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CARDIAC TROPONIN T LEVELS FOR RISK STRATIFICATION IN ACUTE MYOCARDIAL ISCHEMIA

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ABSTRACT

Background The prognosis of patients hospitalized with acute myocardial ischemia is quite variable. We examined the value of serum levels of cardiac troponin T, serum creatine kinase MB (CK-MB) levels, and electrocardiographic abnormalities for risk stratification in patients with acute myocardial ischemia.

Methods We studied 855 patients within 12 hours of the onset of symptoms. Cardiac troponin T levels, CK-MB levels, and electrocardiograms were analyzed in a blinded fashion at the core laboratory. We used logistic regression to assess the usefulness of base-line levels of cardiac troponin T and CK-MB and the electrocardiographic category assigned at admission — ST-segment elevation, ST-segment depression, T-wave inversion, or the presence of confounding factors that impair the detection of ischemia (bundle-branch block and paced rhythms) — in predicting outcome.

Results On admission, 289 of 801 patients with base-line serum samples had elevated troponin T levels (>0.1 ng per milliliter). Mortality within 30 days was significantly higher in these patients than in patients with lower levels of troponin T (11.8 percent vs. 3.9 percent, $P<0.001$). The troponin T level was the variable most strongly related to 30-day mortality (chi-square = 21, $P<0.001$), followed by the electrocardiographic category (chi-square = 14, $P=0.003$) and the CK-MB level (chi-square = 11, $P=0.004$). Troponin T levels remained significantly predictive of 30-day mortality in a model that contained the electrocardiographic categories and CK-MB levels (chi-square = 9.2, $P=0.027$).

Conclusions The cardiac troponin T level is a powerful, independent risk marker in patients who present with acute myocardial ischemia. It allows further stratification of risk when combined with standard measures such as electrocardiography and the CK-MB level. (N Engl J Med 1996;335:1333-41.)

PATIENTS who come to the hospital with acute myocardial ischemic syndromes represent a continuum of disease from unstable angina to acute infarction. The duration, frequency, and timing of ischemic symptoms are important long-term prognostic factors[1,2] and can be used to determine the severity of unstable angina,[3] but these characteristics are not predictive of serious in-hospital events, such as death, infarction, cardiogenic shock, heart failure, or ventricular arrhythmia.[4] Electrocardiography and serum markers are thus the important objective measures of short-term risk in these patients.[1,2,4,5]

Over 90 percent of patients with prolonged ischemic episodes and ST-segment elevation have myocardial infarction.[6,7] In the absence of ST-segment elevation, however, differentiating unstable angina from acute infarction is difficult; few patients have early elevations in creatine kinase MB (CK-MB) that would indicate myocardial infarction or a poor prognosis.[8,9]

Troponin T, the tropomyosin-binding protein of the regulatory complex located on the contractile apparatus of cardiac myocytes,[10] is a sensitive and

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specific marker for myocardial necrosis.[11] Studies of peak troponin T levels measured within 24 hours after admission in small, selected populations have found an increased number of cardiac events in patients with elevated troponin T levels, even those without elevated CK-MB levels.[12-14] We prospectively assessed the prognostic values of base-line cardiac troponin T and CK-MB levels and electrocardiographic abnormalities at admission in a large population of patients with acute ischemic syndromes.

METHODS

This substudy of the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIa) trial was conducted in 96 of 161 participating North American hospitals. All the patients gave informed consent, and the protocol was approved by the review board at each hospital. The Duke Coordinating Center and the Cleveland Clinic Foundation coordinated the trial independently of the sponsors of the main study.

The GUSTO-IIa protocol has been described previously.[15] Patients of any age were eligible if they were enrolled within 12 hours after the onset of chest discomfort with abnormal electrocardiograms — ST-segment elevation or depression of at least 0.05 mV, left bundle-branch block, or T-wave inversion of at least 0.1 mV. Patients with active bleeding, serum creatinine concentrations above 2.5 mg per deciliter (221 μmol per liter), stroke during the year before the study, or contraindications to heparin therapy were excluded.

Medical Care

All patients received 160 mg of aspirin at enrollment and 80 to 325 mg each day thereafter. Patients with ST-segment elevation could receive thrombolytic therapy (streptokinase or an accelerated regimen of alteplase).[16] The patients were randomly assigned according to ST-segment status (elevated or not elevated) to treatment with intravenous heparin, given as a 5000-U bolus followed by an infusion of 1000 U per hour (1300 U per hour if the patient weighed at least 80 kg), or desirudin (Revasc, Ciba–Geigy, Summit, N.J.), given as a bolus of 0.6 mg per kilogram of body weight followed by an infusion of 0.2 mg per kilogram per hour. Both drugs were infused for 72 to 120 hours. All other treatment was provided at the investigators' discretion.

Electrocardiographic Analysis

All 12-lead electrocardiograms were analyzed at the electrocardiographic core laboratory by readers who were not given any information on the patients. All patients underwent 12-lead electrocardiography at randomization, after 8 hours, after 16 to 24 hours, and before discharge. The tracings were assessed for factors that can confound the detection of ischemia, such as left bundle-branch block, left ventricular hypertrophy, and idioventricular or paced rhythms.[17] Each electrocardiogram was categorized according to its predominant feature: ST-segment elevation, ST-segment depression, or T-wave inversion. ST-segment deviation was measured in each lead at the J point, and the duration of the Q wave and the amplitude of the T wave were recorded.

Analysis of Biochemical Markers

Blood samples were obtained as soon as possible after randomization for the measurement of troponin T and CK-MB. The samples were collected in phlebotomy tubes containing no anticoagulant or preservative and were centrifuged at 1000×g for 10 minutes. The resulting aliquots were stored at −20°C, shipped on dry ice within two weeks to the core laboratory, and stored at −70°C until they were thawed. The specimens were assayed in batches within eight hours after thawing. All measurements were performed by personnel with no information about the patients.

Cardiac troponin T was measured by an enzyme-linked immunosorbent assay with an ES 300 automated analyzer with streptavidin-coated tubes (Boehringer Mannheim, Indianapolis).[11,18] The capture antibody (M7) is specific for cardiac troponin T; the detection antibody (1B10), labeled with horseradish peroxidase, has a 12 percent rate of cross-reactivity with skeletal-muscle troponin T.[18] During the first incubation (lasting 60 minutes), the cardiac troponin T antigen binds to one biotinylated antibody (M7) and one horseradish peroxidase–labeled antibody (1B10). After a washing, in the second (25-minute) incubation the biotinylated-antibody complex adheres to the streptavidin-coated tube. After another washing, substrate is added and absorbance is measured at 405 nm to quantify cardiac troponin T. The lower limit of detection of the assay as stated by the manufacturer is 0.04 ng per milliliter, although some investigators have shown the limit to be 0.015 ng per milliliter.[18] The reference range for cardiac troponin T is 0 to 0.1 ng per milliliter, according to the package insert for the assay. The calculated interassay coefficient of variation was 13 percent at the cutoff of 0.1 ng per milliliter (100 percent of the standard deviation divided by the cutoff value of 0.1 ng per milliliter). The coefficient was 8 percent in the range of 5.0 ng per milliliter (with two significant digits).

CK-MB mass was measured by immunoassay with a Stratus II instrument (Baxter Diagnostics, Miami) whose limit of detection was 0.4 ng per milliliter. The upper limit of the reference range was 7.0 ng per milliliter.[19,20] The interassay coefficient of variation was 7 percent at the cutoff value of 7 ng per milliliter and 5 percent in the range of 50 ng per milliliter.

End Points and Definitions

The primary end point of the substudy was a composite end point of death, infarction or reinfarction, bypass surgery, or angioplasty within 30 days. Prospective secondary end points included the events in the composite end point that occurred in an individual patient. Rates of cardiogenic shock, congestive heart failure, atrioventricular block, and ventricular tachycardia or fibrillation were also assessed.

All suspected myocardial infarctions were reviewed by an independent, blinded adjudication committee. We followed the classifications used in the GUSTO-1 study for infarction and reinfarction,[15] cardiogenic shock, and congestive heart failure.[21]

Statistical Analysis

The analyses reported here are of patients for whom serum-marker and electrocardiographic data were complete, except as otherwise indicated. Each patient was assigned to one of four applicable primary categories based on the results of electrocardiography, in the following order: ST-segment elevation, ST-segment depression, T-wave inversion or no abnormality, and confounding electrocardiographic factors present (see the section above on Electrocardiographic Analysis).

We calculated Spearman rank-correlation coefficients comparing the base-line troponin T level with the base-line CK-MB level and comparing the troponin T level with the interval from the onset of the longest-lasting symptom to the time of blood sampling. The time data were plotted against the data on troponin T levels, and a nonparametric smoother (the "super smoother" of Friedman,[22] as implemented in the S-Plus function "supsmu,"[23] with a low-frequency emphasis of 0.0) was used to plot the trend line.

We used all the available data on troponin T levels to plot the predicted probability of death in relation to the troponin T level, using the same nonparametric smoother (and a low-frequency emphasis of 2.0)[22,23] after truncating the troponin T axis at 15 ng per milliliter to highlight the area of interest. Since no cutoff value emerged, we used the value of 0.1 ng per milliliter as the cutoff, according to recommendations of the manufacturer.[18] According to these dichotomous categories of the enzyme measurements and the four electrocardiographic categories, we then expressed

the base-line characteristics and outcomes as numbers of patients and group percentages in the case of discrete variables and medians with interquartile ranges in the case of continuous variables.

We compared the continuous troponin T values with the electrocardiographic categories and the continuous data on CK-MB levels with regard to their ability to predict death within 30 days. A logistic regression was performed, and the log-likelihood chi-square was used to compare the appropriate full and reduced models.[24] We used the concordance-probability index, which represents the area under a receiver-operator-characteristic curve, to assess the discriminatory ability of the models. So as not to assume linearity or any a priori transformations of serum markers, we modeled both variables with restricted cubic-spline functions — piecewise polynomials fitted by including appropriate linear and nonlinear terms in the logistic-regression model.[24] Because of the extreme rightward skewing of the troponin T data (the levels ranged from 0 to 30 ng per milliliter, with 75 percent of the values below 0.27 ng per milliliter), we first transformed this variable by calculating the log (troponin T + 0.001) value before inserting the data into the spline function. In studying the outcome of 30-day mortality, we used a three-knot spline for CK-MB and a four-knot spline for troponin T. We determined these transformations on the basis of the information criteria of Akaike after testing various candidate transformations.[25] Three dummy variables were used for the four-category electrocardiographic variable. The ability of the troponin T level to predict the composite end point was also assessed, and all patients for whom there were troponin T data were included in that analysis. All the analyses were performed with SAS (version 6.09) and S-Plus (version 3.3) software.

RESULTS

Of the 855 patients enrolled,[15] 755 (88 percent) had complete clinical, electrocardiographic, and serum-marker data. Electrocardiographic data obtained on admission were lacking for 46 patients, base-line blood samples were lacking for 48, and both were

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 855 STUDY PATIENTS.*

CHARACTERISTIC	ALL PATIENTS (N = 855)	TROPONIN T	
		>0.1 ng/ml (N = 289)	≤0.1 ng/ml (N = 516)
Age — yr	63 (53–72)	66 (56–75)	62 (52–70)
Male sex	590 (69.0)	187 (64.7)	367 (71.1)
Race†			
White	786 (93.0)	257 (90.8)	481 (93.9)
Black	44 (5.2)	21 (7.4)	23 (4.5)
Other	15 (1.8)	5 (1.8)	8 (1.6)
Hypertension	434 (50.8)	155 (53.6)	252 (48.8)
Diabetes mellitus	184 (21.5)	71 (24.6)	102 (19.8)
Hypercholesterolemia	354 (41.4)	99 (34.3)	234 (45.3)
Medical history			
Infarction	221 (25.8)	64 (22.1)	148 (28.7)
Angina	560 (65.5)	196 (67.8)	336 (65.1)
Angioplasty	91 (10.6)	18 (6.2)	70 (13.6)
Bypass surgery	93 (10.9)	26 (9.0)	63 (12.2)
Stroke or transient ischemic attack	47 (5.5)	21 (7.3)	23 (4.5)
Severe chronic obstructive pulmonary disease	31 (3.6)	17 (5.9)	11 (2.1)
Cancer	33 (3.9)	12 (4.2)	21 (4.1)
Chronic renal failure	22 (2.6)	11 (3.8)	10 (1.9)
Peripheral vascular disease	62 (7.3)	31 (10.7)	28 (5.4)
Heart rate — beats/min	76 (65–88)	60 (68–90)	75 (64–85)
Blood pressure — mm Hg			
Systolic	132 (118–150)	132 (118–149)	133 (118–150)
Diastolic	78 (68–88)	76 (68–86)	78 (68–89)
Killip class‡			
1	733 (86.3)	226 (79.6)	464 (89.9)
2	90 (10.6)	37 (13.0)	48 (9.3)
3	16 (1.9)	12 (4.2)	3 (0.6)
4	10 (1.2)	9 (3.2)	1 (0.2)
Troponin T — ng/ml			
Mean ±SD	0.68±2.44	1.85±3.80	0.02±0.03
Median (interquartile range)	0.04 (0.01–0.27)	0.49 (0.24–1.44)	0.01 (0–0.04)
Range	0–28.47	0.11–28.47	0–0.1
CK-MB — ng/ml			
Mean ±SD	16.37±39.46	39.70±58.42	3.21±6.0
Median (interquartile range)	3.5 (1.2–11.1)	18.7 (7.0–43.9)	1.8 (0.8–3.9)
Range	0–434	0–434	0–103.7

*Except as specified otherwise, the values shown are medians and interquartile ranges or numbers of patients and percentages of the group. All troponin T and CK-MB values were determined at the core laboratory. For 50 patients the troponin T level was not known because blood samples were not available.

†Data on 845 patients were available.

‡Data on 849 patients were available.

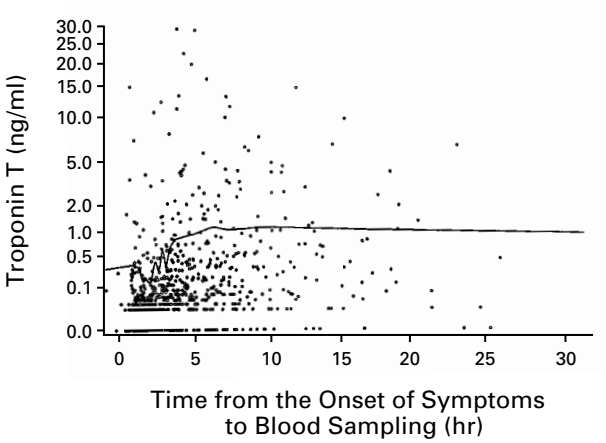

Figure 1. Relation between Serum Troponin T Levels and the Time from the Onset of Symptoms to Blood Sampling.

Each dot represents one patient. A trend line derived by a nonparametric smoothing algorithm is shown.[23] The troponin T levels are plotted on a cube-root scale.

lacking for 6. The base-line characteristics of all 855 patients are shown in Table 1. The median duration of the ischemic episodes qualifying the patients for the study was 2.9 hours. Chest pain was continuous in 38.9 percent and intermittent in 61.1 percent.

A median of 3.5 hours (interquartile range, 2.3 to 6.3) elapsed from the onset of symptoms to the time of blood sampling; a median of 1.6 hours (interquartile range, 0.8 to 3.5) elapsed from arrival at the hospital to the time of blood sampling. There was a weak relation between the troponin T level and the time from the onset of symptoms to the time of blood sampling among patients who had symptoms for less than five hours (Spearman correlation, 0.3; $P<0.001$) (Fig. 1). Troponin T levels were elevated in 33 percent of the patients whose ischemic symptoms had lasted six hours or less and in 43 percent of those whose symptoms had lasted more than six hours ($P=0.06$).

Table 2 shows the patients' characteristics and outcomes according to their electrocardiographic categories at admission. Of the 435 patients with base-line ST-segment elevations, 366 had myocardial infarctions (anterior in 42 percent and inferior in 58 percent). The primary abnormality was ST-segment depression in 12 percent of patients; there were minor electrocardiographic abnormalities (such as T-wave inversion) or a normal tracing in 22 percent, and confounding electrocardiographic factors were present in 9 percent. Myocardial infarction was identified within 18 hours after admission in 50 percent of the patients without ST-segment elevation.

Overall, 36 percent of the patients had elevated troponin T levels (>0.1 ng per milliliter). The patients with confounding electrocardiographic factors had such elevations most often (56.5 percent). The troponin T levels were elevated more often than the CK-MB levels in the patients without ST-segment elevation.

The relation between the troponin T level on admission and death within 30 days is shown in Figure 2. There was no troponin T level at which the probability of death increased stepwise; instead, the relation between the troponin T level and mortality was nearly linear and direct.

There was a strong, positive correlation between the troponin T and CK-MB levels obtained on admission (Spearman correlation, 0.76; $P<0.001$). There was substantial concordance of data among the groups of patients defined according to whether their troponin T and CK-MB levels were above the cutoff values or at or below those values (Table 3). Patients with elevated CK-MB or troponin T levels had a poorer prognosis than patients with normal levels. Median hospital stays were slightly longer in patients with troponin T elevations (eight days, vs. seven days for patients without such elevations; $P=0.047$), but not in patients with CK-MB elevations (seven days with or without CK-MB elevations, $P=0.763$).

In all four electrocardiographic categories, elevated levels of troponin T were associated with higher rates of death and myocardial infarction (Table 4). The 30-day mortality of the patients without ST-segment elevation was 7.6 percent among those with troponin T elevations as compared with 1.2 percent among those without troponin T elevations ($P=0.008$). Regression modeling showed no interaction between the electrocardiographic category and the troponin T level in predicting death within 30 days.

The association of troponin T with mortality was consistent in both CK-MB categories (Table 5). Even among patients with no CK-MB elevations, elevated levels of troponin T were associated with higher mortality ($P=0.001$) and increased rates of cardiogenic shock and congestive heart failure. However, 63 percent of patients without elevations of either CK-MB or troponin T had myocardial infarctions.

The relative values of the electrocardiographic and serum markers in predicting 30-day mortality are shown in Table 6. The troponin T level was most strongly related to mortality, followed by the electrocardiographic category and the CK-MB level. When the electrocardiographic category was forced into a model first (because such a categorization would be available for all patients evaluated for ischemic symptoms), the added value of the troponin T level remained significant (chi-square = 18.1, $P<0.001$), whereas the CK-MB level, although statistically significant, contributed much less (chi-square = 9.67, $P=0.008$). The troponin T level on admission remained significantly predictive of 30-day mortality even after the analysis was adjusted for the electrocardiography category and the CK-MB level, whereas CK-MB was not predictive after the electrocardio-

TABLE 2. CHARACTERISTICS AND OUTCOMES OF THE 755 STUDY PATIENTS WITH COMPLETE DATA, ACCORDING TO THE ELECTROCARDIOGRAPHIC CATEGORY ASSIGNED AT ADMISSION.*

VARIABLE	ST-SEGMENT ELEVATION (N=435)	ST-SEGMENT DEPRESSION (N=88)	T-WAVE DEPRESSION OR NORMAL TRACING (N=163)	ELECTROCARDIOGRAPHIC CONFOUNDERS† (N=69)	P VALUE
Base-line characteristics					
Duration of chest pain — hr	3.0 (1.7–4.7)	2.9 (1.5–5.6)	2.1 (0.8–4.5)	2.6 (1.0–4.0)	0.093
CK-MB >7.0 ng/ml	143 (32.9)	30 (34.1)	44 (27.0)	28 (40.6)	0.218
Troponin T >0.1 ng/ml	138 (31.7)	43 (48.9)	49 (30.1)	39 (56.5)	<0.001
Outcomes at 30 days‡					
Death	32 (7.4)	7 (8.0)	2 (1.2)	8 (11.6)	0.010
Myocardial infarction	366 (84.1)	50 (56.8)	83 (50.9)	46 (66.7)	<0.001
Bypass surgery	63 (14.5)	23 (26.1)	32 (19.6)	7 (10.1)	0.016
Angioplasty	142 (32.6)	20 (22.7)	53 (32.5)	21 (30.4)	0.319
Any of these	393 (90.3)	67 (76.1)	114 (69.9)	51 (73.9)	<0.001

*Values shown are medians and interquartile ranges or numbers of patients and percentages of the group.

†Left bundle-branch block, left ventricular hypertrophy, and idioventricular or paced rhythms were defined as the factors that can confound the detection of ischemia.

‡A patient could have more than one of the outcomes shown.

graphic category and the troponin T level were considered.

The relation between the composite 30-day end point and the troponin T level was also studied by logistic regression. When each patient was counted as having only one event, the rates of the events included in the composite end point were as follows: 54 deaths (7 percent), 538 infarctions (67 percent), and 76 revascularizations (9 percent); in 17 percent of patients, there were no events. The troponin T levels did not significantly predict this composite outcome (chi-square = 2.6, P = 0.46).

DISCUSSION

This prospective study shows that cardiac troponin T levels above 0.1 ng per milliliter on admission are associated with significantly higher mortality within 30 days in patients with acute ischemic syndromes. Furthermore, the base-line cardiac troponin T level provides incremental prognostic information even when there is ST-segment elevation. Therefore, this study not only confirms the observations of small trials in selected patients with unstable angina[12,13] but also extends them in three important ways: by using only a single blood sample obtained early for the stratification of risk; by identifying a new and lower threshold for increased risk; and by verifying these observations in a large, more general population of patients with acute ischemia.

Assessing the condition of patients with acute ischemic syndromes is difficult. The electrocardiogram, when characteristic, provides important information because it is relatively objective.[26] One study has suggested that serum markers provide no prognostic information in addition to that supplied by data on ST-segment and T-wave changes.[27] Our findings in this large cohort indicate that cardiac troponin T levels provide significant incremental prognostic information. Furthermore, the fact that the clinicians were unaware of the troponin T and CK-MB levels provides strong evidence that there was no treatment bias in the study.

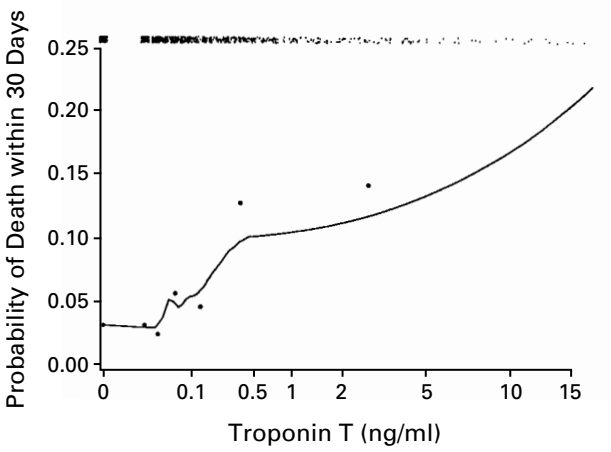

Figure 2. Probability of Death within 30 Days According to the Troponin T Level at Hospital Admission.

Smoothed nonparametric estimates are shown. The troponin T levels are plotted on a cube-root scale. The density of the data is indicated at the top, with each mark representing one patient. The dots represent simple estimates of mortality derived from ranges of the troponin T level that contained at least 70 patients.

TABLE 3. CHARACTERISTICS AND OUTCOMES IN THE 801 PATIENTS WITH BASE-LINE BLOOD SAMPLES, ACCORDING TO THE RESULTS OF BIOCHEMICAL DETERMINATIONS.*

VARIABLE	TROPONIN T		CK-MB	
	>0.1 ng/ml (N=289)	≤0.1 ng/ml (N=512)	>7.0 ng/ml (N=260)	≤7.0 ng/ml (N=541)
Base-line characteristics				
Duration of chest pain — hr	3.0 (1.3–5.2)	3.0 (1.3–4.5)	3.2 (1.5–5.8)	2.8 (1.3–4.3)
CK-MB >7.0 ng/ml	216 (74.7)	44 (8.6)	—	—
Troponin T >0.1 ng/ml	—	—	216 (83.1)	73 (13.5)
Outcome at 30 days				
Death	34 (11.8)	20 (3.9)	26 (10.0)	28 (5.2)
Early infarction†	245 (84.8)	323 (63.1)	251 (96.5)	317 (58.6)
Late infarction	16 (5.5)	29 (5.7)	17 (6.5)	28 (5.2)
Bypass surgery	52 (18.0)	85 (16.6)	39 (15.0)	98 (18.1)
Angioplasty	79 (27.3)	174 (34.0)	81 (31.2)	172 (31.8)
Any of these	269 (93.1)	399 (77.9)	253 (97.3)	415 (76.7)
In-hospital complications				
Shock	25 (8.7)	14 (2.7)	20 (7.7)	19 (3.5)
Congestive heart failure	41 (14.2)	38 (7.4)	34 (13.1)	45 (8.3)
Atrioventricular block	20 (6.9)	20 (3.9)	17 (6.5)	23 (4.3)
Sustained ventricular arrhythmia	17 (5.9)	30 (5.9)	15 (5.8)	32 (5.9)

*Values shown are medians and interquartile ranges or numbers of patients and percentages of the group. All troponin T and CK-MB values were determined at the core laboratory.

†Early infarctions were those occurring within 18 hours of enrollment.

TABLE 4. COMPLICATIONS AND 30-DAY OUTCOMES IN THE 755 STUDY PATIENTS WITH COMPLETE DATA, ACCORDING TO ELECTROCARDIOGRAPHIC CATEGORY AND LEVELS OF TROPONIN T AND CK-MB.*

CATEGORY OF PATIENTS AND OUTCOME	TROPONIN T		CK-MB	
	>0.1 ng/ml	≤0.1 ng/ml	>7.0 ng/ml	≤7.0 ng/ml
ST-segment elevation				
No. of patients	138	297	143	292
Death	18 (13.0)	14 (4.7)	15 (10.5)	17 (5.8)
Myocardial infarction	125 (90.6)	241 (81.1)	137 (95.8)	229 (78.4)
Bypass surgery	22 (15.9)	41 (13.8)	18 (12.6)	45 (15.4)
Angioplasty	35 (25.4)	107 (36.0)	43 (30.1)	99 (33.9)
ST-segment depression				
No. of patients	43	45	30	58
Death	5 (11.6)	2 (4.4)	4 (13.3)	3 (5.2)
Myocardial infarction	33 (76.7)	17 (37.8)	29 (96.7)	21 (36.2)
Bypass surgery	12 (27.9)	11 (24.4)	8 (26.7)	15 (25.9)
Angioplasty	9 (20.9)	11 (24.4)	8 (26.7)	12 (20.7)
T-wave inversion or normal tracing				
No. of patients	49	114	44	119
Death	2 (4.1)	0	1 (2.3)	1 (0.8)
Myocardial infarction	43 (87.8)	40 (35.1)	43 (97.7)	40 (33.6)
Bypass surgery	10 (20.4)	22 (19.3)	8 (18.2)	24 (20.2)
Angioplasty	18 (36.7)	35 (30.7)	16 (36.4)	37 (31.1)
Electrocardiographic confounders†				
No. of patients	39	30	28	41
Death	6 (15.4)	2 (6.7)	5 (17.9)	3 (7.3)
Myocardial infarction	31 (79.5)	15 (50.0)	27 (96.4)	19 (46.3)
Bypass surgery	3 (7.7)	4 (13.3)	0	7 (17.1)
Angioplasty	11 (28.2)	10 (33.3)	10 (35.7)	11 (26.8)

*Values shown are numbers of patients and percentages of the group. All troponin T and CK-MB values were determined at the core laboratory.

†Left bundle-branch block, left ventricular hypertrophy, and idioventricular or paced rhythms were defined as the factors that can confound the detection of ischemia.

TABLE 5. COMPLICATIONS AND 30-DAY OUTCOMES IN THE 801 PATIENTS WITH BASE-LINE BLOOD SAMPLES, ACCORDING TO LEVELS OF SERUM MARKERS STUDIED IN COMBINATION.*

30-DAY OUTCOME†	CK-MB >7.0 ng/ml		CK-MB ≤7.0 ng/ml	
	TROPONIN T >0.1 ng/ml (N=216)	TROPONIN T ≤0.1 ng/ml (N=44)	TROPONIN T >0.1 ng/ml (N=73)	TROPONIN T ≤0.1 ng/ml (N=468)
	no. of patients (%)			
Death	25 (11.6)	1 (2.3)‡	9 (12.3)	19 (4.1)§
Myocardial infarction	210 (97.2)	41 (93.2)	38 (52.1)	294 (62.8)
Bypass surgery	33 (15.3)	6 (13.6)	19 (26.0)	79 (16.9)
Angioplasty	64 (29.6)	17 (38.6)	15 (20.5)	157 (33.6)
Any of these	212 (98.1)	41 (93.2)	57 (78.1)	358 (76.5)

*All troponin T and CK-MB values were determined at the core laboratory.

†A patient could have more than one of the outcomes shown.

‡P=0.04 for the comparison with the group with troponin T levels above 0.1 ng per milliliter.

§P<0.001 for the comparison with the group with troponin T levels above 0.1 ng per milliliter.

TABLE 6. RELATIVE VALUE OF SERUM MARKERS AND 12-LEAD ELECTROCARDIOGRAPHY AS PREDICTORS OF 30-DAY MORTALITY.

PREDICTOR	UNADJUSTED ANALYSIS				ADJUSTED ANALYSIS*		
	CHI-SQUARE	C INDEX†	DF‡	P VALUE	CHI-SQUARE	DF‡	P VALUE
Troponin T	21.0	0.69	3	<0.001	9.2	3	0.027
Electrocardiography	14.2	0.62	3	0.003	11.5	3	0.009
CK-MB	10.9	0.63	2	0.004	0.7	2	0.717

*The analysis of each variable is adjusted for the other two variables, which were forced into the model first.

†This index (the concordance-probability index) represents the area under the receiver-operator-characteristic curve, an indicator of the discriminatory ability of each predictor.

‡DF denotes degrees of freedom.

Although other studies have evaluated serial troponin T levels,[28-31] we examined only one sample obtained within two hours after admission. The substantially higher mortality in patients with elevated troponin T levels and ST segments at base line has not been noted previously, to our knowledge, and may reflect the influence of three factors. First, these patients may have had infarcts that began earlier; patients who present after more than six hours of ischemic symptoms have a higher mortality rate than patients who present earlier.[32,33] Troponin T levels can rise as soon as one hour after the onset of symptoms and can reach 50 percent sensitivity within three to four hours.[18,28] In accordance with this observation, we found a nearly linear increase in the troponin T level among patients who presented after more than four hours of symptoms. Second, these patients may have had brief symptoms of infarction (interpreted as unstable angina), with spontaneous reperfusion and later reocclusion, and associated ST-segment elevation[34]; mortality from reinfarction or reocclusion is significantly greater than mortality from an index infarction.[35] In the latter case, troponin T levels remain elevated for 10 to 14 days after the onset of infarction.[28] Third, the patients who died may have had larger infarcts. Larger infarcts can cause the substantial early release of troponin T due to leakage, the saturation of clearance mechanisms, and the rapid appearance of troponin T in the circulation.[36,37] Whatever the mechanism, elevated base-line troponin T levels were associated with increased morbidity and mortality in all the electrocardiographic categories we studied. Of further importance is that both deaths in the subgroup of patients who had only minor electrocardiographic changes were in patients with elevated troponin T levels.

Patients who are admitted to the hospital with minor elevations in serum creatine kinase or CK-MB have worse long-term prognoses[27,38,39] — a one-to-four-year mortality of 16 to 64 percent — than patients with troponin T elevations. Our study indicates that although CK-MB elevation is associated with a worse short-term prognosis,[40] troponin T is a better prognostic marker when arbitrary cutoff values are not used in either test. Previous studies used a cutoff value of 0.2 ng per milliliter for troponin T,[12,13,29] based on the level used as a marker of acute myocardial infarction.[11,29,41] Recently, a level above 0.1 ng per milliliter was shown to have the best sensitivity and specificity in the diagnosis of infarction.[18] Our results confirm that this lower troponin T level is useful in the diagnosis of infarction and in the identification of patients at increased risk of mortality and morbidity.

Several limitations of our study must be acknowledged. The study population was a somewhat selected, high-risk group with acute ischemic syndromes, and 72 percent of the patients had diagnosed myocardial infarction. Troponin T has been studied in a more general population of patients with chest pain seen in the emergency department.[42] In that study, 58 percent of the 407 patients with unstable angina had elevated troponin T levels (>0.1 ng per milliliter). The rates of death and death or myocardial infarction at 45 days and 6 months were significantly higher in these patients than in patients without troponin T elevations, and they approached the rates seen in patients with myocardial infarction at admission. Another study of similar, unselected patients with chest pain found a significant increase in cardiac events in patients with troponin T levels above 0.1 ng per milliliter as compared with those with normal levels (rates of infarction or revascularization, 96 percent and 40 percent).[43] Thus, these studies provide a consistent message about the diagnostic and prognostic importance of troponin T.

Patients with suspected renal failure (creatinine, >2.5 mg per deciliter) were excluded from GUSTO-IIa. This may have increased the prognostic value of troponin T, because this marker, like CK-MB, may be spuriously elevated in such patients.[44,45]

The time required for the troponin T assay (90 minutes) limits its value as a diagnostic or prognostic tool for short-term use. Bedside assays that indicate qualitative troponin T levels may soon be available,[46] but cutoff values must be established for them that will yield equally compelling prognostic information.

This study shows that the cardiac troponin T level measured within two hours after admission is a powerful, independent marker of risk in patients with acute ischemic syndromes. Using electrocardiographic criteria and cardiac troponin T levels together may facilitate the early care of such patients.

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APPENDIX

The following sites and investigators participated in the GUSTO-IIa Troponin T Substudy: **United States: Northeast** — *Greenwich Hospital:* Seidenstein H, Reilly H; *Falmouth Hospital:* Urbach D, Bull T; *Lowell General Hospital:* Pinsky L, Pelleriti L; *Lahey Clinic Med. Ctr.:* Labib S, Nichter M; *Maine Med. Ctr.:* Lambrew C, Tooker N; *Central Maine Med. Ctr.:* Weiss R, Ridley C; *Lakes Regional General Hospital:* Rosenfeld A, Waldron K; *Dartmouth–Hitchcock Med. Ctr.:* Nilce N, Edkins R; *Concord Hospital:* Deloge K, Flanders R; *Rochester General Hospital:* Gacioch G, Chiodo V; *Northern Westchester Hospital:* Wallach R, Keeler K; *Glens Falls Hospital:* Layden J, Soule R; *St. Joseph's Med. Ctr.:* Bleiberg M, Hoey M; *Ellis Hospital:* Parkes R, Saracco M; *St. Clare's Hospital:* Lindenberg B; *University Hospital South:* McCord D, Viswanathan N; **Mid-Atlantic** — *Franklin Square Hospital:* Strahan N, Heller P; *Suburban Hospital:* Rosing D, Clark C; *Lancaster General Hospital:* Ibarra J, Tuzi J; *St. Joseph Hospital:* Hollywood L; *Chester County Hospital:* Boyek T, Pickering F; *Hershey Med. Ctr.:* Gilchrist I, Zimmerman H; *York Hospital:* Schrading W, Sonin N; *Danville Regional Med. Ctr.:* Miller G, Walker D; *Lynchburg General Hospital* and *Virginia Baptist Hospital:* Nygaard T, McBride J; *Ohio Valley Med. Ctr.:* Noble W, Baltich D; **South** — *East Alabama Med. Ctr.:* Ingram R, Stegall G; *Wuestoff Memorial Hospital:* Sheikh K, Quattrocchi F; *Baptist Med. Ctr.:* Schrank J; *Venice Hospital:* Baga V, Miller K; *Mease Health Care Safety Harbor:* Gibbs K, Hammond P; *Tallahassee Memorial Regional Med. Ctr.:* Williams D, Evans A; *St. Luke's Hospital:* Lane G, Eboner K; *Northwest Regional Hospital:* Schneider R, Bruno G; *Morton Plant Hospital:* Spriggs D, Merriam L; *Piedmont Hospital:* Silverman M, Lowery G; *University Hospital:* Chandler A, Edwards M; *Memorial Med. Ctr.:* Beeson W, Beatie J; *St. Joseph's Hospital:* Gainey P, Smith S; *Audubon Regional Med. Ctr.:* Hanrahan J; *Duke University Med. Ctr.:* Granger C, Brown K; *Memorial Mission Hospital* and *St. Joseph's Hospital:* Maddox W, Allen S; *Margaret Pardee Hospital:* Goodfield P, Goodfield T; *AMI Frye Regional Med. Ctr.:* Hoaron B, Lewis L; *Grace Hospital:* Seagle R, Macopson J; *Anderson Area Med. Ctr.:* Morse H, Blackburn S; **Great Lakes** — *Methodist Med. Ctr.* and *Proctor Hospital:* Schmidt P, Ness C; *Evanston Hospital* and *Glenbrook Hospital:* McDonough T, Coderre P; *St. Joseph Med. Ctr.:* McCriskin J, Hayes M; *Fort Wayne Cardiology:* Wilson W, Dague C; *Ball Memorial Hospital:* Whitaker W, Swinehart M; *St. Mary's Med. Ctr.:* Millsaps R, Ernest J; *Deaconess Hospital:* Becker J, Schaefer C; *Oakwood Hospital:* Riba A, Draus C; *St. Joseph Mercy Hospital:* Heinsimer J, Lentini T; *Christ Hospital:* Kereiakes D, Martin L; *E.M.H. Regional Med. Ctr.:* Schaeffer J, Humphrey D; *Good Samaritan Hospital:* Weinberg S, Wells J; *University Hospital of Cleveland:* Hodgson J, Rowell R; *Lorain Community Hospital:* Schaeffer J, Falasco P; *Licking Memorial Hospital:* Morrice B, Merrick P; *Cleveland Clinic Foundation:* Hejl S; **Midwest** — *St. Luke's Hospital:* Cook L, Soukup M; *Mercy Med. Ctr.:* Murrah L; *St. Paul–Ramsey Med. Ctr.:* Swenson L, Vittum K; *North Memorial Hospital:* Hanovich G, Antolick A; *St. Mary's Med. Ctr.:* Thompson J, Gauthier T; *Missouri Delta Med. Ctr.:* Pfefforken D, Vickery K; *DePaul Health Center:* Drozda J, Mir C; *St. Joseph Health Center:* Forrigni F, Magrew B; *Trinity Med. Ctr.:* Saddin M, Nelson S; *St. Alexius Med. Ctr.:* Oatfield R, McPherson D; *St. Francis Hospital:* Kalbfleisch J, Thompson M; *Midwest City Regional Hospital:* Baber Z, Thompson M; *Sioux Valley Hospital:* Solberg L, Fischer N; *H.C.A. Plano:* Woolbert S, Kistler N; *St. Elizabeth Hospital:* Lombardo T, Long M; *Good Shepherd Med.*

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