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Comparison of Front-Loaded Recombinant Tissue-Type Plasminogen Activator, Anistreplase and Combination Thrombolytic Therapy for Acute Myocardial Infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 4 Trial

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Objectives. **The aim of our study was to determine a superior thrombolytic regimen from three: anistreplase (APSAC), front-loaded recombinant tissue-type plasminogen activator (rt-PA) or combination thrombolytic therapy.**

Background. **Although thrombolytic therapy has been shown to reduce mortality and morbidity after acute myocardial infarction, it has not been clear whether more aggressive thrombolytic-antithrombotic regimens could improve the outcome achieved with standard regimens.**

Methods. **To address this issue, 382 patients with acute myocardial infarction were randomized to receive in a double-blind fashion (along with intravenous heparin and aspirin) APSAC, front-loaded rt-PA or a combination of both agents. The primary end point "unsatisfactory outcome" was a composite clinical end point assessed through hospital discharge.**

Results. **Patency of the infarct-related artery (Thrombolysis in Myocardial Infarction [TIMI] grade 2 or 3 flow) at 60 min after the start of thrombolysis was significantly higher in rt-PA–treated patients (77.8% vs. 59.5% for APSAC-treated patients and 59.3% for combination-treated patients [rt-PA vs. APSAC, p = 0.02; rt-PA vs. combination, p = 0.03]). At 90 min, the incidence of both infarct-related artery patency and TIMI grade 3 flow was significantly higher in rt-PA–treated patients (60.2% had TIMI grade 3 flow vs. 42.9% and 44.8% of APSAC- and combination-treated patients, respectively [rt-PA vs. APSAC, p < 0.01; rt-PA vs. combination, p = 0.02]). The incidence of unsatisfactory outcome was 41.3% for rt-PA compared with 49% for APSAC and 53.6% for the combination (rt-PA vs. APSAC, p = 0.19; rt-PA vs. combination, p = 0.06). The mortality rate at 6 weeks was lowest in the rt-PA–treated patients (2.2% vs. 8.8% for APSAC and 7.2% for combination thrombolytic therapy [rt-PA vs. APSAC, p = 0.02; rt-PA vs. combination, p = 0.06]).**

Conclusions. **Front-loaded rt-PA achieved significantly higher rates of early reperfusion and was associated with trends toward better overall clinical benefit and survival than those achieved with a standard thrombolytic agent or combination thrombolytic therapy. These findings support the concept that more rapid reperfusion of the infarct-related artery is associated with improved clinical outcome.**

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After intravenous thrombolytic therapy was shown to be effective in achieving early coronary reperfusion, the Thrombolysis in Myocardial Infarction (TIMI) 1 trial demonstrated that recombinant tissue-type plasminogen activator (rt-PA) provided a higher reperfusion rate than did streptokinase (1). However, the GISSI-2/International (2,3) and ISIS-3 trials (4) showed no difference in mortality among patients given rt-PA, streptokinase and anistreplase (anisoylated plasminogen streptokinase activator complex [APSAC]) without intravenous heparin. This finding led some to conclude that more aggressive regimens that achieve greater patency would be of no further benefit. However, given the strong evidence that still supported the early open artery hypothesis (5), the TIMI

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Investigators set out in the TIMI 4 trial to evaluate the overall clinical benefit (and the mechanism of benefit) of two promising new regimens—front-loaded rt-PA (6) and combination thrombolytic therapy (7)—and to compare them with those of a standard agent, APSAC (8,9). TIMI 4 was carried out contemporaneously with GUSTO (10), a trial that asked similar questions in a much larger patient cohort.

Methods

Eligibility criteria. Patients were screened for enrollment at 18 clinical centers (see Appendix). To be eligible for study participation, patients had to experience ischemic pain for ≥30 min in association with ST segment elevation ≥0.1 mV in at least two contiguous leads or with new left bundle branch block. The onset of pain had to occur within 6 h of planned initiation of treatment.

Exclusion criteria were age ≥80 years, administration of rt-PA for acute myocardial infarction within the previous 2 weeks or administration of anistreplase or streptokinase at any time, oral anticoagulation, woman of childbearing potential, previously documented left bundle branch block, other serious illness, inability to comply with the protocol or to give informed consent, previous participation in TIMI 4 and contraindications to thrombolytic therapy. The latter included a bleeding disorder or gastrointestinal bleeding within the previous 12 months; a history of cerebrovascular disease at any time, including any form of stroke or transient ischemic attack; a confirmed blood pressure >180/110 mm Hg; severe trauma within the previous 3 months; or a significant surgical procedure, cardiac catheterization or cardiopulmonary resuscitation within the previous 2 weeks. Informed consent was obtained from each patient in accordance with the requirements of each hospital's Institutional Review Board.

Eligible patients were randomly allocated with the use of sealed envelopes to receive, in double-blind fashion, either front-loaded rt-PA (Activase, Genentech) given as a 15-mg bolus, a 0.75-mg/kg (up to 50-mg) infusion over 30 min, followed by a 0.50-mg/kg (up to 35-mg) infusion over 60 min (6); APSAC (Eminase, SmithKline Beecham) given as a 30-U bolus over 2 to 5 min; or combination thrombolytic therapy, which consisted of a 15-mg bolus of rt-PA and a 0.75-mg/kg (up to 50-mg) infusion over 30 min and a 20-U bolus of APSAC.

All patients received immediate intravenous heparin therapy (administered as a 5,000-IU intravenous bolus followed by a 1,000-IU/h infusion, which was then adjusted to maintain an activated partial thromboplastin time between 1.5 and 2 times control level and aspirin ([Ecotrin, SmithKline Beecham] 325 mg chewed immediately on enrollment if they were not already taking aspirin, and 325 mg daily thereafter). In light of the results of the TIMI 2 trial (11), patients also received intravenous followed by oral metoprolol if there were no contraindications. Other medications were administered at the discretion of the treating physician.

Patients underwent coronary arteriography to ascertain patency of the infarct-related artery 90 min after the start of thrombolytic therapy. When possible, arterial patency was also determined at 60 and 75 min. The arterial sheath for the catheterization was secured in place and coronary arteriography was repeated 18 to 36 h after the start of thrombolytic therapy (or earlier if the patient experienced recurrent ischemic pain with ST segment elevation). If the infarct-related artery was occluded at 90 min (TIMI grade 0 or 1 flow) (1) and if coronary occlusion was confirmed at 120 min, rescue percutaneous transluminal coronary angioplasty could be performed at the discretion of the treating physician. Revascularization with angioplasty or coronary artery bypass surgery was recommended only if significant recurrent ischemia developed and was performed at the discretion of the treating physician (11).

Radionuclide perfusion imaging with technetium-99m hexakis 2-methoxyisobutyl isonitrile (sestamibi) was performed according to a standardized protocol (12) immediately after the 18- to 36-h catheterization and before hospital discharge. Rest ventricular function was assessed by radionuclide ventriculography before hospital discharge. Telephone follow-up, obtained at 6 weeks and 1 year, was complete in 96% of patients. Angiograms, radionuclide scans and electrocardiograms were interpreted at the respective Core Laboratories, and suspected clinical end points were reviewed by the Morbidity and Mortality Classification Committee; all interpretations and reviews were made without knowledge of treatment assignment.

Study end points. The primary end point was the composite end point "unsatisfactory outcome," defined as the occurrence of any of the following through hospital discharge (13): death (all-cause mortality), severe congestive heart failure or cardiogenic shock, low ejection fraction (measured by radionuclide ventriculogram as <40% [or as <30% for patients with previous myocardial infarction]), reinfarction, TIMI grade flow <2 at 90 min or 18 to 36 h, reocclusion as assessed by sestamibi imaging, major spontaneous hemorrhage (14) or severe anaphylaxis. A weighted score was calculated for each patient, as previously described (13). A separate analysis of these end points revealed that the definition of ejection fraction <40% for all patients was a stronger predictor of 1-year mortality than when ejection fraction <30% was used for patients with prior myocardial infarction (15). Thus, a secondary end point was the unsatisfactory outcome end point using ejection fraction <40% for all patients as the definition of low ejection fraction.

End point definitions. Severe congestive heart failure was defined as the presence of rales over more than half the lung fields (16), and cardiogenic shock was defined as described elsewhere (17); these end points had to occur ≥4 h after the start of administration of the study drug. Recurrent infarction was defined as in previous TIMI trials (14,18). Reocclusion at hospital discharge as assessed by sestamibi imaging was defined as an increase of >30% in defect size between the 18- to 36-h sestamibi scan and the prehospital discharge scan (12). Major hemorrhage was defined as 1) an intracranial hemorrhage, 2) hemorrhagic pericardial tamponade, 3) a decrease in hemoglobin ≥5 g/dl, or 4) an absolute decrease in hematocrit

Table 1. Baseline Characteristics of the 382 TIMI 4 Study Patients

	Thrombolytic Therapy Group			p Value		
	rt-PA (n = 138)	APSAC (n = 147)	Comb. (n = 97)	3-Way	rt-PA vs. APSAC	rt-PA vs. Comb.
Age (yr)	58.1 ± 11.3	59.5 ± 9.9	58.4 ± 11.6	0.52	0.26	0.84
Age ≥70 yr	18.1%	21.1%	18.6%	0.80	0.53	0.93
Male gender	73.9%	73.5%	72.2%	0.96	0.93	0.77
Race						
White	72.5%	80.3%	75.3%			
Black	13.0%	11.6%	11.3%	0.48	0.30	0.89
Hispanic/other	14.5%	8.2%	13.4%			
Hypertension*	34.6%	39.5%	34.0%	0.62	0.41	0.93
Diabetes	10.2%	9.6%	9.3%	0.97	0.86	0.81
Smoking†	71.3%	74.0%	75.8%	0.74	0.62	0.45
Prior MI‡	13.8%	15.0%	14.4%	0.96	0.77	0.89
Prior CABG	2.2%	3.4%	4.1%	0.68	0.53	0.39
Anterior MI	40.6%	44.2%	35.1%	0.36	0.54	0.39
Hours to treatment						
Mean	3.0 ± 1.4	3.1 ± 1.4	3.0 ± 1.3	0.76	0.54	1.0
0 to <2	21.0%	19.0%	23.7%			
2 to <4	56.5%	55.8%	53.6%	0.92	0.83	0.87
≥4	22.5%	25.2%	22.7%			

* Defined as a history of hypertension requiring treatment with medication or diet, or both. † Defined as a history of smoking at any time. ‡ Defined as a history of a myocardial infarction (MI) that was documented by standard enzyme or electrocardiographic criteria and verified in the medical record by the Thrombolysis in Myocardial Infarction (TIMI) 4 investigator or research coordinator. Data presented are mean value ± 1 SD or percent of patients in the treatment arm. APSAC = anisoylated plasminogen streptokinase activator complex; CABG = coronary artery bypass surgery; Comb. = combination; rt-PA = recombinant tissue-type plasminogen activator.

≥15% (e.g., a hematocrit level of 40% decreasing to 25%), with transfusions being counted as 1 g/dl each (14,19). A decrease in hematocrit after coronary bypass surgery was not classified as a hemorrhagic event.

Sample size considerations and statistical analyses. The initial sample size proposed for this study was based on a power analysis of the primary composite end point. It was estimated from the TIMI 2 experience (11) that ~37% of patients would reach a primary end point. Three hundred patients in each of the three treatment arms would permit the detection of an absolute 13% difference (37% to 24% [a 35% reduction]) between two treatments with a power of 85% at an overall significance level of 5%, using a Bonferroni adjustment for the three treatment comparisons (20). After an interim analysis in October 1992, in which power calculations demonstrated that the combination arm would be unable to achieve significant improvement over either of the other arms, the Data and Safety Monitoring Board recommended discontinuation of the combination arm because of futility (21). At the time that enrollment ended, April 30, 1993, 382 patients were enrolled.

The statistical analyses were carried out in SAS (22) and consisted of chi-square analyses for categoric type variables and *t* tests for continuous type variables. When categoric type variable frequencies were small, the Fisher exact test was used. The survival analysis consisted of a Kaplan-Meier plot and statistical tests using the log-rank statistic.

Results

Open label pilot study. Thirty-four patients were enrolled in a pilot phase of the trial using open label combination thrombolytic therapy. There were no deaths or intracranial hemorrhages; two patients experienced a major spontaneous hemorrhage. Patency of the infarct-related artery (TIMI grade 2 or 3 flow) was achieved in 29 (85.3%) of the 34 patients.

Patients. The baseline characteristics of the 382 patients in the double-blind, randomized phase of the trial are shown in Table 1. The three groups were well matched; overall, ~20% of patients were ≥70 years of age. Twenty-seven percent of patients were women and 14% of all patients had had a prior myocardial infarction; ~76% of patients were white, 12% black, and 12% Hispanic or another race. The average time between the onset of symptoms and the start of double-blind thrombolytic therapy was 3 h, similar to findings in previous trials (10,18) that enrolled patients presenting within 6 h. Fifty-seven percent of patients received intravenous followed by oral beta-adrenergic blocking agents on day 1, 89% received intravenous nitroglycerin, 19% received intravenous magnesium and 4% received angiotensin-converting enzyme inhibitors; there were no significant differences among the treatment arms in the proportion of patients receiving these drugs.

Angiographic results. TIMI grade 2 or 3 flow at 90 min was achieved significantly more often in rt-PA–treated patients (84.2% vs. 72.9% for those receiving APSAC and 67.7% for those receiving the combination [rt-PA vs. APSAC, p = 0.02;

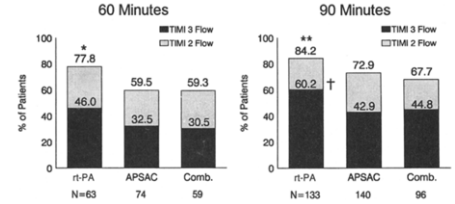


Figure 1. Angiographic results at 60 and 90 min in patients treated with recombinant tissue-type plasminogen activator (rt-PA), anisoylated plasminogen streptokinase activator complex (APSAC) or combination (Comb.) thrombolytic therapy. *p = 0.02, rt-PA versus APSAC; p = 0.03, rt-PA versus combination. **p = 0.02, rt-PA versus APSAC; p < 0.01, rt-PA versus combination. †p < 0.01, rt-PA versus APSAC; p = 0.02, rt-PA versus combination. N = number of patients with angiogram obtained; TIMI = Thrombolysis in Myocardial Infarction perfusion grade (1).

rt-PA vs. combination, p < 0.01]) (Fig. 1). Moreover, TIMI grade 3 flow was achieved in 60.2% of patients treated with front-loaded rt-PA, a significantly higher proportion than the 42.9% for those treated with APSAC and 44.8% for those receiving the combination (rt-PA vs. APSAC, p < 0.01; rt-PA vs. combination, p = 0.02).

Patency of the infarct-related artery (TIMI grade 2 or 3 flow) 60 min after the start of thrombolytic therapy was achieved in 77.8% of rt-PA–treated patients; this patency rate was significantly higher than the 59.5% patency rate achieved with APSAC and the 59.3% rate achieved with combination therapy (rt-PA vs. APSAC, p = 0.02; rt-PA vs. combination, p = 0.03) (Fig. 1). TIMI grade 3 flow was achieved in 46% of patients treated with front-loaded rt-PA compared to 32.5% of APSAC-treated patients and 30.5% of combination-treated patients.

At 18 to 36 h, TIMI grade 3 flow was similar among the three groups: 72.6%, 64.8% and 71.0% for the rt-PA, APSAC and combination groups, respectively (p = NS). TIMI grade 2 or 3 flow was also similar in the three groups: 89.6%, 94.3% and 95.7%, respectively (p = NS). Reocclusion of an initially patent artery occurred in 9 (8.8%) of 112 rt-PA–treated patients versus 2 (2.2%) of 102 APSAC-treated patients and 1 (1.7%) of 65 combination-treated patients (rt-PA vs. APSAC, p = 0.05; rt-PA vs. combination, p = 0.07). All 12 patients with reocclusion underwent subsequent coronary angioplasty, which was carried out immediately in 11 of them. The combination of TIMI grade 3 flow at both 90 min and 18 to 36 h, which has been termed "optimal thrombolysis," (18), was significantly higher for the rt-PA group (53.7% vs. 36.4% for the APSAC group and 40% for the combination group [rt-PA vs. APSAC, p = 0.01; rt-PA vs. combination, p = 0.05]).

In-hospital complications. The in-hospital mortality rate was lowest in the rt-PA group (2.2% vs. 8.8% in the APSAC group and 7.2% in the combination group [rt-PA vs. APSAC, p = 0.02; rt-PA vs. combination, p = 0.06]) (Table 2). New onset of severe congestive heart failure or cardiogenic shock as well as reocclusion by hospital discharge, as assessed by sestamibi imaging, also tended to occur least often in the rt-PA–treated patients (Table 2). Recurrent myocardial infarction was not significantly different among the three groups.

Hemorrhagic events. There were no intracranial hemorrhages in the rt-PA group, but one each occurred in the APSAC and combination groups (Table 3). Major spontaneous hemorrhage occurred in 1.4% of rt-PA–treated patients versus 3.4% and 4.1%, respectively, for patients treated with APSAC and the combination. Overall, the rate of major hemorrhage, including bleeding at instrumented sites, was lower in the rt-PA–treated patients (10.9% vs. 21.8% for the APSAC group and 21.6% for the combination group [rt-PA vs. APSAC, p = 0.01; rt-PA vs. combination, p = 0.02]).

Unsatisfactory outcome. When all these effects were integrated into the composite end point, patients treated with front-loaded rt-PA tended to have a lower incidence of any in-hospital unsatisfactory outcome (41.3% vs. 49% for APSAC-treated patients and 53.6% for combination-treated patients) (Table 2). However, the difference did not achieve statistical significance (for the overall comparison, p = 0.16; rt-PA vs. APSAC, p = 0.19; rt-PA vs. combination, p = 0.06). With use of the secondary definition of unsatisfactory outcome (defining low ejection fraction as <40% for all patients), which has been shown to correlate better with long-term mortality (15), the incidence of unsatisfactory outcome was lower in the rt-PA–treated patients (42% vs. 52.4% for the APSAC group and 56.7% for the combination group [3-way, p = 0.06; rt-PA vs. APSAC, p = 0.08; rt-PA vs. combination, p = 0.03]). The weighted unsatisfactory outcome score showed a similar nonstatistically significant trend favoring rt-PA.

Revascularization procedures. Coronary angioplasty for a persistently occluded infarct-related artery at 90 min was performed in a higher proportion of patients receiving combination therapy (20.6% vs. 10.9% for the rt-PA group and 15% for the APSAC group) (Table 4). This difference was largely due to the lower 90-min patency rate in the APSAC and combination groups. Conversely, angioplasty for recurrent ischemia within the 1st 18 h was performed in a higher proportion of rt-PA–treated patients. Overall, the rate of revascularization with either angioplasty or coronary artery bypass surgery was similar among the three groups.

Long-term follow-up. Patients treated with rt-PA had a lower mortality rate during 1-year follow-up (Fig. 2). At 6 weeks, 2.2% of rt-PA–treated patients had died (vs. 8.8% of

Table 2. Unsatisfactory Outcome End Point

	Thrombolytic Therapy Group						p Value		
	rt-PA (n = 138)		APSAC (n = 147)		Comb. (n = 97)				
	No.	%	No.	%	No.	%	3-Way	rt-PA vs. APSAC	rt-PA vs. Comb.
Death	3	2.2	13	8.8	7	7.2	0.05	0.02	0.06
Intracranial hemorrhage	0	0	1	0.7	1	1.0	0.53	0.33	0.23
Severe CHF or cardiogenic shock	1	0.7	4	2.7	2	2.1	0.45	0.20	0.37
EF <40% (or <30% for patients with prior MI)	23	16.7	17	11.6	13	13.4	0.46	0.22	0.49
Reinfarction	9	6.5	10	6.8	3	3.1	0.43	0.92	0.24
Major spontaneous hemorrhage	2	1.4	5	3.4	4	4.1	0.43	0.29	0.20
TIMI flow <2 (18 to 36 h)	11	8.0	6	4.1	3	3.1	0.19	0.17	0.12
Reocclusion by mibi	6	4.3	10	6.8	6	6.2	0.66	0.37	0.53
TIMI flow <2 (90 min)	21	15.2	38	25.9	31	32.0	0.01	0.03	<0.01
Severe anaphylaxis	0	0	0	0	2	2.1	0.05	0.99	0.09
Any unsatisfactory outcome	57	41.3	72	49.0	52	53.6	0.16	0.19	0.06
Weighted end point (mean ± SEM)	0.20 ± 0.02		0.25 ± 0.03		0.25 ± 0.03		0.32	0.17	0.20
Secondary end point, unsatisfactory outcome	58	42.0	77	52.4	55	56.7	0.06	0.08	0.03

Percentages are based on the total number of patients in the treatment arm. The weighted end point was calculated as previously described (13): Each patient was assigned a weighted score based on the single worst event, ranging from 1.0 for death to 0.5 for reinfarction to 0 for no event. An average weighted score for each treatment group was then calculated (13). The secondary end point, unsatisfactory outcome, was determined using ejection fraction (EF) <40% for all patients as the definition of low ejection fraction (15). CHF = congestive heart failure; mibi = technetium-99m 2-methoxyisobutyl isonitrile; other abbreviations as in Table 1.

the APSAC group and 7.2% of the combination therapy group [rt-PA vs. APSAC, p = 0.02; rt-PA vs. combination, p = 0.06]) (Table 2). By life table analysis, mortality was 5.3% at 1 year for the rt-PA group, 11% for the APSAC group and 10.5% for the combination therapy group (rt-PA vs. APSAC, p = 0.07; rt-PA vs. combination, p = 0.13 [log-rank]) (Fig. 2).

Discussion

It has long been postulated that the benefit of thrombolytic therapy for acute myocardial infarction results from early reperfusion of the infarct-related artery (5,23–25). According to this concept, early reperfusion of the acutely occluded coronary artery *interrupts* the cascade of events that occur after acute myocardial infarction and limits the extent of myocardial necrosis; consequently, it decreases left ventricular dysfunction and improves survival. A thrombolytic regimen that establishes reperfusion more rapidly (i.e., achieves a higher rate of early infarct-related artery patency) would be expected to improve overall outcome and survival (5,23–26).

The present double-blind trial compared three thrombolytic regimens, each with particular features that might improve outcome: 1) Front-loaded rt-PA has shown promise by achieving higher rates of early patency of the infarct-related artery; (6,27,28); 2) APSAC has been associated with a low rate of reocclusion (28,29); 3) combination thrombolytic therapy has appeared to result in the lowest rate of reocclusion (7,30).

Front-loaded rt-PA. Patients treated with front-loaded rt-PA had the lowest incidence of any unsatisfactory outcome end point compared with that of the other two regimens, although this difference between groups did not achieve statistical significance. Use of this composite end point evaluates the

Table 3. Hemorrhagic Events and Strokes

	Thrombolytic Therapy Group						p Value		
	rt-PA (n = 138)		APSAC (n = 147)		Comb. (n = 97)				
	No.	%	No.	%	No.	%	3-Way	rt-PA vs. APSAC	rt-PA vs. Comb.
Total stroke	2	1.4	1	0.7	3	3.1	0.33	0.52	0.39
Intracranial hemorrhage	0	0	1	0.7	1	1.0	0.53	0.33	0.23
Thromboembolic stroke	2	1.4	0	0	2	2.1	0.26	0.14	0.72
Total major hemorrhage	15	10.9	32	21.8	21	21.6	0.05	0.01	0.02
Major spontaneous hemorrhage	2	1.4	5	3.4	4	4.1	0.43	0.29	0.20
Instrumented site hemorrhage	13	9.4	27	18.4	17	17.5	0.07	0.05	0.07

Percentages are based on the total number of patients in the treatment arm. Abbreviations as in Table 1.

Table 4. Revascularization Procedures

	Thrombolytic Therapy Group						p Value		
	rt-PA (n = 138)		APSAC (n = 147)		Comb. (n = 97)				
	No.	%	No.	%	No.	%	3-Way	rt-PA vs. APSAC	rt-PA vs. Comb.
PTCA									
Rescue*	15	10.9	22	15.0	20	20.6	0.12	0.30	0.04
At <18 h for recurrent ischemia	11	8.0	8	5.4	1	1.0	0.06	0.39	0.02
Elective	40	29.0	39	26.5	22	22.7	0.56	0.64	0.28
Total	66	47.8	69	46.9	43	44.3	0.87	0.88	0.60
CABG	27	19.6	18	12.2	10	10.3	0.09	0.09	0.06
PTCA or CABG†	85	61.6	82	55.8	53	54.6	0.49	0.32	0.29

*Performed for occlusion of infarct-related artery at 90 min persistent at 120 min. †Some patients underwent both coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA). Percentages are based on the total number of patients in the treatment arm. Other abbreviations as in Table 1.

overall outcome of the patient, by incorporating both mortality and important nonfatal outcomes in the cascade of events occurring after acute myocardial infarction (13), as well as significant adverse outcomes (e.g., hemorrhagic stroke and major bleeding) and therefore considers both efficacy and important adverse effects (13). Front-loaded rt-PA was also associated with lower mortality rates at hospital discharge and at 6-week and 1-year follow-up, a finding that has also been observed in the much larger GUSTO trial (10). In accord with the findings in the GUSTO angiographic substudy (31) and other reports (28,32–37), the mechanism of improved survival after treatment with front-loaded rt-PA with intravenous heparin and aspirin appears to begin with more rapid reperfusion.

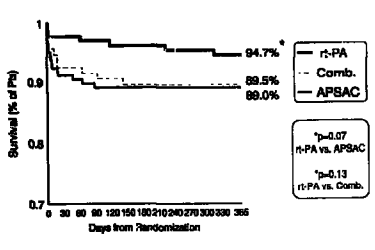
Early infarct-related artery patency. At both the 60- and 90-min time points, rt-PA demonstrated higher rates of reperfusion than did the other two regimens. Front-loaded rt-PA achieved nearly 80% patency (TIMI grade 2 or 3 flow) as early as 60 min after the start of drug administration, in contrast to 60% for APSAC or the combination, with similar improvement at 90 min. This superiority of front-loaded rt-PA in early achievement of infarct–related artery patency at 90 min is similar to that observed in the GUSTO trial (31), which used streptokinase and an rt-PA–streptokinase combination in place of APSAC and the rt-PA–APSAC combination (10). The improved patency at 60 min extends these observations and suggests that the clinical advantage of rt-PA is derived from very early coronary reperfusion.

The benefit of early reperfusion, especially TIMI grade 3 flow, has been associated with smaller infarct size (38,39), improved left ventricular function (36,40,41), a lower rate of reocclusion (34,42,43) and, most important, improved survival (26,31–35,37,43,44). Thus, the improved early achievement of TIMI grade 3 flow by front-loaded rt-PA combined with intravenous heparin and aspirin probably accounts for the improved survival observed in this trial and in the GUSTO trial (23,26). These findings provide further confirmation of the early open artery hypothesis.

Mortality. Although this relatively small trial was not sized to detect changes in mortality, front-loaded rt-PA was associated with a trend toward a lower mortality rate than that associated with APSAC or combination thrombolytic therapy. Very low mortality rates have been observed in other angiographic trials using front-loaded rt-PA, intravenous heparin and aspirin (28,31). The use of angioplasty to help sustain infarct–related artery patency in patients who had reocclusion may help to explain the remarkably low mortality rate in the rt-PA–treated patients, as has been noted in a previous report (45). Conversely, although combination thrombolytic therapy was associated with a low rate of reocclusion in this and other trials (7,30), its failure to improve early patency appears to explain its failure to improve overall outcome or to decrease mortality. These findings are consistent with the hypothesis that the combination of early and sustained infarct–related artery patency is associated with the lowest long-term mortality rate (35,46). Finally, the earlier administration of a thrombolytic agent has also been found to decrease mortality (47–49). Thus, prompt administration after the onset of symptoms (on average by 3 h in this study) of a thrombolytic regimen such as front-loaded rt-PA, which further speeds the achievement of reperfusion, could be expected to have *additive* effects in improving survival (50,51).

Limitations of the study. Several limitations of this trial should be considered. First, the overall number of patients enrolled in the trial was smaller than the planned sample size,

Figure 2. Kaplan-Meier survival curves to 1 year of follow-up. Pts = patients; other abbreviations as in Figure 1.



thereby limiting the power of the trial. Second, this was an angiographic trial and it is possible that the protocol design influenced the results, notably in the availability and use of revascularization procedures. Lastly, the conclusions on mortality must be considered in the context of the small number of deaths in the trial. However, both the angiographic and the clinical results are consistent with those of the larger GUSTO trial (10,31), thereby lending support to the results in this trial. Conversely, this trial was double-blind, thereby diminishing any possible bias by physicians caring for the patients, which serves to support the results of the unblinded GUSTO trial.

Conclusions. Front-loaded rt-PA achieved infarct-related artery patency in nearly 80% of patients after 60 min, a rate significantly higher than that associated with APSAC or combination thrombolytic therapy. Furthermore, early reperfusion with front-loaded rt-PA was associated with trends toward improved overall clinical benefit and 1-year survival. These findings strongly support the early open artery hypothesis, and they suggest that further improvements in outcome of patients with acute myocardial infarction might be achieved with more effective thrombolytic-antithrombotic regimens (18) that improve early (and sustained) infarct-related artery patency.

Appendix

TIMI 4 Coordinating Centers and Core Laboratories

Study Chairman's Office: Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. *Study Chairman*, Eugene Braunwald, MD; *Co-Investigator*, Christopher P. Cannon, MD; *Project Director*, Carolyn H. McCabe, BS.

Data Coordinating Center: Research Triangle Institute, Research Triangle Park, North Carolina. *Principal Investigator*, W. Kenneth Poole, PhD; *Study/Data Coordinator*, Betty K. Hastings; *Statisticians*, Vicki Davis, DrPH, Barbara Alexander, MSPH, Rebecca Perritt, MS; *Systems Analyst*, David Myers, PhD; *Research Associate*, Sandra McGuire.

Angiographic Core Laboratory: Beth Israel Hospital, Boston, Massachusetts. *Co-Principal Investigators*, C. Michael Gibson, MS, MD, Donald S. Baim, MD; *Co-Investigators*, Robert N. Piana, MD, Jeffrey A. Breall, MD, Stacy F. Davis, MD, Kathleen A. Munsour, MD; *Research Coordinator*, Margaret Flatley.

Biochemistry Core Laboratories: *MB Isoforms*: The Methodist Hospital, Baylor College of Medicine, Houston, Texas. *Principal Investigator*, Peter Pelco, MD; *Co-Investigator*, Robert Roberts, MD; *Research Coordinators*, Denise Mayer, MTASCP, Leah White MLT. *MM Isoforms*: Washington University, St. Louis, Missouri. *Principal Investigator*, Dana Abendschein, PhD; *Co-Investigator*, Burt E. Sobel, MD; *Research Coordinator*, Lea Doerr Bullock, MS.

Drug Distribution Center: VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico. *Pharmacist*, Cindy Colling, RPh, MS; *Study Coordinator*, Jenine Peterson, BS; *Co-Investigator*, Mike R. Sather, MS, FASHP.

Hematology Core Laboratory: Brigham and Women's Hospital, Boston, Massachusetts. *Principal Investigator*, Joseph Loscalzo, MD, PhD; *Research Coordinator*, Dorinda George, AB.

Myocardial Infarction Confirmation Core Laboratory: St. Louis University, St. Louis, Missouri. *Principal Investigator*, Bernard R. Chaitman, MD; *Co-Investigators*, BA, Bonpei Takase, MD, Beaver Tunnesis, MD; *Research Coordinators*, Debbie Kargl, BA, Karen Stocke, BS, MBA.

Radionuclide Core Laboratory: Yale University School of Medicine, New Haven, Connecticut. *Co-Principal Investigators*, Barry L. Zaret, MD; Frans J. Th. Wackers, MD; *Research Coordinator*, Michael McMahon, CTNM.

Data and Safety Monitoring Board: Lewis Becker, MD, Joel Karliner, MD, Sheryl Kelsey, PhD, Charles Rackley, MD, Sanford Shattil, MD. *Ex-Officio Members*, Eugene Braunwald, MD, W. Kenneth Poole, PhD.

Morbidity and Mortality Classification Committee: *Chairman*, Daniel J. Diver, MD; *Members*, Christopher P. Cannon, MD, Ferdinand Leya, MD, Donald Palisaitis, MD, Leroy Rabbani, MD.

TIMI 4 Clinical Centers

TIMI 4 clinical centers are listed in the order of the number of patients enrolled.

Beth Israel Hospital, Boston, Massachusetts. *Principal Investigator*, Daniel J. Diver, MD; *Co-Investigator*, Jeffrey A. Breall, MD, Clifford Berger, MD; *Research Coordinator*, Susan Marble, RN. *Satellite center*: Emerson Hospital, Concord, Massachusetts. *Principal Investigator*, Steve Herson, MD; *Research Coordinator*, Gail Carey, RN. **Alta Bates Medical Center,** Berkeley, California. *Principal Investigator*, Robert M. Greene, MD; *Research Coordinators*, Eileen Healy, RN, Vickie Perry, RN. **Cedars-Sinai Medical Center,** Los Angeles, California. *Principal Investigator*, Prediman K. Shah, MD; *Co-Investigator*, Bojan Cercek, MD; *Research Coordinator*, Adrian Mirza, MD. **University of Miami/Jackson Memorial Hospital,** Miami, Florida. *Principal Investigator*, Raphael F. Sequeira, MD; *Co-Investigator*, Alan Fernandez, MD; *Research Coordinator*, Denise A. Francoeur, RN. **Loyola University Hospital,** Maywood, Illinois. *Principal Investigator*, Ferdinand Leya, MD; *Research Coordinator*, Rosita Picchi, RN. **Brigham and Women's Hospital,** Boston, Massachusetts. *Principal Investigator*, James M. Kirshenbaum, MD; *Co-Investigator*, Christopher P. Cannon, MD, *Research Coordinators*, Deborah Bates-Riordan, RN, JD, Paul Sedgwick, RN. **Ohio State University,** Columbus, Ohio. *Principal Investigator*, Raymond D. Magories, MD; *Co-Investigators*, Gregory Eaton, MD, James Peterson, MD; *Research Coordinator*, Jenny Sharp-Wilmer, RN. **Robert Wood Johnson Medical School,** New Brunswick, New Jersey. *Principal Investigator*, Sebastian T. Palmeri, MD; *Co-Investigators*, Abel E. Moreyra, MD, Marybelen Hosler, RN; *Research Coordinator*, Laurie Casazza, RN. **Centre Hospitalier Universitaire de Sherbrooke,** Sherbrooke, Quebec, Canada. *Principal Investigator*, Vincent Dangoisse, MD; *Co-Investigator*, Guy Proulx, MD; *Research Coordinator*, Jackie Dangoisse. **University of Missouri-Columbia,** Columbia, Missouri. *Principal Investigator*, Greg C. Flaker, MD; *Co-Investigators*, Robert Myers, MD, Richard Webel, MD, John Bartolozzi, MD; *Research Coordinator*, Kathy Belew, RN. *Satellite center*: Lake of the Ozarks General Hospital, Osage Beach, Missouri. *Principal Investigator*, T.W. Garrison Jr., MD; *Research Coordinators*, Mary Cope, RN; Roland Vize, RN. **Baystate Medical Center,** Springfield, Massachusetts. *Principal Investigator*, Marc J. Schweiger, MD; *Co-Investigators*, Mark Porway, MD, John Jocelson, MD, Thomas Marauiz, MD, Alan Wiseman, MD; *Research Coordinator*, Deborah Warwick, RN. **Kaiser Permanente Medical Center,** Los Angeles, California. *Principal Investigator*, Peter R. Mahrer, MD; *Research Coordinators*, Joni Noccola, RN; Judy Fleicher, RN. **Hospital of the Good Samaritan,** Los Angeles, California. *Principal Investigator*, Thomas L. Shook, MD; *Co-Investigators*, Steven Burstein, MD, David S. Cannon, MD, Robert A. Kloner, MD, PhD, Joseph M. Ruggio, MD, Ray V. Matthews, MD; *Research Coordinators*, Lucille Junio, RN, C[illegible]yn Gray, RN, BSN. **LDS Hospital,** University of Utah, Salt Lake City, Utah. *Principal Investigator*, Jeffrey L. Anderson, MD; *Co-Investigators*, Labros Karagounis, MD, Miguel Gomez, MD; *Research Coordinator*, Ann Allen, BS. **Hôpital du Sacre Coeur de Montreal,** Montreal, Quebec, Canada. *Principal Investigator*, Donald Palisaitis, MD; *Co-Investigator*, James Nasmith, MD; *Research Coordinators*, Ginette Gaudette, RN, Jocelyne Fouquette, RN. **SUNY Health Science Center at Stony Brook,** Stony Brook, New York. *Principal Investigator*, Peter F. Cohn, MD; *Co-Investigators*, Stephen Vlay, MD, John Dervan, MD, Praveer Jain, MD; *Research Coordinator*, Linda Olson-Vlay, RN. **University of Ottawa Heart Institute,** Ottawa, Ontario, Canada. *Principal Investigator*, Louise A. Laramee, MD; *Co-Investigators*, Richard F. Dawes, MD, Ian G. Stiell, MD; *Research Coordinators*, Ann Baker, RN; Colette Fawreau, RN.

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