ORIGINAL ARTICLE

Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Cardiac troponin testing is central to the diagnosis of acute myocardial infarction. We evaluated a sensitive troponin I assay for the early diagnosis and risk stratification of myocardial infarction.

METHODS

In a multicenter study, we determined levels of troponin I as assessed by a sensitive assay, troponin T, and traditional myocardial necrosis markers in 1818 consecutive patients with suspected acute myocardial infarction, on admission and 3 hours and 6 hours after admission.

RESULTS

For samples obtained on admission, the diagnostic accuracy was highest with the sensitive troponin I assay (area under the receiver-operating-characteristic curve [AUC], 0.96), as compared with the troponin T assay (AUC, 0.85) and traditional myocardial necrosis markers. With the use of the sensitive troponin I assay (cutoff value, 0.04 ng per milliliter) on admission, the clinical sensitivity was 90.7%, and the specificity was 90.2%. The diagnostic accuracy was virtually identical in baseline and serial samples, regardless of the time of chest-pain onset. In patients presenting within 3 hours after chest-pain onset, a single sensitive troponin I assay had a negative predictive value of 84.1% and a positive predictive value of 86.7%; these findings predicted a 30% rise in the troponin I level within 6 hours. A troponin I level of more than 0.04 ng per milliliter was independently associated with an increased risk of an adverse outcome at 30 days (hazard ratio, 1.96; 95% confidence interval, 1.27 to 3.05; P=0.003).

CONCLUSIONS

The use of a sensitive assay for troponin I improves early diagnosis of acute myocardial infarction and risk stratification, regardless of the time of chest-pain onset.

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N Engl J Med 2009;361:868-77.

An early diagnosis of myocardial infarction facilitates rapid decision making and treatment and therefore improves the outcome in patients presenting with symptoms of chest pain.[1,2] The introduction of the testing of necrosis markers in the emergency setting constituted a milestone in the care of patients with chest pain.[3-6] Guidelines recommend the measurement of cardiac troponin levels for the diagnosis of myocardial infarction, with a level above the 99th percentile in a reference population as the discriminatory value, including the detection of a rise or fall in the troponin levels.[7-9] Although conventional necrosis markers have a high diagnostic value, their sensitivity is weak within the first hours after the onset of chest pain.

To overcome this limitation, a new generation of sensitive assays for cardiac troponins with a 10% coefficient of variation for levels below the 99th percentile has been introduced recently.[10-17] This cadre of sensitive troponin assays might further enhance the accuracy of the diagnosis of myocardial infarction and therefore improve diagnostic sensitivity and specificity, even in patients presenting early after the onset of chest pain. There are few data from large-scale prospective studies assessing the use of such assays for the early diagnosis of myocardial infarction. We therefore evaluated the diagnostic accuracy, discrimination, and clinical usefulness of a sensitive troponin I assay for the early diagnosis and risk stratification of myocardial infarction in a large prospective, multicenter study involving patients with chest pain who had a high pretest probability of acute myocardial infarction.

Methods

Study Population

From January 2007 through December 2008, we enrolled 1818 consecutive patients presenting with new-onset chest pain at chest-pain units at three German study centers — the Johannes Gutenberg University Medical Center in Mainz, the Federal Armed Forces Hospital in Koblenz, and University Hospital Hamburg-Eppendorf in Hamburg — in a biomarker-assessment registry. A detailed description of the study population is provided in the Methods section of the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Oversight

The study was approved by local ethics committees in Rheinland-Pfalz and Hamburg. All patients provided written informed consent. The investigational assay of troponin I (Troponin I Ultra) was purchased from Siemens Healthcare Diagnostics, which had no role in the design of the study, the analysis of the data, or the preparation of the manuscript.

Adjudication of the Final Diagnosis

The final discharge diagnosis, which was based on all available clinical, laboratory, and imaging findings, was adjudicated by an expert committee of two independent cardiologists who were unaware of the results of the troponin I assays. If there was disagreement about the final diagnosis, a third cardiologist refereed.

Diagnosis Based on Conventional Troponin Assays

A primary diagnosis of acute myocardial infarction was adjudicated according to current guidelines when there was evidence of myocardial necrosis that was consistent with myocardial ischemia, together with clinical symptoms of ischemia or electrocardiographic changes indicative of new ischemia (new ST-segment or T-wave changes or new left bundle-branch block) or imaging evidence of new loss of viable myocardium or detection of a culprit lesion on coronary angiography; the latter was classified according to the Ambrose criteria.[18] Myocardial necrosis was documented if there was at least one value above the cutoff value for 10% imprecision of the respective conventional troponin test together with a rising or falling pattern of at least 20% within 6 hours after admission to distinguish background elevated troponin levels from acute elevation. Conventional troponin assays that were used for the adjudication of the final diagnosis were Roche Troponin T in Mainz and Hamburg (with a cutoff value for 10% imprecision of 0.03 ng per milliliter) and Siemens Dimension RxL Troponin I in Koblenz (with a cutoff value for 10% imprecision of 0.14 ng per milliliter). The conventional troponin I assay was used only for the diagnosis of myocardial infarction and not for comparisons with the sensitive troponin I assay. Unstable angina pectoris was diagnosed if the electrocardiogram was not diagnostic and if serial conventional troponin testing was negative but ischemia was proved by the

need for intervention during coronary angiography or by a positive stress test and subsequent diagnosis of coronary artery disease by means of coronary angiography. In 95.2% of the patients who were classified as having acute myocardial infarction on the basis of the definition outlined above, coronary angiography identified a culprit lesion that accounted for the increase in the patient's troponin level.

Diagnosis Based on Sensitive Troponin I Assay

To assess the diagnostic value of the sensitive troponin I assay used alone, and to determine how soon a diagnosis could be made on the basis of the assay result, we also used a refined approach for the diagnosis of acute myocardial infarction. First, we used the sensitive troponin I assay in 5000 population-based subjects in the Gutenberg Heart Study and determined that a value of 0.04 ng per milliliter was the 99th percentile for that population. (Fig. 1 in the Supplementary Appendix shows the troponin I distribution, including the 99th percentile and sample characteristics.) We used the concentration of 0.04 ng per milliliter (a 10% coefficient of variation at 0.03 ng per milliliter) as the upper reference limit and established the diagnosis of myocardial infarction if one value of more than 0.04 ng per milliliter was documented, combined with a rise or fall in the value of 30% or more within 6 hours after admission. (A detailed description is available in the Methods section of the Supplementary Appendix.)

With the use of both criteria, we classified all patients who had an elevated troponin level from causes other than coronary origin as having noncoronary chest pain, including 19 patients with proven pulmonary embolism, 18 patients with acute decompensated heart failure, 17 patients with myocarditis, 6 patients with aortic dissection, and 2 patients with decompensated aortic-valve stenosis, as well as all other patients who had no indication of myocardial infarction on the basis of troponin measurements, electrocardiography, coronary angiography, or stress testing. The relatively low number of patients with decompensated heart failure was explained by the primary admission of such patients to the general emergency department.

STATISTICAL ANALYSIS

We calculated receiver-operating-characteristic (ROC) curves on the basis of the continuously measured biomarker levels by taking every measured biomarker level as a cutoff value and then deriving sensitivity and specificity values from the resulting two-by-two tables for each cutoff value. This procedure was repeated for every combination of biomarkers and times of chest-pain onset. The area under the ROC curve (AUC) was calculated with the use of the R package Epicalc.

In addition, we assessed sensitivity, specificity, and positive and negative predictive values for the target markers by applying a marker-specific cutoff value and consecutively calculating the corresponding values from a two-by-two factorial design. Cox regression models were used to determine the association of troponin I levels as measured with the sensitive assay and troponin T levels with the outcome at 30 days. Two models were specified, one adjusted for sex and age and one additionally adjusted for body-mass index; the presence or absence of hypertension, diabetes mellitus, and hyperlipidemia; smoking status; the estimated glomerular filtration rate; and electrocardiographic results. The resulting hazard ratios reflect the risk of an event if biomarker values exceeded the corresponding cutoff value. P values are based on the Wald z-test statistic. All statistical analyses were performed with the use of R software (version 2.8.1) and SAS software (version 9.2). (A detailed description is available in the Methods section of the Supplementary Appendix.)

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

Baseline characteristics of the overall study population at admission to the chest-pain unit are provided in Table 1. The final discharge diagnosis of acute myocardial infarction was made in 413 of 1818 patients (22.7%), including 130 patients (7.2%) who presented with myocardial infarction with ST-segment elevation. The distribution of the time of chest-pain onset was similar in all diagnosis groups. The distribution of troponin T and troponin I values, according to the discharge diagnosis and serial sampling, is shown in Figure 2 in the Supplementary Appendix.

DIAGNOSTIC ACCURACY OF THE SENSITIVE TROPONIN I ASSAY

Figure 1 shows the diagnostic accuracy of a single measurement of troponin I with the sensitive assay as a biomarker for the identification of myo-

cardial infarction, as compared with conventional troponin T measurement and traditional markers of necrosis. Biomarkers were treated as continuous variables and analyzed according to the time of chest-pain onset. The diagnostic accuracy of the sensitive troponin I assay was highest, with an AUC of 0.95 in patients presenting within 3 hours after the onset of chest pain; this value increased marginally, to 0.96, in patients presenting within 6 or 12 hours after chest-pain onset. To assess the diagnostic accuracy over time, serial assays were performed at baseline and at 3 hours and 6 hours after admission (Fig. 3 in the Supplementary Appendix).

For discriminatory analyses of the sensitive troponin I assay, we applied the locally determined upper reference limit of 0.04 ng per milliliter. With testing on admission, the clinical sensitivity for the sensitive troponin I assay was 90.7%, and the specificity was 90.2%, regardless of the interval between the onset of chest pain and admission (Table 2).

A total of 240 of the 1818 patients (13.2%) presented with unstable angina. Of these patients, 53 (22.1%) had troponin I levels of more than 0.04 ng per milliliter as measured with the sensitive assay. With the use of this assay to differentiate unstable angina from noncoronary chest pain, the AUC was 0.62, with a negative predictive value of 84.8%.

ALTERNATIVE DEFINITION OF MYOCARDIAL INFARCTION

As an alternative diagnostic approach, we defined acute myocardial infarction on the basis of a troponin I level, as measured with the sensitive assay, that was above the 99th percentile value of 0.04 ng per milliliter, together with a rise or fall in the level of 30% or more within 3 or 6 hours after hospital admission. We first tested the probability of predicting the rising pattern with the initial sensitive-assay value and calculated the AUC according to the alternative definition of myocardial infarction. Figure 2 shows the association between an elevated value on admission and the diagnosis of acute myocardial infarction, according to the time of chest-pain onset. In patients presenting within 3 hours after the onset of chest pain, 184 of 227 patients with diagnosed myocardial infarction (81.1%) had a single troponin I level of more than 0.04 ng per milliliter on admission, for a negative predictive value of 84.1% and a positive predictive value of 86.7%. Overall, the AUC of the baseline troponin I level was approximately 0.90, regardless of the time of chest-pain onset.

Second, we calculated the time it took to diagnose myocardial infarction in 95 to 100% of patients using the sensitive troponin I assay (Table 3). A total of 88% of myocardial infarctions were detected on admission in patients presenting within 6 hours after the onset of chest pain, and 95% of myocardial infarctions were detected in those presenting between 6 and 12 hours after the onset of chest pain. With serial measurements (on admission and 3 or 6 hours after admission), the rate of detection of myocardial infarction was 100%.

LOW OR MODERATE TROPONIN I LEVELS

Of 585 patients in whom troponin I levels, as measured with the sensitive assay, were between the limit of detection (0.006 ng per milliliter) and the 99th percentile (0.04 ng per milliliter) on admission, 115 patients (19.7%) had levels of more than 0.04 ng per milliliter within 6 hours after hospital admission. Of these patients, only 30 were categorized as having acute myocardial infarction on the basis of conventional troponin measurement; in 29 of the 30 patients, myocardial infarction was confirmed angiographically. A total of 87 patients had moderately elevated troponin I levels (>0.04 ng per milliliter) without a rise or fall of 30% in subsequent samples. Of these patients, 62 had a distinct noncoronary diagnosis (Table 1 in the Supplementary Appendix); none of the 62 patients had an adverse event during the 30-day follow-up.

SHORT-TERM OUTCOME

Measurements with both the sensitive troponin I assay and the conventional troponin T assay predicted the risk of major cardiovascular events within 30 days after presentation. For details, see Table 2 in the Supplementary Appendix.

DISCUSSION

In our study, serial testing in 1818 consecutive patients with chest pain established that a single sensitive troponin I assay at the time of admission, as compared with a conventional troponin T assay and other markers of myocardial necrosis, provided substantially improved levels of diagnostic accuracy and discrimination for the early

diagnosis of myocardial infarction. These findings also point to the clinical significance of very low detectable levels of troponin release.

The use of the sensitive troponin I assay has two major clinical implications. First, a single value, obtained on admission, of more than the 99th percentile reference value provided very high levels of accuracy and discrimination for the diagnosis of myocardial infarction, with an AUC of 0.96, as compared with conventional troponin assays. Second, with the alternative definition of myocardial infarction on the basis of the sensitive troponin I assay, the measurement obtained on admission still had a high diagnostic accu-

Table 1. Baseline Characteristics of the Patients, According to the Final Diagnosis.*

Variable	Noncoronary Chest Pain†	Unstable Angina Pectoris	Acute Myocardial Infarction‡	All Patients
Patients — no. (%)	1165 (64.1)	240 (13.2)	413 (22.7)	1818 (100)
Age — yr	59.7±14.3	65.2±10.6	64.0±11.8	61.4±13.5
Male sex — no./total no. (%)	729/1165 (62.6)	165/240 (68.8)	314/413 (76.0)	1208/1818 (66.4)
Traditional risk factors				
Body-mass index§	27.7±4.9	28±4.4	27.9±4.6	27.8±4.8
Waist-to-hip ratio				
Median	0.98	0.99	1.02	0.99
Interquartile range	0.93–1.03	0.95–1.04	0.96–1.05	0.94–1.04
Coexisting conditions — no./total no. (%)				
Hypertension	822/1165 (70.6)	204/240 (85.0)	313/413 (75.8)	1339/1818 (73.7)
Diabetes mellitus	140/1114 (12.6)	53/230 (23.0)	80/399 (20.1)	273/1744 (15.7)
Hyperlipidemia	824/1165 (70.7)	193/240 (80.4)	311/413 (75.3)	1328/1818 (73.0)
Smoking status — no./total no. (%)				
Current smoker	253/1155 (21.9)	40/234 (17.1)	143/405 (35.3)	436/1794 (24.3)
Former smoker	331/1096 (30.2)	79/221 (35.7)	124/373 (33.2)	534/1690 (31.6)
Cholesterol — mg/dl				
Total	197.7±49.0	196.71±47.5	205.03±50.1	199.23±49.1
High-density lipoprotein	51.8±15.9	49.39±14	47.6±13.8	50.5±15.3
Low-density lipoprotein	117.2±40.8	116.9±41.9	129.6±43.8	119.9±41.9
Triglycerides — mg/dl				
Median	117	134	116	119
Interquartile range	76–188	84–211	76–180	77–189
Coronary artery disease — no./total no. (%)				
Previous diagnosis in parent	379/1134 (33.4)	71/220 (32.3)	118/394 (29.9)	568/1748 (32.5)
Previous diagnosis in patient	360/1132 (31.8)	137/234 (58.5)	136/403 (33.7)	633/1769 (35.8)
Heart failure — no./total no. (%)	47/1114 (4.2)	13/220 (5.9)	15/388 (3.9)	75/1722 (4.4)
Laboratory values on admission				
Troponin T — no./total no. (%)¶				
>0.01 ng/ml	68/1159 (5.9)	30/239 (12.6)	298/410 (72.7)	396/1808 (21.9)
>0.03 ng/ml	33/1159 (2.8)	11/239 (4.6)	261/410 (63.7)	305/1808 (16.9)
Myoglobin — ng/ml				
Median	58.9	65.9	127.0	67.8
Interquartile range	42.8–82.9	47.4–84.1	85.1–235.5	46.7–103.0

Table 1. (Continued.)

Variable	Noncoronary Chest Pain†	Unstable Angina Pectoris	Acute Myocardial Infarction‡	All Patients
Creatine kinase — U/liter				
Median	97	94	148	105
Interquartile range	69–146	65–132	101–259	72–164
Creatine kinase MB — U/liter				
Median	14	15	22	16
Interquartile range	12–19	11–19	15–37	12–21
C-reactive protein — mg/liter				
Median	2.3	2.3	3.4	2.5
Interquartile range	1.1–5.4	1.3–4.5	1.7–8.8	1.3–5.8
Creatinine — mg/dl				
Median	0.94	0.93	0.99	0.95
Interquartile range	0.82–1.08	0.82–1.06	0.88–1.16	0.83–1.10
Estimated glomerular filtration rate — ml/min/1.73 m² of body-surface area	80.1±21.1	79.8±21.1	75.5±22.3	79±21.4
Electrocardiographic results on admission — no./total no. (%)				
ST-segment elevation	27/1153 (2.3)	6/239 (2.5)	56/397 (14.1)	89/1789 (5.0)
ST-segment depression	69/1153 (6.0)	27/239 (11.3)	109/397 (27.5)	205/1789 (11.5)
T-wave inversion	295/1153 (25.6)	77/239 (32.2)	174/397 (43.8)	546/1789 (30.5)
Left or right bundle-branch block	149/1153 (12.9)	35/239 (14.6)	61/397 (15.4)	245/1789 (13.7)
Time since chest-pain onset — no./total no. (%)‖				
<3 hr	446/1165 (38.3)	84/240 (35.0)	166/413 (40.2)	696/1818 (38.3)
<6 hr	693/1165 (59.5)	139/240 (57.9)	237/413 (57.4)	1069/1818 (58.8)
<12 hr	877/1165 (75.3)	171/240 (71.2)	289/413 (70.0)	1337/1818 (73.5)
≥12 hr	288/1165 (24.7)	69/240 (28.8)	124/413 (30.0)	481/1818 (26.5)

* Plus–minus values are means ±SD. Values were missing for body-mass index in 124 patients, for waist-to-hip ratio in 821 patients, for high-density lipoprotein cholesterol in 217 patients, for low-density lipoprotein cholesterol in 218 patients, for triglycerides in 215 patients, for C-reactive protein in 40 patients, for myoglobin in 428 patients, for creatine kinase in 10 patients, for creatine kinase MB in 54 patients, and for creatinine in 9 patients. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† Among patients with the diagnosis of noncoronary chest pain, there were 6 with acute aortic dissection, 2 with decompensated aortic-valve stenosis, 18 with acute decompensated heart failure, 17 with myocarditis, and 19 with pulmonary embolism.

‡ Patients with acute myocardial infarction included those with and those without ST-segment elevation.

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

¶ A troponin T level of 0.01 ng per milliliter represents the 99th percentile of the reference population. A troponin T level of 0.03 ng per milliliter represents the 10% coefficient of variation.

‖ Patients could be included in more than one category.

racy, with a diagnostic rate for myocardial infarction of 88% for patients who presented within 6 hours after the onset of chest pain, 95% for those who presented from 6 to 12 hours after the onset, and 100% for those who presented more than 12 hours after the onset. Measurement of the troponin I level with the use of the sensitive assay within 3 hours after admission ensured a 100% rate of detection of myocardial infarction. The results of our study extend the findings of

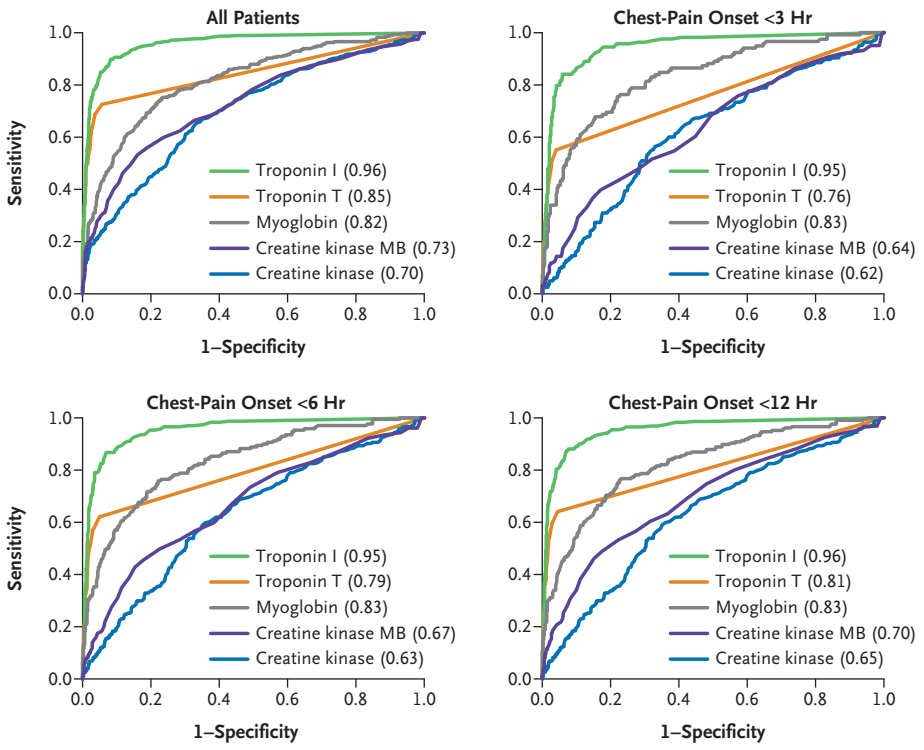

Figure 1. Diagnostic Accuracy of Single Biomarker Testing for Acute Myocardial Infarction.

Shown are receiver-operating-characteristic curves and the corresponding areas under the curve for baseline measurements of troponin I with the sensitive assay (troponin I), troponin T, myoglobin, creatine kinase MB, and creatine kinase, according to the time of the onset of chest pain. Also shown are the sensitivity and specificity of these measures.

two recent single-center pilot studies,[10,12] which showed that with the use of the sensitive troponin I assay, the pattern of a rising troponin I level over time can be predicted from a single sample obtained on admission.

In the absence of clinical evidence of ischemia, an elevated cardiac troponin level should prompt the search for other causes of myocardial necrosis, such as myocarditis, pulmonary embolism, congestive heart failure, renal failure, and aortic-valve disease. However, as in other studies,[17,19] our data provide persuasive evidence that rising troponin I values as measured with sensitive assays, a pattern that reliably establishes the diagnosis of myocardial infarction, can be predicted with a high degree of diagnostic accuracy if the initial value exceeds the upper reference limit for the 99th percentile. Since troponin I levels rise above the upper reference limit of 0.04 ng per milliliter in approximately 20% of patients who present with a lower level, serial testing after 3 hours is also recommended in this subgroup.

For the conventional troponin T assay, we selected a 20% difference between serial troponin T levels to establish the diagnosis of myocardial infarction, since the change represented twice the recommended maximum imprecision (a coefficient of variation of 10%) for that troponin assay. Therefore, changes in the level are unlikely to have been due to analytic imprecision.[20] By contrast, for the sensitive troponin I assay, we selected a difference of 30% to establish the alternative diagnosis of myocardial infarction, since the use of such a differential (in addition to either the baseline or follow-up level) has been

Table 2. Discriminatory Value of Biomarkers for the Diagnosis of Acute Myocardial Infarction.*

Variable	Sensitive Troponin I Assay*	Troponin T, Standard Assay†		Myoglobin‡	Myoglobin or Troponin T	
		99th Percentile	10% CV		99th Percentile	10% CV
	value (95% confidence interval)					
Presentation <3 hr after chest-pain onset						
Sensitivity	84.0 (77.5–89.3)	55.2 (47.2–62.9)	43.6 (35.9–51.6)	61.9 (52.5–70.6)	79.6 (72.2–85.8)	77.6 (69.9–84.2)
Specificity	93.2 (90.4–95.3)	95.7 (93.4–97.4)	98.0 (96.2–99.1)	88.0 (84.1–91.3)	83.5 (79.2–87.2)	86.2 (82.1–89.6)
Positive predictive value	82.0 (75.4–87.5)	82.7 (74.3–89.3)	88.9 (80.0–94.8)	64.0 (54.5–72.8)	66.9 (59.4–73.8)	69.8 (62.0–76.8)
Negative predictive value	94.0 (91.3–96.0)	85.2 (81.7–88.2)	82.4 (78.9–85.5)	87.0 (83.0–90.4)	90.7 (87.0–93.6)	90.3 (86.6–93.3)
Presentation <6 hr after chest-pain onset						
Sensitivity	86.8 (81.7–90.8)	62.1 (55.6–68.4)	50.6 (44.1–57.2)	62.4 (54.6–69.7)	83.8 (78.2–88.4)	80.0 (73.9–85.2)
Specificity	92.2 (90.0–94.1)	94.9 (93.0–96.4)	97.8 (96.4–98.8)	86.9 (83.7–89.6)	82.0 (78.6–85.2)	84.8 (81.5–87.7)
Positive predictive value	79.3 (73.8–84.1)	80.7 (74.1–86.1)	88.8 (82.2–93.6)	59.9 (52.3–67.2)	64.6 (58.7–70.2)	66.9 (60.7–72.7)
Negative predictive value	95.3 (93.4–96.8)	88.0 (85.5–90.3)	85.3 (82.7–87.7)	88.0 (84.9–90.6)	92.8 (90.1–94.9)	91.7 (88.9–93.9)
Presentation <12 hr after chest-pain onset						
Sensitivity	88.1 (83.7–91.6)	64.1 (58.3–69.7)	54.0 (48.1–59.9)	61.2 (54.1–67.9)	83.4 (78.4–87.7)	80.3 (74.9–85.0)
Specificity	92.1 (90.1–93.8)	95.4 (93.8–96.7)	97.9 (96.8–98.8)	86.9 (84.1–89.3)	82.6 (79.6–85.3)	85.0 (82.2–87.6)
Positive predictive value	78.7 (73.8–83.0)	82.1 (76.5–86.9)	89.6 (84.1–93.7)	58.3 (51.5–65.0)	64.4 (59.1–69.5)	66.7 (61.1–71.9)
Negative predictive value	95.9 (94.3–97.1)	89.0 (86.8–90.9)	86.6 (84.3–88.7)	88.2 (85.5–90.5)	92.9 (90.6–94.8)	92.1 (89.7–94.0)
All patients						
Sensitivity	90.7 (87.4–93.3)	72.7 (68.1–76.9)	63.7 (58.8–68.3)	61.3 (55.6–66.9)	87.1 (83.3–90.3)	84.1 (80.0–87.7)
Specificity	90.2 (88.3–91.9)	94.1 (92.6–95.4)	97.2 (96.0–98.0)	86.9 (84.6–89.0)	81.9 (79.3–84.4)	84.6 (82.1–86.9)
Positive predictive value	76.7 (72.7–80.4)	81.4 (77.1–85.3)	88.8 (84.6–92.1)	60.5 (54.8–66.1)	66.6 (62.3–70.7)	69.0 (64.5–73.2)
Negative predictive value	96.4 (95.2–97.5)	90.7 (88.9–92.3)	88.3 (86.4–90.0)	87.3 (85.0–89.4)	93.9 (92.0–95.4)	92.9 (91.0–94.5)

* A cutoff value of 0.04 ng per milliliter for the sensitive troponin I assay was determined to be the 99th percentile on the basis of analysis of samples obtained from 5000 subjects in the Gutenberg Heart Study. The 10% coefficient of variation (CV) was lower than the 99th percentile, so only the 99th percentile is presented.

† A troponin T level of 0.01 ng per milliliter represents the 99th percentile in the reference population. A troponin T level of 0.03 ng per milliliter represents the 10% coefficient of variation.

‡ The cutoff value for myoglobin was 107 ng per milliliter.

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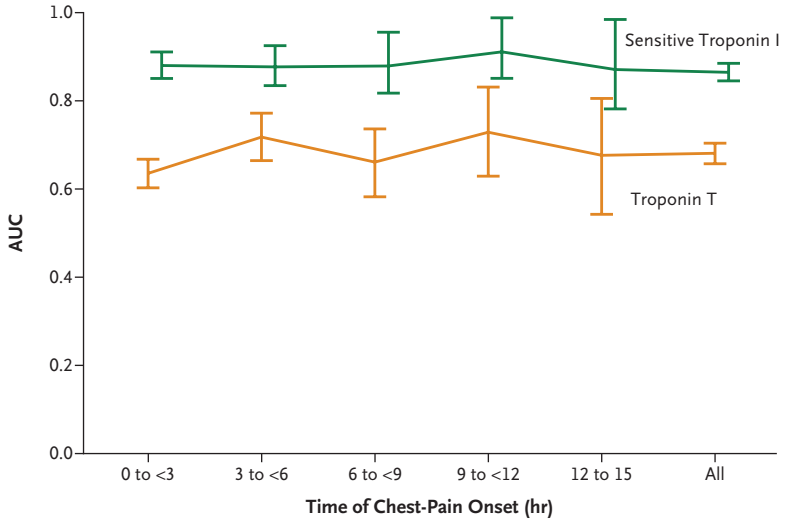

Diagnosis of AMI (no.)	227	97	44	29	17	528
Single Determination (no.)						
Sensitive troponin I >0.04 ng/ml	184	100	38	32	25	534
Troponin T >0.03 ng/ml	81	56	19	21	12	305

Figure 2. Diagnosis of Acute Myocardial Infarction with the Use of Sensitive Troponin I Assay.

Shown is the area under the receiver-operating-characteristic curve (AUC) for the sensitive troponin I assay (troponin I) and a standard troponin T assay, according to the time of chest-pain onset. Criteria for the diagnosis of myocardial infarction with the use of the sensitive troponin I assay were a level of more than 0.04 ng per milliliter within 6 hours after admission and a rise or fall of at least 30% in the level. In addition, the number of patients in whom acute myocardial infarction was diagnosed and the number of patients who were identified as having acute myocardial infarction by means of a single measurement of troponin I (sensitive assay) or troponin T are given for the corresponding time points. AMI denotes acute myocardial infarction.

Table 3. Correct Diagnosis of Acute Myocardial Infarction, According to the Time of a Single Sensitive Troponin I Assay.*

Time of Testing	Detection of Myocardial Infarction
	% of patients
On admission	
0 to <6 hr after chest-pain onset	87.7
6 to 12 hr after chest-pain onset	94.5
>12 hr after chest-pain onset	100
After admission	
At 3 hr	100
At 6 hr	100

* The diagnostic criteria for acute myocardial infarction were a troponin I level (as measured by sensitive assay) above the 99th percentile of 0.04 ng per milliliter in at least one measurement and a rise or fall in the level of at least 30%.

shown to improve both diagnostic specificity and risk assessment in patients presenting with chest pain.[19]

One of the strengths of our study was that prospective serial sampling was performed under standardized conditions in consecutive patients with chest pain who had a high pretest probability of myocardial infarction. This approach allowed for the optimal use of all biomarker measurements. The current guidelines established the 99th percentile of a normal reference population as the diagnostic decision limit for myocardial infarction. Selection of the reference population might influence the determination of the 99th percentile.[21] Therefore, we established and confirmed the upper reference limit of 0.04 ng per milliliter in an independent, population-based study involving 5000 patients and applied this value for the discriminatory analyses.

Several limitations of our study merit consideration. The conventional troponin T assay does not fulfill the requirement of a coefficient of variation of less than 10% at the 99th percentile. Thus, we established a cutoff at the level of the 10% coefficient of variation. This approach might have accentuated the difference of the observed results between the conventional troponin T assay and the sensitive troponin I assay. Troponin I levels are known to be affected by age and renal function. Better sensitivity may thus lead to a higher rate of false positive results. However, the specificity of the new sensitive assays has also increased, for which our data provide persuasive evidence.[11-14] The current investigational assay represents an entire generation of contemporary assays with a 10% coefficient of variation below the 99th percentile population distribution. Finally, whether the classification of unstable angina pectoris will still be necessary in the era of sensitive troponin testing will require further study.

In conclusion, initial use of the sensitive troponin I assay substantially improved the early diagnosis of myocardial infarction and helped to safely rule out or rule in coronary causes of acute chest pain. Future studies will be needed to determine whether the early diagnosis of myocardial infarction facilitates rapid use of invasive strategies and thus improves the outcome in patients with myocardial infarction.

Supported by the University Medical Center of the Johannes Gutenberg University of Mainz and an unrestricted grant from BRAHMS Aktiengesellschaft.

Dr. Peetz reports receiving lecture fees from Siemens Healthcare Diagnostics, Instrumentation Laboratories, and Mitsubishi Chemical Europe; and Dr. Baldus, lecture fees from AstraZeneca and Abbott Diagnostics and grant support from Sanofi Aventis. No other potential conflict of interest relevant to this article was reported.

We thank Margot Neuser for her assistance with an earlier version of the figures.

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