery
( ) other:

1. _____
2. _____

62. Were any of the following cardiovascular complications observed between 24 hours after allocation and discharge (or death)? NO (63) YES (62.1)

62.1 If yes, tick all that apply and give date first noticed:

	DATE:
( ) angina at rest without (re)infarction	__/__/__
( ) effort angina without (re)infarction	__/__/__
( ) chest pain, suggesting (re)infarction	__/__/__
( ) systolic blood pressure under 90 mmHg	__/__/__
( ) cardiogenic shock	__/__/__
( ) pulmonary edema	__/__/__
( ) peripheral edema	__/__/__
( ) hepatomegaly	__/__/__
( ) elevated CVP	__/__/__
( ) bradycardia (pulse rate under 50 bpm)	__/__/__
( ) second degree AV-block	__/__/__
( ) third degree AV-block	__/__/__
( ) IV conduction defect	__/__/__
( ) atrial fibrillation/SVT	__/__/__
( ) accelerated idioventricular rhythm (100 bpm or less)	__/__/__ (d m y)

ID nr:

(62. continued) DATE:

( ) ventricular tachycardia (100 bpm or more)	__/__/__
( ) ventricular fibrillation	__/__/__
( ) mitral regurgitation	__/__/__
( ) papillary muscle rupture	__/__/__
( ) LV aneurysm	__/__/__
( ) LV free wall rupture	__/__/__
( ) ventricular septum rupture	__/__/__
( ) cerebro vascular accident	__/__/__
( ) pulmonary embolus	__/__/__
( ) pericarditis (i.e. at least two of the following three: pain with breathing, friction rub, fever)	__/__/__
( ) other: _____	__/__/__ d m y

63. Give details of use of medication between 24 hours after allocation and discharge or death (tick appropriate drug/time combination(s)):

	after 24 hours	prescribed at discharge*
- anticoagulants - heparin	( )	( )
- coumarin	( )	( )
- antiplatelet drugs	( )	( )
- analgesics (opiates)	( )	( )
- beta-blockers	( )	( )
- calcium antagonists: - oral	( )	( )
- i.v.	( )	( )
- nitrates: - s.l.	( )	( )
- i.v. (continuous)	( )	( )
- other vasodilators	( )	( )
- antiarrhythmics	( )	( )
- digitalis	( )	( )
- dopamine/dobutamine	( )	( )
- other positive inotropics	( )	( )
- diuretics	( )	( )
- thrombolytic agents other than trial medication, specify:		
_____	( )	( )
- any other medication, specify:		
_____	( )	( )
_____	( )	( )
_____	( )	( )
_____	( )	( )
_____	( )	( )

* if patient is discharged alive

ID nr:

64. Were any of the following additional procedures done between 24 hours after allocation and discharge (or death)? NO (65) YES (64.1)

64.1 IF YES, tick all that apply and give date (first time only) and indication (write 'routine' if the procedure at issue is part of your routine work-up):

	DATE	INDICATION
( ) catheterization other than as according to the protocol	_'_/_'_/_'_	_____
( ) PTCA	_'_/_'_/_'_	_____
( ) bypass surgery	_'_/_'_/_'_	_____
( ) other cardiac surgery	_'_/_'_/_'_	_____
( ) intra-aortic balloon pumping	_'_/_'_/_'_	_____
( ) respirator used	_'_/_'_/_'_	_____
( ) electrical counter shock	_'_/_'_/_'_	_____
( ) temporary pacemaker used	_'_/_'_/_'_	_____
( ) permanent pacemaker insertion	_'_/_'_/_'_	_____
( ) blood pool scintigraphy other than as according to the protocol	_'_/_'_/_'_	_____
( ) perfusion scintigraphy	_'_/_'_/_'_	_____
( ) ergometry other than as according to the protocol	_'_/_'_/_'_	_____
( ) Holter ECG	_'_/_'_/_'_	_____
( ) echocardiography	_'_/_'_/_'_ d m y	_____

CONTINUE NEXT PAGE!!

STORE RED COPY OF FORM, READY FOR LATER REFERENCE (NOT IN PATIENT's FILE, USE SPECIAL STUDY BINDER).

SEND ORIGINAL TO THOMAE (USE ENVELOPE PROVIDED).

SEND BLUE COPY TOGETHER WITH RANDOMIZATION ENVELOPE TO DATA CENTER (USE ENVELOPE PROVIDED).

65. Give results of laboratory tests at 0, 12, 24, 36, 48, 72 and 96 hours after treatment allocation. Note actual time and date samples were obtained. OBSERVE DECIMAL POINT!

	0 hours	12 hours	24 hours	36 hours	48 hours	72 hours	96 hours
TIMES:	__:__ h m	__:__ h m	__:__ h m	__:__ h m	__:__ h m	__:__ h m	__:__ h m
DATES:	__/__/__ d m y	__/__/__ d m y	__/__/__ d m y	__/__/__ d m y	__/__/__ d m y	__/__/__ d m y	__/__/__ d m y
Hb (mmol/l)	____	____	____	____	____	____	____
Ht (%)	__	__	__	__	__	__	__
Thrombo's (10^9/l)	___	___	___	___	___	___	___
Na^+ (mmol/l)	___	___	___	___	___	___	___
K^+ (mmol/l)	____	____	____	____	____	____	____
Urea (mmol/l)	____	____	____	____	____	____	____
Creat (mol/l)	___	___	___	___	___	___	___
ASAT(GOT) (U/l)	___	___	___	___	___	___	___
ALAT(GPT) (U/l)	___	___	___	___	___	___	___
LDH (U/l)	____	____	____	____	____	____	____
α-HBDH (U/l)	____	____	____	____	____	____	____
CK (U/l)	____	____	____	____	____	____	____
CK-MB (U/l)	____	____	____	____	____	____	____

66. Supply name and signature of responsible physician:

Dr: _____________________ Signature: _____ Date signed: __/__/__ d m y

SEE INSTRUCTIONS PAGE 20! THANK YOU FOR YOUR CO-OPERATION!

ID Nr: A-27

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT
TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

10-22 DAY EXERCISE TEST FORM

LV-FUNCTION STUDY

(rt-PA versus placebo trial)

ID nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

IF YOU CANNOT SUPPLY THE DATA CENTER AND THOMAE WITH THE PATIENT'S NAME AND ADDRESS, YOU ARE ALLOWED TO CUT OFF THE BOTTOM PART OF THE WHITE AND BLUE COPIES OF THE FORM BEFORE SENDING THEM IN.
YOUR OWN RED COPY MUST ALWAYS BE FILLED OUT AND STORED FOR FUTURE REFERENCE, SEPARATELY FROM PATIENT'S HOSPITAL FILE.

P A T I E N T / C L I N I C I D E N T I F I C A T I O N

1. Identification of clinic where patient was admitted:

   1.1 Name: _____

   1.2 City: _____

2. Give patient identification:

   2.1 Hospital registration number: '_'_'_'_'_'_'_'_'_'_' (double check!)

   2.2 Date of birth: _'_/_'_/_'_
   d m y

   2.3 Sex: ( ) male
   ( ) female

---

3. Give patient name and address:

   Family name: '_' Initials: '_'_'_'_'

   Maiden name: '_'
   (if married)

   Street : '_' Nr: '_'_'_'_'_'

   City : '_'_'_'_'_'_'_'_' '_'
   (postal code)

   Country: '_'

   Telephone: '_'_'_'_'_'_' '_'_'_'_'_'_'_'_'

ID nr:

10 - 22 DAY EXERCISE TEST FORM

BICYCLE PROTOCOL : STEPWISE INCREMENTS OF 10 WATTS/MIN SITTING POSITION.

TREADMILL PROTOCOL : MODIFIED BRUCE (WELD):

TIME (min)	SPEED (mph/kmh)	SLOPE (%)	
1-3	1.7/2.9	0	
4-6	1.7/2.9	5	
7-9	1.7/2.9	10	(=BRUCE 1)
10-12	2.5/4.3	12	(=BRUCE 2)
13-15	3.4/5.8	14	(=BRUCE 3)
16-18	4.2/7.1	16	(=BRUCE 4)

RECORD ECG EITHER CONTINUOUSLY OR INTERMITTENTLY.

MAKE COPIES OF THE MOST ABNORMAL ECG DURING THE TEST AND OF THE ECGs AT PEAK EXERCISE AND AFTER 6 MINUTES RECOVERY.

STORE ORIGINALS FOR TRANSFERRAL TO THE DATA CENTER, MARK WITH DATE, TIME, AND ID NR PEEL-OFF STICKER.

CONTINUE EXERCISE UNTIL SYMPTOMS, DROP OF SYSTOLIC BLOOD PRESSURE, SEVERE ARRHYTHMIAS, OR SIGNIFICANT ST-CHANGES OCCUR OR UNTIL THE PATIENT'S HEART RATE EXCEEDS 200 MINUS AGE.

DO NOT STOP MEDICATION DURING THE TEST.

DO NOT COMBINE EXERCISE TEST WITH RADIONUCLIDE ANGIOGRAPHY OR THALLIUM SCINTIGRAPHY.

4. Make standard 12-lead ECG (store original for transferral to data center, mark with date, time, ID nr peel-off sticker).

   Date: _,_/_,_/_,_ (d m y) Time: _,_:_,_ (h m)

ERRATUM EXERCISE TEST FORM PAGE 2, 135.10

Make 12-lead ECGs at rest, at maximum ST-shift, at peak exercise and at 6 min recovery (or make continuous 12-lead ECG registration). For all these ECGs patient must be in the same position.

Add calibration marks (1 cm = 1 mV)

5. Indicate patient's height and weight:

   Height: ,_,_,_, cm Weight: ,_,_,_, kg

6. Perform symptom limited pre-discharge exercise test:

   6.1 Which equipment is used (tick one)?
   - ( ) bicycle (sitting position)
   - ( ) bicycle (supine)
   - ( ) treadmill

   6.2 Indicate ECG leads used (tick all that apply):

					other, specify:
( ) I	( ) aVR	( ) V1	( ) V4	( ) X	( ) _____
( ) II	( ) aVL	( ) V2	( ) V5	( ) Y	( ) _____
( ) III	( ) aVF	( ) V3	( ) V6	( ) Z	( ) _____

   6.3 Which protocol is used? (tick one):
   - ( ) bicycle, 10 Watts/min increments
   - ( ) bicycle, other. Indicate: ,_,_, Watts/,_,_, min increments
   - ( ) treadmill (modified Bruce)
   - ( ) treadmill, other specify: _____

ID nr:

6.4 Give results of exercise test (measure ST-changes 80 msec after J-point):

	at start of exercise test	onset of symptoms	1 mm ST-depression or -elevation	peak exercise
- min after start of exercise		,_,_, min	,_,_, min	,_,_, min
- bicycle: Watt		,_,_,_, Watt	,_,_,_, Watt	,_,_,_, Watt
- treadmill: slope		,_,_, %	,_,_, %	,_,_, %
speed (km/h)		,_,_, km/h	,_,_, km/h	,_,_, km/h
(mph)		,_,_, mph	,_,_, mph	,_,_, mph
- systolic blood pressure	,_,_,_, mmHg	,_,_,_, mmHg	,_,_,_, mmHg	,_,_,_, mmHg
- heart rate	,_,_,_, bpm	,_,_,_, bpm	,_,_,_, bpm	,_,_,_, bpm

6.5 Any symptoms during the test? NO (6.6) YES ( )

If yes, tick the appropriate symptom/test-phase combination(s) and give time relative to beginning of test-phase:

	During exercise	Onset of symptoms	During recovery	Onset of symptoms
- dyspnea :	( )	,_,_, min	( )	,_,_, min
- typical angina :	( )	,_,_, min	( )	,_,_, min
- a-typical angina :	( )	,_,_, min	( )	,_,_, min
- chest discomfort :	( )	,_,_, min	( )	,_,_, min
- other :	( )	,_,_, min	( )	,_,_, min

6.6 Indicate maximum workload achieved: ,_,_, Watts/Bruce: ,_,_, min

6.7 Indicate expected "normal" value : ,_,_, Watts/Bruce: ,_,_, min.

6.8 What was the workload according to the patient (tick one)?

( ) submaximal
( ) near maximal
( ) maximal

6.9 Was the test terminated by the patient? NO (6.10) YES ( )

If yes, tick reason:
( ) angina
( ) dyspnea
( ) general fatigue
( ) fatigue in the legs
( ) other: _____

6.10 Was the test terminated by the physician? NO (6.11) YES ( )

If yes, tick reason:
( ) arrhythmias
( ) conduction defects
( ) ST-T changes
( ) abnormal blood pressure response
( ) heart rate over (200 - age)
( ) other: _____

ERRATA EXERCISE TEST FORM PAGE 3-4, 135.10

1. Item 6.10: abnormal blood pressure response is at least a 15 mmHg drop in systolic blood pressure
2. Item 6.11: ventricular tachycardia is 100 bpm or more
3. Item 6.13: add generic name and dosage

ID nr:

(6. continued)

6.11 Were any arrhythmias seen? NO (6.12) YES ( )

If yes, tick appropriate arrhythmia/time combination(s):

	before test	during exercise	during recovery
- premature supraventricular complexes	( )	( )	( )
- uniform premature ventricular complexes	( )	( )	( )
- multiform premature ventricular complexes	( )	( )	( )
- bigemini	( )	( )	( )
- couplets	( )	( )	( )
- short run ventricular tachycardia (3-10 complexes)	( )	( )	( )
- ventricular tachycardia (more than 10 complexes)	( )	( )	( )
- other: ________________	( )	( )	( )

6.12 Were any repolarization changes seen? NO (6.13) YES ( )

If yes, tick all that apply: LEADS

( ) junction depression ____________

( ) ST-depression ____________

( ) ST-elevation ____________

If ST-elevation or depression (measure 80 msec after J-point):

- during exercise: maximum: ‚_‚_‚ mm, at: ‚_‚_‚ min
- during recovery: maximum: ‚_‚_‚ mm, at: ‚_‚_‚ min

6.13 Give details of use of medication before and during exercise test (tick appropriate drug/time combination(s)):

	maintenance therapy	added during test
- beta-blockers	( )	( )
- calcium antagonists	( )	( )
- nitrates	( )	( )
- antiarrhythmics	( )	( )
- digitalis	( )	( )

7. Clinic where test was performed: ____________________

Date performed: _‚_/_‚_/_‚_ (d m y) Time: _‚_:_‚_ (h m)

8. Supply name and signature of responsible physician:

Dr: ‚_‚_‚_‚_‚_‚_‚_‚_‚_‚_‚_‚_‚ Signature: ____________ Date signed: _‚_/_‚_/_‚_ (d m y)

THANK YOU FOR YOUR CO-OPERATION!

RETURN RED COPY OF FORM TO CLINIC WHERE PATIENT WAS ADMITTED

SEND ORIGINAL TO THOMAE (USE ENVELOPE PROVIDED)

SEND BLUE COPY AND ORIGINAL ECGs TO DATA CENTER (USE ENVELOPE PROVIDED)

ID Nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT
TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

10-22 DAY RADIONUCLIDE ANGIOGRAPHY FORM

LV-FUNCTION STUDY

(rt-PA versus placebo trial)

ID nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

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P A T I E N T / C L I N I C I D E N T I F I C A T I O N

1. Identification of clinic where patient was admitted:

   1.1 Name: _____

   1.2 City: _____

2. Give patient identification:

   2.1 Hospital registration number: '_'_'_'_'_'_'_'_'_'_'_' (double check!)

   2.2 Date of birth: _'_/_'_/_'_
   d m y

   2.3 Sex: ( ) male
   ( ) female

---

3. Give patient name and address:

   Family name: '_' Initials: '_'_'_'_'

   Maiden name: '_'
   (if married)

   Street : '_' Nr: '_'_'_'_'_'

   City : '_'_'_'_'_'_'_'_' '_'
   (postal code)

   Country: '_'_'_'_'_'_'_'_'_'_'_'_'_'_'_'_'_'_'_'

   Telephone: '_'_'_'_'_'_' '_'_'_'_'_'_'_'_'

ID nr:

10-22 DAY RADIONUCLIDE ANGIOGRAPHY FORM

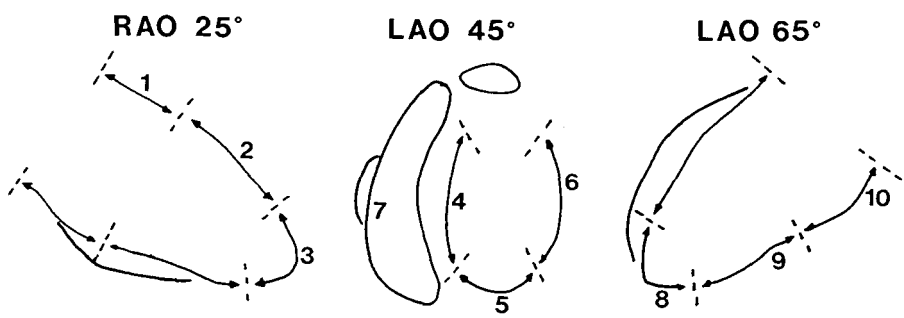
GIVE 1 AMPUL STANNOUS PYROPHOSPHATE INTRAVENOUSLY.

WAIT 20 MINUTES AND ADMINISTER 15 mCI OR MORE TECHNETIUM-99m. DO NOT GIVE STANNOUS PYROPHOSPHATE AND TECHNETIUM THROUGH SAME INTRAVENOUS LINE!

START DATA COLLECTION AFTER ADMINISTRATION OF TECHNETIUM:
- R-WAVE GATED MODE OR GATED LIST MODE.
- A MINIMUM OF 20 FRAMES PER CYCLE AND A MINIMUM OF 5 MINUTES PER VIEW.
- VIEWS: RAO 25°(20°-30°), LAO 45°(30°-60°), SELECT LAO VIEW WITH ±10° TILT FOR OPTIMAL SEPARATION LEFT AND RIGHT VENTRICLE, LAO LATERAL (65°-90°).
- USE TWO REGIONS OF INTEREST FOR CALCULATIONS OF EJECTION FRACTION IF AVAILABLE.

4. Perform radionuclide angiography:

4.1 Indicate results (tick the appropriate):



	NORMAL	HYPOKINETIC	AKINETIC	DYSKINETIC	UNKNOWN
RAO 25°:					
1. antero-basal :	( )	( )	( )	( )	( )
2. antero-lateral :	( )	( )	( )	( )	( )
3. apex :	( )	( )	( )	( )	( )
LAO 45°:					
4. antero-septal :	( )	( )	( )	( )	( )
5. apex :	( )	( )	( )	( )	( )
6. postero-lateral :	( )	( )	( )	( )	( )
7. right ventricle :	( )	( )	( )	( )	( )
LAO 65°:					
8. apex :	( )	( )	( )	( )	( )
9. inferior :	( )	( )	( )	( )	( )
10. posterior :	( )	( )	( )	( )	( )

ID nr:

(4. continued)

4.2 Indicate ejection fraction: left ventricle : _,_,_ %

	NO	YES
4.3 Did you determine quantitative regional ejection fraction?	( )	( )
4.4 Did patient have angina pectoris during radionuclide angiography?	( )	( )

4.5 Give details of use of medication before and during radionuclide angiography (tick appropriate drug/time combination(s)):

	maintenance therapy	added during angio
- beta-blockers	( )	( )
- calcium antagonists	( )	( )
- nitrates	( )	( )
- antiarrhythmics	( )	( )
- digitalis	( )	( )

5. Clinic where radionuclide angiography was performed: _____

Date performed: _,_/_,_/_,_ (d m y) Time: _,_:_,_ (h m)

6. Supply name and signature of responsible physician:

Dr: _,_,_,_,_,_,_,_,_,_,_,_,_,_,_,_,_,_,_,_ Signature: _____ Date signed: _,_/_,_/_,_ (d m y)

THANK YOU FOR YOUR CO-OPERATION!

RETURN RED COPY OF FORM TO CLINIC WHERE PATIENT WAS ADMITTED

SEND ORIGINAL TO THOMAE (USE ENVELOPE PROVIDED)

SEND BLUE COPY TO DATA CENTER (USE ENVELOPE PROVIDED).

ID Nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT
TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

10-22 DAY CATHETERIZATION FORM

LV-FUNCTION STUDY

(rt-PA versus placebo trial)

135.10 - February 26, 1986

ID nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

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P A T I E N T / C L I N I C I D E N T I F I C A T I O N

1. Identification of clinic where patient was admitted:

   1.1 Name: _____

   1.2 City: _____

2. Give patient identification:

   2.1 Hospital registration number: ,_,_,_,_,_,_,_,_,_,_,_, (double check!)

   2.2 Date of birth: _,_/_,_/_,_
   d m y

   2.3 Sex: ( ) male
   ( ) female

---

3. Give patient name and address:

   Family name: ,_, Initials: ,_,_,_,_,

   Maiden name: ,_,
   (if married)

   Street : ,_, Nr: ,_,_,_,_,_,

   City : ,_,_,_,_,_,_,_,_, ,_,
   (postal code)

   Country: ,_,

   Telephone: ,_,_,_,_,_,_,_,_, ,_,

ID nr:

10-22 DAY CATHETERIZATION FORM

- USE BIPLANE X-RAY EQUIPMENT, IF AVAILABLE!
- LEFT VENTRICULOGRAPHY MUST PRECEED CORONARY ANGIOGRAPHY
- USE NON-IONIC CONTRAST MATERIAL AT 37°C
- USE 35 mm CINEFILM, MINIMUM FILM SPEED 50 frames/sec
- BREATH SHOULD BE HELD IN MID-INSPIRATION
- POSITION IMAGE INTENSIFIER AGAINST THE CHEST DURING LEFT VENTRICULOGRAPHY (OF MAJOR IMPORTANCE FOR CALIBRATION)
- NITRATES MAY NOT BE GIVEN ROUTINELY

LEFT VENTRICULOGRAPHY:

- CONTRAST: 0.5-1 ml/kg, flow 6-20 ml/sec.
- PROJECTIONS: 1. RAO 30°, 2. LAO 60°. (IF MONOPLANE SYSTEM IS USED: RAO FIRST)
- IF MORE THAN ONE CONTRAST INJECTION IS GIVEN: WAIT AT LEAST 10 min OR UNTIL END DIASTOLIC LEFT VENTRICULAR PRESSURE HAS RETURNED TO PRE-ANGIOGRAM VALUE
- AT LEAST TWO CONSECUTIVE SINUS BEATS MUST BE FILMED
- NOTE DISTANCE X-RAY TUBE TO IMAGE INTENSIFIER AND FIELD SIZE OF IMAGE INTENSIFIER AT THE TIME OF RAO LEFT VENTRICULOGRAPHY (Item 6.4)

4. Obtain blood sample (5 ml) for anti-body tests. Use provided tube (marked ANT). Put peel-off sticker with tube number in box (all 3 copies!). Store on ice until centrifugation.

sticker

TIME _'_'_:_'_ (h m) DATE _'_'_/_'_'_/_'_'_ (d m y)

5. Indicate details angioroom:

   5.1 Angioroom number: '_'_'

   5.2 System used (tick): ( ) monoplane
   ( ) biplane

6. Perform left ventriculography:

   6.1 Indicate patient's height and weight:

   Height: '_'_'_' cm Weight: '_'_'_' kg

   6.2 Technique used (tick): ( ) femoral
   ( ) brachial

   6.3 Measure pressures and heart rates before each projection:

	MONOPLANE RAO	MONOPLANE LAO	BIPLANE RAO/LAO	
peak systolic pressure :	_'_'_'	_'_'_'	_'_'_'	mmHg
end diastolic pressure :	_'_'_'	_'_'_'	_'_'_'	mmHg
heart rate :	_'_'_'	_'_'_'	_'_'_'	bpm

ID nr:

(6. continued)

6.4 List filming sequence and timing of visualization for left ventriculography: Indicate for RAO view(s) the distance X-ray tube to image intensifier and field size of image intensifier (of major importance for calibration):

	View:	Time:	Distance X-ray - image intensifier:	Field size image intensifier:
1.	RAO 30°	_'_:_'_	_'_'_' cm	'_'_' inch
2.	_____	_'_:_'_	_'_'_' cm	'_'_' inch
3.	LAO 60°	_'_:_'_		'_'_' inch
4.	_____	_'_:_'_ (h m)		'_'_' inch

6.5 Give additional information about left ventriculography:

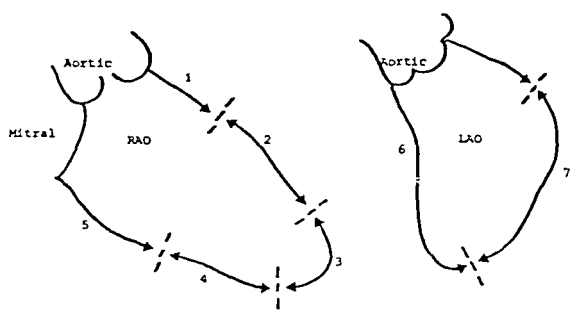
volume of contrast injected : _'_'_' ml

rate of injection : _'_'_' ml/sec

Trade name contrast material: _____

Manufactured by : _____

6.6 Assess segmental wall motion using the drawing below and tick in the diagram all that apply:



1. anterobasal segment
2. anterolateral segment
3. apical segment
4. diaphragmatic segment
5. posterobasal segment
6. septal wall
7. posterolateral

	1	2	3	4	5	6	7	
normal	( )	( )	( )	( )	( )	( )	( )	
hypokinetic	( )	( )	( )	( )	( )	( )	( )	
akinetic	( )	( )	( )	( )	( )	( )	( )	
dyskinetic	( )	( )	( )	( )	( )	( )	( )	
other abnormality	( )	( )	( )	( )	( )	( )	( )	Specify: _____
undefined	( )	( )	( )	( )	( )	( )	( )	

ID nr:

(6. continued)

	NO	YES
6.7 Is mitral regurgitation present?	(6.8)	( )

If yes, indicate grade (tick one):

( ) I, regurgitant jet with minimal opacification of the left atrium which clears rapidly

( ) II, regurgitant jet with moderate opacification of the left atrium which clears rapidly

( ) III, no jet, the left atrial opacification is as intense as that of the left ventricle and aorta on the late films; usually the left atrium is greatly enlarged

( ) IV, the left atrial opacification is more intense than that of the left ventricle and aorta, and the intense opacification persists throughout the entire series of films; left ventricular dilatation and marked left atrial enlargement

	NO	YES
Is mitral regurgitation catheter related?	( )	( )

	NO	YES
6.8 Was global ejection fraction measured?	(7)	( )

If yes, indicate: _ _ _ %

STORE END SYSTOLIC AND END DIASTOLIC CONTOURS FOR LATER REFERENCE (IN CASE FILM IS LOST)

7. Perform coronary angiography

7.1 Indicate type of catheter(s) used (tick):

Right Coronary: ( ) Judkins ( ) Sones ( ) other: _____

Left Coronary: ( ) Judkins ( ) Sones ( ) other: _____

French size: _____

Manufactured by: _____

7.2 List filming sequence of visualization coronary angiogram:

MINIMUM REQUIRED: - 3 VIEWS LEFT CORONARY
- 2 VIEWS RIGHT CORONARY

Artery:	View:	Artery:	View:
1. _____	_____	6. _____	_____
2. _____	_____	7. _____	_____
3. _____	_____	8. _____	_____
4. _____	_____	9. _____	_____
5. _____	_____	10. _____	_____

Item 7 - Measure aortic pressure and heart rate before coronary angiography:

systolic : _ _ _ mmHg

diastolic : _ _ _ mmHg

heart rate: _ _ _ bpm

7.3 Indicate time first view: _ _ : _ _ (h : m)

	NO	YES
7.4 Did you use the same contrast for coronary angiography as for left ventriculography?	( )	(8)

If no, indicate trade name: _____

Manufactured by: _____

ERRATUM 10-22 DAY CATH.FORM 4, 135.10

ID nr:

8. FILM CALIBRATION SPHERE, when patient has left the table:

   8.1 If monoplane system is used:
   Reproduce same distance X-ray tube to image intensifier as used for RAO left ventriculography (item 6.4). Hold calibration sphere with short distance-marker against image intensifier (perpendicular). Film sphere for 5 sec.

   8.2 If biplane system is used:
   Reproduce arm angulations as during left ventriculography. Reproduce same distance X-ray tube to image intensifier as used for RAO left ventriculography. Hold calibration sphere in the isocentric point. Film sphere for 5 sec.

	NO	YES
9. Was catheterization procedure interrupted?	(10)	(9.1)

9.1 If yes, why? _____

➡ COMPLETE MEASUREMENTS AND OBSERVATIONS IF AT ALL POSSIBLE

	NO	YES
10. Did any complications occur?	(11)	(10.1)

10.1 If yes (tick all that apply, give details):

( ) death _____ ( ) arrhythmia _____

( ) MI _____ ( ) vascular _____

( ) CVA _____ ( ) other _____

11. STORE FILM FOR LATER CENTRAL ANALYSIS

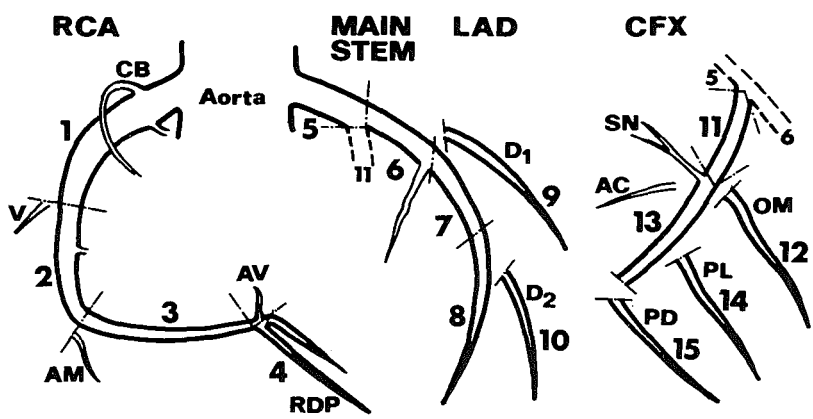
INDICATE ANGIO REGISTRATION NUMBER : '_'_'_'_'_'_'_'_'_'_'

LABEL OUTSIDE OF FILM BOX WITH ID NR PEEL-OFF STICKER AND STORE FILM FOR LATER CENTRAL ANALYSIS

	NO	YES
12. Are you able to identify "infarct related" vessel? (see admission ECG)	(12.1)	(12.2)

12.1 If no, why not: _____

12.2 If yes, give number of vessel segments considered "infarct related": '_'_' (refer to picture below).



(for intermediate, 2nd marginal branch, or deviation from this sketch: indicate on drawing).

ID nr:

13. Indicate grade of perfusion of the "infarct related" segment (tick one):

(13.1) grade 0: non perfusion
(13.1) grade 1: penetration with minimal perfusion (contrast fails to opacify the entire coronary bed distal to the stenosis for the duration of the cine run)
(13.2) grade 2: partial perfusion (contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in coronary bed distal to the obstruction than in comparable areas not perfused by the infarct related vessel)
(13.2) grade 3: complete perfusion (filling and clearance of contrast equally rapid in coronary bed distal to stenosis as in other coronary beds)

13.1 Indicate with a dot in picture (item 12) site of grade 0 or 1 obstruction.

13.2 Is there a diameter stenosis of more than 60% in the "infarct related" segment? NO ( ) YES ( )

13.3 Give details of use of medication before and during catheterization (tick appropriate drug/time combination(s)):

	maintenance therapy	added during cath
- beta-blockers	( )	( )
- calcium antagonists: - oral	( )	( )
- i.v.	( )	( )
- i.c.	( )	( )
- nitrates: - s.l.	( )	( )
- i.v.	( )	( )
- i.c.	( )	( )
- any other medication, specify:		
_____	( )	( )
_____	( )	( )
_____	( )	( )
_____	( )	( )

14. Clinic where catheterization was performed: _____

Date performed: _d_d/_m_m/_y_y

15. Supply name and signature of responsible physician:

Dr: _____ Signature: _____ Date signed: _d_d/_m_m/_y_y

THANK YOU FOR YOUR CO-OPERATION!

CENTRIFUGE BLOOD FOR SPECIAL ANTI-BODY TEST (item 4). TRANSFER PLASMA WITH PIPETTE TO TUBE FROM SET WITH CORRESPONDING NUMBER AND STORE SAMPLE AT -20°C UNTIL FURTHER NOTICE.

RETURN RED COPY OF FORM TO CLINIC WHERE PATIENT WAS ADMITTED.

SEND ORIGINAL TO THOMAE (USE ENVELOPE PROVIDED).

SEND BLUE COPY TO DATA CENTER (USE ENVELOPE PROVIDED).

ID Nr:

EUROPEAN CO-OPERATIVE STUDY GROUP FOR RECOMBINANT
TISSUE-TYPE PLASMINOGEN ACTIVATOR (rt-PA)

L V - F U N C T I O N S T U D Y

O N E - Y E A R F O L L O W - U P F O R M

ID Nr:

THIS PAGE MUST BE COMPLETED FOR EVERY PATIENT ADMITTED TO THE STUDY. HOWEVER, IF YOU CANNOT SUPPLY THE DATA CENTER AND THOMAE WITH THE PATIENT'S NAME AND ADDRESS, YOU ARE ALLOWED TO CUT OFF THE BOTTOM PART OF THE WHITE AND BLUE COPIES OF THE FORM BEFORE SENDING THEM IN. YOUR OWN RED COPY MUST ALWAYS BE FILLED OUT AND STORED FOR FUTURE REFERENCE, SEPARATELY FROM PATIENT'S HOSPITAL FILE.

P A T I E N T / C L I N I C I D E N T I F I C A T I O N

1. Give clinic identification:

   1.1 Name: _____

   1.2 City: _____

2. Give patient identification:

   2.1 Hospital registration number: _'_'_'_'_'_'_'_'_'_'_'_'_' (double check!)

   2.2 Date of birth: _'_/_'_/_'_
   d m y

   2.3 Sex: ( ) male
   ( ) female

---

3. Give patient's name and address:

   Family name: _____ Initials : _____

   Maiden name: _____
   (if married)

   Street : _____ Number : _____

   City : _____ Postal code: _____

   Country : _____

   Telephone : _____

ID Nr:

THIS FORM MUST BE COMPLETED ONE YEAR AFTER ALLOCATION FOR EVERY PATIENT ADMITTED TO THE STUDY AND ALIVE AT THREE-MONTH FOLLOW-UP. INFORMATION IS REQUIRED FOR THE TIME SPAN BETWEEN THREE-MONTH FOLLOW-UP AND ONE YEAR AFTER ALLOCATION OR DEATH. ARRANGE OUT-PATIENT CLINIC VISIT ONE YEAR AFTER ALLOCATION (BETWEEN 12 AND 13 MONTHS). OBTAIN STANDARD 12-LEAD ECG MADE ON THAT DATE. IF IT IS IMPOSSIBLE TO SEE PATIENT, TRY TO OBTAIN AS MUCH INFORMATION AS YOU CAN.

4. Target date for one-year follow-up: _'_/_'_/_'_ (d m y)

5. Actual date of one-year follow-up: _'_/_'_/_'_ (d m y)

6. Was patient alive at actual date of one-year follow-up? UNKNOWN (6.1) NO (6.2) YES (6.3)

   6.1 If unknown, what was date patient last known to be alive? _'_/_'_/_'_ (d m y)
   (e.g. date last out-patient clinic visit)
   GO TO ITEM 17

   6.2 If deceased, COMPLETE ITEMS 7-11 AND ITEMS 16-17

   6.3 If alive, COMPLETE ITEMS 12-17

PATIENT DIED

7. Date patient died: _'_/_'_/_'_ (d m y)

8. Place of death (tick one):
   ( ) in hospital
   ( ) home
   ( ) other: _____

9. Describe briefly the circumstances of death:

   _____

   _____

   _____

   _____

10. Was an autopsy performed? NO (11) YES (10.1)

    10.1 If yes, ATTACH COPY OF REPORT

11. Which factors contributed to death (tick all that apply):
    ( ) re-infarction
    ( ) congestive heart failure
    ( ) cardiac surgery
    ( ) PTCA
    ( ) arrhythmias, describe: _____
    ( ) other cardiac, describe: _____
    ( ) non-cardiac, describe: _____
    ( ) unknown

ID Nr:

PATIENT ALIVE

12. Was patient seen at your out-patient clinic at the actual date of one-year follow-up? NO (12.1) YES (13)

12.1 If no, indicate how information was obtained (tick one):
( ) telephone contact with patient
( ) through patient's family
( ) through general practitioner
( ) cardiologist elsewhere
( ) other means, specify: _____

13. Obtain standard 12-lead ECG (including 1 cm=1 mV calibration) (forward original to data center, mark with date, time, and ID nr peel-off sticker) DATE _'_/_'_/_'_ d m y

14. Indicate current state at one-year follow-up:

Date of re-infarction ___/___/___ d m y

14.1 Tick all that apply:
( ) no complaints
( ) dyspnea
( ) angina at rest
( ) effort angina

14.2 Did a definite (re)infarction occur between three-month and one-year follow-up? NO (14.4) YES (14.3)

14.3 In case of definite (re)infarction, give details:

Site of infarction (tick one):
( ) anterior
( ) infero-posterior
( ) lateral
( ) impossible to determine

Diagnosis based on (tick one):
( ) both ECG and enzymes typical
( ) typical ECG pattern only
( ) typical enzyme pattern only
( ) other grounds, describe: _____

SEND ORIGINAL ECG(s), MARKED WITH TIME, DATE AND ID NR PEEL-OFF STICKER, AND COPY OF YOUR LABORATORY DATA SHEET FOR CARDIAC ENZYMES, TOGETHER WITH THIS FORM TO THE DATA CENTER

14.4 Indicate functional state at one-year follow-up (tick one):
(15) unknown
(15) no limitation of physical activity
(14.5) slight limitation of physical activity but comfortable at rest
(14.5) marked limitation of physical activity but comfortable at rest
(14.5) unable to carry out any physical activity, with or without symptoms at rest

14.5 Limitations due to (tick one):
( ) angina pectoris
( ) congestive heart failure
( ) both
( ) other, describe: _____

ID Nr:

15. Indicate which medication patient currently uses (tick all that apply):

( ) anticoagulants (coumarins)
( ) antiplatelet drugs
( ) beta-blockers
( ) calcium antagonists
( ) long acting nitrates
( ) digitalis
( ) diuretics
( ) any other medication, specify:
_____
_____
_____
( ) none

ALL PATIENTS

16. Has patient been admitted to hospital for any reason between three-month and one-year follow-up or death? NO (17) YES (16.1)

16.1 If yes, give indication, dates of hospital admission and duration of hospital stay (tick all that apply, if more than one admission indicate by different admission dates):

	DATE ADMITTED	DURATION OF HOSPITAL STAY (in days)
( ) angina at rest without (re)infarction	_'_/_'_/_'_	'_'_'_
( ) re-infarction	_'_/_'_/_'_	'_'_'_
( ) congestive heart failure	_'_/_'_/_'_	'_'_'_
( ) rhythm disturbances, specify: _____	_'_/_'_/_'_	'_'_'_
( ) pericarditis	_'_/_'_/_'_	'_'_'_
( ) thrombo-embolism, specify: _____	_'_/_'_/_'_	'_'_'_
( ) catheterization	_'_/_'_/_'_	'_'_'_
( ) PTCA	_'_/_'_/_'_	'_'_'_
( ) bypass surgery	_'_/_'_/_'_	'_'_'_
( ) other cardiac surgery, specify: _____	_'_/_'_/_'_	'_'_'_
( ) other, specify: _____	_'_/_'_/_'_	'_'_'_
( ) unknown	_'_/_'_/_'_	'_'_'_
	d m y	

17. Supply name and signature of responsible physician:

Dr: _____ Signature: _____ Date signed: _'_/_'_/_'_ d m y

STORE RED COPY OF FORM, READY FOR LATER REFERENCE, SEPARATELY FROM PATIENT's HOSPITAL FILE. SEND ORIGINAL TO THOMAE (USE PROVIDED ENVELOPE). SEND BLUE COPY, TOGETHER WITH ORIGINAL ECGs (ITEM 13 AND ITEM 14.3, if applicable) AND COPY OF LABORATORY DATA SHEET (ITEM 14.3, if applicable) TO DATA CENTER (USE PROVIDED ENVELOPE).

THANK YOU FOR YOUR CO-OPERATION!