

CARDIAC-SPECIFIC TROPONIN I LEVELS TO PREDICT THE RISK OF MORTALITY IN PATIENTS WITH ACUTE CORONARY SYNDROMES

ELLIOTT M. ANTMAN, M.D., MILENKO J. TANASIJEVIC, M.D., BRUCE THOMPSON, PH.D., MARK SCHAFTMAN, M.S., CAROLYN H. MCCABE, B.S., CHRISTOPHER P. CANNON, M.D., GEORGE A. FISCHER, PH.D., ANTHONY Y. FUNG, M.B., B.S., CHRISTOPHER THOMPSON, M.D., DONALD WYBENGA, M.D., AND EUGENE BRAUNWALD, M.D.

ABSTRACT

Background In patients with acute coronary syndromes, it is desirable to identify a sensitive serum marker that is closely related to the degree of myocardial damage, provides prognostic information, and can be measured rapidly. We studied the prognostic value of cardiac troponin I levels in patients with unstable angina or non-Q-wave myocardial infarction.

Methods In a multicenter study, blood specimens from 1404 symptomatic patients were analyzed for cardiac troponin I, a serum marker not detected in the blood of healthy persons. The relation between mortality at 42 days and the level of cardiac troponin I in the specimen obtained on enrollment was determined both before and after adjustment for base-line characteristics.

Results The mortality rate at 42 days was significantly higher in the 573 patients with cardiac troponin I levels of at least 0.4 ng per milliliter (21 deaths, or 3.7 percent) than in the 831 patients with cardiac troponin I levels below 0.4 ng per milliliter (8 deaths, or 1.0 percent; $P < 0.001$). There were statistically significant increases in mortality with increasing levels of cardiac troponin I ($P < 0.001$). Each increase of 1 ng per milliliter in the cardiac troponin I level was associated with a significant increase ($P = 0.03$) in the risk ratio for death after adjustment for the base-line characteristics that were independently predictive of mortality (ST-segment depression and age ≥ 65 years).

Conclusions In patients with acute coronary syndromes, cardiac troponin I levels provide useful prognostic information and permit the early identification of patients with an increased risk of death. (N Engl J Med 1996;335:1342-9.)

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IN patients with chest pain at rest but no ST-segment elevation on the electrocardiogram, the diagnoses of unstable angina and non-Q-wave myocardial infarction are usually considered together because they cannot be distinguished clinically or angiographically.¹⁻⁴ The discrimination between these conditions is usually made by testing for elevated levels of a serum cardiac marker that indicates myocardial necrosis when non-Q-wave myocardial infarction is present.⁵ The extent of myocardial necrosis is an important determinant of the risk of death.^{6,7} It is therefore desirable to identify a serum

marker whose release bears a close relation to the degree of myocardial damage. Such a marker should be more sensitive than current markers, should provide prognostic information, and should be measurable in a time frame that permits treatment to minimize further necrosis.^{5,8}

Since the conventional serum cardiac marker, creatine kinase, and its MB isoenzyme (CK-MB) lack sufficient sensitivity and specificity, there is a need for more sensitive and cardiac-specific markers of myocardial necrosis.⁹⁻¹¹ Troponin I, one of the subunits of the troponin regulatory complex, binds to actin and inhibits interactions between actin and myosin. It is encoded by three different genes that are expressed to different degrees in different types of muscle.¹²⁻¹⁴ Cardiac troponin I is not expressed in human skeletal muscle during fetal development, after trauma to skeletal muscle, or during the regeneration of skeletal muscle.¹⁶ Unlike CK-MB, cardiac troponin I is highly specific for myocardial tissue,¹⁷ is not detectable in the blood of healthy persons, shows a greater proportional increase above the upper limit of the reference interval in patients with myocardial infarction,^{18,19} and may remain elevated for 7 to 10 days after an episode of myocardial necrosis.⁵

Given these features of cardiac troponin I as a marker of myocardial necrosis, we designed the present study to evaluate the potential prognostic value of this marker in patients with unstable angina or non-Q-wave myocardial infarction. The data base we used was that of the Thrombolysis in Myocardial Ischemia Phase IIIB (TIMI IIIB) trial.²⁰

METHODS

Study Patients

The TIMI IIIB trial, a prospective, randomized, multicenter study of patients with unstable angina or non-Q-wave myocardial infarction, was conducted in the United States and Canada from

From the Department of Medicine (E.M.A., C.H.M., C.P.C., E.B.) and the Clinical Laboratories (M.J.T., G.A.F., D.W.), Brigham and Women's Hospital, Boston; the Maryland Medical Research Institute, Baltimore (B.T., M.S.); and the University of British Columbia, Vancouver (A.Y.F., C.T.). Address reprint requests to Dr. Antman at the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

October 1989 through June 1992. It used a two-by-two factorial design to compare tissue plasminogen activator with placebo (in a double-blind analysis) and to compare an early, invasive management strategy with an early, conservative strategy.²⁰ All the patients received intravenous heparin and aspirin and other standard medical therapy.

The study patients were from 21 to 76 years of age, had episodes of pain at rest that were presumed to be ischemic in origin and had lasted for at least 5 minutes (but less than 6 hours) within the preceding 24 hours, and had documented evidence of coronary artery disease. Patients were excluded from the study if left bundle-branch block was noted on presentation, a documented myocardial infarction had occurred within the previous 21 days, a treatable cause of angina was present, thrombolytic therapy had been administered within the previous 72 hours, or angioplasty had been performed in the previous 6 months. Patients were considered to have unstable angina or non-Q-wave myocardial infarction on the basis of serial electrocardiograms and determinations of creatine kinase or CK-MB obtained locally at each enrolling center. A non-Q-wave myocardial infarction was considered to have been present at the time of randomization if enzyme elevations were noted at the enrolling site (a CK-MB value in excess of the normal value or, when no CK-MB value was available, a total creatine kinase value more than twice the normal value) at entry into the study or at any time up to 12 hours thereafter.

Blood Specimens

For 1404 of the 1473 patients enrolled in the main TIMI IIIb trial, plasma specimens were available from the time of enrollment. Because it may take several hours from the onset of myocardial necrosis for cardiac troponin I to be detectable in the blood,²¹ we studied the specimens obtained at enrollment from the entire cohort of 1404 patients, as well as from the subgroup of 845 patients who presented at least six hours after the onset of the episode of chest pain qualifying them for the study.

Measurement of Cardiac Troponin I

The blood specimens analyzed in the current study were originally obtained in the main trial to measure various markers of activity of the coagulation system. They were therefore collected in tubes containing aprotinin (200 kallikrein inhibitory units per milliliter of blood), 4.5 mM EDTA, and 40 μ M D-phenylalanyl-L-prolyl-L-arginine (SCAT-I tubes, Haematologic Technologies, Essex Junction, Vt.). After centrifugation at each site, the plasma samples were stored locally at 4°C and then mailed on dry ice to the Hematology Core Laboratory, where they were stored at -70°C.

Before the current study, the specimens were subjected to a single cycle of freezing and thawing (for hematologic analyses), after which they were refrozen and stored at -70°C until their shipment in 1995 to the Cardiac Serum Marker Core Laboratory at the Clinical Chemistry Laboratory of Brigham and Women's Hospital in Boston. Studies have shown that in serum specimens with cardiac troponin I levels between 4.2 and 20.0 ng per milliliter, measurements of cardiac troponin I remain stable, without evidence of either time- or concentration-dependent deterioration, for up to 16 months when they are stored at -70°C (Bauer R, Dade International, Miami: personal communication).

Cardiac troponin I was measured by the Stratus II fluorometric enzyme immunoassay (Dade) for cardiac troponin I by technologists unaware of the clinical data. This assay uses two monoclonal antibodies that recognize two different epitopes on the cardiac troponin I molecule.²¹ No cross-reactivity is seen with troponin I found in human skeletal muscle.²¹ In serum specimens from healthy persons without evidence of cardiac disease, the cardiac troponin I concentration is below the minimal concentration detectable by the assay (i.e., the smallest concentration that can be distinguished from zero), or 0.35 ng of cardiac troponin I per milliliter (Bauer R: personal communication). The within-run coefficient of variation around the discriminator value is 13.3 percent, and the between-run coefficient of variation is 16.0 percent.

Therefore, for the purposes of this study, we chose a cutoff value of 0.4 ng per milliliter as the minimal detectable concentration of cardiac troponin I. All the measured levels of cardiac troponin I that fell below this cutoff value were collectively expressed as less than 0.4 ng per milliliter.

Measurement of Creatine Kinase and CK-MB

The plasma specimens that were analyzed for cardiac troponin I were also studied for CK-MB in the Cardiac Serum Marker Core Laboratory by a mass assay to permit the consistent comparison with cardiac troponin I levels in a single reference laboratory. The mass assay for CK-MB, using monoclonal antibodies, was performed with the Stratus instrument (Dade).

Statistical Analysis

The results of the cardiac troponin I and CK-MB assays were merged with the data base of the main study at the Maryland Medical Research Institute, where the statistical analyses were performed. With regard to base-line characteristics, patients with cardiac troponin I levels of at least 0.4 ng per milliliter were compared with patients who had lower levels by Student's unpaired t-test in the case of continuous variables and by the chi-square test in the case of dichotomous variables. The relation between mortality at 42 days and the presence or absence of at least 0.4 ng of cardiac troponin I per milliliter at enrollment was analyzed by constructing contingency tables. Multivariate analysis of predictors of the risk of death was performed with Cox proportional-hazard regression models that included terms for cardiac troponin I and CK-MB (as measured in the core laboratory). The Cox models were used to estimate the risk ratio for mortality at 42 days that was associated with each increase of 1 ng per milliliter in the level of cardiac troponin I. The statistical comparisons were two-tailed, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Base-Line Characteristics

Only patients who were enrolled in the original study after meeting its criteria for inclusion and from whom plasma specimens were available were included in the analysis. Of 1404 such patients, 573 (41 percent) had cardiac troponin I levels of at least 0.4 ng per milliliter at the time of enrollment, and 831 (59 percent) had levels below 0.4 ng per milliliter. The base-line characteristics of these two groups of patients are compared in Table 1. Patients with at least 0.4 ng of cardiac troponin I per milliliter at enrollment were less likely to have a history of angina, hypertension, or myocardial infarction; to have a prior coronary angiogram showing at least one epicardial vessel with 70 percent or more stenosis; or to have received nitrates, beta-blockers, calcium antagonists, or aspirin before the qualifying episode of ischemic discomfort. However, they had qualifying episodes of pain that lasted significantly longer than those of the patients whose cardiac troponin I levels were below 0.4 ng per milliliter at enrollment (2.3 vs. 1.6 hours, $P=0.001$), and they were significantly more likely to present with ST-segment deviation (either depression or transient elevation).

The angiographic findings in 1150 patients who underwent coronary arteriography are shown in Table 2. There were no significant differences between

TABLE 1. SELECTED BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.

CHARACTERISTIC	ALL PATIENTS (N = 1404)	CARDIAC TROPONIN I		P VALUE
		≥0.4 ng/ml (N = 573)	<0.4 ng/ml (N = 831)	
Mean age (yr)	58.9	59.3	58.6	0.17
Male sex (%)	67	69	65	0.16
White race (%)	80	79	80	0.68
Current smoker (%)	38	41	35	0.03
Medical history (%)				
Angina	86	81	89	<0.001
Hypertension	42	38	45	0.01
Myocardial infarction	40	31	47	<0.001
Angiogram showing stenosis	33	22	40	<0.001
Drugs used in week before randomization (% of patients)				
Nitrates	47	42	50	0.002
Beta-blockers	34	30	36	0.014
Calcium antagonists	43	35	48	<0.001
Aspirin <24 hr before qualifying event	48	43	51	0.002
Continuous heparin infusion	12	13	12	0.35
Pain episodes at presentation				
No. in previous 24 hr	3.1	2.9	3.2	0.10
Mean duration of qualifying episode (hr)	1.9	2.3	1.6	0.001
Mean time from first pain to treatment (hr)	9.2	9.5	8.9	0.10
Electrocardiographic changes (% of patients)				
Transient ST-segment elevation	10	14	8	0.001
ST-segment depression	33	43	25	<0.001
T-wave changes	46	47	46	0.67
Any change	73	84	66	<0.001

TABLE 2. ANGIOGRAPHIC FINDINGS IN 1150 STUDY PATIENTS.

VARIABLE	ALL PATIENTS (N = 1150)	CARDIAC TROPONIN I		P VALUE
		≥0.4 ng/ml (N = 493)	<0.4 ng/ml (N = 657)	
		percentage of patients		
No. of vessels totally occluded*				0.07
0	68	65	71	
1	26	29	23	
2	6	6	6	
3	0.5	0.8	0.3	
Thrombus grade of culprit segment†				0.13
0	46	42	50	
1	38	39	37	
2	7	9	5	
3	5	5	5	
4	4	5	3	

*Because of rounding, percentages do not all total 100.

†Thrombus grades are as described by the TIMI IIIA investigators.²²

patients with cardiac troponin I levels of 0.4 ng per milliliter or higher and those with lower levels.

Classification of the Qualifying Episode of Ischemic Discomfort

On the basis of the CK-MB values measured at the enrolling centers in the specimens obtained at base line or within 12 hours after enrollment, the presenting episodes were classified as unstable angina in 948 patients (68 percent) and non-Q-wave myocardial infarction in 453 patients (32 percent) (Table 3). In 3 of the 1404 patients in whom cardiac troponin I was measured, CK-MB data from the enrolling sites were not available. Thus, data from a total of 1401 patients were used to compare CK-MB measurements at the enrolling site with cardiac troponin I measurements at the core laboratory. The diagnosis of non-Q-wave myocardial infarction or unstable angina was only moderately correlated with the presence or absence of a cardiac troponin I level of at least 0.4 ng per milliliter measured subsequently (Spearman rho, 0.465). Among the 948 patients without CK-MB elevations at enrollment or within 12 hours thereafter, 238 (25 percent) had cardiac troponin I levels of at least 0.4 ng per milliliter at enrollment, whereas among the 453 with such elevations, 335 (74 percent) had cardiac troponin I levels of at least 0.4 ng per milliliter at enrollment.

TABLE 3. CLASSIFICATION OF THE STUDY PATIENTS, AS DETERMINED BY MEASURING CK-MB AND CARDIAC TROPONIN I.

CARDIAC TROPONIN I AT ENROLLMENT	CK-MB INCREASE*		ALL PATIENTS
	YES	NO	
	no. of patients		
≥0.4 ng/ml	335	238	573
<0.4 ng/ml	118	710	828
All patients	453	948	1401
Spearman rho (±SE), 0.465±0.024			

*Patients with an increase in CK-MB were those in whom the CK-MB level measured at the enrolling site exceeded the normal value at base line or within 12 hours after enrollment.

The cardiac troponin I values obtained at enrollment in the patients with diagnoses of non-Q-wave myocardial infarction or unstable angina are shown in Figure 1. As compared with the patients without CK-MB elevations measured at the enrolling hospitals, the patients with elevated CK-MB levels had higher cardiac troponin I values; in 47 percent of the latter, these values were above 2.0 ng per milliliter.

Mortality at 42 Days

Among the 1404 patients with cardiac troponin I measurements, 29 (2.1 percent) died by day 42 after study enrollment. There were 21 deaths among the

573 patients with troponin I levels of at least 0.4 ng per milliliter and 8 deaths among the 831 patients with troponin I levels below 0.4 ng per milliliter. The relation between the presence of a cardiac troponin I measurement of at least 0.4 ng per milliliter at enrollment and mortality by 42 days is shown in Figure 2 for several groups of patients according to the number of hours since the onset of chest pain and the presence of elevated CK-MB measurements. In all the analyses shown, the mortality rate was consistently higher among the patients with cardiac troponin I levels of at least 0.4 ng per milliliter (mortality, 2.4 to 4.0 percent) than among those with values below that level (mortality, 0.5 to 1.7 percent). The difference in the mortality rate between the patients with levels of cardiac-specific troponin I of at least 0.4 ng per milliliter and those with lower levels was greatest for patients who presented at least six hours after the onset of their chest pain, as evidenced by the much higher risk ratio for mortality in that subgroup.

The correlation between mortality at 42 days (without adjustment for base-line characteristics) and the cardiac troponin I level in the plasma specimen obtained at enrollment is shown in Figure 3. There were statistically significant increases in mortality with increasing levels of cardiac troponin I (P<0.001 by the chi-square test for trend). The risk ratio for mortality in the patients with troponin I levels of 0.4 ng per milliliter or more (as compared with those with lower levels) rose progressively with increasing troponin I levels (Fig. 3).

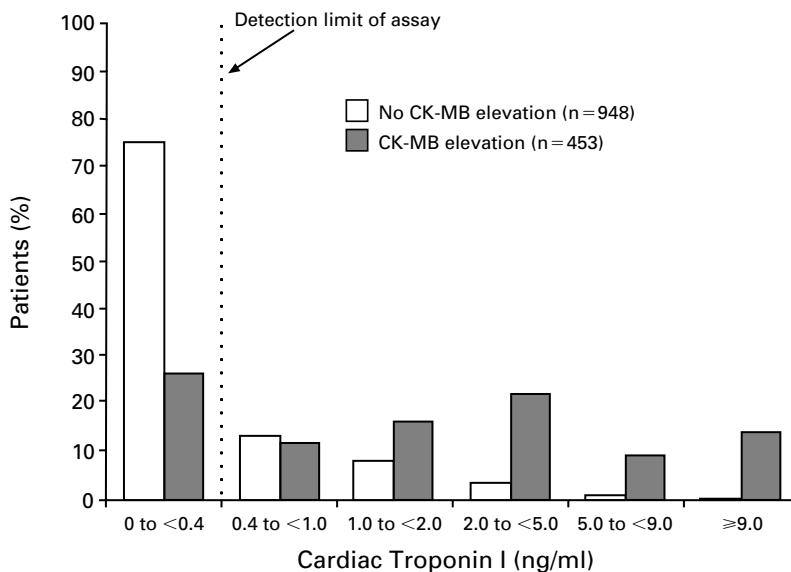


Figure 1. Cardiac Troponin I Measurements at Base Line in 1401 Study Patients.

The cardiac troponin I levels at enrollment are shown for patients with and those without abnormal elevations in CK-MB, as measured at the enrolling centers. The distribution of cardiac troponin I levels was shifted toward higher values in the patients with elevated levels of CK-MB.

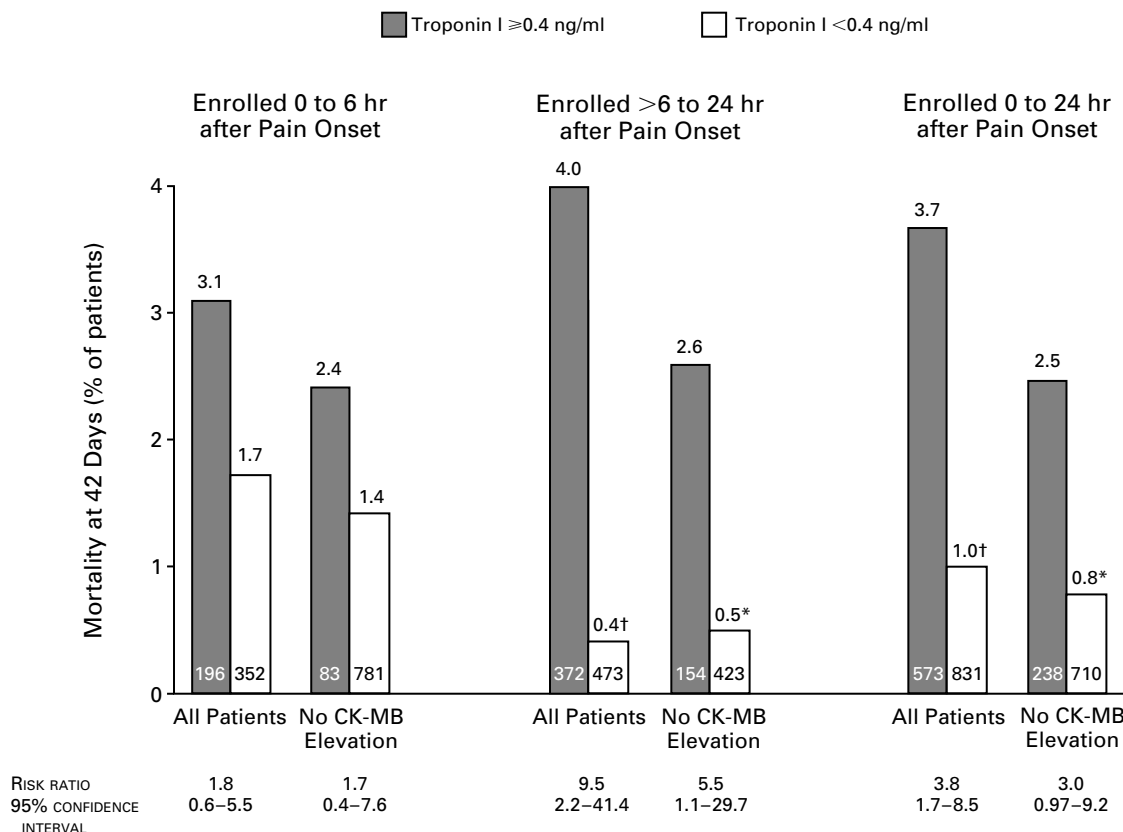


Figure 2. Mortality Rates at 42 Days According to the Time from the Onset of Pain to Study Enrollment and the Base-Line Cardiac Troponin I Levels.

Mortality rates (without adjustment for base-line characteristics) are shown for the study patients according to the time from the onset of chest pain to enrollment (0 to 6, >6 to 24, and 0 to 24 hours). For each subgroup the findings are shown for all patients and those in whom no elevation of CK-MB was found at the enrolling center. The numbers at the bottom of each bar are the numbers of patients in each category, and the numbers above the bars are percentages. For each comparison, the mortality rate was higher in the patients with cardiac troponin I levels of at least 0.4 ng per milliliter. Risk ratios and 95 percent confidence intervals for mortality are shown at the bottom of the figure for the group with cardiac troponin I levels of at least 0.4 ng per milliliter as compared with the group with lower levels. The asterisks indicate $P < 0.05$, and the daggers $P < 0.001$.

Multivariate Models of Mortality

Under the assumption that there was an exponential relation between the cardiac troponin I concentration and mortality, we evaluated the effect of each increase of 1 ng per milliliter in cardiac troponin I on the risk ratio for mortality by day 42, after adjusting for the base-line variables in Table 1 that were found to be statistically significant independent predictors of death. As Table 4 shows, in the overall study population of 1404 patients there was a significant increase in the risk ratio for mortality for each increase of 1 ng per milliliter in cardiac troponin I ($P = 0.03$). Among the 845 patients presenting more than six hours after the onset of chest pain, there was an even stronger correlation between cardiac troponin I and the risk of mortality. Again, for each increase of 1 ng per milliliter in cardiac troponin I, the risk ratio for mortality increased signifi-

cantly ($P = 0.02$), an even more significant increase than was found for an age of 65 years or older (chi-square, 5.47 vs. 1.37).

Because of possible variation in the measurement of CK-MB among the hospital laboratories at the centers where the patients were enrolled in the study, CK-MB was measured again in the Cardiac Serum Marker Core Laboratory by a mass assay. For each increase of 1 ng per milliliter in CK-MB, the risk ratio for mortality increased significantly in both the overall cohort of 1404 patients and the cohort of 845 patients who presented more than six hours after the onset of symptoms (risk ratio in both cohorts, 1.01; $P = 0.03$) when we adjusted the analysis for the base-line characteristics shown in Table 4. However, among the 838 patients with base-line CK-MB levels below the upper limit of the reference interval (5 ng per milliliter), as detected by the mass

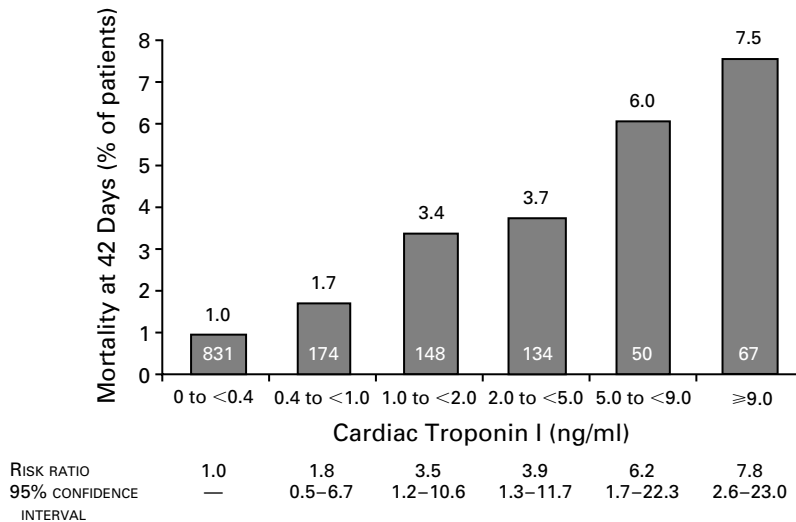


Figure 3. Mortality Rates at 42 Days According to the Level of Cardiac Troponin I Measured at Enrollment. Mortality rates at 42 days (without adjustment for base-line characteristics) are shown for ranges of cardiac troponin I levels measured at base line. The numbers at the bottom of each bar are the numbers of patients with cardiac troponin I levels in each range, and the numbers above the bars are percentages. $P < 0.001$ for the increase in the mortality rate (and the risk ratio for mortality) with increasing levels of cardiac troponin I at enrollment.

assay, those with simultaneously measured cardiac troponin I levels of at least 0.4 ng per milliliter had a higher mortality rate than those with cardiac troponin I levels below 0.4 ng per milliliter (2.6 percent vs. 0.4 percent; risk ratio, 3.1 [95 percent confidence interval, 0.8 to 12.2]).

DISCUSSION

The development of unstable angina or non-Q-wave myocardial infarction indicates that a patient has entered a phase of ischemic heart disease associated with an increased risk of death, one intermediate between the risk in chronic stable exertional angina and the risk in Q-wave myocardial infarction. Postmortem examinations in patients who die suddenly of ischemic causes after presenting with unstable angina often reveal layers of thrombus material of varying ages in the culprit coronary vessel and evidence of the embolic occlusion of small intramyocardial arteries with microinfarcts.^{23,24} It is therefore of interest to determine whether the detection of even minimally elevated levels of serum markers of cardiac necrosis correlates with an increased risk of mortality.

Identifying Patients at Increased Risk of Mortality

Our study indicates that the detection of the highly specific marker cardiac troponin I¹⁷ in blood is an independent risk factor that identifies patients presenting with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death. The prognostic value of cardiac troponin I was greater among patients who presented more than six

hours after the onset of chest discomfort. The likely explanation for the potential of cardiac troponin I to indicate an adverse prognosis is the high sensitivity and specificity of this marker in identifying patients with recent episodes of myocardial necrosis. The patients in this study who had cardiac troponin I levels of at least 0.4 ng per milliliter were less likely than patients with lower levels of the marker to be receiving antianginal medications before enrollment, they had significantly longer qualifying episodes of chest pain, and they were significantly more likely to present with ST-segment deviation on the electrocar-

TABLE 4. RISK RATIOS FOR MORTALITY AFTER ADJUSTMENT FOR BASE-LINE VARIABLES.

VARIABLE	PARAMETER ESTIMATE	RISK RATIO (95% CONFIDENCE INTERVAL)	CHI-SQUARE	P VALUE
All patients (n = 1404)				
ST-segment depression at entry	1.53	4.63 (2.02–10.59)	13.15	<0.001
Age ≥65 yr	0.85	2.34 (1.11–4.96)	4.96	0.026
Troponin I (increase of 1 ng/ml)	0.03	1.03 (1.00–1.05)	4.73	0.030
Patients presenting >6 hr after onset of pain (n = 845)				
ST-segment depression at entry	1.55	4.71 (1.62–13.71)	8.05	0.005
Age ≥65 yr	0.58	1.79 (0.68–4.75)	1.37	0.24
Troponin I (increase of 1 ng/ml)	0.03	1.03 (1.01–1.06)	5.47	0.02

diogram. It is also less likely that they had collateral vessels to the ischemic zone, because their incidence of prior angina was lower and their angiograms were less likely to show substantial stenosis.

The prognostic information conveyed by elevated levels of cardiac troponin I at presentation was evident even in a group of patients with a low overall mortality rate (2.1 percent at 42 days). The prognostic potential of cardiac troponin I persisted even after adjustment for independent base-line variables known to be significantly associated with an increased risk of cardiac events, such as an age of 65 years or older and ST-segment depression on the electrocardiogram.

Furthermore, levels of cardiac troponin I of at least 0.4 ng per milliliter in a single plasma specimen at presentation appear to be associated with an increased risk of mortality even in patients whose CK-MB measurements are not considered abnormally elevated. This is probably due to a reduced sensitivity and specificity of CK-MB in detecting microinfarction.²⁵⁻²⁷ Since CK-MB is found in the skeletal muscle and blood of healthy persons, diagnostic cut-off values for myocardial infarction are typically set above the upper limit of the reference range for the assay. Because cardiac troponin I does not normally circulate in the blood and is 13 times more abundant in the myocardium than CK-MB on a weight basis,¹⁹ the signal-to-noise ratio associated with cardiac troponin I is much more favorable for the detection of minor amounts of cardiac necrosis. The interpretation of minimally elevated CK-MB levels is also confounded by coexisting illnesses that may produce hypoperfusion and injury of skeletal muscles, with expression of the B subunit of creatine kinase.^{19,26,28}

Comparison with Previous Studies

Previous investigators have suggested that the measurement of cardiac troponin T is useful in predicting risk in patients with unstable angina and that it appears to be superior to CK-MB in its predictive potential.²⁹⁻³¹ It is noteworthy that previous studies of troponin T in patients with unstable angina used blood specimens obtained serially 24 to 48 hours after presentation in order to screen for elevated levels of that serum cardiac marker in the evaluation of risk. Our study not only provides data on cardiac troponin I, another cardiac-specific marker measurable in blood, but also emphasizes the use of a single measurement at presentation and describes the quantitative relation between measurements of cardiac troponin I and the risk of mortality.

Clinical Implications

In the context of other reports documenting the usefulness of cardiac troponin I for the diagnosis of myocardial infarction in patients with ST-segment elevation, Q waves, or both, our findings extend

the observations on the benefits of measuring this marker to the entire range of acute coronary syndromes.^{5,17-19} A cardiac troponin I level of at least 0.4 ng per milliliter when a patient with unstable angina is first evaluated predicts an increased risk of short-term mortality, probably because it permits the diagnosis of non-Q-wave myocardial infarction that one might otherwise have overlooked by sampling only for CK-MB. With progressively higher levels of cardiac troponin I, the risk of mortality increases, presumably because the amount of myocardial necrosis increases. Measuring cardiac troponin I is therefore useful in evaluating patients with unstable angina. Elevated levels of this marker provide prognostic information beyond that supplied by the demographic characteristics of the patient or the electrocardiogram at presentation. This permits the early identification of patients at increased risk of death.

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