A COMPARISON OF CONTINUOUS INFUSION OF ALTEPLASE WITH DOUBLE-BOLUS ADMINISTRATION FOR ACUTE MYOCARDIAL INFARCTION

THE CONTINUOUS INFUSION VERSUS DOUBLE-BOLUS ADMINISTRATION OF ALTEPLASE (COBALT) INVESTIGATORS*

ABSTRACT

Background Accelerated infusion of alteplase (tissue plasminogen activator) over a period of 90 minutes induces more rapid lysis of coronary-artery thrombi than a 3-hour infusion. With two bolus doses of alteplase, further shortening the duration of administration, complete reperfusion was achieved in more than 85 percent of the patients in initial angiographic studies. We tested the hypothesis that double-bolus alteplase is at least as effective as accelerated infusion.

Methods In 398 hospitals, 7169 patients with acute myocardial infarction were randomly assigned to weight-adjusted, accelerated infusion of 100 mg of alteplase or to a bolus of 50 mg of alteplase over a period of 1 to 3 minutes followed 30 minutes later by a second bolus of 50 mg (or 40 mg for patients who weighed less than 60 kg). The primary end point was death from any cause at 30 days. The trial was stopped prematurely because of concern about the safety of the double-bolus injection.

Results Thirty-day mortality was higher in the double-bolus group than in the accelerated-infusion group: 7.98 percent as compared with 7.53 percent. The absolute difference was 0.44 percent, with a one-sided 95 percent upper boundary of 1.49 percent, which exceeded the prespecified upper limit of 0.40 percent to indicate equivalence in 30-day mortality between the two regimens. The respective rates of any stroke and of hemorrhagic stroke were 1.92 and 1.12 percent after double-bolus alteplase, as compared with 1.53 and 0.81 percent after an accelerated infusion of alteplase ($P=0.24$ and $P=0.23$, respectively).

Conclusions Double-bolus alteplase was not shown to be equivalent, according to the prespecified criteria, to accelerated infusion with regard to 30-day mortality. There was also a slightly higher rate of intracranial hemorrhage with the double-bolus method. Therefore, accelerated infusion of alteplase over a period of 90 minutes remains the preferred regimen. (N Engl J Med 1997;337:1124-30.)

ADMINISTRATION of 100 mg of alteplase (tissue plasminogen activator) over a period of 90 minutes has been shown to induce more rapid lysis of coronary-artery thrombi than a 3-hour infusion of the same dose.[1,2] This accelerated rate of infusion (with concomitant intravenous heparin) was associated with the lowest mortality rates in the first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial,[3] whereas a three-hour infusion of alteplase or duteplase (without intravenous heparin) was not superior to streptokinase in the second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico,[4] the International Study Group,[5] and the third International Study of Infarct Survival trials.[6] Double-bolus administration of alteplase (two bolus doses given 30 minutes apart) is a further shortening of the duration of administration. The rationale for testing brief infusions or bolus administration of fibrinolytic agents includes the observations that the generation of thrombin, associated with the use of these agents, is less pronounced with short infusions[7] and that the fibrinolytic effects of alteplase on thrombi are sustained after its clearance from the circulation.[8] In two early angiographic studies, high rates of patency were observed after double-bolus administration of alteplase, with no excess of bleeding complications.[9,10] In the largest of these studies, grade 3 flow rates (according to the Thrombolysis in Myocardial Infarction [TIMI] classification) were observed at 60 and 90 minutes in more than 85 percent of patients.[10]

Thus, besides offering the advantage of ease of use, double-bolus alteplase might be at least as effective as the accelerated infusion as used in the GUSTO I study. The current trial was performed to test this hypothesis.

METHODS

Organization of the Study

A total of 398 centers in 26 countries participated in the trial. For each patient, after inclusion and exclusion criteria were checked and demographic data provided, a unique study-treatment number was allocated by telephone with the use of an interactive voice-response computer system. This number corresponded with the number on a sealed envelope at the enrolling site that contained the instruction for the administration of alteplase: double bolus or infusion. Thus, the trial had a randomized, open design.

Patient Population

The inclusion and exclusion criteria were identical to those of the GUSTO I trial.[3] Patients who had had ischemic chest pain for

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Dr. Van de Werf, as chairman of the trial, assumes full responsibility for the overall content and integrity of the manuscript.

*The investigators participating in the COBALT trial are listed in the Appendix.

at least 20 minutes who came to the hospital within 6 hours after the onset of symptoms were eligible if the electrocardiogram showed ST-segment elevation of at least 0.1 mV in two or more limb leads, ST-segment elevation of at least 0.2 mV in two or more contiguous precordial leads, or both. The following were reasons for exclusion: active bleeding, a history of stroke or structural damage of the central nervous system, recent noncompressible vascular puncture, major surgery or trauma within the preceding 6 months, current participation in any other study of experimental drugs or devices, previous enrollment in this study, pregnancy, or lactation or parturition within the preceding 30 days. A systolic blood pressure of ≥180 mm Hg, a diastolic blood pressure of ≥110 mm Hg, or both, in spite of treatment, were considered a relative contraindication to enrollment. The protocol was approved by local and national ethics committees and local institutional review boards, and informed consent was obtained before randomization.

Trial Medications and Additional Therapy

Patients who were randomly assigned to be given an accelerated infusion of alteplase received an intravenous bolus of 15 mg followed by an infusion of 0.75 mg per kilogram of body weight over a 30-minute period, not to exceed 50 mg, and then by an infusion of 0.5 mg per kilogram, up to a total of 35 mg, for 60 minutes. The maximal dose was therefore 100 mg. Patients assigned to receive double-bolus alteplase were given 50 mg intravenously over a period of 1 to 3 minutes followed 30 minutes later by a second bolus of 50 mg, or 40 mg if the patient weighed less than 60 kg.

All patients were given aspirin (160 to 325 mg) as soon as possible after randomization, followed by a daily dose of 80 to 325 mg. Heparin was administered as a bolus dose of 5000 U followed by an infusion of 1000 U per hour for at least 48 hours. The target activated partial-thromboplastin time was 60 to 85 seconds. Doses were adjusted with the use of a heparin nomogram similar to the one used in the GUSTO I trial.[3] The use of all other medications and invasive procedures was left to the discretion of the investigator.

Data Monitoring and Management

For each patient a safety summary form was faxed to the coordinating center in Leuven, Belgium, at the time of discharge from the hospital, on day 30, or at the time of death, whichever came first. This form provided information on whether a stroke or other life-threatening complication had occurred. Serious events were also reported to the safety officer according to national regulatory requirements.

Case-report forms were also forwarded to the coordinating center so that data could be entered and missing or inconsistent data could be identified. We further ensured the quality of the data by verifying all reported data against medical records and by double entering the data at the coordinating center. When a patient died or when a stroke or reinfarction occurred, special forms with additional questions regarding the event had to be completed. Furthermore, an independent stroke-assessment panel reviewed all stroke data (clinical information, computed axial tomographic scans or magnetic resonance images, and autopsy reports) and classified the stroke as primary hemorrhagic, ischemic, ischemic with conversion to hemorrhagic, or of unknown cause (in which case there were no brain scans or autopsy results available).

An independent data and safety monitoring board was responsible for continuously monitoring the data on safety and efficacy, according to the Peto–Haybittle criteria for stopping a study.[11,12]

End Points and Statistical Analysis

The primary end point was death from any cause at 30 days. The aim of the trial was to demonstrate therapeutic equivalence. Double-bolus alteplase was to be considered at least equivalent to accelerated infusion if the upper boundary of the one-sided 95 percent confidence interval of the difference in 30-day mortality did not exceed 0.40 percentage point. This value represented the lower 95 percent confidence limit of the 1 percent absolute difference in 30-day mortality between an accelerated infusion of alteplase and streptokinase that was observed in the GUSTO I trial.[3] The null hypothesis of interest was therefore that 30-day mortality with double-bolus alteplase would exceed mortality with accelerated infusion, with an upper boundary of the 95 percent confidence interval of 0.40 percentage point; the alternative was that mortality with double-bolus alteplase would equal or be less than mortality with accelerated infusion, with an upper boundary of the 95 percent confidence interval of 0.40 percentage point. Thus, if equivalence was demonstrated according to this criterion, superiority over streptokinase could be claimed.

We assumed a 30-day mortality rate of 6.3 percent with accelerated infusion of alteplase, similar to that observed in the GUSTO I trial, and a 30-day mortality rate with double-bolus alteplase of 5.4 percent. The reduction in the 30-day mortality rate to 5.4 percent is proportional to the increase in the TIMI grade 3 flow rate at 90 minutes, from 54 percent with accelerated infusion (as in the GUSTO I trial) to 88 percent with double-bolus alteplase (as in the study by Purvis et al.[10]).

Accordingly, we calculated that a sample size of 4029 patients per treatment group was needed to reject the null hypothesis (of nonequivalence) with a power of 80 percent at the one-sided significance level of 5 percent if the specified alternative hypothesis (of equivalence) were true. A binomial test for equivalence was used.[13] This sample size also had 80 percent power to detect a 0.66 percent difference in the rates of hemorrhagic stroke between the two alteplase regimens at a two-sided nominal significance level of 5 percent with Fisher's exact test and with the assumption of a 0.70 percent rate of hemorrhagic stroke at 30 days with the accelerated infusion.[3]

For the primary end point a one-sided 95 percent upper boundary and P value (testing for equivalence) are reported, whereas for all other exploratory analyses two-sided 95 percent confidence intervals and P values (testing for superiority) are given. All patients who underwent randomization with the computer system and for whom an envelope with the code had been opened at the enrolling site were considered to be in the study and were analyzed according to the intention-to-treat principle.

RESULTS

A total of 7169 patients underwent randomization between January 23, 1995, and January 5, 1996, with a temporary suspension of enrollment for 11 days in August 1995 to allow the data and safety monitoring board to consider a possible imbalance in the rates of intracranial hemorrhage that had been reported to the safety officer. On January 5, 1996, the board recommended stopping the trial because of poorer clinical outcomes in the double-bolus group than in the accelerated-infusion group. This recommendation was based on a finding of higher rates of death (7.9 percent, vs. 6.7 percent in the accelerated-infusion group), stroke (2.0 percent vs. 1.4 percent), and cardiogenic shock (4.5 percent vs. 3.2 percent), as reported on the safety summary form for 5595 patients. The results for all 7169 patients enrolled in the trial by that time are presented here. Mortality and stroke data up to 30 days after enrollment were available on all patients.

Characteristics of the Patients

The base-line characteristics of the patients are given in Table 1. Slightly more patients in the dou-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	DOUBLE BOLUS (N=3585)	ACCELERATED INFUSION (N=3584)
Median age (yr)	63 (53, 70)	62 (53, 70)
Female sex (%)	23	24
Diabetes (%)	13	13
Current smoker (%)	45	44
History of smoking (%)	70	69
Hypertension (%)	38	37
Previous infarction (%)	17	16
Previous bypass surgery (%)	2	2
Previous angioplasty (%)	2	2
Median systolic blood pressure (mm Hg)	140 (120, 156)	140 (120, 160)
Median heart rate (beats/min)	75 (63, 88)	75 (63, 88)
Killip class >1 (%)	17	16
Anterior infarction (%)	45	43
Median interval between onset of symptoms and randomization (min)	162 (108, 230)	158 (104, 228)
Median interval between onset of symptoms and treatment (min)	180 (120, 247)	175 (120, 240)

*Values in parentheses are the 25th and 75th percentiles. There were no significant differences between groups.

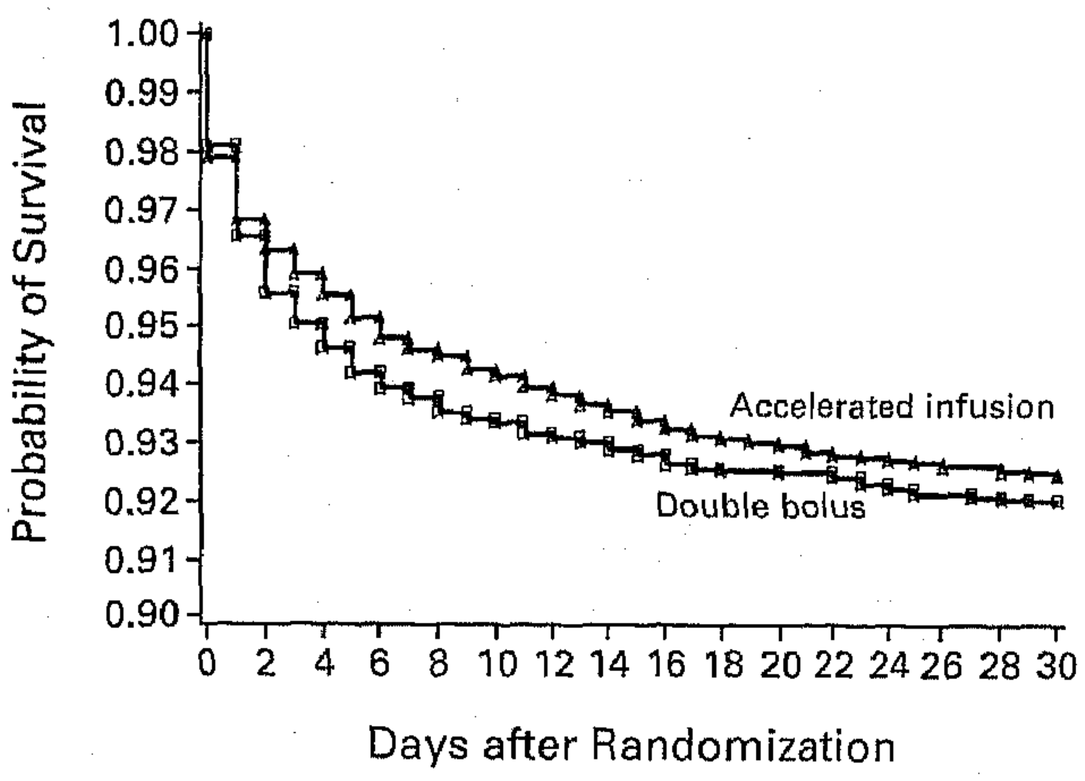

Figure 1. Kaplan–Meier Survival Curves in the Two Treatment Groups.

ble-bolus group had had a previous infarction, sustained an anterior infarction, or were in a Killip class higher than 1. None of these differences were statistically significant (Table 1).

In-Hospital Treatments and Diagnosis

The complete dose of study medication was given to 97 percent of the patients assigned to receive double-bolus alteplase and to 95 percent of the patients assigned to receive an accelerated infusion. Compliance with antithrombotic therapy was excellent and was similar in both groups. The heparin bolus was given to 96 percent of the patients in the double-bolus group and 95 percent of the patients in the accelerated-infusion group, and the heparin infusion was given to 90 percent and 89 percent, respectively. Aspirin was given to 89 percent of the patients in both groups. The median activated partial-thromboplastin time at 6 hours was significantly longer in the double-bolus group (101 seconds, vs. 84 seconds in the accelerated-infusion group; $P<0.001$), whereas at later times the results were similar.

The diagnosis of acute myocardial infarction was confirmed in 97 percent of the patients in both groups. The diagnosis was based on cardiac-enzyme levels and electrocardiographic changes in 85 percent of the double-bolus group and 86 percent of the accelerated-infusion group; on cardiac-enzyme levels alone in 1 percent and 0.8 percent, respectively; and on electrocardiographic changes alone in 14 percent and 13 percent.

Mortality and Major Cardiac Events

Mortality at 30 days, the primary end point of the study, was higher with two bolus doses of alteplase than with an accelerated infusion of alteplase (7.98 percent vs. 7.53 percent). The absolute difference in 30-day mortality was 0.44 percent, with a one-sided 95 percent upper boundary of 1.49 percent ($P=0.53$). Thus, according to the prespecified definition of equivalence of this trial, the two treatments were not shown to be equivalent. Additional statistical tests, including simulation analyses and the method of stochastic curtailment for sequential trials,[14] showed that even if the trial had enrolled the planned 8058 patients, the probability of showing equivalence according to the prespecified criteria was almost zero. The mortality rates at 24 hours were almost identical in the two groups: 3.01 percent for the double-bolus group and 2.99 percent for the accelerated-infusion group. The mortality rates in this trial, both at 24 hours and at 30 days, were higher than those reported in the GUSTO I trial (2.3 and 6.3 percent, respectively).[3] The Kaplan–Meier survival curves for the two alteplase regimens are shown in Figure 1.

The incidence of major cardiac events and the use of invasive procedures were similar in the two treatment groups (Table 2). The incidence of anaphylaxis was 0.1 percent in both groups.

Stroke and Bleeding Complications

The rate of any stroke and the rate of hemorrhagic stroke with the double-bolus regimen were 1.92 percent and 1.12 percent, as compared with 1.53 percent and 0.81 percent for the accelerated-infu-

TABLE 2. INCIDENCE OF MAJOR CARDIAC EVENTS AND PROCEDURES AT 30 DAYS.*

EVENT	DOUBLE BOLUS (N=3585)	ACCELERATED INFUSION (N=3584)
	percent	
Cardiogenic shock	4.2	4.0
Reinfarction	3.9	4.1
Ventricular fibrillation	5.9	6.3
Sustained ventricular tachycardia	4.6	4.0
Angioplasty	9.8	9.7
Bypass surgery	2.8	3.1
Sustained hypotension	9.2	9.3
Second- or third-degree atrioventricular block	6.6	6.5
Asystole	5.4	5.1
Recurrent angina	14.9	14.8
Acute mitral regurgitation	0.8	0.6
Acute ventricular septal defect	0.4	0.3

*There were no significant differences between groups.

TABLE 3. INCIDENCE OF STROKE AND BLEEDING COMPLICATIONS AT 30 DAYS.*

VARIABLE	DOUBLE BOLUS (N=3585)	ACCELERATED INFUSION (N=3584)
	no. of patients (%)	
Stroke		
Any stroke	69 (1.9)	55 (1.5)
Primary hemorrhagic	40 (1.1)	29 (0.8)
Primary ischemic	21 (0.6)	19 (0.5)
With hemorrhagic conversion	2 (0.06)	4 (0.11)
Unknown type	6 (0.2)	3 (0.1)
Bleeding complications		
Any bleeding	790 (22.0)	727 (20.3)
Severe or life-threatening	24 (0.7)	22 (0.6)
Mild or moderate	755 (21.1)	691 (19.3)
Not classified	11 (0.3)	14 (0.4)
Units of blood transfused		
1–2	51 (1.4)	52 (1.4)
3–4	20 (0.6)	17 (0.5)
≥5	8 (0.2)	8 (0.2)

*There were no significant differences between groups.

sion group (P=0.24 and P=0.23, respectively). The incidence of nonhemorrhagic stroke was similar in the two treatment groups (Table 3). The incidence of the combined end point of death or nonfatal stroke at 30 days was 8.8 percent in the double-bolus group and 8.3 percent in the accelerated-infusion group (a difference of 0.5 percentage point; 95 percent confidence interval, −0.8 to 1.8; P=0.45).

The incidence and severity of bleeding complications were similar in the two groups (Table 3).

Subgroup Analyses

The treatment effects were analyzed according to age, location of infarct, and time to treatment. No criteria of equivalence were prespecified for any subgroup analysis. Odds ratios and their 95 percent confidence intervals for 30-day mortality in the subgroups are shown in Figure 2. The 30-day mortality rates were similar in the two groups among patients 75 years of age or younger, patients with an anterior infarction, and those treated within two hours after the onset of symptoms, but the confidence intervals were large. There was an increase in the mortality rate in the double-bolus group with longer delays in treatment.

Major clinical outcomes with the two treatments are shown in Table 4 according to age. In the large group of patients who were 75 years of age or younger (87 percent of the study population), net clinical outcomes (death or nonfatal stroke) were identical: 6.3 percent. However, the 95 percent confidence interval is large (−1.2 to 1.2 percent) and does not exclude the possibility of a 1 percent worse or better outcome with double-bolus alteplase. Furthermore, the rate of intracranial hemorrhage after double-bolus alteplase was 0.19 percentage point higher in this age category.

DISCUSSION

The aim of this multicenter trial was to assess whether accelerated infusion and double-bolus administration of alteplase were equivalent therapeutically. The trial failed to show equivalence of the two treatments according to our prespecified criteria. Our definition of equivalence was more stringent than the one used in the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial,[15] the first large trial to compare the equivalence of two thrombolytic agents, reteplase and streptokinase. In that trial a 1 percent difference was chosen as the absolute outer limit for the confidence interval of the difference in mortality rates between reteplase and streptokinase, thus inferring from historical, controlled trials that the new regimen was likely to be significantly better than placebo and equivalent to streptokinase. In the present trial we chose a 0.40 percent absolute difference in 30-day mortality between the two regimens as the upper boundary. This value represents the lower 95 percent confidence limit of the 1 percent absolute difference in 30-day mortality observed between an accelerated infusion of alteplase and streptokinase in the GUSTO I trial.[3] Thus, if the upper boundary of the difference in 30-day mortality between double-bolus alteplase and an accelerated infusion of alteplase in this trial had been 0.40 percent or below, we could have concluded

Variable	Percentage of Patients	Mortality (%)		Odds Ratio and 95% Confidence Interval
		Double Bolus	Accelerated Infusion	
Age				
≤75 yr	87	5.6	5.7	
>75 yr	13	23.6	19.9	
Location of infarction				
Anterior	44	10.0	10.2	
Other	56	6.4	5.6	
Time to treatment				
0 to <2 hr	25	6.6	6.7	
2 to <4 hr	48	7.7	7.1	
4 to 6 hr	23	9.0	8.0	
>6 hr	2	12.9	9.2	(4.3)

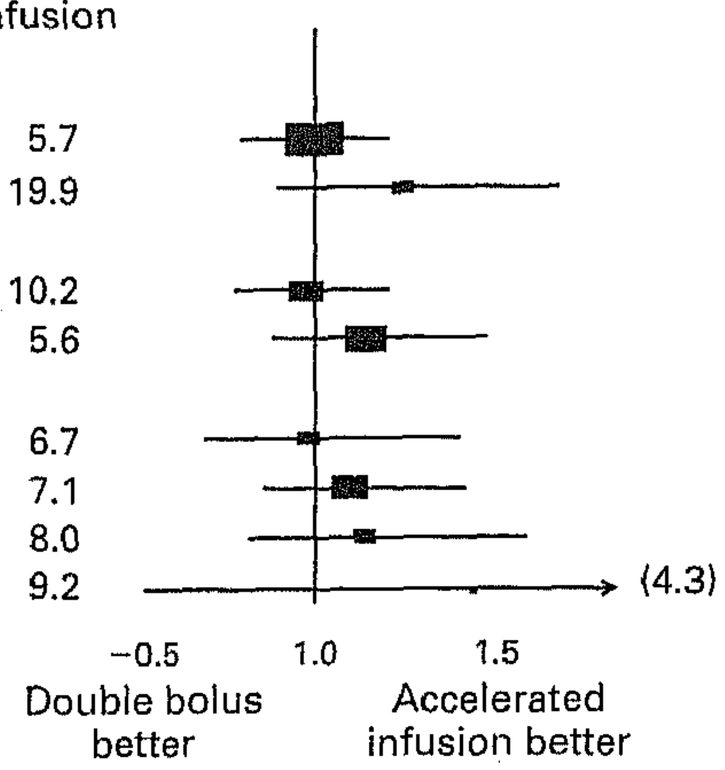

Figure 2. Odds Ratios and 95 Percent Confidence Intervals for Death within 30 Days, According to Age, Location of Infarction, and Time from Onset of Symptoms to Treatment.

The value in parentheses is the upper boundary of the confidence interval. Data on the time to treatment were missing for 2 percent of the patients.

that the effect of double-bolus alteplase on mortality was at least equivalent to that of accelerated infusion and better than that of streptokinase. We thought a stringent equivalence criterion was needed to allow a general recommendation of the new dosing schedule, in the case of a positive result, with confidence that this new regimen has at least the same degree of superiority over streptokinase as an accelerated alteplase regimen has.

The 30-day mortality rate for double-bolus alteplase was 0.44 percentage point higher than that for accelerated infusion. The upper boundary for this difference was 1.49 percent. Therefore, according to our definition, double-bolus alteplase was not shown to be equivalent to the accelerated infusion as used in the GUSTO I trial. To show a difference in mortality between reteplase and a historical placebo control, the INJECT investigators calculated that the upper boundary of the difference between reteplase and streptokinase should be less than 2.1 percent.[15] According to this definition, our results also show that double-bolus alteplase is better than placebo and equivalent to streptokinase in reducing mortality after acute myocardial infarction. If we take into account the theoretical improvement in mortality that should be achieved with an increase in the percentage of patients with TIMI grade 3 flow rates,[16,17] the mortality rates after double-bolus alteplase in this trial suggest that early reperfusion with this regimen occurs less frequently than in the population studied by Purvis et al.[10] Our mortality data are more concordant with the patency data obtained in a larger angiographic study by Bleich et al.[18] In that trial, 58 percent of 216 patients assigned to the double-bolus regimen had a TIMI grade 3 flow rate at 90 minutes, as compared with 66 percent of 221 patients assigned to accelerated infusion.

In the present study, the rate of hemorrhagic stroke was higher after double-bolus alteplase than after accelerated infusion of alteplase ($P=0.23$) and may have been related to the induction of a more pronounced systemic lytic effect, as suggested by the longer activated partial-thromboplastin times in this group at six hours. These data suggest that a less aggressive regimen of heparin may be sufficient when given in conjunction with double-bolus alteplase and may reduce the incidence of hemorrhagic stroke. As in the GUSTO I trial, the rates of death and stroke were higher in elderly patients than in younger ones.[19] These differences were particularly striking in patients over 85 years of age.

On the basis of our results, an accelerated infusion of alteplase over a period of 90 minutes should remain the preferred approach to alteplase therapy in patients with acute myocardial infarction who present within 6 hours after the onset of symptoms. In the subgroup of patients who were 75 years of age or younger (6235 patients, or 87 percent of the study population), however, mortality rates and net clinical outcomes were remarkably similar with both regimens. Similar 30-day mortality rates were also observed in patients who were treated very soon after the onset of symptoms. Although from a statistical point of view the equivalence of the two treatments has not been demonstrated in these subgroups, these post hoc analyses suggest that there

TABLE 4. CLINICAL OUTCOMES AT 30 DAYS ACCORDING TO AGE.*

AGE AND OUTCOME	DOUBLE BOLUS		ACCELERATED INFUSION	
	NO. OF PATIENTS	VALUE	NO. OF PATIENTS	VALUE
		no. (%)		no. (%)
Patients ≤55 years	1041		1093	
Death		25 (2.4)		20 (1.8)
Any stroke		7 (0.7)		4 (0.4)
Hemorrhagic stroke		1 (0.1)		1 (0.09)
Death or nonfatal stroke		31 (3.0)		24 (2.2)
Patients >55 to ≤65 years	1010		1001	
Death		55 (5.4)		62 (6.2)
Any stroke		11 (1.1)		14 (1.4)
Hemorrhagic stroke		7 (0.7)		8 (0.8)
Death or nonfatal stroke		59 (5.8)		69 (6.9)
Patients >65 to ≤75 years	1068		1022	
Death		96 (9.0)		95 (9.3)
Any stroke		25 (2.3)		16 (1.6)
Hemorrhagic stroke		15 (1.4)		8 (0.8)
Death or nonfatal stroke		108 (10.1)		104 (10.2)
All patients ≤75 years	3119		3116	
Death		176 (5.6)		177 (5.7)
Any stroke		43 (1.4)		34 (1.1)
Hemorrhagic stroke		23 (0.7)		17 (0.6)
Death or nonfatal stroke		198 (6.3)		197 (6.3)
Patients >75 to ≤85 years	417		421	
Death		91 (21.8)		82 (19.5)
Any stroke		22 (5.3)		16 (3.8)
Hemorrhagic stroke		14 (3.4)		11 (2.6)
Death or nonfatal stroke		99 (23.7)		87 (20.7)
Patients >85 years	49		47	
Death		19 (38.8)		11 (23.4)
Any stroke		4 (8.2)		5 (10.6)
Hemorrhagic stroke		3 (6.1)		1 (2.13)
Death or nonfatal stroke		19 (38.8)		13 (27.7)
All patients >75 years	466		468	
Death		110 (23.6)		93 (19.9)
Any stroke		26 (5.6)		21 (4.5)
Hemorrhagic stroke		17 (3.6)		12 (2.6)
Death or nonfatal stroke		118 (25.3)		100 (21.4)

*There were no significant differences between groups.

may be a role for a double bolus of alteplase in selected populations (e.g., those who are treated in the ambulance and patients who are 75 or younger).

The mortality rates associated with an accelerated infusion of alteplase in this trial were higher than those in the GUSTO I trial in spite of the use of identical inclusion and exclusion criteria. The most likely explanations are the enrollment of a population at higher risk (more patients with anterior infarction and in a Killip class higher than 1), the longer delay between the onset of symptoms and the start of thrombolytic therapy, and possibly, the less frequent use of revascularization procedures. The incidence of stroke and bleeding complications, on the other hand, was very similar in the two trials.

This multicenter study failed to show equivalence between double-bolus administration of alteplase and accelerated infusion of alteplase according to the prespecified criteria. Furthermore, we observed a higher incidence of intracranial hemorrhage with the double-bolus method. Thus, this method cannot be recommended for general use in patients with acute myocardial infarction.

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APPENDIX

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