ORIGINAL ARTICLE

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays

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ABSTRACT

BACKGROUND

The rapid and reliable diagnosis of acute myocardial infarction is a major unmet clinical need.

METHODS

We conducted a multicenter study to examine the diagnostic accuracy of new, sensitive cardiac troponin assays performed on blood samples obtained in the emergency department from 718 consecutive patients who presented with symptoms suggestive of acute myocardial infarction. Cardiac troponin levels were determined in a blinded fashion with the use of four sensitive assays (Abbott–Architect Troponin I, Roche High-Sensitive Troponin T, Roche Troponin I, and Siemens Troponin I Ultra) and a standard assay (Roche Troponin T). The final diagnosis was adjudicated by two independent cardiologists.

RESULTS

Acute myocardial infarction was the adjudicated final diagnosis in 123 patients (17%). The diagnostic accuracy of measurements obtained at presentation, as quantified by the area under the receiver-operating-characteristic curve (AUC), was significantly higher with the four sensitive cardiac troponin assays than with the standard assay (AUC for Abbott–Architect Troponin I, 0.96; 95% confidence interval [CI], 0.94 to 0.98; for Roche High-Sensitive Troponin T, 0.96; 95% CI, 0.94 to 0.98; for Roche Troponin I, 0.95; 95% CI, 0.92 to 0.97; and for Siemens Troponin I Ultra, 0.96; 95% CI, 0.94 to 0.98; vs. AUC for the standard assay, 0.90; 95% CI, 0.86 to 0.94). Among patients who presented within 3 hours after the onset of chest pain, the AUCs were 0.93 (95% CI, 0.88 to 0.99), 0.92 (95% CI, 0.87 to 0.97), 0.92 (95% CI, 0.86 to 0.99), and 0.94 (95% CI, 0.90 to 0.98) for the sensitive assays, respectively, and 0.76 (95% CI, 0.64 to 0.88) for the standard assay. We did not assess the effect of the sensitive troponin assays on clinical management.

CONCLUSIONS

The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain. (ClinicalTrials.gov number, NCT00470587.)

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Acute myocardial infarction is a major cause of death and disability. Approximately 15 million patients per year in the United States and Europe present to the emergency department with chest pain or other symptoms suggestive of acute myocardial infarction.[1-3] Rapid identification of acute myocardial infarction is critical for the initiation of effective evidence-based medical treatment and management.[2-4]

Electrocardiography (ECG) and measurement of cardiac troponins are the current diagnostic cornerstones and complement the clinical assessment.[2-4] ECG by itself is often insufficient to diagnose an acute coronary syndrome or acute myocardial infarction, since ST-segment deviation may be observed in other conditions, such as acute pericarditis, left ventricular hypertrophy, left bundle-branch block, the Brugada syndrome, and early repolarization patterns.[2-6] Cardiac troponins, which are structural proteins unique to the heart, are sensitive and specific biochemical markers of myocardial damage.[2-4,7-12] They are very helpful in clinical practice for identifying patients with acute coronary syndromes who are at high risk and for selecting patients who will benefit from an early invasive strategy and glycoprotein IIb/IIIa blockade.[2-4,7-12] In addition, cardiac troponin levels, as measured by fully automated standard assays such as the current fourth-generation Roche Troponin T, are superior to all other clinically available biomarkers, including myoglobin, the MB fraction of creatine kinase (CK-MB), myeloperoxidase, and heart fatty acid–binding protein, for the diagnosis of acute myocardial infarction.[8,10,13,14]

The major limitation of standard cardiac troponin assays is their low sensitivity at the time of a patient's presentation, owing to a delayed increase in circulating levels of cardiac troponins.[2-4,15] The diagnosis of acute myocardial infarction consequently requires prolonged monitoring over a period of 6 to 12 hours and serial blood sampling. A delay in confirming a diagnosis of acute myocardial infarction may increase the risk of complications associated with the condition,[2-4] and a delay in ruling out the diagnosis contributes to overcrowding in the emergency department, with the associated costs probably exceeding several billion U.S. dollars each year.[16] Recently, improvements in the technology of cardiac troponin assays have allowed manufacturers to provide fully automated assays that meet the recommendations set out by the International Federation of Clinical Chemistry and Laboratory Medicine[4,17,18]: higher sensitivity than the previous assays and improved precision at the lower limit of detection. These assays have a lower limit of detection that is below the 99th percentile in a normal reference population.[19-21] We conducted a multicenter study to examine the diagnostic performance of new, sensitive cardiac troponin assays, performed on blood samples obtained at the time of a patient's presentation to the emergency department, for the early diagnosis of acute myocardial infarction.

METHODS

STUDY DESIGN AND POPULATION

The Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study is an ongoing prospective, international, multicenter study designed and coordinated by the University Hospital Basel. From April 2006 through April 2008, we recruited a total of 786 consecutive patients who presented to the emergency department with symptoms, such as chest pain and angina pectoris, that were suggestive of an acute myocardial infarction and in whom the onset or peak of symptoms had occurred within 12 hours before presentation. Patients were included if values from all five investigational cardiac troponin assays were obtained at presentation, even if some follow-up values were missing. Patients with terminal kidney failure requiring dialysis were excluded. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee at each participating institution. Written informed consent was obtained from all patients. The authors designed the study, gathered and analyzed the data, wrote the article and made the decision to submit it for publication, and vouch for the accuracy and completeness of the data, the analysis, and the presentation. The assays were donated by the manufacturers, who had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

CLINICAL ASSESSMENT

All patients underwent an initial clinical assessment that included a clinical history taking, a

physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood measurements, and chest radiography. Cardiac troponin I or cardiac troponin T, CK-MB, and myoglobin were measured at presentation and 6 to 9 hours after presentation or as long as clinically indicated. The precise timing of clinical post-baseline measurements and the treatment of patients were left to the discretion of the attending physician.

ADJUDICATED FINAL DIAGNOSIS

To determine the final diagnosis for each patient, two independent cardiologists reviewed all available medical records — the clinical history, findings on physical examination, and results of laboratory tests (including cardiac troponin values obtained at the participating hospitals but not those being assessed as part of this study), radiologic studies, ECG, echocardiography, cardiac exercise testing, and coronary angiography — from the time of the patient's arrival in the emergency department to the end of the 60-day follow-up period. When there was disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

An acute myocardial infarction was defined in accordance with current guidelines.[4] In brief, an acute myocardial infarction was diagnosed when there was evidence of myocardial necrosis in association with clinical signs of myocardial ischemia. Necrosis was diagnosed on the basis of a rising or falling pattern of the local cardiac troponin level, with at least one value above the 99th percentile, at a level of imprecision of less than 10%.[17,18] The following cardiac troponin assays were used for the adjudication of the final diagnosis at the participating hospitals: Abbott AxSYM Troponin I ADV, Beckman Coulter AccuTnI, and Roche Troponin T. All three are well-validated, current, standard cardiac troponin assays with similar performance in the diagnosis of acute myocardial infarction.[17,18] Unstable angina was diagnosed when a patient had normal troponin levels and typical angina at rest, a deterioration of previously stable angina, a positive result on a cardiac exercise test, or cardiac catheterization showing coronary arteries with stenosis of 70% or more of the vessel diameter, or when the diagnosis was uncertain but follow-up information showed that the patient had an acute myocardial infarction or a sudden, unexpected cardiac death within 60 days after presentation. Further predefined diagnostic categories included cardiac but not coronary causes (e.g., perimyocarditis or tachyarrhythmias), noncardiac causes, and symptoms of unknown origin. If acute myocardial infarction was ruled out in the emergency department but no further diagnostic procedures were performed that were sufficient to establish a conclusive diagnosis, symptoms were classified as being of unknown origin.

INVESTIGATIONAL ASSAYS OF CARDIAC TROPONINS

Blood samples for the determination of five investigational cardiac troponin assays (four sensitive and one standard) and traditional markers of necrosis were collected in tubes containing potassium EDTA (in the case of Abbott–Architect Troponin I[19] and Siemens Troponin I Ultra[20,21]) or serum (in the case of the standard assay,[14,19] Roche High-Sensitive Troponin T,[19] and Roche Troponin I) at the time of the patient's presentation to the emergency department. Additional samples were obtained 1, 2, 3, and 6 hours after presentation. Serial sampling was discontinued when the diagnosis of acute myocardial infarction was certain and treatment required transferring the patient to the catheterization laboratory or coronary care unit. After centrifugation, samples were frozen at −80°C until they were assayed in a blinded fashion in two batches in a dedicated core laboratory. In contrast to the standard assay, the four sensitive cardiac troponin assays have a limit of detection below the 99th percentile in a normal reference population.[19-21]

The Abbott–Architect Troponin I assay was performed with the use of the Architect system (Abbott Diagnostics), with a limit of detection of 0.01 μg per liter, a 99th-percentile cutoff point of 0.028 μg per liter, and a coefficient of variation of less than 10% at 0.032 μg per liter, as specified by the manufacturer. All Roche assays were performed with the use of the Elecsys 2010 system (Roche Diagnostics): Troponin T (fourth generation) with a limit of detection of 0.01 μg per liter, a 99th-percentile cutoff point of less than 0.01 μg per liter, and a coefficient of variation of less than 10% at 0.035 μg per liter; High-Sensitive Troponin T with a limit of detection of 0.002 μg per liter, a 99th-percentile cutoff point of 0.014 μg per liter, and a coefficient of variation of less than 10% at 0.013 μg per liter; and Troponin I with a limit of detection of 0.10 μg

per liter, a 99th-percentile cutoff point of 0.16 μg per liter, and a coefficient of variation of less than 10% at 0.30 μg per liter, as specified by the manufacturer. The Siemens Troponin I Ultra assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens), with a limit of detection of 0.006 μg per liter, a 99th-percentile cutoff point of 0.04 μg per liter, and a coefficient of variation of less than 10% at 0.03 μg per liter, as specified by the manufacturer.[20,21]

CK-MB and myoglobin were measured with the use of immunoassays (CK-MB by means of mass assay) (Elecsys 2010, Roche Diagnostics). The glomerular filtration rate was calculated with the use of the abbreviated Modification of Diet in Renal Disease formula.

STATISTICAL ANALYSIS

Continuous variables are presented as means (±SD) or medians (with the interquartile range), and categorical variables as numbers and percentages. Continuous variables were compared with the use of the Mann–Whitney U test and categorical variables with the use of the Pearson chi-square test. Receiver-operating-characteristic (ROC) curves were constructed to assess the sensitivity and specificity of cardiac troponin measurements obtained at specific times with the five assays and to compare their ability to diagnose acute myocardial infarction. Logistic regression was used to combine cardiac troponin levels at presentation with early changes in cardiac troponin levels. The comparison of areas under the ROC curves (AUC) was performed as recommended by DeLong et al.[22] All hypothesis testing was two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS for Windows, version 15.0 (SPSS), and MedCalc software, version 9.6.4.0 (MedCalc).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Baseline values from all five assays were available for 718 of the 786 consecutive patients; values from fewer than five assays were available for the remaining 68 patients. Baseline characteristics of the 718 patients with suspected acute myocardial infarction are shown in Table 1. The adjudicated final diagnosis was acute myocardial infarction in 17% of the patients, unstable angina in 16%, cardiac symptoms from causes other than coronary artery disease in 13%, noncardiac causes in 46%, and symptoms of unknown origin in 8%.

DIAGNOSTIC ACCURACY OF CARDIAC TROPONIN LEVELS AT PRESENTATION

Cardiac troponin levels at presentation, as assessed by all the assays, were significantly higher in patients in whom acute myocardial infarction was the final diagnosis than in patients in whom there was a different final diagnosis (Fig. 1). The diagnostic accuracy for acute myocardial infarction, as quantified by the AUC, was significantly higher with the four sensitive cardiac troponin assays than that with the standard assay (AUC for Abbott–Architect Troponin I, 0.96; 95% confidence interval [CI], 0.94 to 0.98; for Roche High-Sensitive Troponin T, 0.96; 95% CI, 0.94 to 0.98); for Roche Troponin I, 0.94; 95% CI, 0.92 to 0.97; and for Siemens Troponin I Ultra 0.96; 95% CI, 0.94 to 0.98; vs. AUC for the standard assay, 0.90; 95% CI, 0.86 to 0.94; P=0.01, P=0.008, P=0.06, and P=0.009, respectively, for the comparisons of the four sensitive assays with the standard assay) and was also significantly higher than that with the traditional markers of necrosis, CK-MB and myoglobin (AUC for CK-MB, 0.88; 95% CI, 0.85 to 0.92; and for myoglobin, 0.84; 95% CI, 0.80 to 0.88) (Table 2 and Fig. 2A). The diagnostic accuracy was similar among the four sensitive assays (P values for all comparisons were not significant).

The diagnostic performance of the four sensitive cardiac troponin assays was similar in the case of non–ST-segment-elevation acute myocardial infarction and in the case of ST-segment-elevation acute myocardial infarction (AUC in non–ST-segment-elevation acute myocardial infarction: Abbott–Architect Troponin I, 0.96; 95% CI, 0.93 to 0.98; Roche High-Sensitive Troponin T, 0.96; 95% CI, 0.94 to 0.98; Roche Troponin I, 0.95; 95% CI, 0.92 to 0.98; and Siemens Troponin Ultra, 0.96; 95% CI, 0.93 to 0.98; AUC in ST-segment-elevation acute myocardial infarction: Abbott–Architect Troponin I, 0.96; 95% CI, 0.94 to 0.98; Roche High-Sensitive Troponin T, 0.96; 95% CI, 0.94 to 0.98; Roche Troponin I, 0.95; 95% CI, 0.90 to 0.99; and Siemens Troponin Ultra, 0.97; 95% CI, 0.95 to 0.99. The diagnostic performance of the four sensitive assays was also similar in the analyses of men and of women, of pa-

Table 1. Baseline Characteristics of the Patients.

Characteristic	All Patients (N=718)	Patients Who Had an Acute Myocardial Infarction (N=123)	Patients Who Did Not Have an Acute Myocardial Infarction (N=595)	P Value
Age — yr				<0.001
Median	64	72	62	
Interquartile range	51–75	59–80	49–74	
Male sex — no. (%)	471 (66)	88 (72)	383 (64)	0.13
Risk factors — no. (%)				
Hypertension	438 (61)	87 (71)	351 (59)	0.02
Hypercholesterolemia	311 (43)	63 (51)	248 (42)	0.05
Diabetes	116 (16)	25 (20)	91 (15)	0.17
Current smoking	173 (24)	35 (28)	138 (23)	0.21
History of smoking	242 (34)	37 (30)	205 (34)	0.35
History — no. (%)				
Coronary artery disease	251 (35)	43 (35)	208 (35)	1.00
Previous myocardial infarction	182 (25)	32 (26)	150 (25)	0.85
Previous revascularization	202 (28)	29 (24)	173 (29)	0.22
Peripheral artery disease	47 (7)	13 (11)	34 (6)	0.05
Previous stroke	45 (6)	14 (11)	31 (5)	0.01
Clinical findings				
Heart rate — beats/min				0.18
Median	75	80	75	
Interquartile range	66–88	66–89	66–88	
Blood pressure — mm Hg				
Systolic				0.04
Median	141	135	142	
Interquartile range	127–160	123–158	127–160	
Diastolic				0.55
Median	86	84	86	
Interquartile range	77–95	76–97	77–95	
Body-mass index*				0.94
Median	26.3	26.6	26.3	
Interquartile range	23.8–29.4	23.6–29.0	23.9–29.4	
Electrocardiographic findings — no. (%)				
Left bundle-branch block	25 (3)	11 (9)	14 (2)	<0.001
ST-segment elevation	51 (7)	35 (28)	16 (3)	<0.001
ST-segment depression	68 (9)	25 (20)	43 (7)	<0.001
T-wave inversion	50 (7)	18 (15)	32 (5)	<0.001
No clinically significant abnormalities	524 (73)	34 (28)	490 (82)	<0.001
Glomerular filtration rate — ml/min/1.73 m^2				<0.001
Median	93	83	94	
Interquartile range	74–109	61–104	76–111	

* The body-mass index is the weight in kilograms divided by the square of the height in meters.

tients 70 years of age or older, and of patients with renal dysfunction and an estimated glomerular filtration rate below 60 ml per minute per 1.73 m² of body-surface area (data not shown).

CARDIAC TROPONIN LEVELS AT PRESENTATION IN PATIENTS WITH RECENT ONSET OF CHEST PAIN

The superiority of the sensitive cardiac troponin assays was most pronounced among patients with recent onset of chest pain (Fig. 2B and Fig. 3, and Table 3A in the Supplementary Appendix, available with the full text of this article at NEJM.org). Among patients who presented within 3 hours after the onset of chest pain, the AUCs for the five assays were as follows: Abbott–Architect Troponin I, 0.93 (95% CI, 0.88 to 0.99); Roche High-Sensitive Troponin T, 0.92 (95% CI, 0.87 to 0.97); Roche Troponin I, 0.92 (95% CI, 0.86 to 0.99); Siemens Troponin I Ultra, 0.94 (95% CI, 0.90 to 0.98); and standard assay, 0.76 (95% CI, 0.64 to 0.88) (P=0.01, P=0.01, P=0.02, and P=0.005, respectively, for the comparisons of the sensitive assays with the standard assay) (Fig. 3). The AUC for CK-MB was 0.80 (95% CI, 0.72 to 0.88) and the AUC for myoglobin was 0.79 (95% CI, 0.69 to 0.89). The combination of the results of the sensitive cardiac troponin assays and the measurement of CK-MB or myoglobin did not further increase the AUC provided by the results of the sensitive cardiac troponin assays alone (data not shown). Moreover, the AUC for the sensitive cardiac troponin assays 2 hours after the onset of pain was significantly higher than that of the standard assay 2 hours after the onset of pain (AUC, 0.92, 0.91, 0.90, and 0.94 with the four sensitive assays, respectively, vs. 0.71 with the standard assay; P=0.02, P=0.02, P=0.04, and P=0.005, respectively) and was even higher than the AUC for the standard assay at 10 hours (0.85).

SERIAL CARDIAC TROPONIN LEVELS

The AUC for all cardiac troponin assays increased further at the later sampling points (Table 3B in the Supplementary Appendix). For example, 3 hours after presentation, the AUC for the sensitive and the standard cardiac troponin assays was 0.98.

The diagnostic performance of the absolute value of changes in cardiac troponin levels from presentation to 1 hour and to 2 hours was similar to the performance of cardiac troponin levels at presentation (Table 3C in the Supplementary Appendix). The combination of the baseline level and early changes resulted in a nonsignificant further improvement in diagnostic performance as compared with the baseline level alone.

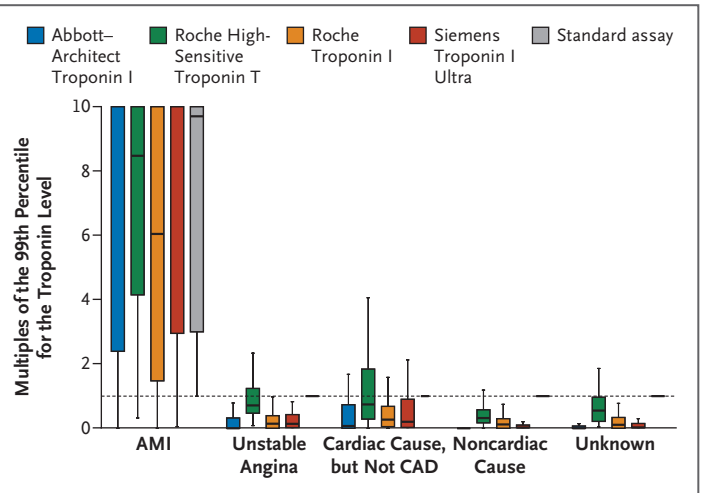

Figure 1. Levels of Cardiac Troponins at Presentation, as Assessed by Four Sensitive Assays and a Standard Assay, According to the Final Diagnosis.

Troponin levels at the time of patients' presentation to the emergency department are shown as multiples of the 99th-percentile level, according to the adjudicated final diagnosis. The boxes represent interquartile ranges, the horizontal line in each box represents the median (the absence of a horizontal line indicates a median >10 times the 99th percentile), and the whiskers show the minimum and maximum values (excluding outliers that were more than 1.5 times the values represented at each end of the box). AMI denotes acute myocardial infarction, and CAD coronary artery disease.

CARDIAC TROPONIN LEVELS IN PATIENTS WITH UNSTABLE ANGINA

As assessed by the sensitive assays, cardiac troponin levels at presentation in patients whose final diagnosis was unstable angina were significantly lower than those in patients whose final diagnosis was acute myocardial infarction, were similar to those in patients whose final diagnosis was other cardiac causes of chest pain, and were significantly higher than those in patients whose final diagnosis was noncardiac causes of chest pain. The diagnostic accuracy of the sensitive assays in differentiating unstable angina from noncardiac causes of chest pain was low to moderate, with substantial differences among the assays (AUC for Abbott–Architect Troponin I, 0.65; 95% CI, 0.59 to 0.71; for Roche High-Sensitive Troponin T, 0.76; 95% CI, 0.71 to 0.81; for Roche Troponin I, 0.56; 95% CI, 0.50 to 0.63; and for Siemens Troponin I Ultra, 0.68; 95% CI, 0.62 to 0.74). For the

Table 2. Diagnostic Performance of Cardiac Troponin Assays at Presentation.

Troponin Assay	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
	percent (95% confidence interval)			
Sensitive troponin assays				
Abbott–Architect Troponin I				
Limit of detection, 0.010 μg/liter	94 (88–97)	87 (84–89)	98 (97–99)	59 (52–66)
99th percentile, 0.028 μg/liter	86 (79–92)	92 (90–94)	97 (95–98)	69 (61–76)
10% coefficient of variation, 0.032 μg/liter	85 (77–90)	93 (90–95)	97 (95–98)	70 (62–78)
Roche High-Sensitive Troponin T				
Limit of detection, 0.002 μg/liter	100 (97–100)	14 (12–18)	100 (96–100)	19 (16–23)
99th percentile, 0.014 μg/liter*	95 (90–98)	80 (77–83)	99 (97–100)	50 (43–56)
Roche Troponin I				
Limit of detection, 0.100 μg/liter	92 (86–96)	88 (86–91)	98 (97–99)	62 (55–69)
99th percentile, 0.160 μg/liter	84 (76–90)	94 (91–95)	97 (95–98)	73 (65–80)
10% coefficient of variation, 0.300 μg/liter	75 (66–82)	97 (95–98)	95 (93–97)	83 (75–89)
Siemens Troponin I Ultra				
Limit of detection, 0.006 μg/liter	97 (91–99)	68 (64–72)	99 (97–100)	38 (32–44)
99th percentile, 0.040 μg/liter*	89 (82–94)	92 (89–94)	98 (96–99)	68 (60–76)
Standard assay				
Roche Troponin T 4th Generation				
99th percentile, unknown				
Limit of detection, 0.010 μg/liter	83 (76–90)	93 (91–95)	97 (95–98)	72 (64–79)
10% coefficient of variation, 0.035 μg/liter	72 (64–80)	97 (96–98)	94 (92–96)	85 (76–91)

* The criterion of 10% coefficient of variation was fulfilled at the 99th percentile.

diagnosis of acute myocardial infarction or unstable angina, the negative predictive value of a negative assay result (defined as a value below the 99th percentile with a level of imprecision of less than 10%) was 77%, 82%, 74%, and 79% for the four sensitive assays, respectively.

DISCUSSION

This prospective, multicenter study involving unselected patients examined the diagnostic performance of new, sensitive cardiac troponin assays for the early diagnosis of acute myocardial infarction at the time of the patient's presentation to the emergency department. We report four major findings with the potential to improve the ability both to rule in and to rule out acute myocardial infarction. First, the diagnostic accuracy of the four sensitive cardiac troponin assays was already very high at presentation. The AUCs ranged from 0.94 to 0.96. The diagnostic performance of cardiac troponin levels observed in this study is even superior to the accuracy of B-type natriuretic peptides in the diagnosis of heart failure.[23,24]

Second, the accuracy of the four sensitive cardiac troponin assays was higher than that of the standard assay. This multicenter study corroborated the hypothesis that cardiac troponin assays with increased sensitivity would improve the early diagnosis of acute myocardial infarction.[4,13-15,17-21,25] We also confirm and extend findings from two recent single-center pilot studies evaluating the Siemens Troponin I Ultra assay.[20,21]

Third, the superiority of the sensitive cardiac troponin assays was most pronounced among patients with a recent onset of chest pain. Improvement in the early diagnosis of acute myocardial infarction in such patients is of paramount importance, since it offers the opportunity to

extend early treatment options to all patients with acute myocardial infarction — not just those with ST-segment elevation.[2-4] More rapid diagnosis of acute myocardial infarction may reduce complications by allowing for earlier revascularization, earlier transfer to the coronary care unit, and earlier initiation of evidence-based treatment for acute myocardial infarction.[2-4]

Fourth, the sensitive cardiac troponin assays may make it possible to reliably rule out the diagnosis of acute myocardial infarction in many patients on the basis of the initial measurement. The negative predictive value of the 99th percentile of the sensitive cardiac troponin assays, used as a single variable, was 97 to 99%. When sensitive cardiac troponin assays are used in conjunction with a clinical assessment and ECG, they will substantially reduce the percentage of patients in whom the diagnosis is uncertain after the first cardiac troponin measurement and for whom continuous ECG monitoring and serial blood sampling are necessary. The cost savings associated with this increase in early diagnostic accuracy might be substantial.[16]

Despite the excellent performance of sensitive cardiac troponin assays in the early diagnosis of acute myocardial infarction, they should be used only in conjunction with a detailed clinical assessment. For example, differentiating acute myocardial infarction from other medical conditions associated with elevations in cardiac troponin levels, including myocarditis and heart failure, will continue to require a full clinical evaluation. Also, despite its low sensitivity, ECG remains an indispensable tool for immediately identifying patients who have had an acute myocardial infarction with ST-segment elevation.[2-6]

Although the prognosis for patients with unstable angina is much better than that for patients with acute myocardial infarction, detection of unstable angina is important so that appropriate medical management can be initiated.[2-4] The accuracy of sensitive cardiac troponin assays for the detection of unstable angina was low to moderate in our study, suggesting that these assays may remain of limited value for the diagnosis of unstable angina. Further research is necessary to identify biomarkers that reliably detect myocardial ischemia without necrosis.[26-28]

The current study has several limitations. First, we evaluated four sensitive cardiac troponin as-

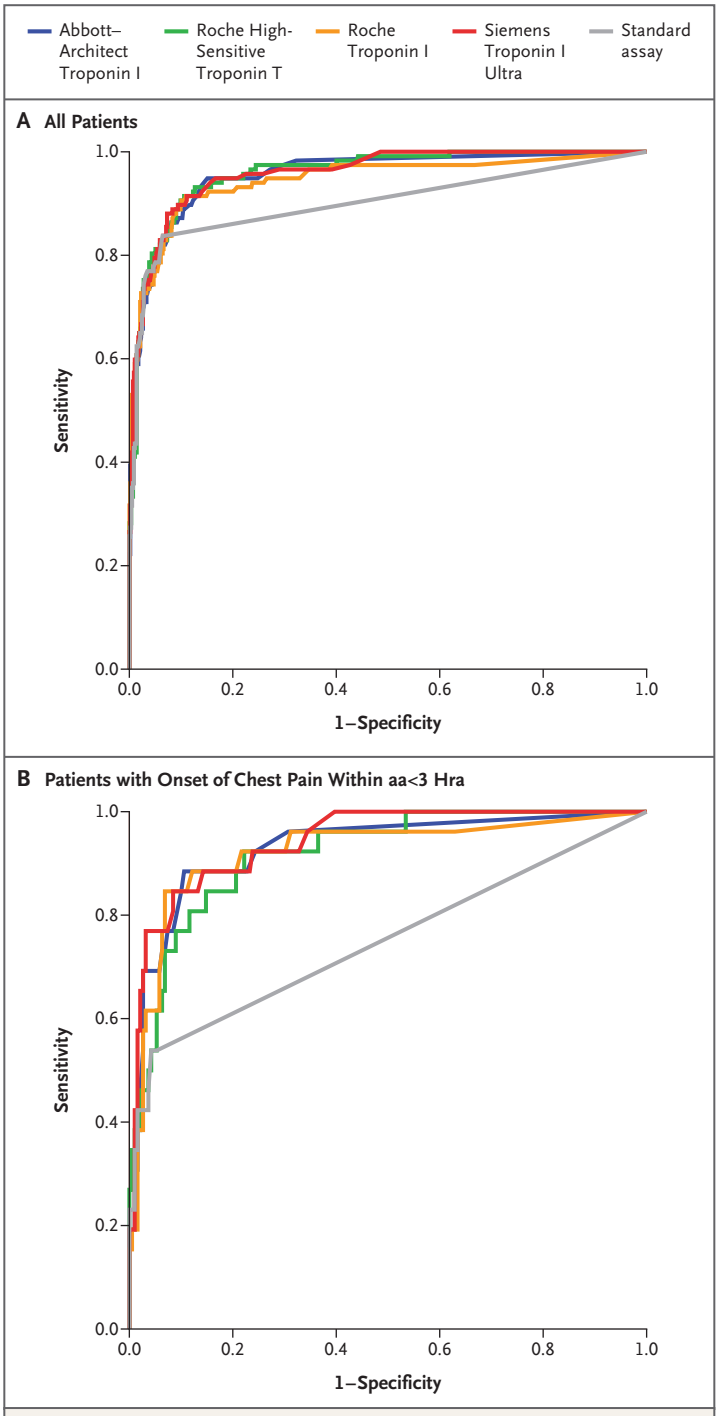

Figure 2. Diagnostic Performance of Cardiac Troponin Assays at Presentation.
Receiver-operating-characteristic (ROC) curves show the diagnostic performance of the four sensitive cardiac troponin assays and the standard assay performed on blood samples obtained at presentation for the diagnosis of acute myocardial infarction in the overall cohort (Panel A) and in the subgroup of patients presenting within 3 hours after the onset of chest pain (Panel B).

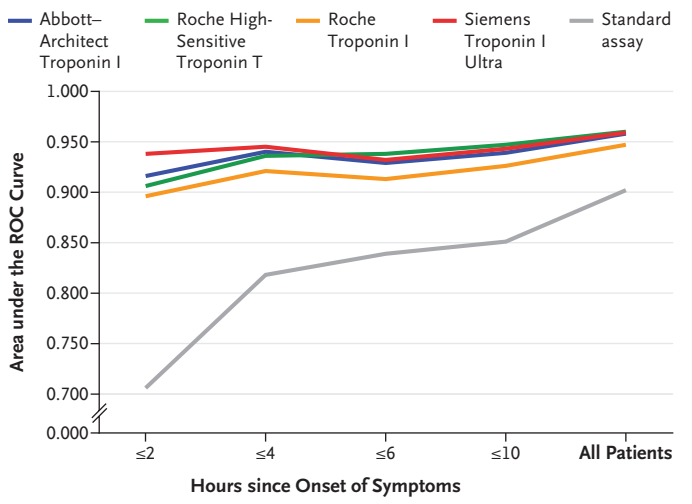

Figure 3. Diagnostic Accuracy of Cardiac Troponin Assays at Presentation According to Time since Onset of Chest Pain.

The area under the receiver-operating-characteristic curve (AUC) is shown, according to the time since the onset of chest pain, for the four sensitive cardiac troponin assays and the standard assay performed on blood samples obtained at presentation for the diagnosis of acute myocardial infarction.

says. We hypothesize that our findings can be generalized to other cardiac troponin assays that have similar sensitivity and precision. However, additional large, multicenter studies are needed to confirm this hypothesis. Second, since this was a prospective, observational study, we cannot quantify the clinical effect associated with the increase in early diagnostic accuracy. Intervention studies are warranted to provide this important additional information. Third, our study showed a high diagnostic accuracy of sensitive cardiac troponin assays among patients with impaired renal function; however, we cannot comment on the accuracy among patients with terminal kidney failure requiring dialysis, since such patients were excluded from our study. Fourth, some of the patients with positive results of sensitive cardiac troponin assays whose final diagnosis was classified as a condition other than an acute myocardial infarction might have had small acute myocardial infarctions that were below the limit of detection of the conventional assays, a result that might have led to an underestimate of the specificity of the sensitive assays.

In conclusion, sensitive cardiac troponin assays have an excellent diagnostic performance as early as at the time of a patient's presentation in the emergency department and may thereby substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain.

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REFERENCES

1. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. Advance data from vital and health statistics. No. 386. Hyattsville, MD: National Center for Health Statistics, 2007.
2. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116(7):e148-e304.
3. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-660.
4. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.
5. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163-70.
6. Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. N Engl J Med 2003;349:2128-35.
7. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. JAMA 2001;286:2405-12.
8. Morrow DA, Antman EM, Tanasijevic M, et al. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy. J Am Coll Cardiol 2000;36:1812-7.
9. Mueller C, Neumann FJ, Perruchoud AP, Zeller T, Buettner HJ. Prognostic value of quantitative troponin T measurements in unstable angina/non-ST-segment elevation acute myocardial infarction treated early and predominantly with percutaneous coronary intervention. Am J Med 2004;117:897-902.
10. Hochholzer W, Buettner HJ, Trenk D, et al. New definition of myocardial infarction: impact on long-term mortality. Am J Med 2008;121:399-405.
11. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients

with refractory unstable angina in relation to serum troponin T levels. N Engl J Med 1999;340:1623-9. [Erratum, N Engl J Med 1999;341:548.]
12. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. JAMA 2006;295:1531-8.
13. Eggers KM, Oldgren J, Nordenskjöld A, Lindahl B. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. Am Heart J 2004;148:574-81.
14. McCann CJ, Glover BM, Menown IB, et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. Eur Heart J 2008; 29:2843-50.
15. Macrae AR, Kavsak PA, Lustig V, et al. Assessing the requirement for the 6-hour interval between specimens in the American Heart Association Classification of Myocardial Infarction in Epidemiology and Clinical Research Studies. Clin Chem 2006;52:812-8.
16. Forberg JL, Henriksen LS, Edenbrandt L, Ekelund U. Direct hospital costs of chest pain patients attending the emergency department: a retrospective study. BMC Emerg Med 2006;6:6.
17. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Circulation 2007;115(13):e352-e355.
18. Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. Am Heart J 2002;144:981-6.
19. Mingels A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, van Dieijen-Visser M. Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. Clin Chem 2009;55:101-8.
20. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. Am J Clin Pathol 2007;128:282-6.
21. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. Clin Chem 2008; 54:723-8.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
23. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647-54.
24. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161-7.
25. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? J Am Coll Cardiol 2006;48:1763-4.
26. Lindahl B. Multimarker approach for diagnosis of acute myocardial infarction: better answers need better questions. Clin Chem 2009;55:9-11.
27. Apple FS, Smith SW, Pearce LA, Murakami MM. Assessment of the multiple-biomarker approach for diagnosis of myocardial infarction in patients presenting with symptoms suggestive of acute coronary syndrome. Clin Chem 2009;55:93-100.
28. Peacock WF. Will SCUBE1 solve the ischemia marker deficit? J Am Coll Cardiol 2008;51:2181-3.