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Time From Symptom Onset to Treatment and Outcomes After Thrombolytic Therapy

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Objectives. **This study sought to examine the relations among patient characteristics, time to thrombolysis and outcomes in the international GUSTO-I trial.**

Background. **Studies have shown better left ventricular function and decreased infarct size as well as increased survival with earlier thrombolysis, but the relative benefits of various thrombolytic agents with earlier administration are uncertain.**

Methods. **We evaluated the relations of baseline characteristics to three prospectively defined time variables: symptom onset to treatment, symptom onset to hospital arrival (presentation delay) and hospital arrival to treatment (treatment delay). We also examined the relations of delays to clinical outcomes and to the relative 30-day mortality benefit with accelerated tissue-type plasminogen activator (t-PA) versus streptokinase.**

Results. **Female, elderly, diabetic and hypertensive patients had longer delays at all stages. Previous infarction or bypass surgery was an additional risk factor for treatment delay. Early thrombolysis was associated with lower overall mortality rate (<2 h, 5.5%; >4 h, 9.0%), but no additional relative benefit resulted from earlier treatment with accelerated t-PA versus streptokinase (p = 0.38). Longer presentation and treatment delays were both associated with increased mortality rate (presentation delay <1 h, 5.6% and >4 h, 8.6%; treatment delay <1 h, 5.4%, and >90 min, 8.1%). As time to treatment increased, the incidence of recurrent ischemia or reinfarction decreased, but the rates of shock, heart failure and stroke increased.**

Conclusions. **Earlier treatment resulted in better outcomes, regardless of thrombolytic strategy. Elderly, female and diabetic patients were treated later, adding to their already substantial risk.**

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Studies show that the timing of thrombolytic therapy is a major factor in determining the magnitude of the mortality reduction with these agents in the treatment of acute myocardial infarction (1–3). Although the survival benefit from thrombolysis persists with administration up to 12 h after symptom onset, the largest effect is observed when treatment begins within the first hour, with attenuation of the treatment benefit over time (4). These clinical observations are consistent with animal models of acute coronary occlusion, which show that restoration of arterial patency within 1 to 2 h salvages myocardium and preserves ventricular function (5). Although many trials have shown better improvement in left ventricular function and limitation of infarct size with very early treatment (6–9), none of the large mortality trials have actually collected time to treatment. They showed a significant relation of time to randomization to treatment effect (2,10–12), but exclusion of the variable time from randomization to treatment may have resulted in an imprecise estimate of the importance of delay. In addition, the relations between patient characteristics and delay in seeking treatment (presentation delay) and delay in initiating thrombolysis after hospital arrival (treatment delay) have been of interest, but limited sample sizes in individual studies have led to instability in the estimate of factors associated with these delays (13).

Using the 41,021 patients in the GUSTO-I trial, we examined patient characteristics as they relate to time-to-treatment variables and assessed the relations between time to treatment and its major components, presentation delay and treatment delay, and the risk of death. We also examined the time-dependent mortality benefit of treatment with

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Table 1. Changes in Time to Treatment as a Result of Data Auditing

Initial Data*	Final Data*	Changes	t-PA	SK+IV	Combination	SK+SQ
Missing	0–2 h	1,147	272	311	266	298
Missing	2–4 h	2,332	604	571	588	569
Missing	4–6 h	1,016	256	235	266	259
Missing	>6 h	262	68	64	69	61
0–2 h	Missing	5	2	3	0	0
2–4 h	Missing	9	1	2	3	3
4–6 h	Missing	4	0	2	1	1
>6 h	Missing	3	0	0	1	2
0–2 h	2–4 h	15	3	2	7	3
0–2 h	4–6 h	0	0	0	0	0
0–2 h	>6 h	1	0	0	0	1
4–6 h	0–2 h	3	2	0	0	1
4–6 h	2–4 h	4	1	0	2	1
4–6 h	>6 h	4	1	1	1	1
>6 h	0–2 h	6	1	3	0	2
>6 h	2–4 h	7	1	1	3	2
>6 h	4–6 h	7	0	2	3	2

*Time to treatment. Unless otherwise indicated, data presented are number of patients. IV = intravenous heparin; SK = streptokinase; SQ = subcutaneous heparin.

accelerated tissue-type plasminogen activator (t-PA) versus two streptokinase monotherapies.

Methods

Patient population. The 41,021 patients in GUSTO-I comprised our study population. Complete methods of the trial have been published (14). In brief, patients were randomized to one of four thrombolytic treatments if they presented within 6 h of symptom onset (minimum duration 20 min), met electrocardiographic criteria for acute myocardial infarction (≥0.1 mV ST elevation in two or more limb leads or ≥0.2 mV ST elevation in at least two contiguous precordial leads) and had no contraindications to thrombolysis.

Time variables. For this study, three time variables were prospectively defined: time from symptom onset to hospital arrival (presentation delay), time from hospital arrival to initiation of thrombolytic therapy (treatment delay), and total time from symptom onset to thrombolytic therapy. The patient (or a surrogate if the patient could not communicate) provided the time of onset of symptoms resulting in hospital presentation. Time of hospital arrival and time of thrombolysis (initiation of infusion) were obtained from hospital records.

Before publication of this manuscript, an extensive quality-control effort was completed that resulted in some changes in the data published in the initial report of GUSTO-I (14–16). In the original publication, for missing data on the time of symptom onset, an estimate made by the clinician during randomization was used. After completion of case report forms and an audit of 12% of these forms against source documentation, in addition to systematic checks at the Coordinating Center, numerous corrections had been made in the initial data. The final quality-controlled information reflects the following changes: time to treatment changed from missing to complete in 4,757 patients, from complete to missing in 21 patients and to an earlier or later interval in 47 patients. A detailed summary of these changes is shown in Table 1.

Statistical analysis. Descriptive statistics (percentages for discrete variables; medians with 25th and 75th percentiles for continuous variables) were generated for baseline characteristics and events for all time-to-treatment variables. For analysis, each time-to-treatment variable was prospectively divided into four intervals. Because of the large size of the data base and to avoid confusion as to their interpretation, we do not present p values.

We investigated the relations of enrollment site (United States or non-United States) and baseline characteristics to overall time to treatment and presentation and treatment delays. Outcomes assessed in relation to time variables were

Figure 1. Cumulative distributions of time to treatment overall (**solid line**) and for patients treated in the United States (**long dashes**) versus outside the United States (**short dashes**).

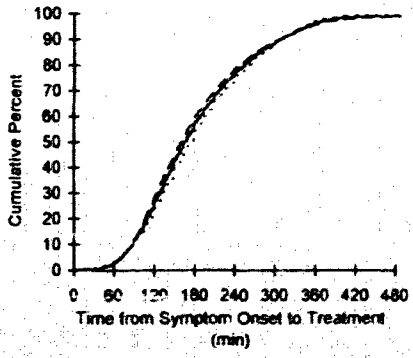

Table 2. Time From Symptom Onset to Treatment: Baseline Characteristics

	≤2 h (n = 10,611)	>2–4 h (n = 20,213)	>4–6 h (n = 7,650)	>6 h (n = 1,359)
Demographics				
Age (yr)	59 (50, 68)	62 (52, 70)	63 (54, 72)	63 (53, 71)
Male	80	75	70	68
Race				
White	93	92	90	89
Black	2	3	4	7
Other	5	5	6	7
Height (cm)	173 (167, 179)	172 (165, 178)	170 (163, 177)	170 (163, 177)
Weight (kg)	80 (70, 89)	78 (69, 88)	77 (68, 86)	78 (69, 88)
Risk factors				
Hypertension	34	38	41	46
Diabetes	12	14	18	21
Current smoker	46	43	39	41
Previous smoker	72	70	65	67
Hypercholesterolemia	36	34	32	36
Family history	44	42	39	45
Cardiac history				
Previous angina	36	36	39	40
Previous infarction	16	16	16	17
Previous bypass	4	4	4	5
Previous angioplasty	5	4	3	4
Presentation characteristics				
Heart rate (beats/min)	72 (60, 84)	73 (63, 85)	76 (64, 88)	76 (65, 90)
Systolic BP (mm Hg)	126 (110, 140)	130 (113, 144)	130 (115, 146)	130 (115, 143)
Diastolic BP (mm Hg)	80 (69, 89)	80 (70, 90)	80 (70, 90)	79 (68, 89)
Killip class				
I	88	85	83	83
II	11	13	14	15
III	1	1	2	2
IV	1	1	1	0.4
Location of infarction				
Anterior	39	38	41	40
Inferior	58	59	55	55
Other	3	3	4	4
ECG variables				
Sum of ST elevation (mm)	8 (5, 13)	7 (4, 12)	7 (4, 12)	6 (4, 10)
No. of leads with ST elevation	4 (3, 6)	4 (3, 5)	4 (3, 5)	4 (3, 5)
Max ST elevation (mm)	3 (2, 4)	3 (2, 4)	2 (2, 4)	2 (1, 3)
Left bundle branch block	0.7	0.7	1.2	0.9
Right bundle branch block	3.2	3.5	3.7	3.8
Left anterior hemiblock	3.6	3.6	3.6	3.9
Left posterior hemiblock	0.1	0.2	0.2	0.1
Time from symptom onset to arrival (h)	0.77 (0.5, 1.0)	1.7 (1.2, 2.1)	3.3 (2.5, 4.0)	4.8 (3.6, 5.3)
Time from arrival to treatment (min)	46 (35, 60)	70 (50, 93)	85 (57, 130)	113 (75, 205)

Data presented are percent of patients or median (25th, 75th percentiles). BP = blood pressure; ECG = electrocardiographic; Max = maximal.

30-day and in-hospital mortality, stroke subtypes, reinfarction, recurrent ischemia, shock, and congestive heart failure and the combined end points of death or stroke, death or primary intracranial hemorrhage and death or disabling stroke.

Results

Time to treatment. Complete data for time from symptom onset to thrombolysis were available for 39,833 of the 41,021 patients (97.1%). Cumulative distributions of time to treatment overall and by enrollment site (United States versus non-United States) are shown in Figure 1. Overall time to treatment was < 4 h in 77.4% of patients; most of the rest were treated between 4 and 6 h. Only 26.6% of patients were treated within 2 h of symptom onset.

Baseline characteristics by time from symptom onset to treatment are shown in Table 2. Female, hypertensive, and diabetic patients were found in greater proportions in the later-treated groups, and current or former cigarette smokers were more often in the earlier-treated groups. Prior myocar-

Table 3. Time From Symptom Onset to Treatment: Clinical Events

	≤2 h (n = 10,611)	>2–4 h (n = 70,213)	>4–6 h (n = 7,650)	>6 h (n = 1,359)
In-hospital mortality	5.3	5.9	8.5	8.9
30-day mortality	5.5	6.3	9.0	9.0
Stroke	1.3	1.5	1.6	2.0
Primary intracranial hemorrhage	0.5	0.7	0.8	1.0
Nonhemorrhagic	0.6	0.6	0.7	1.0
Hemorrhagic conversion	0.1	0.1	0.1	0
Unknown	0.1	0.1	0.1	0
Death or stroke	6.2	7.1	9.8	10.2
Death or hemorrhagic stroke	5.7	6.5	9.2	9.4
Death or disabling stroke	6.0	6.7	9.5	9.6
Reinfarction	4.7	4.0	3.2	3.6
Recurrent ischemia	21	20	19	18
Shock	5.7	5.6	6.4	7.0
Congestive heart failure	14	16	19	19

Data presented are percent of patients.

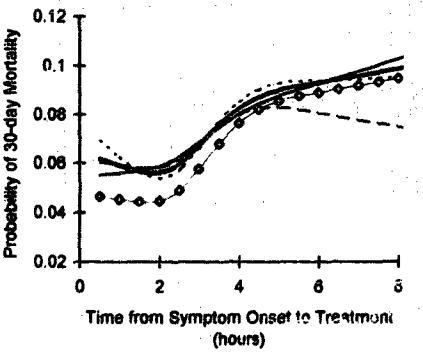

Figure 3. Probability of 30-day mortality as a function of time from symptom onset to treatment and assignment to streptokinase with subcutaneous heparin (**short dashes**), streptokinase with intravenous heparin (**light solid line**), streptokinase and tissue-type plasminogen activator (t-PA) with intravenous heparin (**long dashes**) or accelerated t-PA with intravenous heparin (**line with diamonds**). The probability for the combined streptokinase groups is shown by the **heavy solid line.**

dial infarction was more frequent in the later-treated groups, and patients treated after 2 h were older, weighed less, had higher systolic blood pressures and heart rates and were more likely to be nonwhite and to have congestive heart failure (Killip class ≥II). Other than a slight delay (median 5 min) in patients treated with combination thrombolytic therapy, there were no differences in time to treatment as a function of treatment assignment.

Table 3 shows the relations between time to treatment and selected clinical end points. As time to treatment increased, 30-day mortality increased (Fig. 2). The incidence of stroke also increased as time to treatment increased, mostly through an increase in primary intracranial hemorrhage. Reinfarction and recurrent ischemia were less frequent, and the incidence of shock and congestive heart failure greater, as time to treatment increased.

Figure 3 shows treatment benefit of each thrombolytic strategy as a function of time from symptom onset to treatment. Although the relative treatment effect was slightly greater for patients treated earlier, the formal test for time-to-treatment interaction for t-PA versus the combined streptokinase groups was not significant ($p = 0.38$).

Presentation delay. Cumulative distributions of time from symptom onset to hospital arrival are shown in Figure 4. Patients enrolled in the United States arrived earlier than patients elsewhere (median 85 vs. 105 min). Overall, most patients arrived within 2 h of symptom onset.

Relations between presentation delay and baseline characteristics are shown in Table 4. The distribution of baseline characteristics was similar to that for the total-time-to-treatment group. However, patients with a family history of

Figure 2. Probability (**solid line**) and 95% confidence intervals (**dashed lines**) for 30-day mortality as a function of time to treatment.

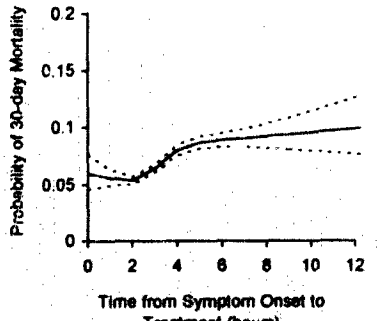

Figure 4. Cumulative distribution of time from symptom onset to hospital arrival overall (**solid line**) and for patients enrolled in the United States (**long dashes**) versus outside the United States (**short dashes**).

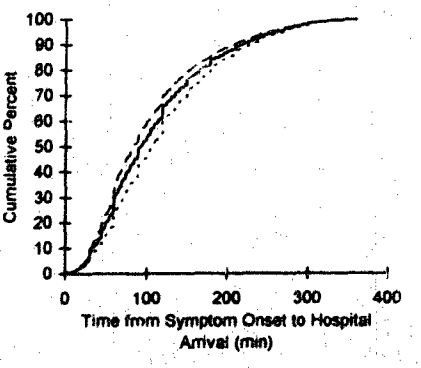

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Table 4. Time From Symptom Onset to Hospital Arrival: Baseline Characteristics

	<1 h (n = 9,275)	1–2 h (n = 14,208)	2–4 h (n = 12,441)	>4 h (n = 2,462)
Demographics				
Age (yr)	59 (50, 68)	61 (52, 69)	63 (54, 71)	63 (54, 72)
Male	79	76	72	71
Race				
White	91	92	92	92
Black	3	3	3	3
Other	6	5	5	5
Height (cm)	173 (167, 179)	173 (165, 175)	170 (165, 177)	170 (164, 177)
Weight (kg)	80 (70, 96)	78 (70, 89)	77 (68, 87)	77 (68, 86)
Risk factors				
Hypertension	35	37	39	41
Diabetes	13	14	16	17
Current smoker	45	45	42	41
Previous smoker	73	71	67	56
Hypercholesterolemia	37	34	32	33
Family history	46	42	40	39
Cardiac history				
Previous angina	34	35	37	46
Previous infarction	17	16	15	13
Previous bypass	5	4	4	4
Previous angioplasty	5	4	3	3
Presentation characteristics				
Heart rate (beats/min)	72 (62, 84)	72 (62, 84)	75 (64, 88)	76 (65, 90)
Systolic BP (mm Hg)	127 (110, 142)	128 (111, 142)	130 (115, 146)	130 (118, 148)
Diastolic BP (mm Hg)	79 (69, 89)	80 (70, 90)	80 (70, 90)	80 (70, 90)
Killip class				
I	87	86	84	84
II	12	12	13	14
III	1	1	2	1
IV	1	1	1	1
Location of infarction				
Anterior	41	38	38	40
Inferior	56	59	58	56
Other	3	3	3	3
ECG variables				
Sum ST elevation (mm)	7 (4, 12)	8 (5, 12)	7 (4, 12)	7 (4, 12)
No. of leads with ST elevation	4 (3, 6)	4 (3, 5)	4 (3, 5)	4 (3, 5)
Max ST elevation (mm)	3 (2, 4)	3 (2, 4)	3 (2, 4)	2 (2, 4)
Left bundle branch block	0.8	0.7	0.8	1.2
Right bundle branch block	3.0	3.5	3.6	4.2
Left anterior hemiblock	3.6	3.6	3.8	4.9
Left posterior hemiblock	0.2	0.1	0.2	0.1

Data presented are percent of patients or median (25th, 75th percentiles). Abbreviations as in Table 2.

coronary artery disease or with a previous infarction presented earlier, whereas those with previous angina alone presented later. There was no relationship between presentation delay and ethnicity.

Outcomes as a function of time to presentation (Table 5) generally mirrored those of the overall time-to-treatment group analysis.

Treatment delay. Figure 5 presents cumulative distributions of time from hospital arrival to treatment. Non-United States patients had a slightly shorter treatment delay than U.S. patients (median 60 vs. 66 min). Only 43% of patients were treated within an hour of arrival.

Table 6 shows the baseline characteristics for each treatment delay category. For most variables, the associations were similar to those for total time to treatment and presentation delay. However, patients with prior bypass surgery or angina had longer treatment delays, as did black and other nonwhite patients. Those with a family history of coronary artery disease or a prior infarction had longer treatment delays, even though they presented sooner.

Patients with longer treatment delays had more adverse outcomes such as death, stroke, shock and heart failure (Table 7). As with the other delay times, reinfarction was less common in patients with a longer treatment delay.

Table 5. Time From Symptom Onset to Hospital Arrival: Clinical Events

	<1 h (n = 9,275)	1–2 h (n = 14,208)	2–4 h (n = 12,441)	>4 h (n = 2,462)
In-hospital mortality	5.3	5.9	7.2	8.5
30-day mortality	5.6	6.2	7.6	8.6
Stroke	1.4	1.4	1.5	1.8
Primary intracranial hemorrhage	0.65	0.61	0.68	0.85
Nonhemorrhagic	0.59	0.58	0.54	0.73
Hemorrhagic conversion	0.08	0.07	0.11	0.04
Unknown	0.08	0.14	0.17	0.18
Death or stroke	6.4	7.0	8.4	9.8
Death or hemorrhagic stroke	5.9	6.5	7.8	9.1
Death or disabling stroke	6.1	6.7	8.1	9.2
Reinfarction	3.7	4.0	3.7	3.4
Recurrent ischemia	21	20	19	17
Shock	5.6	6.0	5.7	6.7
Congestive heart failure	15	16	17	19

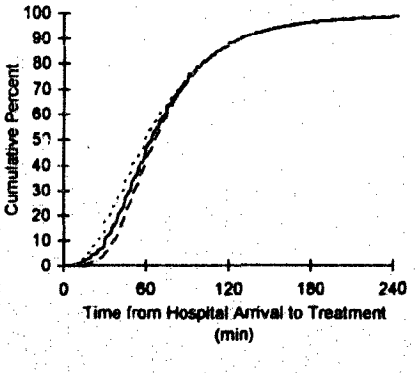
Data presented are percent of patients.

Discussion

This evaluation of the 41,021 GUSTO-I patients shows that substantial differences in baseline characteristics and outcomes exist between patients who pursue and receive thrombolysis promptly and those whose treatment is delayed. Further, although a trend is present, the relative reduction in mortality from accelerated t-PA treatment is not significantly affected by this delay. Most characteristics associated with longer presentation delay are also associated with longer treatment delay, raising the possibility that focusing attention on female, elderly, diabetic and more critically ill patients can greatly improve outcomes by reducing time to treatment.

Time to treatment. Defined as time from symptom onset to initiation of infusion, time to treatment provides an estimate of the total time of vessel occlusion. Accurate assessment of treatment effect as a function of time is difficult, however, because the measurement of time to treatment is inherently imprecise; time of symptom onset and time of thrombolytic initiation do not correlate exactly with the relevant events—vessel occlusion and reperfusion, respectively. Further, the variable time to treatment does not capture the additional time from thrombolytic initiation to reperfusion, nor is infarct-artery patency achieved in each case. Indeed, when successful, reperfusion occurs 45 to 60 min after initiation of thrombolytic therapy (17,18).

Figure 5. Cumulative distribution of time from hospital arrival to treatment overall (**solid line**) and for patients enrolled in the United States (**long dashes**) and outside the United States (**short dashes**).



In GUSTO-I, the median time to treatment was 2.8 h, similar to that seen in actual practice (median 2.75 h) during the same time period, as suggested by comparison with data from the National Registry of Myocardial Infarction (NRMI) survey (19). To better assess risk factors for this delay in treatment, we prospectively divided overall delay into two components: presentation delay, which reflects patient-related delays, and treatment delay, which reflects the response of hospitals to patients.

Presentation delay. Studies show that presentation delay accounts for the greater proportion of total time to treatment (20,21). The median presentation delay in GUSTO-I was 92 minutes, 55% of total time to treatment. Studies suggest that patients take much of this time to decide to seek medical treatment (13,20–24). Many factors have been shown to affect this decision, including time of day, day of the week, location of the patient when symptoms occur, symptom severity or typicality and whether advice is sought from co-workers, family members or the family physician (13,21,23,25–27).

Our analysis, based on over 41,000 patients, adds substantial information and clarification to smaller, less detailed observations (13,18,22,28,29). It supports the finding that advanced age, diabetes, hypertension and prior angina are indeed risk factors for presentation delay, as is female gender. Contrary to previous studies, we noted an association between earlier presentation and prior infarction or family history of coronary disease. Further, there was no relation of race to presentation delay. Although median blood pressure was lower in the groups presenting earlier, other markers of a complicated infarction—faster heart rate and higher Killip class—

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Table 6. Time From Hospital Arrival to Treatment: Baseline Characteristics

	<30 min (n = 2,728)	30–60 min (n = 13,403)	60–90 min (n = 11,246)	>90 min (n = 10,227)
Demographics				
Age (yr)	60 (51, 68)	60 (51, 69)	62 (52, 70)	63 (53, 71)
Male	81	79	74	70
Race				
White	95	93	92	89
Black	1	2	3	4
Other	4	5	5	7
Height (cm)	172 (167, 178)	173 (166, 178)	172 (165, 178)	170 (164, 177)
Weight (kg)	77 (70, 86)	79 (70, 89)	79 (70, 89)	77 (68, 88)
Risk factors				
Hypertension	30	35	39	42
Diabetes	11	12	14	18
Current smoker	48	47	43	39
Previous smoker	71	71	70	68
Hypercholesterolemia	32	35	35	34
Family history	37	42	44	43
Cardiac history				
Previous angina	35	33	35	40
Previous infarction	14	13	16	19
Previous bypass	2	3	4	5
Previous angioplasty	3	4	4	4
Presentation characteristics				
Heart rate (beats/min)	72 (60, 84)	72 (61, 85)	73 (63, 86)	75 (64, 88)
Systolic BP (mm Hg)	130 (110, 144)	129 (112, 144)	130 (113, 144)	130 (113, 144)
Diastolic BP (mm Hg)	80 (70, 90)	80 (70, 90)	80 (70, 90)	79 (69, 89)
Killip class				
I	87	87	85	83
II	11	11	13	14
III	1	1	1	2
IV	1	1	1	1
Location of infarction				
Anterior	39	37	38	42
Inferior	58	60	59	54
Other	3	3	3	5
ECG variables				
Sum ST elevation (mm)	9 (5, 14)	8 (5, 13)	7 (4, 12)	6 (4, 11)
No. of leads with ST elevation	4 (3, 6)	4 (3, 6)	4 (3, 5)	4 (3, 5)
Max ST elevation (mm)	3 (2, 4)	3 (2, 4)	3 (2, 4)	2 (1, 3)
Left bundle branch block	0.5	0.6	0.7	1.2
Right bundle branch block	3.1	3.4	3.4	3.8
Left anterior hemiblock	3.3	3.4	4.8	4.4
Left posterior hemiblock	0.1	0.1	0.1	0.2
Time to arrival (h)	1.8 (1.0, 2.8)	1.5 (1.0, 2.5)	1.5 (1.0, 2.5)	1.5 (1.0, 2.4)

Data presented are percent of patients or median (25th, 75th percentiles). Abbreviations as in Table 2.

were associated with longer presentation delay in GUSTO-I. Table 8 summarizes these comparisons.

Treatment delay. In GUSTO-I, the median treatment delay was 64 min. Little information exists regarding the relation of baseline characteristics to treatment delay. One study did show that the degree of ST segment deviation on initial electrocardiography was important (30). In our study, most characteristics associated with longer presentation delay were also associated with longer treatment delay. Nonwhite race was associated only with longer treatment delay (not presentation delay). In addition, prior bypass surgery and previous infarction, which were associated with no effect on and shorter presentation delays, respectively, were associated with longer treatment delay. Groups with longer treatment delays were those whose initial symptoms are more likely atypical (women, diabetics, the elderly) or for whom the benefit relative to the risks of thrombolysis are uncertain (the elderly, hypertensives). Although differences existed in the distribution of electrocardiographic variables (other than infarct location) between earlier- and later-treated patients, these were small and unlikely to be of major clinical significance (Tables 2, 4 and 6).

Time to treatment—importance of delay to clinical outcomes. The Fibrinolytic Therapy Trialists' meta-analysis suggested that outcome was significantly better with shorter time

Table 7. Time From Hospital Arrival to Treatment: Clinical Events

	<30 min (n = 2,728)	30–60 min (n = 13,403)	60–90 min (n = 11,246)	>90 min (n = 10,227)
In-hospital mortality	5.4	5.1	6.1	7.6
30-day mortality	5.4	5.4	6.4	8.1
Stroke	1.0	1.3	1.4	1.7
Primary intracranial hemorrhage	0.4	0.6	0.7	0.8
Nonhemorrhagic	0.4	0.5	0.7	0.8
Hemorrhagic conversions	0.04	0.07	0.11	0.08
Unknown	0.1	0.2	0.1	0.1
Death or stroke	5.9	6.2	7.3	9.0
Death or hemorrhagic stroke	5.6	5.6	6.7	8.4
Death or disabling stroke	5.8	5.9	6.9	8.7
Reinfarction	4.3	4.2	3.7	3.5
Recurrent ischemia	16	19	20	21
Shock	5.1	5.7	6.0	5.7
Congestive heart failure	13	15	16	18

Data presented are percent of patients.

from symptom onset (1.6 additional lives saved per 1,000 treated for each hour earlier that treatment began) (1). The absolute and relative treatment effects for therapy 1 h earlier were greater the earlier treatment began, presumably reflecting the important time-dependent effect of vessel occlusion on the extent of irreversible myocardial damage. Similarly in GUSTO-I, independent of thrombolytic assignment, delays at any point adversely affected mortality and the development of heart failure or shock, underscoring the importance of early recognition of and response to ischemic symptoms. Although stroke, mostly hemorrhagic, seemed to increase with increased time to treatment, a multivariable analysis of stroke risk factors in GUSTO-I found no relation with time to treatment (31).

Overall mortality increased as time to treatment increased, but patients treated very early (<1 h) after symptom onset appeared to have higher mortality than those treated between 1 and 3 h (Fig. 2). It may be that patients who present and are treated very early are sicker, with a higher expected mortality. The small number of patients treated within 1 h may have limited the ability to detect a difference in severity of illness between these groups. Further, patients with acute myocardial infarction have the greatest risk of lethal ventricular arrhythmias during the first hour of symptoms. Perhaps the higher mortality observed in patients with a shorter time to thrombolysis simply reflects this pathophysiology. Finally, the small size of the group treated within 1 h and the wide 95% confidence intervals suggest that caution should be used in interpreting these results.

Table 8. Association of Baseline Characteristics With Presentation Delay: Comparison of Previous Reports With GUSTO-I

	Previous Reports	GUSTO-I
Presentation characteristics		
Advanced age	+	+
Female gender	+/0	+
Nonwhite race	+	0
Hemodynamic instability		+
Cardiac risk factors		
Diabetes	+	+
Hypertension	+	+
Hypercholesterolemia	ND	0
Cigarette use	ND	-
Family history of CAD	+/0	-
Cardiac history		
Prior angina	+	+
Prior infarction	+/0	-
Prior angioplasty	ND	-
Prior bypass	ND	0

CAD = coronary artery disease; + = increases presentation delay; 0 = no effect on presentation delay; - = decreases presentation delay; ND = no data.

Because presentation delay primarily reflects patient response to symptoms, public education programs have been the main focus for its improvement. To date, mass-media campaigns and public education programs have had variable results in improving presentation delay (32–35). Programs and services focused on groups identified as being at highest risk for presentation delay may be more helpful.

Because it reflects the medical system response to patients, time to treatment may be most easily decreased through procedural and diagnostic strategies focused on treatment delay. Institution of specific emergency room protocols can significantly reduce treatment delay (25,36–38), as can administration of thrombolysis by emergency room physicians without mandatory cardiology consultation (25), arrival by ambulance (22) and transmission of an initial electrocardiogram from the field (39,40).

Time to treatment—accelerated t-PA versus streptokinase. The GUSTO-I investigators postulated that more rapid reperfusion with accelerated t-PA would result in proportionately more myocardial salvage in patients treated early and would be reflected in a greater survival advantage in these patients. The original GUSTO-I report noted an apparent interaction between earlier treatment with accelerated t-PA and a greater relative survival benefit (14). However, after careful quality-

control measures, the trend toward a greater survival benefit with accelerated t-PA in patients treated early did not reach statistical significance (15,16). This result may emanate from two major factors: the timing of symptom onset is not precisely related to the initial coronary occlusion, and because patients with longer times to treatment are generally sicker (with a higher expected mortality), they therefore have a greater mathematical opportunity for clinical benefit, although pathophysiologically their chances for benefit are less. Several statistical issues regarding this finding also must be addressed. First, because the analysis for treatment interaction uses time to treatment as a continuous variable, the relatively few (4,825) changes in data that resulted from the quality-control process, although not altering the shape of the data, were sufficient in this setting to change a borderline statistically significant result ($p = 0.04$) to a nonsignificant one ($p = 0.38$). Further, for the comparison of t-PA versus the combined streptokinase strategies, post hoc analysis shows that the power of the test for an interaction of treatment effect with time to treatment is only about 0.18. However, with a sample size of over 40,000 patients for the overall analysis, the p value of 0.38 indicates strong evidence of no differential effect rather than a lack of power to detect a difference. Although the relative benefit from t-PA in the first hour seems greater, as does that for the combination therapy after 5 h, the number of patients in each group at these intervals was small, precluding any definitive statements about these observations.

Conclusions. Although imprecision in measurement may limit our ability to detect subtle time-dependent treatment effects somewhat, we found no additional relative advantage for earlier treatment with accelerated t-PA versus streptokinase, although a trend was present. Regardless of the agent, earlier thrombolysis resulted in better outcomes, with the best effects for treatment within 2 h of symptom onset. Focused educational, diagnostic and management strategies to facilitate early identification and rapid treatment, especially of those at high risk for delay, should help maximize the benefits of thrombolytic therapy.

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