

# Association of Duration of Symptoms at Presentation With Angiographic and Clinical Outcomes After Fibrinolytic Therapy in Patients With ST-Segment Elevation Myocardial Infarction

C. Michael Gibson, MS, MD,\* Sabina A. Murphy, MPH,\* Ajay J. Kirtane, MD,\*† Robert P. Giugliano, MD, SM,\* Christopher P. Cannon, MD,\* Elliott M. Antman, MD,\* Eugene Braunwald, MD,\* for the TIMI Study Group

Boston, Massachusetts

---

<b>OBJECTIVES</b>	We sought to determine if an underlying mechanism of the association between prolonged symptom-to-treatment times and adverse outcomes may be an association of symptom-to-treatment times with impaired Thrombolysis In Myocardial Infarction myocardial perfusion grades (TMPGs).
<b>BACKGROUND</b>	Prolonged symptom duration among ST-segment elevation myocardial infarction (STEMI) patients undergoing fibrinolytic therapy is associated with adverse outcomes.
<b>METHODS</b>	Angiography was performed 60 min after fibrinolytic administration in 3,845 Thrombolysis In Myocardial Infarction (TIMI) trial patients.
<b>RESULTS</b>	The median time from symptom onset to treatment was longer among patients with impaired myocardial perfusion (3.0 h for TMPG 0/1 vs. 2.7 h for TMPG 2/3; $p = 0.001$ ). In a multivariate model, impaired tissue perfusion (TMPG 0/1) remained associated with increased time to treatment (odds ratio 1.14 per hour of delay; $p = 0.007$ ) even after adjusting for Thrombolysis In Myocardial Infarction flow grade (TFG) 3, left anterior descending infarct location, and baseline clinical characteristics. Impaired myocardial perfusion after rescue/adjunctive percutaneous coronary intervention (PCI) was associated with longer median times to treatment (3.0 h for TMPG 2/3 vs. 2.7 h for TMPG 0/1; $p = 0.017$ ), as was abnormal epicardial flow after rescue/adjunctive PCI (3.3 h for TFG 0/1/2 vs. 2.8 h for TFG 3; $p = 0.005$ ). Thirty-day mortality was associated with longer time from onset of symptoms to treatment (6.6% mortality for time to treatment $>4$ h vs. 3.3%; $p < 0.001$ ), even among patients undergoing rescue PCI.
<b>CONCLUSIONS</b>	A prolonged symptom to treatment time among STEMI patients is associated with impaired myocardial perfusion independent of epicardial flow both immediately after fibrinolytic administration and after rescue/adjunctive PCI. These data provide a pathophysiologic link between prolonged symptoms due to vessel occlusion, impaired myocardial perfusion, and poor clinical outcomes. (J Am Coll Cardiol 2004;44:980–7) © 2004 by the American College of Cardiology Foundation

---

A prolonged duration of symptoms (longer “symptom to treatment times”) among patients with ST-segment elevation myocardial infarction (STEMI) is associated with poorer clinical outcomes (1–3). The time-dependent nature of clinical outcomes after the administration of fibrinolytics has been attributed previously, at least in part, to a failure to achieve successful epicardial reperfusion among patients treated at longer intervals from symptom onset, a concept referred to as “thromboresistance” (1). However, there also may be other mechanisms that contribute to the correlation between time to treatment and clinical outcomes. In an

analysis of the Stent versus Thrombolysis for Occluded coronary arteries in Patients with Acute Myocardial Infarction (STOP-AMI) trials, Schomig et al. (4) demonstrated that longer symptom-to-treatment times are associated with worsened myocardial salvage among patients treated with fibrinolytic therapy.

Insofar as improved myocardial salvage has been linked to the restoration of normal myocardial perfusion (5), the goal of the present study was to examine the association of delays in symptom-to-treatment times with the restoration of myocardial as well as epicardial perfusion. We hypothesized that, in patients, a prolonged duration of symptoms at presentation would be associated with impaired myocardial perfusion after fibrinolytic administration in the setting of STEMI.

## METHODS

Clinical and angiographic data were pooled from the Thrombolysis In Myocardial Infarction (TIMI)-4, TIMI-10, TIMI-14, Integrilin and Tenecteplase in Acute Myo-

---

From the \*TIMI Study Group, Cardiovascular Division, Brigham & Women's Hospital and the †Cardiovascular Division, Beth Israel Deaconess Medical Center, Department of Medicine, Harvard Medical School, Boston, Massachusetts. Supported in part by a grant from Smith Kline Beecham, Philadelphia, Pennsylvania (TIMI-4); Genentech Inc., South San Francisco, California (TIMI-10A and TIMI 10-B); Centocor and Eli Lilly Inc., Malvern, Pennsylvania, and Indianapolis, Indiana (TIMI-14); Millenium Pharmaceuticals, Cambridge, Massachusetts (INTEGRITI); Aventis, Antony, France (TIMI-23-ENTIRE); and Merck & Co. Inc., Whitehouse Station, New Jersey (FASTER).

Manuscript received March 12, 2004; revised manuscript received May 6, 2004, accepted May 11, 2004.

#### Abbreviations and Acronyms

CHF	= congestive heart failure
CTFC	= corrected Thrombolysis In Myocardial Infarction frame count
LAD	= left anterior descending
PCI	= percutaneous coronary intervention
OR	= odds ratio
rt-PA	= recombinant tissue-type plasminogen activator
STEMI	= ST-segment elevation myocardial infarction
TFG	= Thrombolysis In Myocardial Infarction flow grade
TIMI	= Thrombolysis In Myocardial Infarction
TMPG	= Thrombolysis In Myocardial Infarction myocardial perfusion grade
TNK	= tenecteplase
t-PA	= tissue-type plasminogen activator

cardial Infarction (INTEGRITI), Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction (ENTIRE-TIMI-23), and Fibrinolytic and Aggrastat ST-Elevation Resolution (FASTER) studies in STEMI. Briefly, the TIMI-4 trial was a randomized double-blind comparison of anistreplase (Eminase, Glaxo-SmithKline, Research Triangle Park, North Carolina) versus front-loaded tissue-type plasminogen activator (t-PA) (alteplase or Activase, Genetech Inc., South San Francisco, California) versus combination therapy in 416 patients (6). The TIMI-10A trial was a nonrandomized, open-label, dose-escalation study of eight ascending doses of tenecteplase (TNK) (7). TIMI-10B was a randomized trial comparing 30, 40, and 50 mg of TNK versus front-loaded t-PA (8). In the TIMI-14 trial, patients were randomized to receive either full-dose fibrinolytic (t-PA or reteplase [r-PA]) or abciximab in combination with a reduced dose of fibrinolytic agents, which also included streptokinase (9,10). In the INTEGRITI trial, patients were randomized to full-dose TNK versus combinations of eptifibatid and reduced-dose TNK (11). In ENTIRE-TIMI-23 (n = 483), patients were randomized to: 1) full-dose TNK plus unfractionated heparin, 2) full dose TNK plus enoxaparin, or 3) half-dose TNK plus abciximab in addition to either unfractionated heparin or enoxaparin (12). FASTER was a phase II trial evaluating the efficacy of a combination of tirofiban, TNK, and unfractionated heparin in patients with acute STEMI. In each of the trials, an angiography was performed at both 60 min and 90 min after the initiation of fibrinolytic agents. The primary angiographic end point was assessed at 90 min in TIMI-4, TIMI-10, and TIMI-14 and at 60 min in INTEGRITI, ENTIRE-TIMI-23, and FASTER. All data reported in the present analysis are for the 60-min time point unless otherwise specified. Rescue or adjunctive percutaneous coronary intervention (PCI) after index angiography was performed at the discretion of individual operators in the TIMI trials.

**Assessment of flow and perfusion.** Angiographic end points were prospectively assessed at 60 min after the

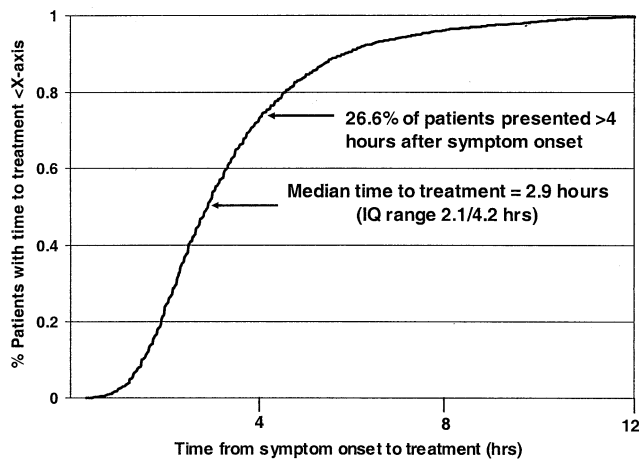
administration of fibrinolytics. Thrombolysis In Myocardial Infarction myocardial perfusion grades (TMPGs), Thrombolysis In Myocardial Infarction flow grades (TFG), and corrected Thrombolysis In Myocardial Infarction frame counts (CTFCs) were assessed as defined previously (13-15) by a single blinded observer (C.M.G.). The CTFC was converted when necessary to be based on the most common filming speed in the U.S. of 30 frames per second (14). Digital subtraction angiography was performed as described previously, and the intensity of blush within the region of interest was quantitated using a grayscale standard (16).

**Statistical analysis.** All analyses were performed using Stata version 7.0 (Stata Corp., College Station, Texas). All continuous variable values are reported as the median with 25% and 75% confidence intervals (median [25th, 75th confidence intervals]) unless otherwise stated. The nonparametric Wilcoxon rank-sum test was used for the analysis of continuous variables when they were not normally distributed. The chi-square test was used for the analysis of categorical variables when sample size was  $\geq 5$  for all cells in a table. When the sample size was  $< 5$  in a given cell of a table, the Fisher exact test was used. A multivariate model was used to assess the association between TMPG and time from symptom onset to treatment, adjusting for TFG, left anterior descending (LAD) infarct location, and baseline clinical characteristics, including TIMI risk score.

## RESULTS

**Baseline characteristics.** Among the 3,913 patients with acute STEMI enrolled in the trials, 422 were treated with non-fibrin-specific agents (streptokinase, anistreplase, or a combination of APSAC and t-PA), 1,908 were treated with fibrin-specific agents alone (t-PA, rt-PA, TNK), and 1,551 patients were treated with a combination of a fibrin-specific agent plus a glycoprotein IIb/IIIa inhibitor or a glycoprotein IIb/IIIa inhibitor alone. Among the 3,845 patients with available time of symptom onset, the median time from onset of chest pain to fibrinolytic therapy was 2.9 h (2.1, 4.2), with 26.6% of patients (1,022, 3,845) presenting  $> 4$  h after symptom onset (Fig. 1). Patients with shorter symptom-to-treatment times were younger and more likely to be male (Table 1). In contrast, those with prolonged symptom-to-treatment times were more likely to be female ( $p < 0.001$ ) and diabetic ( $p = 0.059$ ). The pulse and systolic blood pressure were higher among these patients on admission (Table 1). Patients with shorter symptom-to-treatment times had lower TIMI risk scores than patients with longer symptom-to-treatment times ( $p < 0.001$ ).

**Angiographic data.** The median time from symptom onset to treatment was longer among patients with impaired myocardial perfusion at 60 min (TMPG 0/1, median 3.0 h vs. 2.7 h for TMPG 2/3;  $p = 0.001$ ) (Fig. 2A). Likewise, patients with a delay in symptom onset to treatment  $> 4$  h were less likely to have TMPG 2/3 (46.5% vs. 55.1%;  $p = 0.04$ ) (Fig. 2B), and the myocardium was paler on digital



**Figure 1.** Cumulative distribution function of time from symptom onset to treatment in hours.

subtraction angiography (median 6.6 vs. 8.0 gray scale;  $p = 0.02$ ) (Fig. 2C).

The median symptom-to-treatment time was longer among patients with a closed epicardial artery (TFG 0/1, median 3.3 h vs. 2.8 h for TFG 2/3;  $p < 0.001$ ) (Fig. 3A) and among patients with any abnormality in epicardial flow (TFG 0/1/2) vs. patients with TFG 3 (median 2.8 [2.0, 3.9] h vs. 3.0 [2.1, 4.2] h;  $p = 0.02$ ). Similarly, patients who experienced a delay in symptom onset to treatment ( $>4$  h time-to-treatment) were less likely to achieve TFG 2/3 (71.3% vs. 79.5%;  $p < 0.001$ ) (Fig. 3B) or TFG 3 (47.6% vs. 52.3%,  $p = 0.035$ ). The median CTFC at 60 min was higher among patients with symptom onset to treatment  $>4$  h (42.9 [27.6, 100] frames vs. 38.2 [25, 100] frames;  $p =$

**Table 1.** Baseline Characteristics and Time From Symptom Onset to Treatment

	Time to Treatment $>4$ h (n = 1022)	Time to Treatment $\leq 4$ h (n = 2823)	p Value
Time from symptom onset to treatment, h	Median = 5.3 IQ 4.6/6.7	Median = 2.4 IQ 1.9/3.1	
Age, yrs	59.2 $\pm$ 11.3	57.7 $\pm$ 10.6	0.0002
Age $\geq 65$ yrs	37.1%	29.8%	$<0.001$
Female gender	26.5%	20.7%	$<0.001$
Previous MI	11.5%	12.8%	0.279
History of diabetes	15.4%	13.1%	0.059
History of hypertension	33.0%	32.0%	0.552
Current smokers	48.2%	49.8%	0.390
Previous PCI	6.7%	8.2%	0.126
Pulse on admission, beats/min	78.5 $\pm$ 18.0	74.6 $\pm$ 17.4	$<0.0001$
Systolic blood pressure on admission	140.1 $\pm$ 21.6	137.6 $\pm$ 22.4	0.0019
Anterior MI per ECG	40.5%	37.2%	0.065
TIMI risk score			
0-1	36.0%	64.4%	$<0.001$
2-4	35.4%	26.1%	
$\geq 5$	28.6%	9.5%	

MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

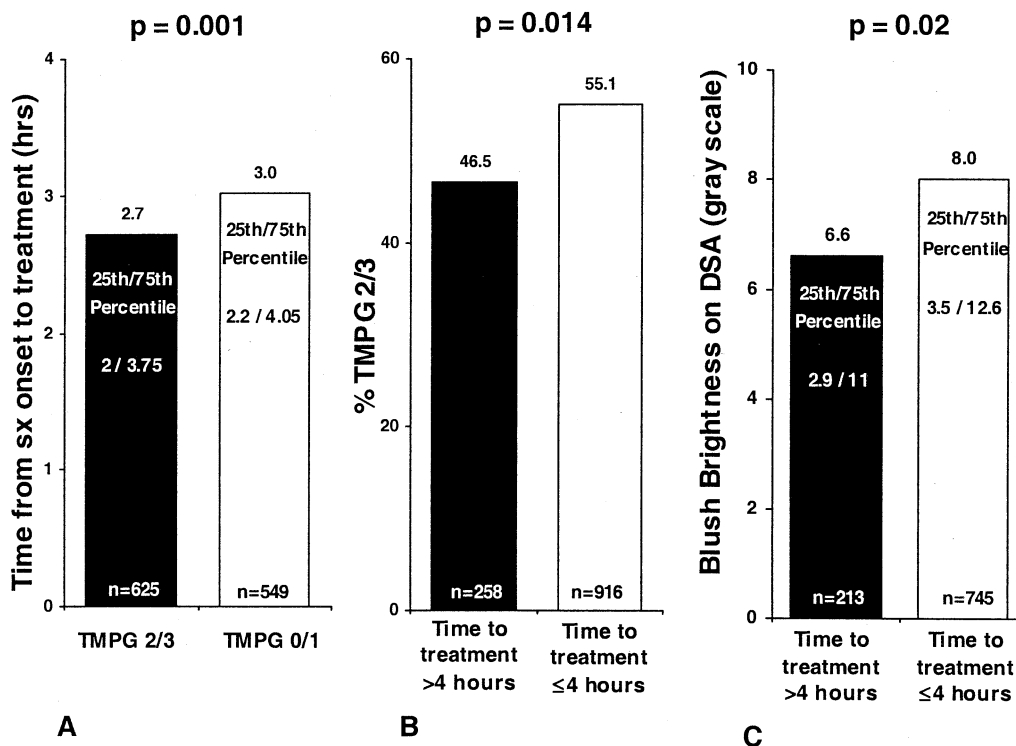
0.001) (Fig. 3C). Even when restricted to patients with TFG 3, the CTFC at 60 min trended higher among patients with symptom onset to treatment  $>4$  h (mean  $\pm$  SD of 27.6  $\pm$  9.4 frames vs. 26.4  $\pm$  8.7 frames;  $p = 0.058$ ). Patients with time from symptom onset to treatment  $>4$  h also had lower ejection fractions measured during left ventriculography (mean  $\pm$  SD of 55.3  $\pm$  15.5% vs. 58.8  $\pm$  14.5%;  $p < 0.0001$ ) (Table 2, Fig. 4A) and more frequently had collaterals present on the angiogram (16.1% vs. 12.4%;  $p = 0.004$ ) (Table 2, Fig. 4B).

In a multivariate model adjusting for TIMI risk score, TFG 3, and LAD infarct location, impaired tissue perfusion at 60 min (TMPG 0/1) was associated with increased time to treatment (odds ratio [OR] 1.13 per hour of delay;  $p = 0.013$ ). In an analysis adjusting for age, gender, pulse and blood pressure on admission, TFG 3, and LAD infarct location, impaired tissue perfusion at 60 min (TMPG 0/1) remained associated with increased time to treatment (OR 1.14 per hour of delay;  $p = 0.007$ ). In a similar model restricted to patients with TFG 3, impaired tissue perfusion at 60 min (TMPG 0/1) remained associated with increased time to treatment (OR 1.13 per hour of delay;  $p = 0.049$ ).

**Perfusion and flow after rescue/adjunctive PCI.** Among the 1,464 patients who underwent rescue/adjunctive PCI immediately after index angiography, the median time from symptom onset to treatment was longer among patients with impaired myocardial perfusion after PCI (median 3.0 h for TMPG 0/1 vs. 2.7 h for TMPG 2/3;  $p = 0.017$ ) (Fig. 5). The median time to treatment also was longer among patients with TFG  $<3$  after PCI (2.75 h vs. 3.25 h;  $p = 0.005$ ) (Fig. 6A). Likewise, TFG 3 was achieved less frequently after PCI among patients whose time from symptom onset to treatment was  $>4$  h (81.3% vs. 87.0%;  $p = 0.007$ ) (Fig. 6B). The median CTFC after PCI was higher in patients with symptom onset to treatment  $>4$  h (24.4 [17, 37] frames vs. 22.0 [16, 32] frames;  $p = 0.008$ ) (Fig. 6C).

**Analyses stratified by fibrin specificity and glycoprotein IIb/IIIa inhibitor usage.** In a separate analysis restricted to patients treated with fibrin-specific fibrinolytic monotherapy, the median time from symptom onset to treatment was greater among patients with impaired myocardial perfusion (3.0 [2.0, 4.1] h for TMPG 0/1 vs. 2.6 [1.9, 3.7] h for TMPG 2/3;  $p = 0.03$ ) and was greater among patients with a closed epicardial artery (3.2 [2.3, 4.6] h vs. 2.8 [2.0, 3.9] h for an open artery;  $p = 0.0002$ ). Similar findings were observed among patients treated with combination therapy with a fibrin-specific agent plus a glycoprotein IIb/IIIa inhibitor (median time from symptom onset to treatment of 3.0 [2.2, 4.0] h for TMPG 0/1 vs. 2.8 [2.1, 3.8] h for TMPG 2/3;  $p = 0.03$ ; median time of 3.3 [2.3, 4.6] h for patients with a closed artery vs. 2.8 [2.1, 3.9] h for open artery;  $p = 0.001$ ).

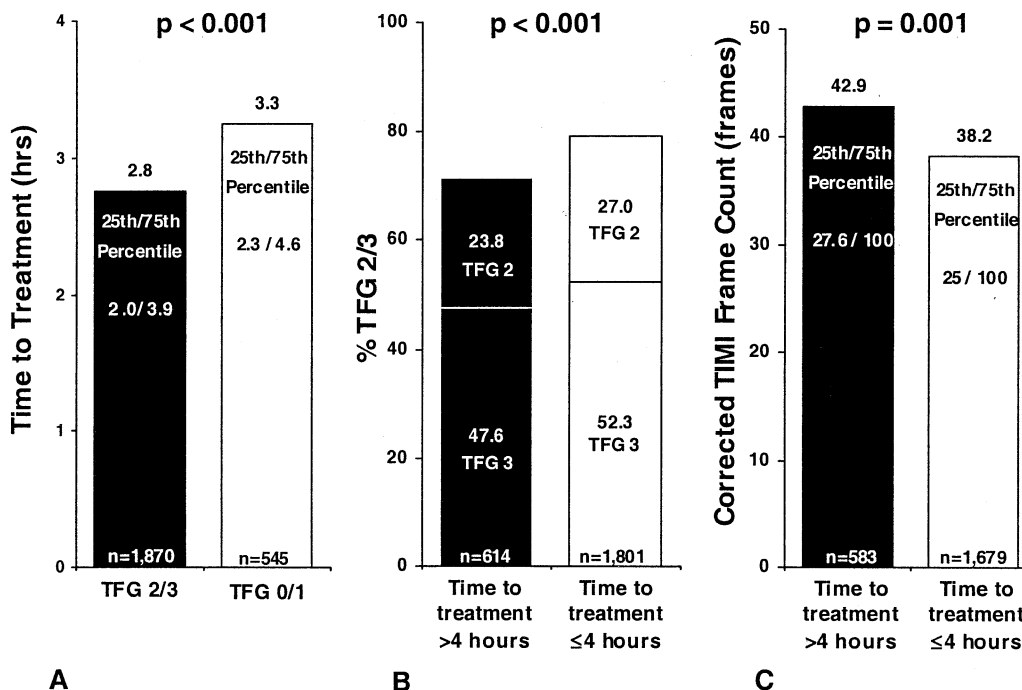
**Clinical outcomes.** Death at 30 days occurred more frequently among patients who presented  $>4$  h from symptom onset (Table 3, Fig. 7). The median time to treatment was



**Figure 2.** (A) Median time from symptom (sx) onset to treatment stratified by Thrombolysis In Myocardial Infarction myocardial perfusion grade (TMPG) at 60 min; (B) percent of patients with TMPG 2 or 3 at 60 min stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset; (C) blush brightness (gray scale) stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset. DSA = digital subtraction angiography.

longer in patients who died by 30 days (3.5 [2.4, 5.0] h vs. 2.9 [2.1, 4.1] h;  $p = 0.0001$ ). There was no difference in rates of recurrent myocardial infarction at 30 days by time to

treatment, but congestive heart failure (CHF) tended to occur more frequently in patients who presented >4 h from symptom onset (Table 3). Similar results in outcomes were



**Figure 3.** (A) Median time from symptom onset to treatment by Thrombolysis In Myocardial Infarction flow grade (TFG) at 60 min; (B) percent of patients with TFG 2 or 3 at 60 min stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset; (C) median corrected TIMI frame count stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset.

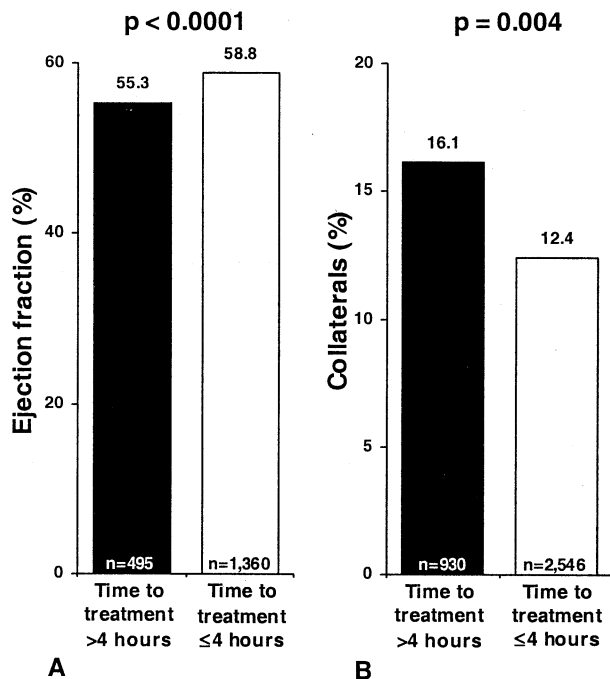
**Table 2.** Angiographic Characteristics and Time From Symptom Onset to Treatment

	Time to Treatment >4 h (n = 1,022)	Time to Treatment ≤4 h (n = 2,823)	p Value
LAD infarction	38.8%	34.3%	0.010
	391/1,009	956/2,791	
Thrombus present	38.1%	38.8%	0.724
	374/981	1,049/2,706	
Collaterals present	16.1%	12.4%	0.004
	150/930	316/2,546	
Calcified	7.7%	7.3%	0.656
	68/880	174/2,394	
Disease extent			0.287
Single-vessel	44.9%	47.2%	
Double-vessel	35.3%	35.0%	
Triple-vessel	19.8%	17.8%	
Ejection fraction	55.3 ± 15.5, n = 495	58.8 ± 14.5, n = 1,360	<0.0001
Brightness of blush on digital subtraction angiography, gray scale	Median = 6.6, IQ 2.9/11, n = 213	Median = 8.0, IQ 3.5/12.6, n = 745	0.022

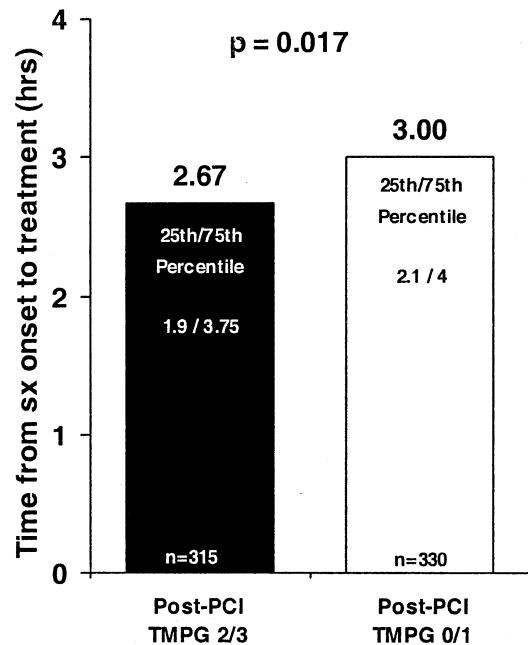
LAD = left anterior descending.

observed in an analysis restricted to patients who underwent rescue/adjunctive PCI during the index catheterization (Table 3). In patients undergoing rescue/adjunctive PCI after the initial angiogram, the median time to treatment among patients who died by 30 days was 4.1 (2.3, 5.3) h vs. 2.8 (2.0, 4.2) h for those who survived (p = 0.004).

Similar findings of increased rates death or CHF by 30



**Figure 4.** (A) Ejection fraction (%) stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset; (B) presence of collaterals (%) stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset.



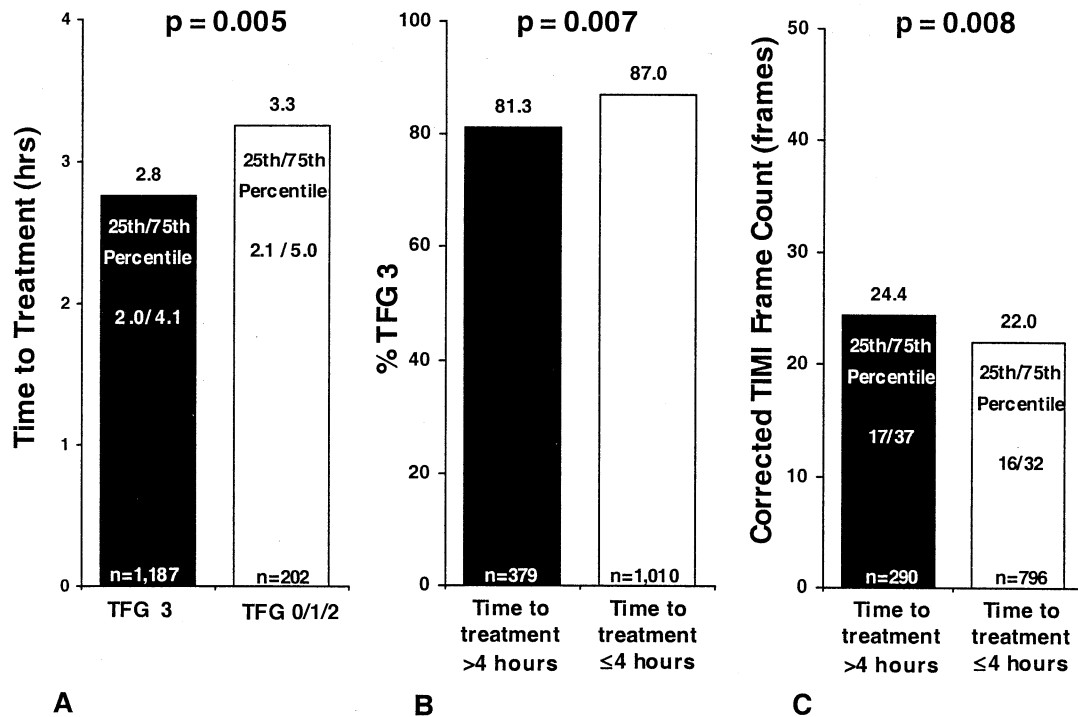
**Figure 5.** Median time from symptom (sx) onset to treatment stratified by post-percutaneous coronary intervention (PCI) Thrombolysis In Myocardial Infarction myocardial perfusion grade (TMPG).

days in patients with time from symptom onset to treatment >4 h were observed when restricted to the cohort of female patients (n = 851; 15.24% vs. 9.79%; p = 0.021) or to the cohort of male patients (n = 2,974; 8.3% vs. 4.85%; p < 0.001). Likewise, in patients who underwent rescue/adjunctive PCI after the initial angiogram, the rate of death or CHF at 30 days was higher in patients with time from symptom onset to treatment >4 h when restricted to the subgroup of female patients (n = 293; 19.09% vs. 9.84%; p = 0.024) or to the subgroup of male patients (n = 1,171; 9.83% vs. 4.91%; p = 0.002).

Median time to treatment was greater in patients who died at 30 days in analyses restricted to patients treated with fibrin-specific agents only (t-PA, TNK, rt-PA; 2.8 [2.0, 4.1] h vs. 3.3 [2.4, 4.7] h for fibrin-specific lytic alone, n = 1,875; p = 0.02) and among patients treated with a combination of fibrin-specific agents and glycoprotein IIb/IIIa inhibitors (2.9 [2.2, 4.1] h vs. 4.2 [2.7, 5.5] h for combination therapy, n = 1,531; p = 0.0001).

## DISCUSSION

This analysis demonstrates that prolonged symptom-to-treatment times are associated with impaired myocardial perfusion grades as well as poorer epicardial flow grades across a variety of fibrinolytic regimens. The association between prolonged symptom-to-treatment times and impaired myocardial perfusion remained when adjusting for epicardial flow, infarct artery location, and other baseline clinical characteristics. After rescue/adjunctive PCI, myocardial and epicardial perfusion remained poorer among patients with prolonged symptom-to-treatment times. As in



**Figure 6.** (A) Median time from symptom onset to treatment stratified by post-percutaneous coronary intervention Thrombolysis In Myocardial Infarction flow grade (TFG); (B) percent of patients with open/closed epicardial artery post-percutaneous coronary intervention stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset; (C) median corrected TIMI frame count post-percutaneous coronary intervention stratified by presentation >4 h from symptom onset versus ≤4 h from symptom onset.

earlier studies (1-3), mortality rates were higher in patients with longer symptom-to-treatment times. This study extends these observations to demonstrate this association even among those patients who underwent rescue/adjunctive PCI.

In addition to confirming an association between prolonged symptom-to-treatment times and impaired epicardial flow grades, this study extends previous observations to demonstrate that prolonged symptom-to-treatment times also are associated with impaired myocardial perfusion grades independent of epicardial flow. Impaired myocardial perfusion after the administration of fibrinolytics has in turn been associated with larger infarct sizes (17), worsened myocardial salvage (5), and increased mortality (15,18) among STEMI patients. Prolonged symptom-to-treatment times also are associated with less-intense myocardial blush on digital subtraction angiography, which could be speculated to reflect a greater extent of myocardial and or endothelial edema in these patients. Similar observations were described in a recent study in which 24- to 36-h ST-segment resolution was worse among patients with prolonged symptom-to-treatment times and correlated with adverse clinical outcomes (19).

Although the association of prolonged duration of symptoms with adverse clinical outcomes is clear in studies of fibrinolytic therapy, the same association is somewhat more controversial among patients undergoing primary PCI rather than fibrinolytic therapy (4,20-22). Although several studies have observed no association between symptom-to-

treatment times and myocardial function (4) or clinical outcomes (21) in patients undergoing primary PCI, a report from the Zwolle investigators that adjusted for baseline clinical and angiographic characteristics demonstrated a significant and independent association between symptom-to-treatment times and outcomes in high-risk patients and in patients with closed epicardial arteries upon initial diagnostic angiography (23). In the present study, 30-day mortality was significantly associated with a longer time from symptom onset to fibrinolytic treatment, even in patients undergoing rescue/adjunctive PCI during the index catheterization. Although this observation is retrospective, it suggests that the higher risk conferred by a prolonged symptom-to-treatment time is not entirely offset by the performance of PCI after fibrinolytic therapy. The finding of poorer myocardial perfusion and epicardial and flow after rescue/adjunctive PCI among patients with prolonged symptoms may also explain in part these patients' poorer clinical outcomes.

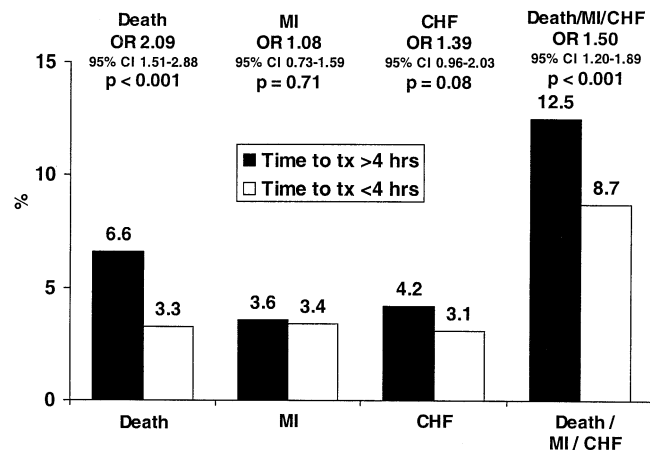
Abnormal coronary flow after fibrinolytic administration has been associated with increased mortality (24), and previous studies have demonstrated that longer times from symptom onset to fibrinolytic treatment in STEMI may be linked to reduced epicardial patency, particularly after treatment with less fibrin-specific agents (1,25,26). Although these original observations were made in trials using streptokinase, subsequent studies of more fibrin-specific agents have demonstrated little or no association between symptom-to-treatment times and rates of epicardial patency

**Table 3.** Clinical Outcomes at 30 Days and Time from Symptom Onset to Treatment

	Time to Treatment >4 h (n = 1,022)	Time to Treatment ≤4 h (n = 2,823)	p Value
<b>All patients</b>			
Death	6.6%	3.3%	<0.001
	67/1,015	92/2,809	
Recurrent MI	3.6%	3.4%	0.707
	36/993	93/2,758	
CHF	4.2%	3.1%	0.083
	42/992	85/2,765	
Death or MI	9.4%	6.3%	0.001
	95/1,016	176/2,809	
Death or CHF	10.1%	5.9%	<0.001
	103/1,016	165/2,809	
Death, MI, or CHF	12.5%	8.7%	<0.001
	127/1,016	244/2,809	
<b>Patients who underwent rescue/adjunctive PCI</b>			
Death	7.6%	2.7%	<0.001
	31/405	29/1,059	
Recurrent MI	2.5%	2.3%	0.793
	10/395	24/1,045	
CHF	5.3%	3.6%	0.143
	21/393	38/1,048	
Death or MI	9.4%	4.6%	0.001
	38/405	49/1,059	
Death or CHF	12.4%	5.8%	<0.001
	50/405	61/1,059	
Death, MI, or CHF	13.6%	7.5%	<0.001
	55/405	79/1,059	

CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

(25,26). In contrast to these previous studies, the sample size in the present study was significantly greater, epicardial flow grades were assessed in a core laboratory, and similar time dependency was observed among patients treated with fibrin-specific, non-fibrin-specific, or “combination therapy” (fibrin-specific agent plus a glycoprotein IIb/IIIa inhibitor) regimens.



**Figure 7.** Clinical outcomes at 30 days stratified presentation >4 h from symptom onset versus ≤4 h from symptom onset. CHF = congestive heart failure; MI = myocardial infarction; OR = odds ratio.

**Study limitations.** This analysis was a non-randomized retrospective analysis of pooled data from several clinical trials and, as such, it is possible that both identified and unidentified confounders may have influenced the outcomes. Nonetheless, similar enrollment criteria were used in each of these trials, and outcomes were ascertained in a blinded fashion by a core laboratory. Because the analysis is based upon randomized trial data, the results observed here might not be applicable to all patients in clinical practice.

**Conclusions.** Prolonged symptom-to-treatment times among STEMI patients are associated with impaired myocardial perfusion independent of epicardial flow both immediately after fibrinolytic administration and after rescue/adjunctive PCI. These data provide a pathophysiologic link between prolonged symptoms due to vessel occlusion, impaired myocardial perfusion, and poor clinical outcomes.

**Reprint requests and correspondence:** Dr. C. Michael Gibson, 350 Longwood Avenue, First Floor, Boston, Massachusetts 02115. E-mail: mgibson@timi.org.

## REFERENCES

- Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis In Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987; 76:142-54.
- Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1,000 patients. *Lancet* 1994;343:311-22.
- Newby LK, Rutsch WR, Califf RM, et al. Time from symptom onset to treatment and outcomes after thrombolytic therapy. GUSTO-1 Investigators. *J Am Coll Cardiol* 1996;27:1646-55.
- Schomig A, Ndrepepa G, Mehilli J, et al. Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. *Circulation* 2003;108:1084-8.
- Dibra A, Mehilli J, Dirschinger J, et al. Thrombolysis in myocardial infarction myocardial perfusion grade in angiography correlates with myocardial salvage in patients with acute myocardial infarction treated with stenting or thrombolysis. *J Am Coll Cardiol* 2003;41:925-9.
- Cannon CP, McCabe CH, Diver DJ, et al. 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. *J Am Coll Cardiol* 1994;24:1602-10.
- Cannon CP, McCabe CH, Gibson CM, et al. TNK-tissue plasminogen activator in acute myocardial infarction. Results of the Thrombolysis In Myocardial Infarction (TIMI) 10A dose-ranging trial. *Circulation* 1997;95:351-6.
- Cannon CP, Gibson CM, McCabe CH, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis In Myocardial Infarction (TIMI) 10B Investigators. *Circulation* 1998;98:2805-14.
- Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis In Myocardial Infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation* 1999;99:2720-32.
- Antman EM, Gibson CM, de Lemos JA, et al. Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14. The Thrombolysis In Myocardial Infarction (TIMI) 14 Investigators. *Eur Heart J* 2000;21:1944-53.

11. Giugliano RP, Roe MT, Harrington RA, et al. Combination reperfusion therapy with eptifibatid and reduced-dose tenecteplase for ST-elevation myocardial infarction: results of the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) phase II angiographic trial. *J Am Coll Cardiol* 2003;41:1251-60.
12. Antman EM, Louwrenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis In Myocardial Infarction (TIMI)-23 Trial. *Circulation* 2002;105:1642-9.
13. The Thrombolysis In Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med* 1985;312:932-6.
14. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879-88.
15. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;101:125-30.
16. Gibson CM, Cohen DJ, Cohen EA, et al. Effect of eptifibatid on coronary flow reserve following coronary stent implantation (an ESPRIT substudy). Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. *Am J Cardiol* 2001;87:1293-5.
17. Angeja BG, Gunda M, Murphy SA, et al. TIMI myocardial perfusion grade and ST-segment resolution: association with infarct size as assessed by single photon emission computed tomography imaging. *Circulation* 2002;105:282-5.
18. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation* 2002;105:1909-13.
19. Fu Y, Goodman S, Chang WC, Van De Werf F, Granger CB, Armstrong PW. Time to treatment influences the impact of ST-segment resolution on one-year prognosis: insights from the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial. *Circulation* 2001;104:2653-9.
20. Berger PB, Ellis SG, Holmes DR Jr., et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO-IIb) trial. *Circulation* 1999;100:14-20.
21. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;283:2941-7.
22. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2-4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur Heart J* 2002;23:550-7.
23. De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2003;42:991-7.
24. Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation* 1999;99:1945-50.
25. Steg PG, Laperche T, Golmard JL, et al. Efficacy of streptokinase, but not tissue-type plasminogen activator, in achieving 90-minute patency after thrombolysis for acute myocardial infarction decreases with time to treatment. PERM Study Group. Prospective Evaluation of Reperfusion Markers. *J Am Coll Cardiol* 1998;31:776-9.
26. Zeymer U, Tebbe U, Essen R, Haarmann W, Neuhaus KL. Influence of time to treatment on early infarct-related artery patency after different thrombolytic regimens. ALKK-Study Group. *Am Heart J* 1999;137:34-8.