The New England Journal of Medicine -- September 2, 1993 -- Vol. 329, No. 10
ORIGINAL ARTICLE

An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction

The GUSTO Investigators

Abstract

Background. The relative efficacy of streptokinase and tissue plasminogen activator and the roles of intravenous as compared with subcutaneous heparin as adjunctive therapy in acute myocardial infarction are unresolved questions. The current trial was designed to compare new, aggressive thrombolytic strategies with standard thrombolytic regimens in the treatment of acute myocardial infarction. Our hypothesis was that newer thrombolytic strategies that produce earlier and sustained reperfusion would improve survival.

Methods. In 15 countries and 1081 hospitals, 41,021 patients with evolving myocardial infarction were randomly assigned to four different thrombolytic strategies, consisting of the use of streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, accelerated tissue plasminogen activator (t-PA) and intravenous heparin, or a combination of streptokinase plus t-PA with intravenous heparin. ("Accelerated" refers to the administration of t-PA over a period of 1 1/2 hours -- with two thirds of the dose given in the first 30 minutes -- rather than the conventional period of 3 hours.) The primary end point was 30-day mortality.

Results. The mortality rates in the four treatment groups were as follows: streptokinase and subcutaneous heparin, 7.2 percent; streptokinase and intravenous heparin, 7.4 percent; accelerated t-PA and intravenous heparin, 6.3 percent; and the combination of both thrombolytic agents with intravenous heparin, 7.0 percent. This represented a 14 percent reduction (95 percent confidence interval, 5.9 to 21.3 percent) in mortality for accelerated t-PA as compared with the two streptokinase-only strategies ($P = 0.001$). The rates of hemorrhagic stroke were 0.49 percent, 0.54 percent, 0.72 percent, and 0.94 percent in the four groups, respectively, which represented a significant excess of hemorrhagic strokes for accelerated t-PA ($P = 0.03$) and for the combination strategy ($P<0.001$), as compared with streptokinase only. A combined end point of death or disabling stroke was significantly lower in the accelerated-t-PA group than in the streptokinase-only groups (6.9 percent vs. 7.8 percent, $P = 0.006$).

Conclusions. The findings of this large-scale trial indicate that accelerated t-PA given with intravenous heparin provides a survival benefit over previous standard thrombolytic regimens. (N Engl J Med 1993;329:673-82.)

Since the landmark trial of intravenous streptokinase by the Gruppo Italiano per lo Studio

della Streptochinasi nell'Infarto Miocardico (GISSI) in 1986, (1) there has been no confirmation that other thrombolytic regimens provide additional survival benefit in patients with acute myocardial infarction, except for the important addition of aspirin (2). Collectively, the large trials of thrombolytic therapy demonstrated a 25 percent reduction in 30-to-35-day mortality in patients presenting to the hospital within six hours of the onset of symptoms (3). Neither the GISSI-2/International trial nor the Third International Study of Infarct Survival (ISIS-3) trial (4,5,6) of more than 60,000 patients found a difference in associated mortality between the use of streptokinase and the use of tissue plasminogen activator (t-PA) (4,5) or between the use of these agents and that of anistreplase (6). Furthermore, the addition of subcutaneous heparin to the regimens did not significantly reduce mortality as compared with no use of heparin (5,6). Although clear differences between thrombolytic agents are evident in the speed with which the agents achieve reperfusion, the similar survival rates in these previous trials suggested that factors other than rapid or sustained coronary reperfusion might be important in reducing mortality.

Recent data suggest that more rapid and effective infarct-artery patency can be achieved with accelerated t-PA, (7,8,9) that lower rates of reocclusion are observed with the use of combination thrombolytic therapy, (10,11,12) and that infarct-artery patency can be sustained longer with the use of intravenous heparin as an adjunct to thrombolytic therapy (13,14,15). ("Accelerated" t-PA refers to the rapid intravenous administration of t-PA over a period of 1 1/2 hours -- with two thirds of the dose given in the first 30 minutes -- rather than the conventional period of 3 hours.) The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial was conceived in 1989 to test the hypothesis that early and sustained infarct-vessel patency was associated with better survival rates in patients with evolving myocardial infarctions. To this end, we compared the effects of four thrombolytic strategies on mortality: streptokinase with subcutaneous heparin, streptokinase with intravenous heparin, accelerated t-PA with intravenous heparin, and streptokinase with t-PA and intravenous heparin.

Methods

Study Organization

Before the trial began, the Food and Drug Administration requested a pilot study of 100 patients treated with a combination of t-PA and streptokinase along with intravenous heparin. After the dose regimen was found not to be associated with excessive bleeding, (16) enrollment in the main trial began on December 27, 1990, and was completed on February 22, 1993. A total of 1081 hospitals in 15 countries in North America and Europe and in Israel, Australia, and New Zealand participated (see the Appendix).

Patient Population

Patients presenting to a participating hospital less than 6 hours after the onset of symptoms, with chest pain lasting at least 20 minutes and accompanied by electrocardiographic signs of greater than or equal to 0.1 mV of ST-segment elevation in two or more limb leads or greater than or equal to 0.2 mV in two or more contiguous precordial leads were eligible for enrollment. The criteria for exclusion were previous stroke, active bleeding, previous treatment with streptokinase or anistreplase, recent trauma or major surgery, previous participation in the trial, or noncompressible vascular punctures. Patients with severe, uncontrolled hypertension (systolic blood pressure greater than or equal to 180 mm Hg, unresponsive to therapy) were considered to have a relative contraindication to enrollment. Patients gave informed consent for participation, and the protocol was approved by the institutional review board at each hospital.

Randomization and Treatment Strategies

The investigators and study coordinators telephoned a 24-hour-per-day, seven-day-per-week randomization center to review patient eligibility and receive a treatment assignment to one of four intravenous thrombolytic strategies: (1) streptokinase (Kabikinase, Kabi Vitrum, Sweden), 1.5 million U over a 60-minute period, with subcutaneous heparin (sodium heparin, Sanofi, Paris) in a dose of 12,500 U twice daily, beginning 4 hours after the start of thrombolytic therapy (the treatment regimen tested in ISIS-3 (6)); (2) streptokinase, 1.5 million U over a 60-minute period, with intravenous heparin (porcine-derived) in a bolus dose of 5000 U and 1000 U per hour (a dose of 1200 U per hour was recommended for patients weighing more than 80 kg), with the dose adjusted to raise the activated partial-thromboplastin time to between 60 and 85 seconds; (3) accelerated t-PA (Genentech, San Francisco) in a bolus dose of 15 mg, 0.75 mg per kilogram of body weight over a 30-minute period, not to exceed 50 mg, and 0.5 mg per kilogram, up to 35 mg, over the next 60 minutes with the same intravenous heparin regimen; or (4) the combination of intravenous t-PA (1.0 mg per kilogram over a 60-minute period, not to exceed 90 mg, with 10 percent given in a bolus dose) and streptokinase (1.0 million U over a 60-minute period), given simultaneously but through separate intravenous catheters, along with intravenous heparin as described for the other treatment strategies. For subcutaneous heparin, the treatment was continued for seven days or until the patient was discharged from the hospital; intravenous heparin was given for at least 48 hours or longer at the investigators' discretion. The activated partial-thromboplastin time was monitored at 6, 12, and 24 hours for titration of the dose of intravenous heparin. Individual drug kits for each patient were forwarded to each study site for use according to the random assignment; these were sealed and coded with a numerical sequence, and the actual treatment was not identifiable until the seal was broken.

The trial began in December 1990 with only three groups but was modified in March 1991 after the first 1160 patients had been enrolled. At that time, the ISIS-3 results were reported, (6) and it was suggested that there would not be a reference group within the three groups of the GUSTO trial for adequate comparison of the results with those of ISIS-3. Therefore, the Steering Committee unanimously decided to include a treatment group receiving streptokinase and subcutaneous heparin, which had the most favorable results with regard to mortality, on the basis of the preliminary results of ISIS-3 in March 1991, supported by the results obtained with a similar regimen in the GISSI-2/International trial (4,5).

Additional Therapy

Chewable aspirin (Bayer, New York) was administered as soon as possible in a dose of greater than or equal to 160 mg, followed by a daily dose of 160 to 325 mg per day. For patients without a contraindication to beta-blockade, 5 mg of intravenous atenolol (ICI Pharmaceuticals, Wilmington, Del.) was given in two divided doses, followed by oral therapy with 50 to 100 mg once daily. All other medications, including nitrates, antiarrhythmic drugs, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, and digitalis were prescribed at the discretion of the attending physician. Similarly, the use of coronary angiography, angioplasty, and coronary-artery bypass surgery was left to the discretion of the investigator.

End Points

The primary end point was death from any cause at 30 days of follow-up. Other related major clinical outcomes that were prospectively defined and assessed were the combined end

points of death and nonfatal stroke, death and nonfatal hemorrhagic stroke, and death and nonfatal disabling stroke. In all cases of focal neurologic dysfunction, every attempt was made to determine the cause by computerized axial tomography of the head, magnetic resonance imaging, or in the case of death, by autopsy. Strokes were classified as caused by a primary hemorrhage (including cerebral hemorrhage and subdural hematomas), a cerebral infarct with conversion to hemorrhage, a nonhemorrhagic cerebral infarct, or an unknown cause (in which case there was no brain imaging or autopsy). The stroke data were independently reviewed by a Stroke Review Committee whose members were unaware of the treatment assignments. A patient who had a stroke was classified as disabled if at the time of hospital discharge he or she had a moderate deficit (substantial limitation of activity and capabilities) or a severe deficit (inability to live independently or work) or as not disabled if he or she had no sequelae or only a minor deficit (with the functional status unchanged). This classification was validated by direct interviews with patients about their quality of life.

Bleeding complications were classified as severe or life-threatening if they were intracerebral or if they resulted in substantial hemodynamic compromise requiring treatment. Moderate bleeding was defined by the need for transfusion. Minor bleeding referred to other bleeding, not requiring transfusion or causing hemodynamic compromise. The lowest hematocrit during the hospitalization was recorded.

Data Management and Quality Assurance

A simplified three-page case-report form was used to enter the primary data, with additional one-to-two-page data-collection forms used for all patients who had stroke, cardiogenic shock, or reinfarction. The case-report forms were forwarded to either the international coordinating centers (Catholic University, Leuven, Belgium, and the National Health and Medical Research Council Clinical Trials Centre, Sydney, Australia) or the main coordinating center (Duke University, Durham, N.C.) for data entry and the generation of queries about missing or inconsistent data. Patients who survived the hospitalization were given a postcard to mail to the coordinating center at the 30-day follow-up. Missing data on follow-up mortality were obtained by telephone, by registered mail, at follow-up clinics, or through locator services, as well as by cross-checking with national-registry indexes in countries where such data are promptly and accurately tabulated and available. The quality of the data was ensured by auditing 10 percent of the data forms. The audits involved at least one visit to each enrolling site, during which cross-checks between the case-report forms and the source medical records were made. In addition to this verification, similar audits were performed for all patients who had strokes. For each patient randomized, a safety summary form was sent by facsimile transmission to the coordinating center at the time of discharge from the hospital, on day 30, or at the time of death, whichever came first. This form provided details about whether there had been a stroke or a life-threatening bleeding event. The electrocardiographic core laboratory, which was unaware of the treatment assignments, read all electrocardiograms obtained at enrollment, before discharge, and at the time of any subsequent infarction. No investigator or sponsor had access to any of the data until the trial was complete and the prespecified analyses had been performed by the two biostatisticians who coordinated the data analyses. The data reported herein are based on a 99.9 percent level of completeness of 30-day mortality outcomes and a 99.8 percent level of completeness for other outcome data derived from case reports.

Statistical Analysis

The trial was designed to provide high power for detecting a 15 percent reduction in

mortality or an absolute decrease of 1 percent, whichever was larger, for the experimental treatments as compared with the controls. The two groups assigned to monotherapy with streptokinase were considered the control groups. It was prospectively determined that if there was no difference in mortality between these two groups ($P>0.10$), the analysis would proceed with these patients pooled together. If a difference was observed between the two streptokinase groups, the plan called for a comparison of the two experimental groups with the streptokinase group that had the best results. With a projection that mortality in the control patients would be approximately 8 percent, the target enrollment of 41,000 was chosen to provide at least 90 percent power for detecting the desired differences if mortality among the controls was 8 percent or higher, and at least 80 percent power if mortality among the controls was less than 8 percent. These calculations were based on an alpha of 0.05 and two-tailed testing.

Continuous data are summarized as medians with 25th and 75th percentiles unless otherwise indicated. Selected base-line characteristics and clinical outcomes were compared between treatments by the chi-square test for discrete variables and by nonparametric analysis of variance for continuous variables. Odds ratios and 95 percent confidence intervals were used to compare treatments with regard to major clinical outcomes. Mortality during the 30-day follow-up period was characterized with Kaplan-Meier mortality curves. The consistency of treatment effects among prespecified subgroups (interactions) defined according to age, location of infarct, and time to treatment was assessed with logistic regression. Prespecified interim analyses of safety were performed when enrollment reached 11,274, 21,926, and 28,312 patients, with the data reviewed by an independent Data and Safety Monitoring Board. Comparisons of efficacy at the interim analyses were monitored with two-sided, symmetric O'Brien-Fleming boundaries generated with the Lan-DeMets approach to group-sequential testing (17,18). All tests of significance were two-tailed, and treatments were compared according to the intention-to-treat principle.

Relationship with Sponsors

When the study was designed, the Steering Committee undertook specific measures to avoid financial conflicts of interest, as reported elsewhere (19). All the members of the Steering Committee, the Data and Safety Monitoring Board, and the Data Coordinating Center declared in writing that neither they nor their immediate family members had any financial relationship with any of the sponsors, including equity interest, receipt of honorariums, consulting relationships, and reimbursement for travel expenses. Principal investigators at the enrolling hospitals were required to acknowledge in writing that they had no equity interest in the sponsoring companies.

Results

Characteristics of the Patients

A total of 41,021 patients were enrolled between December 27, 1990, and February 22, 1993 (Table 1). The imbalance in the number of patients assigned to receive streptokinase and subcutaneous heparin reflects the slight delay in initiating this group during the trial. There were no differences in base-line characteristics among the four treatment groups. The time from the onset of symptoms to treatment, although not a base-line variable, differed among the groups ($P<0.001$); it was five minutes longer for the group assigned to combined streptokinase and t-PA because of the longer time required to prepare and initiate this treatment regimen. The diagnosis of acute myocardial infarction was confirmed in at least 97 percent of the patients in each group.

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Table 1: Base-Line Characteristics of the Four Treatment Groups.

Characteristic	Streptokinase and Subcutaneous Heparin (N = 9841)	Streptokinase and Intravenous Heparin (N = 10,410)	Accelerated t-PA and Intravenous Heparin (N = 10,396)
Age (yr)	62 (52, 70)	62 (52, 70)	62 (52, 70)
Female sex (%)	25	25	25
Diabetes (%)	15	15	15
Cigarette smoker (%)	43	43	43
Hypertension (%)	39	38	38
Systolic blood pressure (mm Hg)	130 (111, 144)	129 (112, 144)	130 (113, 144)
Heart rate (beats/min)	73 (62, 85)	74 (63, 86)	73 (62, 86)
Previous infarction (%)	16	17	17
Previous CABG† (%)	4	4	5
Time to randomization (min)	120 (90, 180)	120 (90, 180)	120 (90, 180)
Time to treatment (min)	164 (115, 232)	165 (120, 230)	165 (120, 230)

*Values followed by numbers in parentheses are medians, with the 25th and 75th percentiles shown inside the parentheses. There were no di characteristics among the four groups. Time to treatment, although not strictly a base-line characteristic, did differ among the groups (P<0.001).

†CABG denotes coronary-artery bypass surgery.

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Study Medications

The rate of compliance with the randomly assigned thrombolytic regimens was 97 to 98 percent for all four groups. In each group, the initial aspirin dose was given to 97 percent of the patients, and oral aspirin was administered subsequently to approximately 93 percent, with no significant differences between treatment groups. In the three groups assigned to intravenous heparin, 99.5 percent of the patients received this therapy on the first hospital day, and 86 percent received at least 40 hours of continuously infused intravenous heparin during the first 48 hours. The median activated partial-thromboplastin times at 12 hours in the groups assigned to streptokinase and intravenous heparin, accelerated t-PA and intravenous heparin, and the combination of t-PA and streptokinase with intravenous heparin were 82, 72, and 83 seconds, respectively; at 24 hours the corresponding values were 62, 63, and 62 seconds. These data demonstrate that the target value of in vitro anticoagulation was achieved in at least half the patients assigned to intravenous heparin throughout the first 24 hours. Lack of compliance with subcutaneous heparin therapy, defined as failure to start this regimen in the first 24 hours, occurred in 11 percent of the patients, more often in the United States (14 percent) than in the other countries (7 percent). Overall, 36 percent of the patients in this group received intravenous heparin at some point during their hospitalization. The predominant reason for switching to intravenous heparin was recurrent ischemia, in more than 60 percent of the patients.

Beta-blockers were administered intravenously to 46 percent of the patients and orally to 71 percent. Prophylactic lidocaine was given to 18 percent of the patients, a calcium-channel blocker to 31 percent, preparations of digitalis to 14 percent, other inotropic agents to 19 percent, intravenous nitroglycerin to 77 percent, and an angiotensin-converting-enzyme inhibitor to 21 percent.

Major Clinical Outcomes

The data on the principal end points are summarized in Table 2 for the four treatment groups. For 30-day mortality, there was no significant difference between the streptokinase groups ($P = 0.731$). There was a significant reduction in mortality with accelerated t-PA as compared with the two streptokinase strategies (10 lives saved per 1000 patients treated; risk reduction, 14 percent; 95 percent confidence interval, 5.9 to 21.3; $P = 0.001$). In addition, comparing the accelerated-t-PA group separately with each streptokinase group demonstrated significant reductions in mortality (t-PA vs. streptokinase with subcutaneous heparin, $P = 0.009$; t-PA vs. streptokinase with intravenous heparin, $P = 0.003$). There was no difference in mortality between the combination strategy using both t-PA and streptokinase and the two strategies involving streptokinase monotherapy (risk reduction, 4 percent; 95 percent confidence interval, -4.2 to 12.2; $P = 0.352$). There was a significant difference in 30-day mortality between accelerated t-PA and the combination therapy (6.3 vs. 7.0 percent; risk reduction, 10 percent; 95 percent confidence interval, 0.8 to 19.2; $P = 0.04$). As shown in Table 2, there were similar statistically significant differences between accelerated t-PA and each of the streptokinase strategies with regard to the combined end points of mortality and stroke. In Figure 1, the mortality data are plotted with an actuarial analysis for the 30-day end point. Figure 2 shows the benefit in the accelerated-t-PA group as compared with either streptokinase group with regard to reduction in mortality and the combined end point of death or disabling stroke. There were significant reductions in the risk of this combined end point with accelerated t-PA as compared with the two streptokinase strategies together ($P = 0.006$) and as compared with each streptokinase group separately (t-PA vs. streptokinase with subcutaneous heparin, $P = 0.03$; t-PA vs. streptokinase with intravenous heparin, $P = 0.01$).

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Table 2: Major Clinical Outcomes.

Outcome	Streptokinase and Subcutaneous Heparin (N = 9796)	Streptokinase and Intravenous Heparin (N = 10,377)	Accelerated t-PA and Intravenous Heparin (N = 10,344)	Both Thrombolytic Agents and Intravenous Heparin (N = 10,328)	P Value, Accelerated t-PA vs. Both Streptokinase Groups
	percent of patients				
24-hr mortality	2.8	2.9	2.3	2.8	0.005
30-day mortality	7.2	7.4	6.3	7.0	0.001
Or nonfatal stroke	7.9	8.2	7.2	7.9	0.006
Or nonfatal hemorrhagic stroke	7.4	7.6	6.6	7.4	0.004
Or nonfatal disabling stroke	7.7	7.9	6.9	7.6	0.006

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Figure 1: Thirty-Day Mortality in the Four Treatment Groups.

The group receiving accelerated treatment with t-PA had lower mortality than the two streptokinase groups (P = 0.001) and than each individual treatment group: streptokinase and subcutaneous (SC) heparin (P = 0.009), streptokinase and intravenous (IV) heparin (P = 0.003), and t-PA and streptokinase combined with IV heparin (P = 0.04).

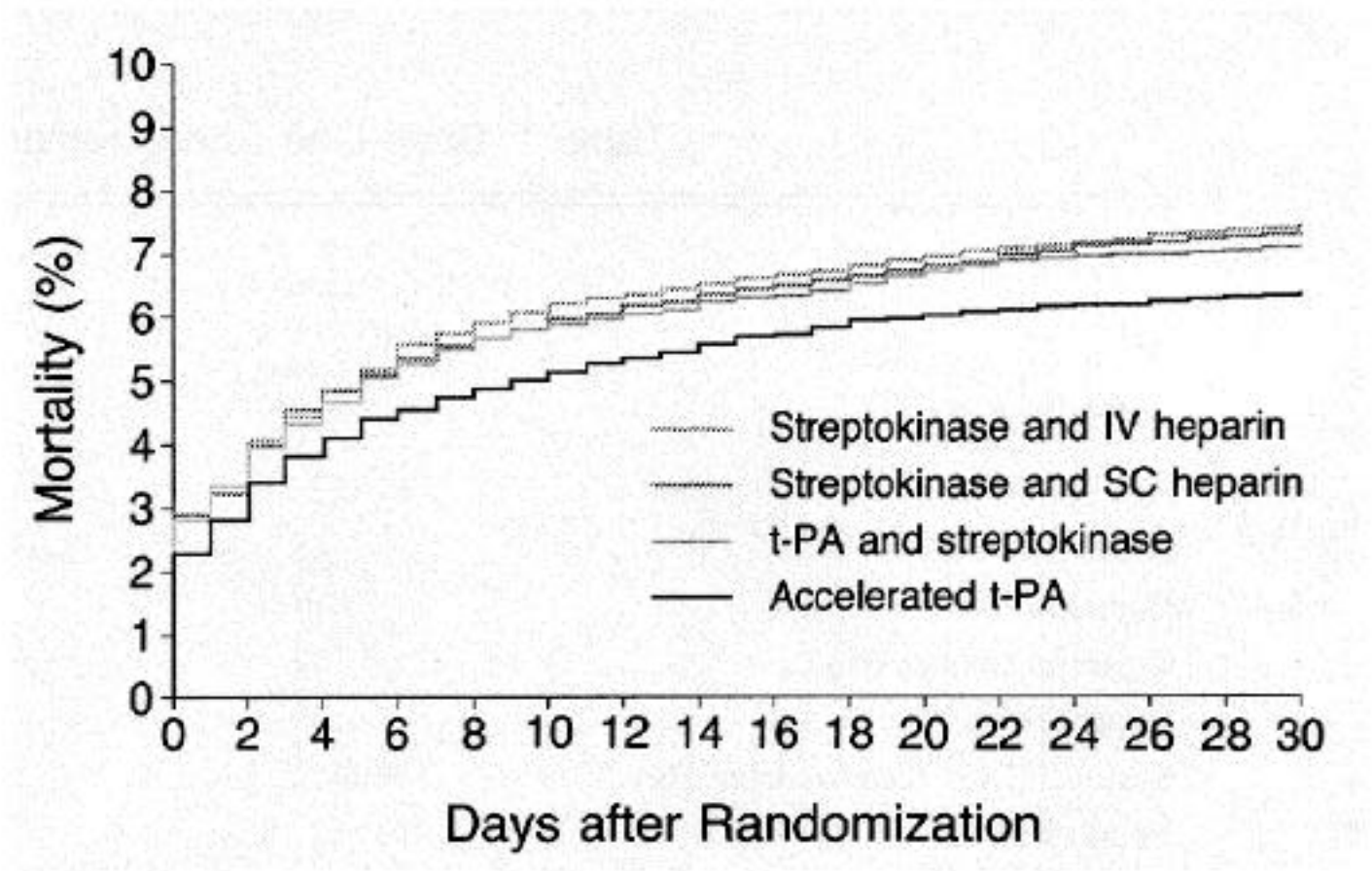

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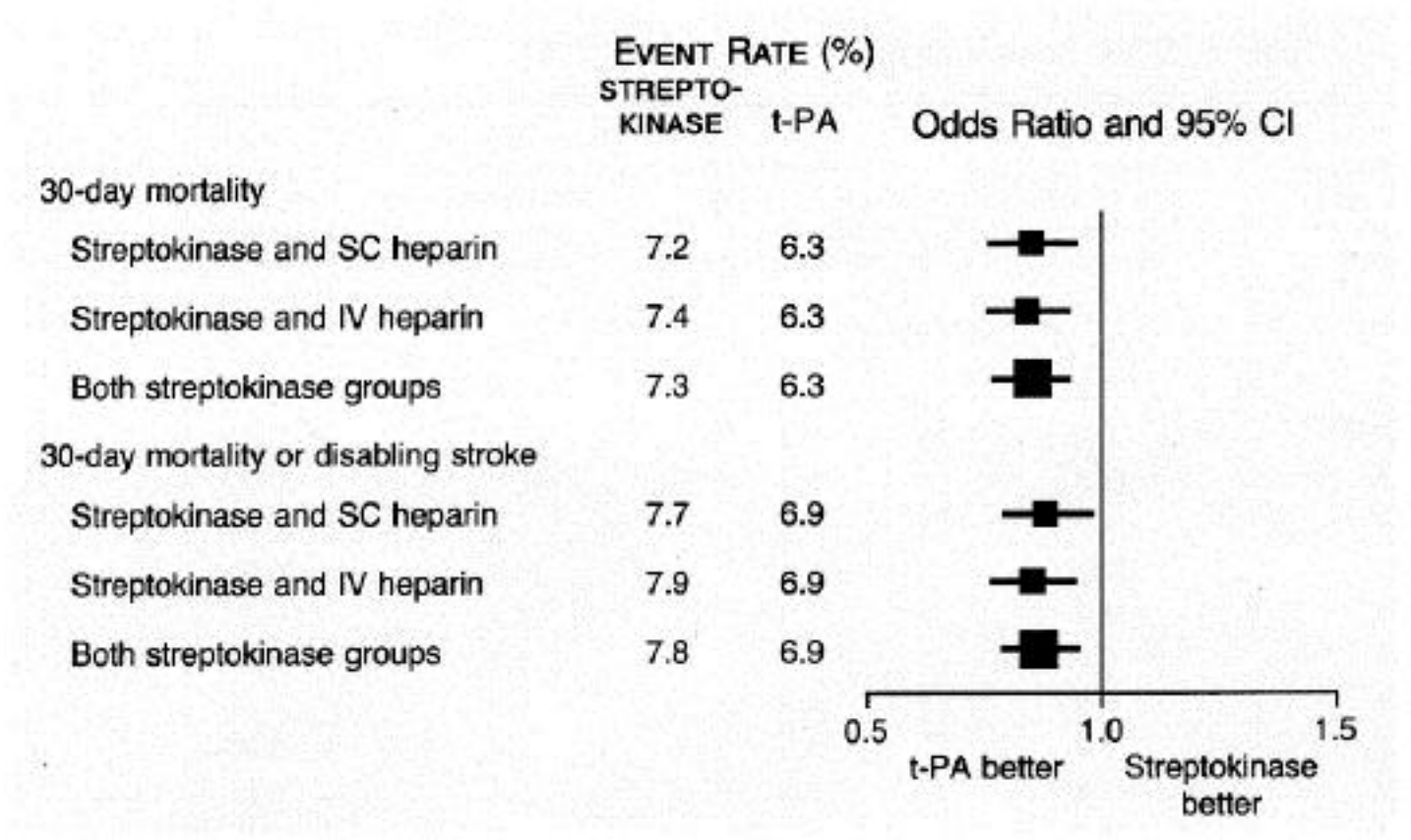
Figure 2: Odds Ratios and 95 Percent Confidence Intervals (CI) for Reduction in Mortality and Net Benefit, Defined as Reduction in Mortality and Disabling Stroke, in the Group Assigned to Accelerated t-PA as Compared with the Streptokinase Groups.



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Stroke and Bleeding Complications

In Table 3, the data on strokes, broken down according to the presence or absence of hemorrhage, show an approximate excess of 2 hemorrhagic strokes per 1000 patients treated (absolute excess, 0.2 percent) for t-PA as compared with streptokinase (P = 0.03) and an excess of 4 hemorrhagic strokes per 1000 for the combination of thrombolytic agents (P< 0.001). With regard to all strokes, there was an excess of approximately 2 per 1000 in the accelerated-t-PA group (P = 0.09) and of more than 3 per 1000 in the combination group (P = 0.02). The incidence of other bleeding events or indexes tended to be more favorable with accelerated t-PA than with the other treatments. Although differences between groups in the nadir hematocrit during hospitalization were statistically significant, the magnitude of the differences clinically was small.

Clinical Outcomes Other Than Mortality and Stroke

A consistent pattern of fewer complications was noted in the accelerated-t-PA group, particularly with respect to allergic reactions, clinical indicators of left ventricular dysfunction, and arrhythmias (Table 4). No differences were observed in the rate of complications reflecting recurrent ischemia, including reinfarction. The use of coronary revascularization procedures was similar in the four treatment groups (angioplasty in 15 percent of the patients and bypass surgery in 9 percent). Procedures to treat arrhythmia or heart failure were used less often in the patients receiving accelerated t-PA.

Prespecified Subgroups

Three groups of patients were prospectively defined according to age (>75 years vs. less than or equal to 75 years), infarct location (anterior vs. inferior), and the time to randomization. The relative reduction in the mortality rate was lower in the patients over 75 who were given accelerated t-PA than in the patients less than or equal to 75 who were given streptokinase, and the excess risk of hemorrhagic stroke or stroke of any type was higher in those over 75 (Table 5). However, as shown in Table 5, the absolute net benefit with respect to mortality and disabling stroke was similar in both younger and older patients. The results of the test to determine whether treatment varied according to age (interaction between treatment and age) were not significant (P = 0.098). Both patients with anterior and those with inferior myocardial infarctions derived a mortality benefit from accelerated t-PA as compared with streptokinase, although the benefit in those with anterior infarctions was greater (anterior infarction, 8.6 percent vs. 10.5 percent, respectively; odds ratio, 0.81; 95 percent confidence interval, 0.71 to 0.92; inferior infarction, 4.7 percent vs. 5.3 percent; odds ratio, 0.89; 95 percent confidence interval, 0.78 to 1.03). When the time to treatment was categorized in intervals of 0 to 2 hours, 2 to 4 hours, and 4 to 6 hours, there was a consistent benefit for accelerated t-PA as compared with streptokinase with respect to the extent of the reduction in mortality (4.3 percent vs. 5.4 percent, 5.5 percent vs. 6.7 percent, and 8.9 percent vs. 9.3 percent for the respective intervals), although a significant interaction was observed between time to treatment and reduction in mortality (P = 0.015), with a greater reduction in mortality associated with early treatment with t-PA (Figure 3).

Discussion

Our findings indicate that a thrombolytic strategy consisting of accelerated t-PA with intravenous heparin was superior to both of the streptokinase regimens in reducing mortality and achieving a net clinical benefit, as defined by survival without a disabling stroke. As compared with the streptokinase regimens, t-PA led to an actual benefit of 10 additional lives saved per 1000 patients treated, or the prevention of death and disabling

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Table 3: Incidence of Stroke and Bleeding Complications.

Event	Streptokinase and Subcutaneous Heparin	Streptokinase and Intravenous Heparin	Accelerated t-PA and Intravenous Heparin	Both Thrombolytic Agents and Intravenous Heparin
Stroke	**N = 9709**	**N = 10,314**	**N = 10,268**	**N = 10,248**
		percent of patients		
All types	1.22	1.40	1.55	1.64
Hemorrhagic	0.49	0.54	0.72	0.94
Nonhemorrhagic	0.53	0.65	0.64	0.53
With conversion to hemorrhagic	0.04	0.05	0.06	0.08
Unknown type	0.15	0.16	0.13	0.10
Bleeding	**N = 8663**	**N = 9249**	**N = 9222**	**N = 9184**
		percent of patients		
Severe or life-threatening	0.3	0.5	0.4	0.6
Moderate	5.6	5.8	5.1	5.6
Moderate or worse	5.8	6.3	5.4	6.1
Units transfused				
0	89	88	90	88
1–2	5	6	5	6
3–4	3	3	3	3
≥5	3	3	2	3
Lowest hematocrit — median (25th, 75th percentile)	37 (33, 41)	37 (32, 41)	37 (33, 41)	37 (32, 41)

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Table 4: Other Complications.

Complication	Streptokinase and Subcutaneous Heparin (N = 8669)	Streptokinase and Intravenous Heparin (N = 9260)	Accelerated t-PA and Intravenous Heparin (N = 9235)	Both Thrombolytic Agents and Intravenous Heparin (N = 9193)
		percent of patients		
Allergic reaction	5.7	5.8	1.6	5.4
Anaphylaxis	0.7	0.6	0.2	0.6
Congestive heart failure	17.5	16.8	15.2	16.8
Cardiogenic shock	6.9	6.3	5.1	6.1
Sustained hypotension	13.3	12.5	10.1	12.4
Atrioventricular block*	9.5	8.7	7.3	8.4
Sustained ventricular tachycardia	6.8	6.5	5.6	6.1
Ventricular fibrillation	7.1	6.9	6.3	6.9
Asystole	6.0	6.4	5.3	6.4
Atrial fibrillation or flutter	9.9	9.8	8.6	9.1
Reinfarction	3.4	4.0	4.0	4.0
Recurrent ischemia	19.9	19.6	19.0	18.8
Acute mitral regurgitation	1.6	2.6	1.3	1.4
Acute ventricular septal defect	0.5	0.4	0.4	0.6

*Refers to second- or third-degree block.

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Table 5: Effect of Treatment According to Age.

Outcome	Treatment Group		Odds Ratio (95% CI*)
	Both streptokinase groups	Accelerated t-PA	
Age ≤75 yr	**N = 17,804**	**N = 9039**	
	% of patients		
Death	5.5	4.4	0.79 (0.70–0.89)
Any stroke	1.08	1.20	1.21 (0.88–1.42)
Hemorrhagic stroke	0.42	0.52	1.24 (0.86–1.78)
Death or nonfatal disabling stroke	6.0	5.0	0.83 (0.74–0.93)
Age >75 yr	**N = 2358**	**N = 1297**	
	% of patients		
Death	20.6	19.3	0.92 (0.78–1.10)
Any stroke	3.05	3.93	1.30 (0.90–1.87)
Hemorrhagic stroke	1.23	2.08	1.71 (1.01–2.88)
Death or nonfatal disabling stroke	21.5	20.2	0.93 (0.78–1.10)

*CI denotes confidence interval.

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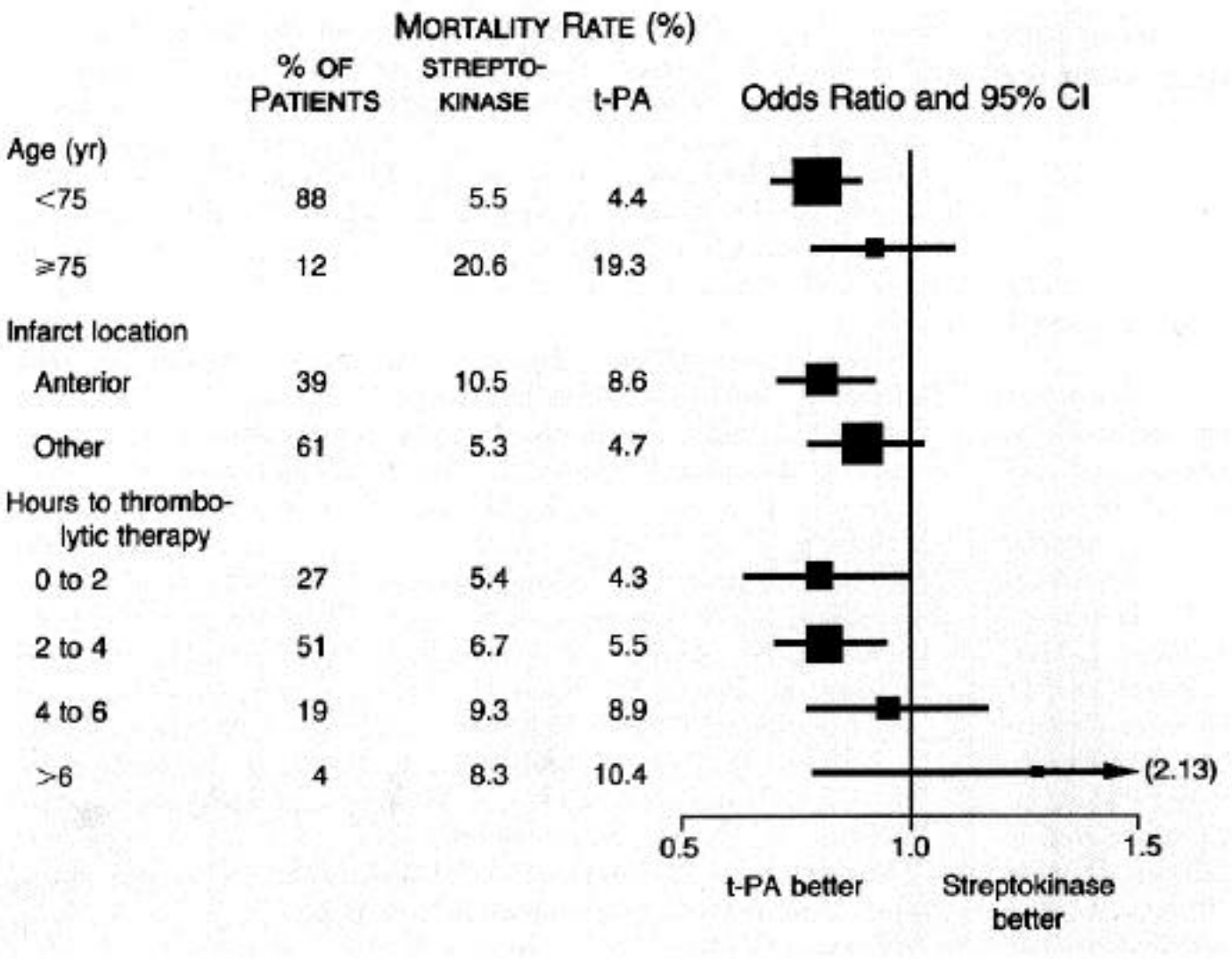
Figure 3: Odds Ratios and 95 Percent Confidence Intervals (CI) for 30-Day Mortality in the Prespecified Subgroups Defined by Age, Infarct Location, and Time to Thrombolytic Therapy.



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stroke in 9 patients per 1000 treated. There was also a significant reduction in the mortality rate with accelerated t-PA as compared with the combination regimen including both t-PA and streptokinase. The superiority of the accelerated t-PA treatment was statistically robust across all the comparisons of prespecified subgroups. Even though this regimen was associated with a small excess of strokes, the end points of survival without a stroke, survival without a disabling stroke, and survival without a nonfatal hemorrhagic stroke all demonstrated the net advantage of this treatment approach over either streptokinase regimen.

The patency rate of the infarct-related artery at 90 minutes with accelerated t-PA has been reported to be 85 percent in previous angiographic trials (7,8,9,20) and was confirmed to be significantly higher than with the other thrombolytic regimens in the current trial (these data will be reported on fully in a subsequent paper). On the other hand, the combination of t-PA and streptokinase, in which there was less initial loading of t-PA, has not been associated with a higher early patency rate (10,11,12). We suggest that the superiority of accelerated t-PA over the combination strategy is probably related to faster recanalization of the infarct-related vessel achieved by the more rapid administration of t-PA.

Even at 24 hours, the mortality rate was reduced significantly, by 19 percent, with accelerated t-PA as compared with the other regimens, showing that fully half the absolute benefit in survival occurred very early. These favorable survival data were paralleled by a lower incidence of arrhythmia, congestive heart failure, and cardiogenic shock. Although the importance of early infarct-artery patency has been a subject of debate, the current trial supports the idea that in the setting of acute myocardial infarction, rapid restoration of myocardial blood flow improves survival.

As compared with previous, placebo-controlled thrombolytic trials (1,2) that collectively showed a 2.5 to 3.3 percent absolute reduction in mortality (relative reduction, 27 percent), the current study demonstrated an additional survival benefit with the accelerated-t-PA strategy that represents an important additional step forward in thrombolytic therapy. Like our trial, future trials using an active-treatment control group cannot be expected to demonstrate as extensive an incremental survival benefit as did earlier placebo-controlled trials.

The cost effectiveness of widespread use of the most favorable thrombolytic regimen in this trial (accelerated t-PA with intravenous heparin) is likely to attract substantial interest. As compared with a regimen of streptokinase and aspirin (and no heparin), which has been thoroughly evaluated in the GISSI-2 and ISIS-3 trials, accelerated t-PA is more expensive ($320 vs. $2,300, respectively, in the United States) and more complex to administer, because it requires the titration of intravenous heparin according to the activated partial-thromboplastin time in addition to weight-adjusted dosing of t-PA as specified in the current trial. Given the different margins of benefit in certain prespecified subgroups, further analysis of this issue will be useful in determining the most cost-effective application of the survival benefit realized in the overall study population.

On the basis of the survival advantage and net clinical benefit, along with the lower incidence of allergic reactions and other complications, the GUSTO trial provides evidence that accelerated t-PA combined with intravenous heparin is the best thrombolytic strategy to date for patients with acute myocardial infarction. This development, however, should not lead to complacency about further clinical investigation of better therapeutic approaches to myocardial infarction, (20) given the 6.3 percent mortality rate and the 1.5 percent incidence of stroke. It is possible that even more aggressive strategies to promote earlier and complete coronary reperfusion will further improve these outcomes.

Source Information

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Supported by a combined grant from Bayer, CIBA-Corning, Genentech, ICI Pharmaceuticals, and Sanofi Pharmaceuticals.

Dr. Topol, as chairman of the study, assumes full responsibility for the overall content and integrity of the manuscript.

A list of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) investigators appears in the Appendix.

Appendix

The following investigators collaborated on the GUSTO study. The numbers shown are the numbers of patients enrolled from each area or country.

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Correction

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ORIGINAL ARTICLE

An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction

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