Recombinant tissue-type plasminogen activator and immediate angioplasty in acute myocardial infarction. One-year follow-up. The European Cooperative Study Group [published errata appear in Circulation 1993 May;87(5):1775 and 1993 Jun;87(6):2070]

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Recombinant Tissue-Type Plasminogen Activator and Immediate Angioplasty in Acute Myocardial Infarction

One-Year Follow-up

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Background. **The European Cooperative Study Group conducted two randomized trials in patients with suspected myocardial infarction to assess the effect of 100 mg single-chain recombinant tissue-type plasminogen activator (rt-PA, alteplase) on enzymatic infarct size, left ventricular function, morbidity and mortality relative to placebo (alteplase/placebo trial) and to assess the effect of immediate percutaneous transluminal coronary angioplasty (PTCA) in addition to alteplase (alteplase/PTCA trial). One-year follow-up results are reported.**

Methods and Results. **In the alteplase/placebo trial, 721 patients with chest pain of less than 5 hours and extensive ST-segment elevation were allocated at random to 100 mg alteplase or placebo (double-blind) over 3 hours. In the alteplase/PTCA trial, 367 similar patients received alteplase and subsequently were allocated at random to immediate coronary angiography and angioplasty of the infarct-related vessel or control. All patients received aspirin and intravenous heparin. In the alteplase/placebo trial, mortality during the first year was reduced by 36% with alteplase (from 9.3% to 5.6%; difference, −3.7%; 95% confidence interval, −7.5% to 0.2%). Revascularization was performed more frequently after alteplase, and more patients in the alteplase group were in New York Heart Association functional class I or II. Reinfarction tended to occur more frequently after alteplase than after placebo. In the alteplase/PTCA trial, reinfarction was less common after immediate PTCA, and revascularization procedures were less frequent. However, this benefit was offset by a high rate of immediate reocclusion and early recurrent ischemia and by higher mortality at 1 year (9.3% versus 5.4%; difference, 3.9%; 95% confidence interval, −1.5% to 9.2%) in the invasive group. In a multivariate analysis of 1,043 hospital survivors, mortality after discharge was related to coronary anatomy, left ventricular function, age, and previous infarction but not to initial treatment allocation. Reinfarction after hospital discharge tended to be more common after alteplase and related to coronary anatomy.**

Conclusions. **Benefit from treatment with alteplase, heparin, and aspirin is not diminished at 1 year. Routine immediate PTCA does not confer additional benefit. Prognosis after hospital discharge mainly is determined by coronary anatomy and residual left ventricular function and is unrelated to initial treatment assignment. (*Circulation* 1992;86:111–120)**

KEY WORDS • **percutaneous transluminal coronary angioplasty** • **plasminogen activator, tissue-type** • **clinical trials** • **thrombolytic therapy** • **myocardial infarction**

In 1988, the European Cooperative Study Group reported two randomized clinical trials with single-chain recombinant tissue-type plasminogen activator (alteplase). In the alteplase/placebo trial, 721 patients were allocated at random to alteplase 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 alteplase. Mortality was reduced by 51% at 2 weeks and by 36% at 3 months. In the alteplase/percutaneous transluminal coronary angioplasty (PTCA) trial, 367 patients were allocated at random to a noninvasive strategy of alteplase, heparin, and aspirin or to an invasive strategy of alteplase, heparin, and aspirin followed by immediate coronary angiography and PTCA.[2] No additional benefit of immediate coronary angioplasty

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

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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 for 1 year to answer the following questions. Is the reduction of mortality by alteplase maintained during follow-up? Are clinical course and functional class influenced by alteplase and immediate angioplasty? Which are the determinants of mortality and reinfarction after hospital discharge?

Methods

Patients with ECG evidence of extensive myocardial infarction were enrolled in two different trials provided that thrombolytic therapy could be started within 5 hours after the onset of symptoms. Details of patient selection and baseline characteristics have been published previously.[1,2] All patients entered in both trials had given their informed consent, and the ethical committee in each participating center had approved the study protocol. In the alteplase/placebo trial, patients were randomized to alteplase or placebo. All patients received a bolus of 5,000 IU heparin followed by an infusion of 1,000 IU/hr and 250 mg aspirin i.v. Alteplase was given as a 10-mg bolus injection followed by 50 mg in 1 hour and 40 mg in the subsequent 2 hours. In the alteplase/PTCA trial, patients were allocated to a noninvasive strategy of alteplase, heparin, and aspirin or to an invasive strategy of alteplase, heparin, and aspirin followed by immediate angiography and PTCA. In both trials, aspirin (75–120 mg on alternating days) as well as anticoagulation with heparin and/or coumarin were continued until predischarge angiography, which was required in all patients between days 10 and 22 after admission. Investigators had to choose a 4-day time window for this angiography before the start of the study to avoid the clinical condition of the patient determining the timing of the angiography between days 10 and 22. After discharge, long-term treatment with β-blockers was recommended (100 mg metoprolol b.i.d.). In case of recurrent ischemia resistant to medical treatment, PTCA or coronary bypass surgery was to be performed. In the alteplase/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 diameter stenosis in the infarct-related vessel was assessed visually and categorized into <50%, 50–90%, or 90–99% (but with complete distal filling within three cardiac cycles) diameter stenosis and (sub)total occlusion (incomplete distal filling within three cardiac cycles). Left ventricular ejection fraction was determined from contrast left ventricular angiography in the right anterior oblique projection.[1]

In both trials, contrast left ventricular ejection fraction on angiography between days 10 and 22 was used for trial size calculation. 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 with analyzable angiograms were necessary in each group. Assuming missing or inadequate angiograms in 15%, 700 patients were foreseen.[1] In the alteplase/PTCA trial, patient entry was stopped by the Data Monitoring and Ethical Committee when interim analysis revealed an adverse effect of the invasive treatment. In that study, 367 patients were entered.[2]

Follow-up information was obtained by the investigators at each participating center during a visit of the patient to the outpatient clinic a few weeks more than 3 months and a few weeks more than 1 year after myocardial infarction. Data regarding survival, date and cause of death, dates and duration of any hospital admission, reinfarction, coronary angioplasty and bypass surgery, New York Heart Association functional 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.

Statistical Analysis

Incidence of events and use of medication were reported as proportions of patients. Patient groups were compared using rate differences or ratios with test-based confidence intervals.

Survival and survival without events (reinfarction, revascularization) were determined according to Kaplan-Meier to account for patients with incomplete follow-up.[3] Relative risk in one patient group compared with a reference group is reported as hazard ratio and was obtained with Cox regression analysis.[4] In the Cox regression analyses, complete follow-up was used without truncation at 1 year.

There has been some doubt whether randomization in the alteplase/PTCA trial was successful in segregating treatment groups with equal risk of death before randomization (baseline risk) since patients in shock before randomization were more common in the invasive than in the noninvasive group.[2] Baseline risk was assessed in each individual patient by calculating a baseline risk score based on multiple determinants of mortality available before treatment allocation. The contribution of each determinant of mortality was assessed in the alteplase/placebo trial by Cox multivariate regression analysis. The obtained risk model subsequently was applied in the alteplase/PTCA trial. Baseline risk was assessed in three steps. First, a Cox multivariate model describing the relation between baseline characteristics and mortality was assessed in the alteplase/placebo trial. Only baseline characteristics known to be related to mortality after myocardial infarction were considered: age, sex, history of previous infarction, sum of ST-segment elevation, infarct localization, hemodynamic status before thrombolytic treatment, and delay from symptom onset to start of treatment.[5] In a stepwise manner (BMDP statistical software), determinants of which the coefficient value was $p<0.10$ for entry into the model were included. Indicator variables for treatment allocation were forced into the model, as was the case with indicator variables for missing values. Second, the probability of dying within the first year was calculated from this multivariate model for each individual patient as the following:

$$1-0.969\ \exp(a\times x_1+b\times x_2+\ldots)$$

where 0.969 is the estimated survival at 1 year for a patient without any risk factor x_i; a and b represent the Cox regression coefficients of the indicator variables for age, history of previous myocardial infarction, Killip class III or IV, sum ST-segment elevation, anterior

TABLE 1. Mortality, Reinfarction, and Revascularization Procedures Within First Year

	Alteplase/placebo trial			Alteplase/PTCA trial		
	Placebo*	Alteplase*	Difference (95% CI)	Alteplase†	PTCA†	Difference (95% CI)
Patients with events (%) (*n*)‡						
Death						
14 Days	5.7 (21)	2.8 (10)	−2.9 (−5.9, 0.0)	2.7 (5)	6.6 (12)	3.8 (−0.5, 8.1)
1 Year	9.3 (34)	5.6 (20)	−3.7 (−7.5, 0.2)	5.4 (10)	9.3 (17)	3.9 (−1.5, 9.2)
Reinfarction						
14 Days	4.1 (15)	3.9 (14)	−0.2 (−3.0, 2.7)	6.0 (11)	4.4 (8)	−1.6 (−6.1, 2.9)
1 Year	6.8 (25)	8.2 (29)	1.3 (−2.5, 5.2)	11.4 (21)	6.6 (12)	−4.9 (−10.7, 1.0)
PTCA						
14 Days	2.5 (9)	2.5 (9)	0.1 (−2.2, 2.4)	6.0 (11)	4.9 (9)	−1.1 (−5.7, 3.6)
1 Year	7.7 (28)	7.3 (26)	−0.3 (−4.2, 3.5)	16.3 (30)	7.7 (14)	−8.7 (−15.3, −2.0)
CABG						
14 Days	0.3 (1)	2.3 (8)	2.0 (0.4, 3.6)	0.0 (0)	2.2 (4)	2.2 (0.5, 3.9)
1 Year	7.4 (27)	10.1 (36)	2.8 (−1.4, 6.9)	7.6 (14)	8.2 (15)	0.6 (−4.9, 6.1)
PTCA and CABG						
14 Days	0.3 (1)	0.3 (1)	0.0 (−0.8, 0.8)	0.5 (1)	0.0 (0)	−0.5 (−1.6, 0.5)
1 Year	0.5 (2)	1.1 (4)	0.6 (−0.7, 1.9)	1.6 (3)	0.5 (1)	−1.1 (−3.2, 1.0)
Revascularization						
14 Days	3.0 (11)	5.1 (18)	2.1 (−0.8, 4.9)	6.5 (12)	7.1 (13)	0.6 (−4.6, 5.7)
1 Year	15.8 (57)	18.8 (66)	3.0 (−2.5, 8.5)	25.5 (47)	16.9 (30)	−9.2 (−17.5, −0.8)
Patient status at 14 days (%)§						
Survival	94.3	97.5	3.2 (0.2, 6.2)	97.3	94.0	−3.3 (−7.6, 1.0)
Survival without re-MI	91.3	94.7	3.4 (−0.4, 7.3)	92.9	90.7	−2.2 (−8.0, 3.6)
Survival without re-MI, PTCA, or CABG	89.3	90.4	1.1 (−3.6, 5.7)	90.2	86.9	−3.3 (−10.2, 3.6)
Patient status at 1 year (%)§						
Survival	90.7	94.4	3.7 (−0.3, 7.7)	94.4	90.6	−3.8 (−9.8, 2.3)
Survival without re-MI	86.3	87.6	1.3 (−4.0, 6.6)	85.2	85.8	0.5 (−7.4, 8.4)
Survival without re-MI, PTCA, or CABG	72.7	72.4	−0.3 (−8.0, 7.4)	67.1	73.1	6.0 (−5.4, 17.3)

PTCA, percutaneous transluminal coronary angioplasty; CI, confidence interval; CABG, coronary artery bypass grafting; MI, myocardial infarction.

*No. of placebo patients with complete follow-up, 366 at 14 days and 361 at 1 year; no. of alteplase patients, 355 at 14 days and 351 at 1 year.

†No. of alteplase patients with complete follow-up, 184 at 14 days and 177 at 1 year; no. of PTCA patients, 183 at 14 days and 178 at 1 year.

‡Cumulative incidences, patients with incomplete follow-up are included to avoid exclusion of patients with events.

§Patient status at 14 days and 1 year were determined by Kaplan-Meier survival analysis.

infarct localization, female sex, and treatment allocation; and x_1 and x_2 are 0 or 1 depending on the absence or presence of each risk factor for each patient. For this calculation, the indicator variable for treatment allocation was set at 0 (indicating placebo treatment). This predicted 1-year mortality assuming placebo treatment for each individual patient was used as a composite risk score. Patients were subdivided into low, medium, and high baseline risk groups according to their predicted probability of death within the first year using arbitrary cutoff values of 5.3% and 12.0% to obtain similarly sized subgroups in the alteplase/placebo trial.

As for baseline risk assessment, multivariate Cox models were designed to assess the determinants of mortality after discharge. In addition to the variables used in the model for assessment of baseline risk, contrast left ventricular ejection fraction,[1] grade of stenosis of the infarct-related vessel,[2] and number of coronary arteries with ≥50% diameter stenosis were evaluated.

For all Cox regression analyses, the assumption of proportionality was checked in the data as described previously.[6] Ninety-five percent confidence intervals for the relative risk of a determinant x_i was calculated as the natural antilogarithm of the Cox regression coefficient of $x_i \pm 1.96 \times$standard error of the coefficient of the indicator variable for x_i. A 95% confidence interval including 1 indicates borderline significance since a relative risk of 1 indicates identical risk in the subgroup under study and in the reference group.

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, testing the same variables as for the model for mortality after hospital discharge. Adjusted rate ratios and 95% confidence intervals were calculated from this logistic model according to Miettinen.[7]

Results

Mortality

Eighty-seven of 1,088 patients died during follow-up. In 1,001 surviving patients, follow-up ranged from 50 to 1,124 days (median, 402 days). In 21 patients (2.1%), information was not available for as long as 365 days after myocardial infarction.

In the alteplase/placebo trial, mortality was 9.3% at 1 year in the placebo group and 5.6% in the alteplase group (difference, −3.7%; 95% confidence interval, −7.5% to +0.2%; Table 1). Mortality reduction by alteplase was 36% with univariate and multivariate Cox regression analysis (95% confidence interval, −62% to

TABLE 2. Determinants of Mortality in Alteplase/Placebo Trial

Determinant	No. of patients	Mortality within first year (%)	Relative risk	
			Crude	Adjusted (95% CI)
Age (years)				
<60	412	3.9	...	...
≥60	309	12.3	3.18	3.17 (1.81, 5.56)
History of previous MI				
No	668	6.3	...	...
Yes	53	22.6	3.87	3.63 (1.94, 6.82)
Killip III or IV				
No	693	6.6	...	...
Yes	28	28.6	4.33	3.37 (1.56, 7.26)
Sum ST				
<2.0 mV	500	5.8	...	...
≥2.0 mV	189	12.2	1.97	2.12 (1.24, 3.62)
Missing	32	6.3		
Anterior infarct localization				
No	446	5.8	...	...
Yes	275	10.2	1.73	1.72 (1.02, 2.92)
Sex				
Male	617	6.5	...	...
Female	104	13.5	2.10	1.75 (0.96, 3.17)
Treatment allocation				
Placebo	366	9.3	...	...
Alteplase	355	5.6	0.64	0.64 (0.38, 1.09)

CI, confidence interval; MI, myocardial infarction.

Proportions of patients are given as percentages and were obtained by Kaplan-Meier survival analysis. Crude relative risk is determined by univariate Cox regression analysis; adjusted relative risk is determined by multivariate Cox regression analysis. Predicted mortality for a patient without any risk factor and allocated to placebo is 0.021 at 365 days after discharge. Indicator variables for treatment allocation were forced into the model.

+9%; Table 2). The greatest benefit was found for patients treated within 3 hours after onset of symptoms; mortality was 9.7% (20 of 207) at 1 year in the placebo group and 3.9% (seven of 180) in the alteplase group (difference, −5.8; 95% confidence interval, −10.9% to −0.7%).

In the alteplase/PTCA trial, mortality appeared higher after invasive therapy, both at 14 days and at 1-year follow-up. Mortality was 60% higher in patients allocated to the invasive strategy (95% confidence interval, −25% to +340%) according to Cox regression analysis.

In both trials, heart failure was the most common cause of death, and it occurred in 34 patients. Death was preceded by reinfarction in one third of these patients (12 of 34). Other common causes of death were ventricular arrhythmia (nine patients), sudden death (eight patients), tamponade (seven patients in the placebo group), and bleeding (six patients).

In the alteplase/placebo trial, determinants of mortality were age, history of previous myocardial infarction, Killip class III or IV on admission, sum of ST-segment elevation on admission, anterior infarct localization, sex, and allocation to alteplase. In Table 2, the relative risks with 95% confidence intervals for these determinants are listed. The multivariate regression model with covariates listed in Table 2 was used to calculate a composite risk score by setting the indicator variable for treatment allocation to placebo treatment. On the basis of this composite risk score, patients were categorized into a low-, medium-, or high-risk group to assess whether randomization was successful in segregating treatment groups with similar baseline risk in the alteplase/PTCA trial.

Baseline Risk

In the alteplase/PTCA trial, mortality (Kaplan-Meier) in the low-, medium-, and high-risk groups was 2.4%, 8.0%, and 15.2% at 1 year, respectively, indicating that the baseline risk score was successful in segregating low-risk from high-risk patients in a separate group of patients.

In the alteplase/PTCA trial, 31.7% of invasively treated patients (58 of 183) were in the high-risk group versus 22.3% in the noninvasive group (41 of 184). For the medium-risk group, these proportions were 29.0% in the invasive treatment group (53 of 183) and 25.5% in the noninvasive group (47 of 184). This indicates that in the alteplase/PTCA trial, randomization did not result in treatment groups with equal baseline risks. Therefore, relative risk for mortality in the alteplase/PTCA trial was adjusted for imbalanced baseline risk by Cox multivariate regression analysis in which indicator variables for treatment allocation and high baseline risk were forced. After adjustment, mortality was 38% higher in the invasive group (95% confidence interval, −36% to +295%). When 59 patients with an occluded infarct-related vessel on angiography between days 10 and 22 and/or reinfarction before angiography between days 10 to 22 were excluded in the present analysis, mortality thereafter was reduced by immediate angioplasty with 18% (95% confidence interval, −69% to +216%) in a Cox regression model with indicator variables for baseline risk and missing angiography between days 10 and 22.

Reinfarction

Reinfarction was diagnosed on the basis of a combination of enzyme elevation and ECG pattern (57% of

TABLE 3. Proportion of Patients With Medication at Hospital Discharge and 3-Month and 1-Year Follow-up for Patients Alive and With Information Available

Medication	Alteplase/placebo trial			Alteplase/PTCA trial		
	Placebo*	Alteplase*	Difference (95% CI)	Alteplase†	PTCA†	Difference (95% CI)
Coumarins						
Discharge	59 (202)	55 (188)	−4 (−12, 3)	20 (36)	17 (29)	−3 (−11, 5)
3 Months	55 (186)	54 (183)	−1 (−9, 7)	27 (47)	20 (34)	−7 (−16, 2)
1 Year	21 (69)	24 (78)	3 (−4, 9)	14 (23)	15 (24)	1 (−6, 9)
Antiplatelets						
Discharge	35 (119)	35 (119)	0 (−7, 7)	59 (105)	50 (84)	−9 (−20, 1)
3 Months	41 (139)	43 (144)	2 (−6, 9)	55 (96)	52 (87)	−3 (−14, 8)
1 Year	50 (163)	43 (141)	−7 (−14, 1)	54 (90)	54 (87)	0 (−10, 11)
None of these						
Discharge	22 (76)	24 (83)	2 (−4, 8)	25 (44)	36 (60)	11 (1, 20)
3 Months	16 (55)	13 (45)	−3 (−8, 2)	22 (39)	30 (50)	8 (−2, 17)
1 Year	30 (98)	35 (113)	5 (−3, 12)	33 (56)	33 (53)	0 (−11, 10)
β-Blockers						
Discharge	56 (192)	51 (174)	−5 (−13, 2)	39 (69)	37 (62)	−2 (−12, 8)
3 Months	59 (197)	59 (200)	0 (−7, 8)	42 (74)	48 (81)	6 (−5, 17)
1 Year	59 (192)	54 (175)	−5 (−13, 3)	45 (75)	42 (68)	−3 (−13, 8)
Calcium antagonists						
Discharge	16 (56)	17 (59)	1 (−5, 6)	39 (69)	38 (64)	−1 (−11, 9)
3 Months	20 (68)	20 (67)	0 (−6, 6)	44 (77)	38 (63)	−7 (−17, 4)
1 Year	26 (86)	25 (81)	−1 (−8, 5)	42 (71)	42 (68)	0 (−11, 11)
Nitrates						
Discharge	12 (41)	8 (27)	−4 (−9, 0)	35 (62)	31 (53)	−4 (−13, 7)
3 Months	16 (54)	13 (44)	−3 (−8, 2)	57 (100)	54 (91)	−3 (−14, 8)
1 Year	18 (59)	17 (54)	−1 (−7, 4)	45 (76)	44 (70)	−1 (−13, 9)

PTCA, percutaneous transluminal coronary angioplasty; CI, confidence interval. Patients using combinations of medication are counted in each group.

*No. of placebo patients, 341 at discharge, 336 at 3 months, and 327 at 1 year; no. of alteplase patients, 343 at discharge, 337 at 3 months, and 326 at 1 year.

†No. of alteplase patients, 178 at discharge, 175 at 3 months, and 168 at 1 year; no. of PTCA patients, 169 at discharge, 168 at 3 months, and 161 at 1 year.

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 within 1 year after myocardial infarction was reported for 87 of 1,088 patients and occurred within 14 days in 48 patients (Table 1). Twenty-one of 87 patients with reinfarction died within the first year after infarction compared with 60 of 1,001 patients without reinfarction (risk of death in patients with reinfarction, 4.03-fold that of patients without reinfarction; 95% confidence interval, 2.59% to 6.26%). Reinfarction occurred in 78% of cases at the same site as the index infarct but in 10 patients at a distant site. In six cases, the localization of reinfarction could not be determined, and for two patients, data were missing. Reinfarction was slightly more common among alteplase-allocated patients (8.2% versus 6.8% for placebo patients; difference, 1.3%; 95% confidence interval, −2.5% to +5.2%; Table 1). In the invasive group, reinfarction was less frequent than in the noninvasive group (6.6% versus 11.4%; difference, −4.9%; 95% confidence interval, −10.7% to +1.0%). However, recurrent ischemia during the first 24 hours after allocation was more frequent in the invasive group (17% versus 3%).[2]

Similar differences in occurrence of reinfarction between the treatment groups were observed if a more restricted definition for reinfarction was applied requiring ECG signs of reinfarction. With this definition, 4.9% of placebo patients (18 of 366) and 5.9% of patients in the alteplase group suffered from reinfarction (difference, 1.0%; 95% confidence interval, −2.3% to +4.3%). In the alteplase/PTCA trial, 8.7% of patients in the noninvasive group (16 of 184) and 5.5% of patients in the invasive group (10 of 183) had reinfarction (difference, −3.2%; 95% confidence interval, −8.5% to +2.0%).

Revascularization and Medication

Revascularization within 1 year was performed in 18.8% of patients in the alteplase group and 15.8% of patients in the placebo group (difference, 3.0%; 95% confidence interval, −2.5% to +8.5%). Most interventions were made after the first 2 weeks. Overall, interventions were more frequent in the alteplase/PTCA trial than in the alteplase/placebo trial. In the invasive group, revascularization was performed less often than in the noninvasive group (16.9% and 25.5% of patients, respectively; difference, −9.2%; 95% confidence interval, −17.5% to −0.8%).

At 1 year, approximately 72% of patients in both studies were alive and had no reinfarction or additional revascularization procedures (Table 1).

Approximately two thirds of patients were treated with anticoagulant or antiplatelet drugs (Table 3). In the alteplase/placebo trial, the most often prescribed antithrombotic medications at hospital discharge were coumarins, whereas antiplatelet drugs were more often used in the alteplase/PTCA trial. This difference disappeared at 1 year follow-up, when antiplatelet drugs were used by half of the patients in both trials. β-Blockade

TABLE 4. Functional Class According to New York Heart Association at Hospital Discharge and 1-Year Follow-up

	Alteplase/placebo trial		Alteplase/PTCA trial	
	Placebo (n=366)	Alteplase (n=355)	Alteplase (n=184)	PTCA (n=183)
At hospital discharge				
Median number of days to follow-up	14	14	20	20
90% Range	10–29	10–23	11–40	11–39
% Dead	6.6 (24)	3.1 (10)	3.3 (6)	7.1 (14)
Canadian functional class				
I	73.2 (268)	78.6 (279)	77.2 (142)	69.9 (128)
II	14.5 (53)	12.4 (44)	13.0 (24)	16.4 (30)
III	4.1 (15)	3.9 (14)	6.5 (12)	5.5 (10)
IV	1.4 (5)	0.8 (3)	. . .	. . .
Unknown	0.3 (1)	1.1 (5)	. . .	1.1 (1)
At 1-year follow-up				
Median number of days to follow-up	399	399	404	412
90% Range	365–643	365–615	366–599	365–663
% No follow-up	0.5 (2)	0.6 (2)	1.6 (3)	1.6 (3)
% Dead	9.8 (36)	6.5 (23)	6.0 (11)	9.3 (17)
Canadian functional class				
I	60.1 (220)	63.9 (227)	60.9 (112)	51.9 (95)
II	21.3 (78)	22.8 (81)	22.3 (41)	25.1 (46)
III	7.4 (27)	4.5 (16)	7.6 (14)	9.8 (18)
IV	0.5 (2)	1.1 (4)	1.1 (2)	1.6 (3)
Unknown	0.3 (1)	0.6 (2)	0.5 (1)	0.5 (1)

PTCA, percutaneous transluminal coronary angioplasty. Proportions of patients are given as percentages (absolute number in parentheses).

was used more often in the alteplase/placebo trial than in the alteplase/PTCA trial (56.2% [367 of 653] and 43.5% [143 of 329], respectively; difference, 12.7%; 95% confidence interval, +6.1% to +19.4%). Calcium antagonists were prescribed less frequently in the alteplase/placebo trial than in the alteplase/PTCA trial (25.6% [167 of 653] and 42.3% [139 of 329], respectively; difference, −16.7%; 95% confidence interval, −22.8% to −10.5%). The same was true for nitrates (17.3% [113 of 653] and 44.4% [146 of 329], respectively; difference, −27.1%; 95% confidence interval, −32.9% to −21.2%). Medications such as digitalis, diuretics, or antiarrhythmics were used rarely in either trial.

Functional Class

Functional class at hospital discharge and 1-year follow-up are listed in Table 4. In the alteplase/placebo trial, more patients treated with alteplase were in functional class I or II than were those allocated to placebo (87.7% [308 of 351] and 82.1% [298 of 363], respectively; difference, 5.7%; 95% confidence interval, +0.4% to +10.9%). Functional impairment at 1 year was due primarily to angina pectoris (44% of cases in the alteplase group and 49% of placebo patients), symptoms of congestive heart failure (18% versus 17%), or both (2% and 1%, respectively). Among patients allocated to invasive strategy, functional class appeared worse compared with the noninvasive strategy throughout the follow-up period. Reasons for functional impairment were angina pectoris and/or congestive heart failure in 88% and 81% in the noninvasive and invasive groups, 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 1-year follow-up for all treatment groups.

Hospital Stay

In the alteplase/placebo trial, duration of the initial hospitalization was 14 days in both treatment groups (median, 90%; range, 9 to 28 in the alteplase group and 9 to 23 in placebo patients), and the total duration of hospitalization during the first year was 17 days in both treatment groups (median, 90%; range, 10 to 47 in the alteplase group and 10 to 43 in placebo patients). In the alteplase/PTCA trial, initial hospitalization was longer—20 days in each treatment group (median, 90%; range, 11 to 36 in the invasive group and 11 to 37 in the noninvasive group). The difference in initial hospital stay between the two trials was due to a longer stay in German clinics: Hospital stay was 17 days in non-German clinics (median, 90%; range 12 to 25) and was 24 days in German centers (median, 90%; range, 13 to 66). Including readmissions, patients of both treatment groups stayed 22 days in the hospital during the first year (median, 90%; range, 12 to 65 in the invasive and 12 to 58 in the noninvasive group).

Determinants of Death and Reinfarction After Discharge

To identify determinants of mortality and reinfarction after hospital discharge, data were analyzed from 1,043 hospital survivors.

Mortality in the first year after discharge was low (3.4% by Kaplan-Meier survival analysis) and appeared related to coronary anatomy, left ventricular function, and, to a lesser extent, age and history of previous infarction (Table 5). The degree of residual diameter stenosis in the infarct-related vessel on angiography between days 10 and 22 was related to mortality, regardless of the number of diseased coronary arteries, and left ventricular ejection fraction. The relation between residual diameter stenosis in the infarct-related coronary segment on angiography between days 10 and 22 and 1-year mortality tended to be present among both placebo- and alteplase-treated patients. In the placebo group, mortality was 2.4-fold higher (95% confidence interval, +0.8 to +7.7) among patients with ≥90% residual stenosis than among patients with <90%

TABLE 5. Determinants of Mortality After Hospital Discharge in 1,043 Hospital Survivors in Order of Decreasing Importance

Determinant	No. of patients	Mortality within first year after discharge (%)	Relative risk	
			Crude	Adjusted (95% CI)
No. 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 (years)				
<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				
Placebo	345	3.8	...	...
Alteplase	346	3.2	0.92	0.97 (0.47 to 2.02)
Alteplase*	180	3.4	0.88	1.13 (0.45 to 2.85)
PTCA	172	3.5	0.80	0.98 (0.36 to 2.69)

CI, confidence interval; PTCA, percutaneous transluminal coronary angioplasty.

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; the adjusted relative risk is determined by multivariate Cox regression analysis. Predicted mortality for a patient without any risk factor and allocated to placebo is 0.006 at 365 days after discharge. Indicator variables for treatment allocation were forced into the model.

*Alteplase in alteplase/PTCA trial.

residual stenosis. For patients who were allocated to placebo, in both trials combined, mortality was 1.8 times higher in patients with severe residual stenosis (95% confidence interval, 0.7 to 4.8). In the invasive group, only 25 of 172 hospital survivors had a ≥90% residual infarct-related stenosis on angiography between days 10 and 22 (of whom two died within the first year). Assessment of the relation between residual diameter stenosis and mortality in this treatment group separately therefore was impossible.

It should be noted that the initial treatment allocation did not affect mortality after hospital discharge.

Reinfarction within the first year after hospital discharge occurred in only 39 of 1,043 patients (3.7%). It occurred 2.4-fold more frequently among patients with a patent infarct-related vessel with a diameter stenosis of 50–99% than among patients with <50% diameter stenosis and was about twice as common in alteplase-allocated patients as in the placebo group (Table 6). Residual stenosis on angiography between days 10 and 22 was the only variable that passed the $p<0.10$ limit for entry into a stepwise logistic regression analysis.

The combined end point of mortality and/or reinfarction after hospital discharge occurred in 76 of 1,043 patients. In a stepwise Cox regression analysis, only poor left ventricular ejection fraction and multivessel coronary artery disease were entered into the model. None of the other determinants of mortality or reinfarction as reported for the models for mortality (Table 5) and reinfarction (Table 6) separately passed the $p<0.10$ limit for entry.

Discussion

The reduction in mortality by alteplase noted during the first 3 months[1] was still present at 1 year. Other investigators also have reported that the initial benefits of thrombolytic therapy are maintained at 7 months,[8,9] 1 year,[10,11] and 5 years.[12] In both alteplase/placebo and alteplase/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 reported in any trial with similar inclusion criteria. This probably is due to the combination of effective early thrombolytic therapy and simultaneous antithrombotic therapy with aspirin[13] and intravenous heparin.[14] As in other studies,[8,12] revascularization procedures were more common after thrombolytic therapy. This may be explained by a smaller infarct size and thus more myocardium susceptible for ischemia 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. One-year survival rates were strikingly similar in patients treated with alteplase but without coronary angioplasty in both trials (94%). Some patient management differences between the trials were apparent. In the noninvasive group of the alteplase/PTCA trial, PTCA was

TABLE 6. Reinfarction Within the First Year After Hospital Discharge in Various Categories of Residual Stenosis in the Infarct Coronary Artery in 1,043 Hospital Survivors

Determinant	No. of patients	Reinfarction within first year after discharge (%)	Relative risk	
			Crude	Adjusted (95% CI)
Diameter stenosis in infarct-related vessel (%)				
≥50	193	2.1	...	...
50 to 90	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	...	...
Alteplase	346	4.9	1.88	1.95 (0.88 to 4.34)
Alteplase*	180	5.0	1.92	2.06 (0.82 to 5.17)
PTCA	172	2.3	0.89	1.43 (0.39 to 5.23)

CI, confidence interval; PTCA, percutaneous transluminal coronary angioplasty.

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 ratios and 95% CI were calculated according to Miettinen[7] with the following multivariate logistic regression coefficients (standard error in parentheses): constant, −4.32 (0.67); alteplase, 0.69 (0.42); alteplase,* 0.75 (0.49); invasive, 0.37 (0.68); missing diameter stenosis, −0.56 (1.15); stenosis, 50–99%, 0.89 (0.61); and (sub)total occlusion, 0.31 (0.72). Above variables were forced into the model to obtain adjusted relative risks.

*Alteplase in the alteplase/PTCA trial.

performed more often than in the corresponding group in the alteplase/placebo trial. This might be related to an excess of patients with a history of angina before the qualifying myocardial infarction in the alteplase/PTCA trial (70% versus 48% in the alteplase/placebo trial). Furthermore, the initial hospital stay was longer, coumarins and β-blockers were prescribed less frequently, and calcium antagonists were prescribed more frequently in the alteplase/PTCA trial. Also, hospital stay was substantially longer in German centers due to prolonged clinical revalidation after myocardial infarction. These differences may reflect differences in medical culture among university hospitals in Germany, France, Belgium, The Netherlands, and Spain participating in the alteplase/PTCA trial and large district hospitals in Belgium, United Kingdom, The Netherlands, Spain, and Switzerland cooperating in the alteplase/placebo trial.[2] However, these differences in medical culture had no major impact on patient outcome at 1 year since mortality and functional state at 1 year were similar in patients treated with alteplase in the alteplase/placebo trial and patients in the noninvasive group of the alteplase/PTCA trial.

Reinfarction

Reinfarction was slightly more common after treatment with alteplase. 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 other trials, a higher incidence of reinfarction than among controls was reported after thrombolytic therapy,[8,12,15,16] except in one trial.[17] In another trial, the reinfarction rate after alteplase was higher than that in the present study (18.1% at 1 year).[18] In that trial, aspirin was started only 8–10 days after myocardial infarction, whereas reinfarctions tend to occur earlier (Table 1).

Because reinfarction is related to mortality (fourfold higher after reinfarction in the present trials) and reinfarction appears to occur more often after thrombolytic treatment, benefit of thrombolytic therapy may be increased if reinfarction could be prevented. The low incidence of reinfarction after invasive treatment in the alteplase/PTCA trial is probably misleading since recurrent ischemia during the first 24 hours was much more common in the invasive group,[2] and reinfarctions among patients with early recurrent ischemia are difficult to define because the ECG and enzymatic patterns of the evolving initial myocardial infarction are blurring the diagnosis of reinfarction.

Functional Class

Functional class in patients initially treated with alteplase, heparin, and aspirin was superior to that in patients treated with heparin, aspirin, and placebo. Thus, thrombolytic therapy improves survival after myocardial infarction without negatively influencing the quality of life. More than half of the patients treated with alteplase were asymptomatic at 1-year follow-up. This is similar to earlier observations after intracoronary streptokinase.[15] Only a few patients were treated for heart failure (vasodilators, digitalis, and diuretics), which corresponds with the small number of class III and IV patients during follow-up.

Immediate Angioplasty

Immediate angioplasty was not beneficial. Because only hospitals with extensive PTCA experience were allowed to participate in the alteplase/PTCA trial and because similar conclusions were drawn by other investigators,[19,20] it is unlikely that immediate angioplasty will turn out to be beneficial in the hands of other operators. Routine coronary angioplasty later during hospitalization also proved not to be beneficial[21]; therefore, we recommend that coronary angioplasty be restricted to patients with recurrent ischemia 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 (seven patients) than in the noninvasive group (one patient).[22] However, correction for difference in baseline risk did not alter the trial outcome. This remained

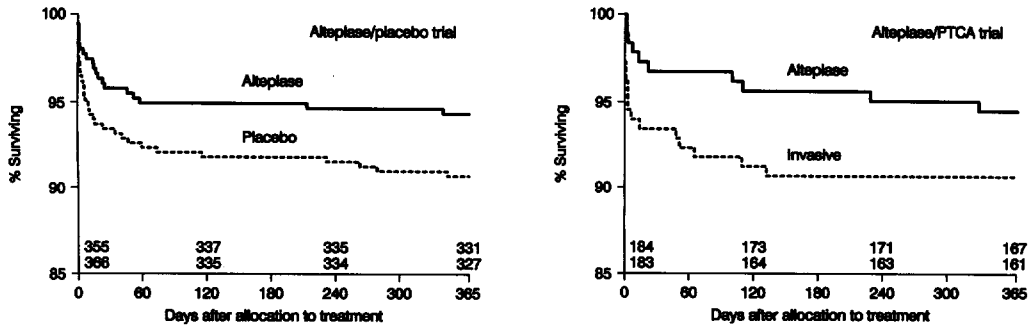

FIGURE 1. *Plots of survival until 1 year after initial treatment allocation in the alteplase/placebo trial and the alteplase/percutaneous transluminal coronary angioplasty (PTCA) trial of the European Cooperative Study Group.*

true when another method for adjustment for unequal baseline risk was applied. After exclusion of patients in Killip class III or IV, mortality was 7.4% in the invasive group and 5.5% in the noninvasive group (difference, 1.9%; 95% confidence interval, −3.4% to +7.3%) with Kaplan-Meier survival analysis. In the future, immediate angioplasty in selected patients might be beneficial if reocclusion of the infarct-related vessel and reinfarction could be prevented. After exclusion of patients with an occluded infarct-related vessel on angiography between days 10 and 22 and/or reinfarction before angiography between days 10 and 22, there was a trend toward benefit of the invasive treatment strategy with 18% reduction of mortality. A similar trend was observed for regional wall motion in the same patients.[23] This is compatible with the finding in the present analysis that the degree of residual stenosis is related to the occurrence of reinfarction.

Mortality and Reinfarction After Hospital Discharge

Mortality after hospital discharge was determined mainly by left ventricular function and coronary anatomy. Determinants of mortality were identical as reported in an intracoronary streptokinase trial with similar patient selection.[12] Many studies have stressed the predictive value of left ventricular function determined on admission[24] or before hospital discharge.[25–27] In addition, the importance of coronary patency for mortality has been described.[12,24,27] Initial treatment, although an important determinant of mortality during hospital stay (Table 1), did not influence mortality after hospital discharge independent of coronary anatomy and left ventricular function. Sophisticated analyses in other trials suggested that the same is true for intracoronary streptokinase.[12,24]

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. The alteplase/PTCA trial was designed because earlier reports suggested that reduction in residual stenosis would be beneficial.[28,29] 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 to be related to both mortality and reinfarction. This suggests that routine revascularization may turn out to be beneficial provided that patients are properly selected and reocclusion and restenosis are sufficiently prevented.

Patients with a 90–99% diameter stenosis in the infarct-related segment had mortality rates similar to those with an occluded infarct-related vessel and, therefore, were grouped together in Table 5. Reinfarction tended to be less common in patients with an occluded infarct-related vessel than in patients with a significant residual stenosis (Table 6), which might be related to the pathophysiological mechanism for reinfarction (thromboembolism in the infarct-related vessel). The inhomogeneous relation between residual stenosis and mortality on one hand and reinfarction on the other were reflected in the Cox regression model for the combined end point of mortality and/or reinfarction in which indicator variables for residual stenosis did not pass the $p<0.10$ limit for entry, regardless of how categories of residual stenosis were offered for stepwise entering in the model, although the number of events was greater (76 versus 42).

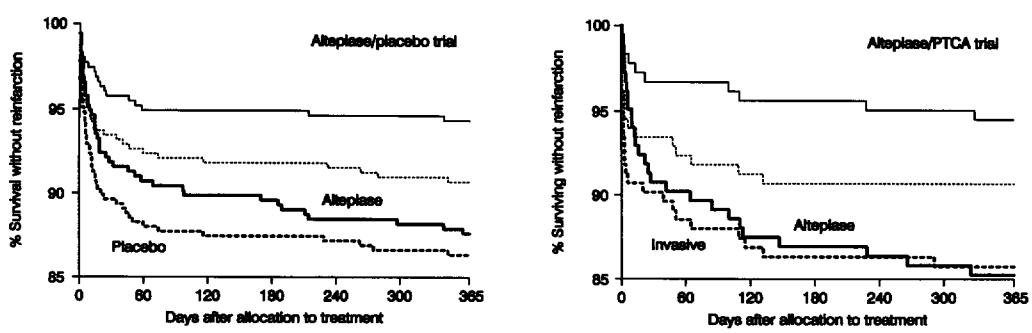

FIGURE 2. *Plots of survival without reinfarction in first year after initial treatment allocation in the alteplase/placebo trial and the alteplase/percutaneous transluminal coronary angioplasty (PTCA) trial of the European Cooperative Study Group. Thin solid and dotted lines at top represent survival shown in Figure 1.*

Possible Hazards of Pooling

One might be concerned that pooling the data of two trials for the multivariate models at discharge would result in erroneous prognostic models (Tables 5 and 6) and argue that it would be more appropriate to design a prognostic model for each trial separately. The two trials were conducted by different investigators working in different countries, and theoretically, the accuracy of the estimates for relative risk might be impaired by differences in data collection between the trials. But this is not very likely in the present study since most determinants in the models were assessed centrally by the same assessors in both trials. Other determinants such as age and previous infarction also could be assessed reliably, and the definition of the end point death was equal for all investigators. Separate analysis in each trial would result in considerable loss of statistical power in the analysis (loss of precision with which the estimates for relative risk in Tables 5 and 6 are known, i.e., wider 95% confidence interval) and therefore would complicate rather than facilitate the interpretation of the results.

Finally, with regard to the results with borderline statistical significance (risk differences with 95% confidence intervals including 0 or relative risks with 95% confidence intervals including 1), one should realize that trial size calculations were performed for left ventricular ejection fraction such as end point, and for end points such as mortality and reinfarction, in general, larger trial sizes are required. Results with borderline or no statistical significance therefore must be interpreted with caution and with reference to evidence from other thrombolysis trials.

Conclusions

Benefit from a treatment strategy of alteplase, heparin, and aspirin appears to be mainly due to its effect during hospital stay and is not diminished at 1 year. Routine immediate angioplasty as currently applied does not appear to confer benefit. Prognosis after hospital discharge is determined mainly by coronary anatomy and residual left ventricular function but is unrelated to initial treatment assignment.

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