

## EMERGENCY ROOM TRIAGE OF PATIENTS WITH ACUTE CHEST PAIN BY MEANS OF RAPID TESTING FOR CARDIAC TROPONIN T OR TROPONIN I

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### ABSTRACT

**Background** Evaluation of patients with acute chest pain in emergency rooms is time-consuming and expensive, and it often results in uncertain diagnoses. We prospectively investigated the usefulness of bedside tests for the detection of cardiac troponin T and troponin I in the evaluation of patients with acute chest pain.

**Methods** In 773 consecutive patients who had had acute chest pain for less than 12 hours without ST-segment elevation on their electrocardiograms, troponin T and troponin I status (positive or negative) was determined at least twice by sensitive, qualitative bedside tests based on the use of specific monoclonal antibodies. Testing was performed on arrival and four or more hours later so that one sample was taken at least six hours after the onset of pain. The troponin T results were made available to the treating physicians.

**Results** Troponin T tests were positive in 123 patients (16 percent), and troponin I tests were positive in 171 patients (22 percent). Among 47 patients with evolving myocardial infarction, troponin T tests were positive in 44 (94 percent) and troponin I tests were positive in all 47. Among 315 patients with unstable angina, troponin T tests were positive in 70 patients (22 percent), and troponin I tests were positive in 114 patients (36 percent). During 30 days of follow-up, there were 20 deaths and 14 nonfatal myocardial infarctions. Troponin T and troponin I proved to be strong, independent predictors of cardiac events. The event rates in patients with negative tests were only 1.1 percent for troponin T and 0.3 percent for troponin I.

**Conclusions** Bedside tests for cardiac-specific troponins are highly sensitive for the early detection of myocardial-cell injury in acute coronary syndromes. Negative test results are associated with low risk and allow rapid and safe discharge of patients with an episode of acute chest pain from the emergency room. (N Engl J Med 1997;337:1648-53.)

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**T**HE assessment of patients with acute chest pain in the emergency room is a time-consuming diagnostic challenge. If the electrocardiogram reveals ST-segment elevation, the probability of acute myocardial infarction is high, and further management is well established. However, the sensitivity of the electrocardiogram may be as low as 50 percent,<sup>1-4</sup> and up to 4 percent of patients with evolving myocardial infarctions are

sent home inappropriately.<sup>5-8</sup> Electrocardiographic changes in patients with unstable angina are even less specific.<sup>9</sup> When the electrocardiogram fails to provide conclusive diagnostic information, serial measurements of creatine kinase and its MB isoenzyme are widely used for decision making. This traditional biochemical gold standard for myocardial-cell injury has limited prognostic power, however.<sup>10,11</sup> Accordingly, many patients are unnecessarily hospitalized and occupy expensive beds in coronary care units.

Recently, it was shown that measurements of the cardiac-specific contractile proteins troponin T and troponin I are superior to conventional measurement of creatine kinase MB for the detection of minor myocardial injury<sup>12,13</sup> and are valid predictors of adverse events in patients with acute coronary syndromes.<sup>10,11,14-18</sup> However, the use of troponin measurements in the emergency room is impaired by the limited availability of refined analytic techniques and by the long turnover times. Newly developed bedside test kits that provide a qualitative result (positive or negative) within 15 to 20 minutes could represent a major advance in decision making in emergency rooms.<sup>19-21</sup> In this prospective study, we investigated the diagnostic and prognostic value of rapid bedside troponin T and troponin I testing for early triage in the emergency room.

### METHODS

#### Patients

The study population consisted of 773 patients (317 women and 456 men; mean [ $\pm$ SD] age,  $62 \pm 11$  years) who were recruited from among 870 consecutive eligible patients of all ages presenting between June 1, 1994, and March 31, 1996, to the emergency room of the University Hospital in Hamburg, Germany. To be eligible, the patients had to have acute anterior, precordial, or left-sided chest pain lasting 12 hours or less that was unexplained by obvious local trauma or abnormalities on chest films. Patients with ST-segment elevations ( $n=97$ ) or with documented acute myocardial infarctions during the preceding two weeks were excluded. The mean duration of the qualifying episode of chest pain was  $5.0 \pm 3.2$  hours (less than 2 hours in 21 patients); the chest pain was continuous in 32.8 percent of patients and intermittent in 67.2 percent.

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### Study Protocol

The study protocol was approved by the ethics committee of the Hamburg Medical Board. After oral informed consent had been obtained from the patient, 10 ml of blood was collected within 15 minutes after arrival for measurement of troponin T and I, and each patient underwent 12-lead electrocardiography. These tests were repeated four hours later. For patients who presented less than two hours after the onset of chest pain, these tests were performed for a third time six hours after the onset of pain, so that tests were performed in all patients at least six hours after the onset of pain.

The rapid troponin T test was routinely performed in the emergency room by a trained assistant, and the result was provided to the treating physicians. The decision about the treatment of each patient was left to the physician on duty. The rapid troponin I test was performed on heparin-treated plasma in a separate laboratory by a trained assistant blinded to the patient's data. Serum samples for quantitative measurements and rapid qualitative measurements of troponin I were kept at room temperature for 20 minutes to allow clotting, then centrifuged at 3000 rpm for 10 minutes and stored at  $-80^{\circ}\text{C}$ .

Clinical data from the emergency room evaluation, including the history, results of the physical examination, results of cardiac-enzyme tests, and interpretation of the electrocardiograms, were recorded as part of a detailed protocol by the physicians in the emergency room.

Patients were followed until discharge from the hospital and for 30 days thereafter by telephone or questionnaire to record cardiac events (complete data were obtained for 97.2 percent of patients). Patients admitted to the hospital stayed for a mean of  $4.2 \pm 2.5$  days. The study end points were death from cardiac causes and nonfatal acute myocardial infarction during hospitalization (excluding the first 24 hours) or after discharge from the hospital, as shown by hospital records. Death from myocardial infarction was counted only as a death from cardiac causes, not as a myocardial infarction.

### Electrocardiographic Criteria

On the basis of the interpretation by the physician on duty, each patient was placed into one of the following electrocardiographic categories: ST-segment elevation  $\geq 0.20$  mV, suggestive of acute myocardial infarction (exclusion criterion); ST-segment depression  $\geq 0.15$  mV, with or without T-wave inversion; T-wave inversion only; nondiagnostic electrocardiogram (paced rhythm, bundle-branch block); and normal electrocardiogram. All electrocardiograms were reevaluated by an independent observer.

### Definitions

Unstable angina was defined as type IIIB in the Braunwald classification.<sup>22</sup> An acute myocardial infarction in a patient without ST-segment elevation was considered to be present when the total creatine kinase activity within 24 hours after admission was more than twice the upper limit of normal associated with elevated creatine kinase MB.

### Analytic Techniques

For qualitative determination of serum cardiac troponin T, we used a whole-blood rapid-assay device (Boehringer Mannheim, Mannheim, Germany).<sup>23</sup> In 150  $\mu\text{l}$  of whole blood treated with heparin, the cellular fraction was separated from the plasma with a glass-fiber fleece. In this assay, immunocomplexes are formed by a cardiac-specific gold-labeled monoclonal antibody and a biotinylated monoclonal antibody binding to a different epitope of troponin T. The immunocomplexes are immobilized by means of streptavidin technology in the reading zone, indicating by a color line the presence of troponin T in the sample at a concentration above the discriminator value of 0.18 ng per milliliter, within 20 minutes.<sup>19</sup>

The results were controlled quantitatively with a one-step en-

zyme immunoassay (ES 300, Boehringer Mannheim). The lower limit of detection was 0.02 ng per milliliter, and a discriminator value of 0.1 ng per milliliter was used.<sup>17</sup> The interassay coefficients of variation were 9.7 percent at 0.35 ng per milliliter and 7.4 percent at 5.55 ng per milliliter.

The qualitative determination of serum cardiac troponin I was carried out by a rapid assay with chromatographic immunologic solid-phase technology (Spectral Diagnostics, Toronto).<sup>24</sup> This test requires two color-labeled mouse monoclonal antibodies and a biotinylated polyclonal goat capture antibody forming a sandwich complex with the troponin I molecule that adheres to streptavidin in the signal zone.<sup>21</sup> Enrichment of color-labeled antibodies binding to troponin I (discriminator value, 0.10 ng per milliliter) results in a color line within 15 minutes.

The results of the rapid troponin I assay were controlled quantitatively by the Access Analyzer (Sanofi Diagnostics-Pasteur, Marnes, France), which is based on chemiluminescence and magnetic particles.<sup>25,26</sup> The limit of detection of this test is 0.03 ng per milliliter, and values of 0.1 ng or more per milliliter were considered positive. The day-to-day coefficient of variation was 9.5 percent at 0.2 ng per milliliter and 4.6 percent at 2.4 ng per milliliter according to internal controls.

The correspondence between the results of the rapid bedside tests and the quantitative controls in 1479 samples was 94.8 percent for troponin T and 98.7 percent for troponin I. A negative bedside-test result in the presence of a quantitative result above the predefined cutoff point (false negative) was found for troponin T in one sample and for troponin I in five samples.

In all samples, the concentration of creatine kinase MB was determined with a Stratus II Analyzer (Dade, Miami) with a limit of detection of 0.4 ng per milliliter and a cutoff of 4.7 ng per milliliter.<sup>27</sup> The interassay coefficient of variation was 12.5 percent at 6 ng per milliliter and 6.3 percent at 35 ng per milliliter. The total creatine kinase activity was routinely measured at room temperature in the emergency room laboratory by a Hitachi 717 colorimeter (Boehringer Mannheim) with a cutoff point of 80 units per liter in men and 70 units per liter in women. All biochemical analyses were performed by technicians unaware of the patients' histories and the results of the rapid assays for troponin T.

### Statistical Analysis

All results for continuous variables are expressed as means  $\pm$  SD. The Mann-Whitney test was used to compare continuous variables between two subgroups. The P values for comparisons of categorical variables were generated by the chi-square test for proportions with appropriate degrees of freedom, and P values of less than 0.05 according to the two-sided McNemar test were considered to indicate statistical significance. The negative predictive value was calculated as the percentage of all negative test results observed that were true negative results. Stepwise logistic-regression analysis was used to adjust for the effects of possible confounding by clinical, electrocardiographic, and cardiac-marker differences on the rates of mortality and infarction during follow-up.<sup>28,29</sup> All variables in the model were dichotomous. Relative risk was expressed in terms of odds ratios with 95 percent confidence intervals. All calculations were done with SPSS 6.1 (SPSS, Chicago) or StatXact-3 (Cytel Software, Cambridge, Mass.).

## RESULTS

### Final Clinical Diagnoses

Of 773 consecutive patients without ST-segment elevation presenting to the emergency room with acute chest pain, 47 (6 percent) had a final diagnosis of acute myocardial infarction on the basis of routine measurements of creatine kinase activity within 24 hours after arrival. Among the other 726 patients, unstable angina was diagnosed in 315, sta-

ble angina in 121, pulmonary embolism in 12, acute heart failure in 15, and myocarditis in 5; 258 patients had no evidence of coronary heart disease.

A total of 487 patients (63 percent) were admitted to the hospital, including 224 (29 percent) admitted to the intensive care unit. All patients with acute myocardial infarction or unstable angina were admitted.

#### Troponin Results and Clinical Diagnoses

Of the 773 patients, 123 (16 percent) had at least one positive bedside-test result for troponin T, and 171 (22 percent) had at least one positive test for troponin I ( $P < 0.001$  by two-sided McNemar test). Patients with positive test results presented to the hospital earlier than patients with negative results (3.1 vs. 5.4 hours after the beginning of pain,  $P < 0.001$  by the Mann-Whitney test) and were younger (mean age, 57.6 vs. 62.5 years;  $P < 0.006$  by the Mann-Whitney test). On arrival, 71 patients (9 percent) had a positive troponin T result, and 109 patients (14 percent) had a positive troponin I result. In the second test, done approximately four hours later, 51 additional patients had a positive troponin T result and 61 additional patients had a positive troponin I result. In the third test, which was performed in the 21 patients with pain of less than two hours' duration on arrival, 1 additional patient had a positive troponin T result, and 1 had a positive troponin I result. Thus, among the patients who had at least one positive result for troponin, only 58 percent of those with a positive troponin T result and 64 percent of those with a positive troponin I result had a positive result when they were first tested on arrival at the emergency room.

Among 47 patients with acute myocardial infarction but without ST-segment elevation, 24 (51 percent) had a positive troponin T test on arrival, and 44 (94 percent) had a positive troponin T test four hours later. Thirty-one (66 percent) of these patients had a positive troponin I test on arrival, and all of them had a positive troponin I test four hours later. Creatine kinase MB was elevated in 25 of these patients (53 percent) on arrival and in 43 patients (91 percent) four hours later.

Among 315 patients with unstable angina, 70 (22 percent) had at least one positive troponin T test, and 114 (36 percent) had at least one positive troponin I test. Creatine kinase MB was elevated in only 16 (5 percent) of the patients with unstable angina in any test.

Among the other patients with at least one positive troponin T test, one had pulmonary embolism, one had cardiac failure, and one had suspected myocarditis. Among the other patients with at least one positive troponin I test, two had pulmonary embolism, five had cardiac failure, two had myocarditis, and one had unexplained chest pain. Seven patients

had a positive troponin T test but a negative troponin I test. In six of these patients, this result was associated with renal failure and is therefore regarded as a false positive result.

Creatine kinase MB was elevated in 27 patients who had no detectable troponins. In none of these patients could an acute myocardial ischemic event be confirmed during clinical follow-up.

#### Troponins and the Electrocardiogram

Electrocardiographic ST-T alterations other than ST-segment elevations were found in 355 patients (46 percent); 158 patients had ST-segment depressions, and 197 patients had T-wave inversions. In 87 patients (11 percent), the electrocardiogram was nondiagnostic (paced rhythm, bundle-branch block); 23 of these patients had myocardial infarctions. Among the other patients with myocardial infarctions, 8 had ST-segment depressions, 15 had T-wave inversions, and 1 had a normal electrocardiogram.

Among 158 patients with ST-segment depressions, 51 patients (32 percent) had at least one positive troponin T test, and 88 patients (56 percent) had at least one positive troponin I test. Among 197 patients with T-wave inversions, 12 patients (6 percent) had at least one positive troponin T test, and 9 patients (5 percent) had at least one positive troponin I test. Among 331 patients with normal electrocardiograms, 32 patients (10 percent) had at least one positive troponin T test, and 33 patients (10 percent) had at least one positive troponin I test. Among 87 patients with nondiagnostic electrocardiograms, 28 patients (32 percent) had at least one positive troponin T test, and 41 patients (47 percent) had at least one positive troponin I test.

#### Follow-up Events

All patients with a positive troponin T test were admitted to the hospital. Of the 286 patients who were not admitted, 7 patients had a positive troponin I test, as determined in a separate laboratory. Two of these patients had adverse events during follow-up (one death after 23 days and one nonfatal myocardial infarction after 5 days).

Cardiac events occurred in 34 patients during follow-up. Four additional deaths from noncardiac causes were not included in the evaluation. All 20 deaths included in the evaluation were related to cardiac disease or were sudden deaths; 11 of them occurred in the hospital (Table 1). Nine of the 14 myocardial infarctions occurred during the initial hospitalization.

Four of the 20 patients who died had negative results on all troponin T tests, and 1 had negative results on all troponin I tests. Three of the 14 patients who had myocardial infarctions had negative results on all troponin T tests, and 1 had negative results on all troponin I tests. The second test performed four

hours after arrival (or, for patients who presented less than two hours after the onset of pain, the third test performed six hours after the onset of pain) considerably increased the predictive value (Table 2). The total event rate was 1.1 percent in patients in whom all troponin T tests were negative and 0.3 percent in patients in whom all troponin I tests were negative ( $P < 0.001$  by the McNemar test). Thus, the negative predictive value was 98.9 percent for troponin T and 99.7 percent for troponin I. Only one patient with negative results on all troponin T tests had a cardiac event within two weeks after discharge (Fig. 1).

Table 3 shows event rates according to the electrocardiographic results and the results of the troponin tests. No cardiac event occurred in a patient with a normal electrocardiogram and a negative troponin I test.

Table 4 shows the relative value of serum markers and electrocardiographic results for the prediction of major cardiac events. After the electrocardiogram is forced into the logistic-regression model first, the independent prognostic value of troponin I and troponin T remains evident. If the results of tests for creatine kinase MB and troponins are available, the electrocardiogram provides no additional prognostic value.

## DISCUSSION

In recent years several studies have shown that detectable blood levels of cardiac-specific troponin T and troponin I in patients with acute coronary syndromes are associated with unfavorable outcomes.<sup>10,11,14-18</sup> In the present prospective study, these findings were extended to patients arriving at the emergency room with acute chest pain. The aim was to investigate how clinical decision making for patients with acute chest pain but without ST-segment elevation may be facilitated and improved. Accordingly, the troponin T test result obtained at the point of care in the emergency room was made available to the treating physicians.

When the troponin T bedside test was routinely used, no patient with myocardial infarction was inappropriately discharged. When patients were tested four hours after arrival (or six hours after the onset of pain for those who presented less than two hours after the onset of pain), 94 percent of patients with myocardial infarction and without ST-segment elevation had a positive test for troponin T, and 100 percent had a positive test for troponin I. However, the diagnostic specificity of these tests for myocardial infarction was low, since 22 percent of patients with unstable angina had a positive result for troponin T and 36 percent of them had a positive result for troponin I.

In patients with negative test results, the risk of major cardiac events during the 30-day follow-up period was very low. Only 1.1 percent of patients with negative troponin T results and 0.3 percent of pa-

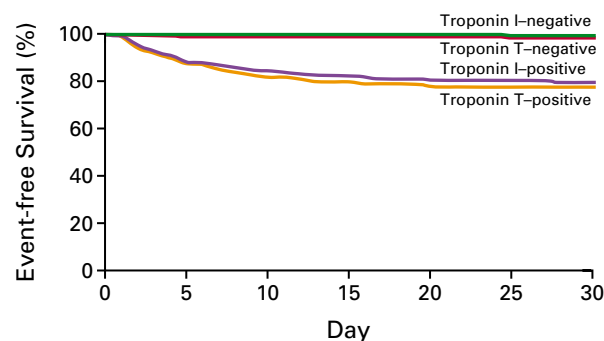
**TABLE 1.** NUMBERS OF DEATHS AND NONFATAL ACUTE MYOCARDIAL INFARCTIONS OCCURRING IN THE HOSPITAL AND WITHIN 30 DAYS AFTER DISCHARGE, ACCORDING TO TROPONIN STATUS.

EVENT	TROPONIN I— POSITIVE (N = 171)	TROPONIN I— NEGATIVE (N = 602)	TROPONIN T— POSITIVE (N = 123)	TROPONIN T— NEGATIVE (N = 650)
Death in hospital	11	0	9	2
Acute myocardial infarction in hospital	9	0	7	2
Death after discharge	8	1	7	2
Acute myocardial infarction after discharge	4	1	4	1
All events	32	2	27	7

**TABLE 2.** CARDIAC EVENTS AS PREDICTED BY ELEVATED SERUM MARKERS AND ELECTROCARDIOGRAPHIC ABNORMALITIES ON ARRIVAL AND FOUR HOURS LATER (OR AT LEAST SIX HOURS AFTER ONSET OF PAIN).

PREDICTOR	ON ARRIVAL		≥6 HR AFTER ONSET OF PAIN	
	NO. OF PATIENTS WITH POSITIVE RESULTS	NO. OF EVENTS (% OF EVENTS DETECTED)*	NO. OF PATIENTS WITH POSITIVE RESULTS	NO. OF EVENTS (% OF EVENTS DETECTED)*
Troponin T	79	15 (44)	123	27 (79)
Troponin I	109	19 (56)	171	32 (94)
Creatine kinase MB	60	10 (29)	86	12 (35)
ST-segment depression	138	11 (32)	158	14 (41)
T-wave inversion	194	4 (12)	197	4 (12)

\*The percentage of the 34 detected events that were predicted represents the sensitivity.



**Figure 1.** Survival without Cardiac Events (Death or Nonfatal Acute Myocardial Infarction) during 30 Days of Follow-up, according to Troponin T and Troponin I Status. Events that occurred during the initial 24 hours are excluded.

**TABLE 3.** CARDIAC EVENTS ACCORDING TO ELECTROCARDIOGRAPHIC FINDINGS AND TROPONIN STATUS.

ELECTROCARDIOGRAPHIC FINDING	NO. OF PATIENTS	NO. OF CARDIAC EVENTS	TROPONIN T-	TROPONIN T-	TROPONIN I-	TROPONIN I-
			POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
no. of events (% of patients in subgroup)						
ST-segment depression	158	14	11 (22)	3 (2.8)	13 (15)	1 (1.4)
T-wave inversion	197	4	3 (25)	1 (0.5)	3 (33)	1 (0.5)
Normal electrocardiogram	331	5	4 (12)	1 (0.3)	5 (15)	0
Nondiagnostic electrocardiogram	87	11	9 (32)	2 (3.4)	11 (27)	0
Total		34	27 (22)	7 (1.1)	32 (19)	2 (0.3)

**TABLE 4.** RELATIVE VALUE OF SERUM MARKERS AND ELECTROCARDIOGRAPHIC ABNORMALITIES AS PREDICTORS OF CARDIAC EVENTS AT 30 DAYS.

PREDICTOR	NO. OF PATIENTS	ODDS RATIO (95% CI)*	P VALUE
Troponin T†	123	25.8 (9.6–48.6)	<0.001
Troponin I†	171	61.4 (14.9–511.7)	<0.001
Creatine kinase MB†	40	3.5 (1.4–8.9)	0.008
ST-segment depression	158	2.9 (1.47–5.9)	0.003
T-wave inversion	197	0.4 (0.1–1.1)	0.07
Troponin T after ST-segment depression‡		20.0 (8.6–46.4)	<0.001
Troponin I after ST-segment depression‡		55.1 (14.2–467.3)	<0.001
Creatine kinase MB after ST-segment depression‡		3.4 (1.3–8.5)	0.01
Troponin T after creatine kinase MB		15.6 (6.5–37.5)	<0.001
Troponin I after creatine kinase MB		52.4 (12.8–285.6)	<0.001

\*CI denotes confidence interval.

†Values over the analytic cutoff points are as follows: troponin T,  $\geq 0.18$  ng per milliliter; troponin I,  $\geq 0.10$  ng per milliliter; creatine kinase MB,  $>4.7$  ng per milliliter.

‡Odds ratios are as calculated when the electrocardiographic data were forced into the model first.

tients with negative troponin I results had nonfatal myocardial infarctions or died. Only one patient with a negative troponin T result had a cardiac event within two weeks after discharge (Fig. 1). Because all patients with a positive troponin T result were admitted to the hospital, the event rate may have been lower than that with conventional decision making. However, the primary aim of this study was to demonstrate that two negative test results on admission and four hours later (or at least six hours from the onset of chest pain) allow safe early discharge.

Our experience shows that highly sensitive bedside tests for troponin T and troponin I result in

more accurate diagnoses than do previous, more time-consuming methods<sup>30-33</sup> and allow safer and more rapid decision making for most patients with acute chest pain. A high-risk acute coronary syndrome is very unlikely in a patient with a negative test result. All patients with at least one positive test result should be admitted to the hospital and will require further evaluation, including coronary angiography in most cases. A single test at the time of arrival is inadequate for clinical decision making.<sup>34,35</sup>

Previous studies demonstrated that increasing troponin levels were correlated with a higher risk of future adverse events.<sup>11,14,18</sup> However, for routine clinical practice, the qualitative results obtained with the bedside tests seem to be sufficient. The analytic reliability of the tests was confirmed in our study by quantitative controls. The slightly higher sensitivity of the troponin I test as compared with the troponin T test may be related to different release kinetics and different limits of detection of the versions of the test that are currently available.

The finding of false positive results for troponin T, but not troponin I, in patients with renal failure may, however, represent a true difference between the two tests.<sup>36</sup> Both test systems are superior to creatine kinase MB measurements with respect to sensitivity and specificity, as was previously shown for the quantitative assays.<sup>13,14</sup>

These new biochemical tests should not be considered substitutes for the electrocardiogram, which remains the unquestioned standard for the diagnosis of acute myocardial infarction and the initiation of thrombolytic therapy.<sup>37</sup> However, in patients without ST-segment elevation and in patients with unstable angina, thrombolysis is of no established benefit.<sup>33,37</sup> Troponin measurements allow the detection of minor myocardial injuries that are most likely due to thrombotic microembolization from ruptured atherosclerotic plaques.<sup>38,39</sup> Therapy for patients in this high-risk group still needs to be established, but the use of glycoprotein IIb/IIIa receptor inhibitors may be a promising strategy.<sup>40</sup>

The troponin tests cannot replace the clinical evaluation of the patient with chest pain.<sup>32</sup> Life-threatening noncardiac diseases need to be excluded. However, this new diagnostic tool, with its superior predictive value, should be made available to emergency rooms and chest-pain units.

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