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Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction

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Background—Current guidelines for the diagnosis of acute myocardial infarction (AMI), among other criteria, also require a rise and/or fall in cardiac troponin (cTn) levels. It is unknown whether absolute or relative changes in cTn have higher diagnostic accuracy and should therefore be preferred.

Methods and Results—In a prospective, observational, multicenter study, we analyzed the diagnostic accuracy of absolute (Δ) and relative (Δ%) changes in cTn in 836 patients presenting to the emergency department with symptoms suggestive of AMI. Blood samples for the determination of high-sensitive cTn T and cTn I ultra were collected at presentation and after 1 and 2 hours in a blinded fashion. The final diagnosis was adjudicated by 2 independent cardiologists. The area under the receiver operating characteristic curve for diagnosing AMI was significantly higher for 2-hour absolute (Δ) versus 2-hour relative (Δ%) cTn changes (area under the receiver operating characteristic curve [95% confidence interval], high-sensitivity cTn T: 0.95 [0.92 to 0.98] versus 0.76 [0.70 to 0.83], $P<0.001$; cTn I ultra: 0.95 [0.91 to 0.99] versus 0.72 [0.66 to 0.79], $P<0.001$). The receiver operating characteristic curve–derived cutoff value for 2-hour absolute (Δ) change was 0.007 μg/L for high-sensitivity cTn T and 0.020 μg/L for cTn I ultra (both cutoff levels are half of the 99th percentile of the respective cTn assay). Absolute changes were superior to relative changes in patients with both low and elevated baseline cTn levels.

Conclusions—Absolute changes of cTn levels have a significantly higher diagnostic accuracy for AMI than relative changes, and seem therefore to be the preferred criteria to distinguish AMI from other causes of cTn elevations.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00470587.

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Key Words: acute myocardial infarction ■ chest pain diagnosis ■ high sensitive cardiac troponin assay ■ troponin

Cardiac troponin (cTn) I and T are the current gold standard for the detection of myocardial necrosis, and acute myocardial infarction (AMI) is the most important cause of myocardial necrosis.[1] The current universal definition of AMI requires a rise and/or fall in cTn in patients with evidence of myocardial ischemia, with at least 1 cTn value above the 99th percentile.[2] Blood samples for measurement of cTn are recommended to be drawn at presentation and 6 to 9 hours later to optimize clinical sensitivity for ruling in AMI. It is unknown whether absolute or relative changes in cTn have higher accuracy, and should therefore be preferred. There is also emerging evidence suggesting that with the use of sensitive or high-sensitive cTn assays, a blood sample collected 2 or 3 hours after presentation might be appropriate for an earlier rule in and rule out compared with the recommended second blood draw 6 to 9 hours after admission.[3]

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Recently, improved cTn assay technology has led to the development of fully automated cTn assays with higher sensitivity and improved precision.[2,4,5] These improvements allow the measurement of cTn levels even in healthy individuals,[6–9] and the novel assays have been shown to improve

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early diagnostic accuracy for AMI in patients with acute chest pain.[10,11] The clinical introduction of the sensitive assays, however, markedly increases the number of chest pain patients presenting with cTn values exceeding the 99th percentile as a result of causes other than AMI, thus raising a dilemma in the appropriate triage of patients.[10,12–14] It is therefore critical to assess the rising and/or falling pattern of cTn levels to distinguish between increased levels caused by chronic cardiac disorders from acute cardiac conditions such as AMI.

The purpose of this study was to determine the diagnostic accuracy of early absolute (Δ) and relative (Δ%) changes in sensitive cTn within the first hour and the first 2 hours for the diagnosis of AMI as adjudicated on the basis of standard cTn assays in a nonselected heterogeneous population of patients presenting with acute chest pain to the emergency department (ED).

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, Basel, Switzerland.[10,15] From April 2006 to June 2009, 1247 consecutive white patients who presented to the ED with symptoms suggestive of AMI, such as chest pain and angina pectoris with onset or peak of symptoms within the last 12 hours, were recruited. Patients with terminal kidney failure requiring dialysis were excluded. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the local ethics committee at each participating institution. Written informed consent was obtained from all patients.

Patients with ST-segment elevation myocardial infarction (n=50) were excluded from this analysis because cardiac biomarkers are of limited clinical value in these patients. Among the remaining 1197 patients, samples at presentation as well as after 1 hour for measurement of both high-sensitive cardiac troponin T (hs-cTnT) and cardiac troponin I ultra (cTnI-ultra) were available in 836 patients. Of these, additional samples after 2 hours were available in 590 patients.

Clinical Assessment

All patients underwent an initial clinical assessment that included clinical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood tests, and chest radiography. Standard cTn levels were measured at presentation and after 6 to 9 hours or as long as clinically indicated. Timing and treatment of patients were left to the discretion of the attending physician.

Adjudicated Final Diagnosis

To determine the final diagnosis for each patient, 2 independent cardiologists blinded to measurements of hs-cTnT and cTnI-ultra reviewed all available medical records (including patient history, physical examination, results of laboratory testing, including local cTn values, radiological testing, ECG, echocardiography, cardiac exercise test, coronary angiography) pertaining to the patient from the time of ED presentation to 60-day follow-up. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and cTn levels were interpreted as recommended in current guidelines.[1,2,4,5] In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. Cardiac necrosis was diagnosed when there was at least 1 value of the local standard cTn above the 99th percentile (or above the 10% imprecision value if not fulfilled at the 99th percentile). In the absence of uniformly accepted published guidelines, a significant rise and/or fall was defined as a change of at least 30% of the 99th percentile (or the 10% coefficient of variation level) within 6 to 9 hours.[1,2,4,5] The following cTn assays were used for the adjudication of the final diagnosis on-site: Abbott Axsym cTnI ADV, Beckmann Coulter Accu cTnI, and Roche cTnT fourth generation. All 3 are well-validated current standard cTn assays with comparable performance in the diagnosis of AMI (see the online-only Data Supplement for details on use of local cTn assays for final diagnosis adjudication).[4,5] Unstable angina was diagnosed in patients with normal cTn levels and typical angina at rest, in patients with deterioration of a previously stable angina, in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have a stenosis of ≥70%, and in ambiguous cases in which follow-up information revealed AMI or a sudden, unexpected cardiac death within 60 days. Additional predefined diagnostic categories included cardiac but not coronary symptoms (eg, perimyocarditis, tachyarrhythmias), noncardiac chest pain, and symptoms of unknown origin. If AMI was excluded in the ED but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified as being of unknown origin.

Biochemical Analysis

Blood samples for the determination of Roche hs-cTnT and Siemens cTnI-ultra were collected in serum tubes or EDTA tubes, respectively, at the time of the patient's presentation to the ED. Additional samples were obtained 1, 2, 3, and 6 hours after presentation. Serial sampling was discontinued when the diagnosis of AMI 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 a dedicated core laboratory.

The hs-cTnT assay was performed with the use of the Elecsys 2010 system (Roche Diagnostics). Limit of detection has been determined to be 0.003 μg/L; an imprecision corresponding to a 10% coefficient of variation was reported at 0.013 μg/L with the 99th percentile of a healthy reference population at 0.014 μg/L.[9]

The cTnI-ultra assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens). Limit of detection has been determined to be 0.006 μg/L; a 10% coefficient of variation was reported at 0.030 μg/L with the 99th percentile cutoff point of 0.04 μg/L.[7,8]

Estimated glomerular filtration rate was calculated with the use of the abbreviated Modification of Diet in Renal Disease formula.[16]

Statistical Analysis

The data are presented as proportions, mean±SD, and, in the case of nonnormal distribution, as median with interquartile range. Comparisons were made with the *t* test for normally distributed continuous variables, Mann-Whitney *U* test for nonnormally distributed continuous variables, Fisher exact test for categorical variables with any field including <6 patients, and χ^2 test for the other categorical variables. The Kolmogorov-Smirnov test was used to test for normality. The absolute values were used because we were interested in the magnitude of the change and also because we were testing for 2-tailed significance. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy for the diagnosis of AMI for absolute values of the absolute (Δ) and relative (Δ%) changes in hs-cTnT and cTnI-ultra within the first hour and within the first 2 hours after presentation. The comparison of areas under the ROC curves (AUC) was performed as recommended by DeLong et al.[17] Optimal cutoff values were derived from ROC curves as described by Youden,[18] and sensitivity, specificity, negative predictive value, and positive predictive value were calculated. All hypothesis testing was 2 tailed, and a *P* value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS for Windows 19.0 (SPSS Inc, Chicago, IL) and MedCalc 9.6.4.0 (MedCalc Software).

Table 1. Baseline Characteristics of the Patients

	All Patients (n=836)	AMI (n=108)	No AMI (n=728)	*P*
Male gender, No. (%)	563 (67)	73 (68)	490 (67)	0.95
Age, y	64 (51–76)	74 (63–82)	63 (50–74)	<0.001
Body mass index, kg/m^2	27 (24–30)	26 (24–29)	27 (24–30)	0.19
Medical history, No. (%)				
Coronary artery disease	308 (37)	49 (45)	259 (36)	0.05
Previous myocardial infarction	212 (25)	36 (33)	176 (24)	0.04
Arterial hypertension	536 (64)	81 (75)	455 (63)	0.01
Hypercholesterolemia	390 (47)	55 (51)	335 (46)	0.34
Previous stroke	51 (6)	17 (16)	34 (5)	<0.001
Peripheral artery disease	58 (7)	13 (12)	45 (6)	0.03
Diabetes mellitus	173 (22)	26 (24)	146 (21)	0.24
Smoker (current and past)	499 (60)	75 (62)	430 (60)	0.75
eGFR, mL/min per m^2	89 (70–106)	75 (59–100)	91 (73–107)	<0.001
Medications, No. (%)				
Platelet inhibitor	357 (43)	52 (48)	305 (42)	0.22
β-Blocker	324 (39)	45 (42)	279 (38)	0.51
ACE inhibitor/angiotensin receptor blocker	346 (41)	50 (46)	296 (41)	0.27
Calcium antagonist	144 (17)	22 (20)	122 (17)	0.35
Statin	306 (37)	40 (37)	266 (37)	0.92
BNP ≥400 pg/mL	93 (13)	34 (35)	59 (9)	<0.001

AMI denotes acute myocardial infarction; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; and BNP, B-type natriuretic peptide (available in 727 of 836 patients [87%]).

Results

Characteristics of Patients

The baseline characteristics of all 836 patients are shown in Table 1. AMI was the adjudicated final diagnosis in 108 patients (13%). The other adjudicated final diagnoses were unstable angina in 120 (14%), cardiac symptoms from causes other than coronary artery disease in 118 (14%), noncardiac causes in 417 (50%), and symptoms of unknown origin in 73 patients (9%). Baseline levels of cTn measured at presentation were significantly higher in patients in whom AMI was the final diagnosis than in patients in whom there was a different final diagnosis (Figure 1).

Additional samples after 2 hours were available in 590 of 836 patients. Of these, 11% suffered from AMI, 15% from unstable angina, 14% from cardiac symptoms from causes other than coronary artery disease, 49% from noncardiac causes, and 11% from symptoms of unknown origin. Baseline characteristics of these patients are displayed in Table I of the online-only Data Supplement.

Early Absolute Cardiac Troponin Changes

The absolute changes (Δ) between cTn levels at presentation and after 1 hour and 2 hours were significantly higher in patients diagnosed with AMI than in the rest of the patients ($P<0.001$ for Δ1-hour and Δ2-hour values and for both assays) (Figure 2A).

Figure 3 shows the proportion of patients according to the amount of absolute (Δ) 2-hour changes in hs-cTnT and cTnI-ultra stratified to AMI or other diagnoses of chest pain. In patients with AMI, an absolute 2-hour change >+0.010 μg/L was observed in 79% and 93% of patients, according to hs-cTnT and cTnI-ultra, respectively. In patients without AMI, an absolute 2-hour change of hs-cTnT of <0.006 μg/L

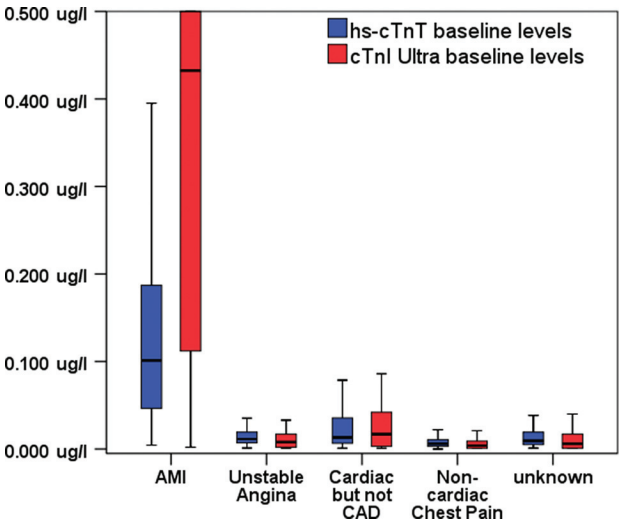

Figure 1. Baseline cardiac troponin levels according to adjudicated final diagnoses. Baseline levels of high-sensitive cardiac troponin T (hs-cTnT) (blue) and cardiac troponin I ultra (cTnI-ultra) (red) according to the final diagnosis. The boxes represent interquartile ranges, the horizontal line in each box represents the median, and the whiskers show the minimum and maximum values (excluding outliers that were >1.5 times the values represented at each end of the box). The 75th percentile of cTnI-ultra in patients with acute myocardial infarction (AMI) was 1.90 μg/L, and the upper box plot whisker was 4.11 μg/L. CAD indicates coronary artery disease.

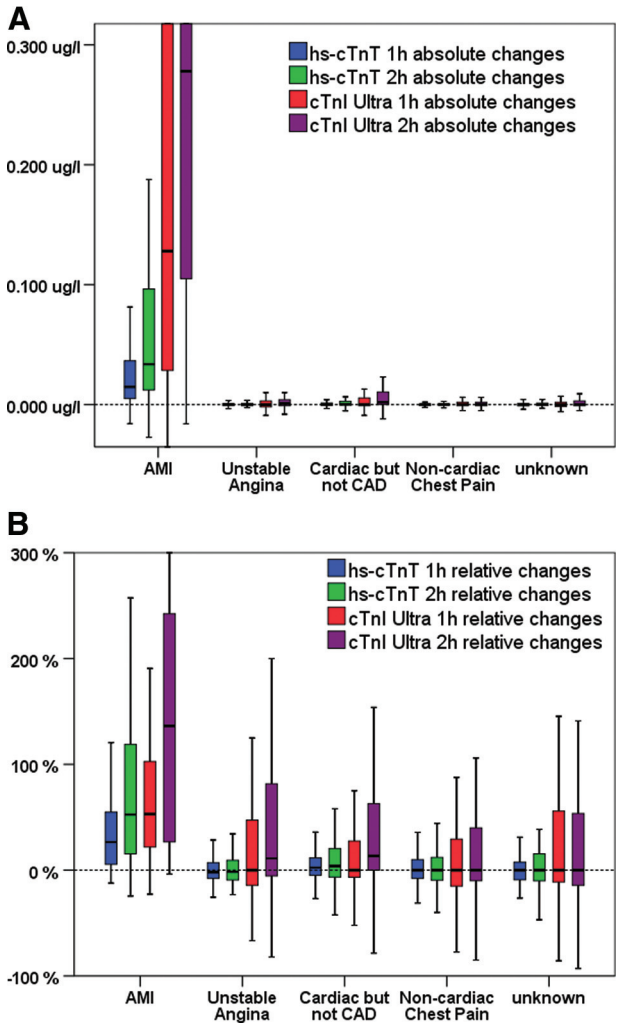

Figure 2. Absolute and relative cardiac troponin changes according to adjudicated final diagnoses. Absolute (**A**) and relative (**B**) changes according to the final diagnosis are shown. The boxes represent interquartile ranges, the horizontal line in each box represents the median, and the whiskers show the minimum and maximum values (excluding outliers that were >1.5 times the values represented at each end of the box). hs-cTnT indicates high-sensitive cardiac troponin T; cTnI-ultra, cardiac troponin I ultra; AMI, acute myocardial infarction; and CAD, coronary artery disease.

(ie, between −0.006 and +0.006 μg/L) within the first 2 hours was seen in 92%, according to hs-cTnT, and in 76%, according to cTnI-ultra.

Early Relative Cardiac Troponin Changes

Similar to absolute changes, the relative changes (Δ%) between the values of cTn at presentation and after 1 hour and 2 hours were significantly higher among AMI patients compared with patients with other diagnoses ($P<0.001$ for Δ% 1-hour and Δ% 2-hour values and for both assays) (Figure 2B).

Figure 4 shows the proportion of patients according to the amount of relative (Δ%) 2-hour changes in hs-cTnT and cTnI-ultra stratified to AMI or other diagnoses of chest pain. In patients with AMI, a relative 2-hour change of >25% (ie, >+25% or <−25%) was observed in 64% and 75% of patients, according to hs-cTnT and cTnI-ultra, respectively, whereas in patients without AMI, a relative 2-hour change of <25% (ie, in between +25% and −25%) was observed in 80% and 51%, respectively.

Diagnostic Accuracy of Absolute and Relative Cardiac Troponin Changes

The diagnostic accuracy of absolute cTn changes for the diagnosis of AMI was very high both after 1 hour (AUC, 0.93; 95% confidence interval, 0.90 to 0.96 for hs-cTnT and AUC, 0.94, 95% confidence interval, 0.91 to 0.97 for cTnI-ultra) and after 2 hours (AUC, 0.95; 95% confidence interval, 0.92 to 0.98 for hs-cTnT and AUC, 0.95; 95% confidence interval, 0.91 to 0.99 for cTnI-ultra), and was significantly higher compared with that of relative changes at both time points ($P<0.001$ for comparisons; Figure 5 and Table 2). The ROC curve–derived optimal cutoff values for absolute changes within 2 hours were 0.007 μg/L for hs-cTnT and 0.020 μg/L for cTnI-ultra. The use of these cutoff values resulted in sensitivity, specificity, positive predictive value, and negative predictive value of 89%, 93%, 64%, and 98% for hs-cTnT and 93%, 91%, 58%, and 99% for cTnI-ultra, respectively (Table 2).

For the differentiation of unstable angina from noncardiac causes of chest pain, the diagnostic accuracy was low for absolute (AUC, 0.59 for hs-cTnT and 0.60 for cTnI-ultra) as well as relative 2-hour cTn changes (AUC, 0.46 for hs-cTnT and 0.58 for cTnI-ultra), and was comparable to the diagnostic accuracy of baseline cTn levels (AUC, 0.72 for hs-cTnT and 0.63 for cTnI-ultra).

Diagnostic Accuracy of Absolute and Relative Changes According to Baseline Cardiac Troponin Values

At presentation, a total of 296 patients (35%) had hs-cTnT levels above the 99th percentile (0.014 μg/L), and 170 patients (20%) had cTnI-ultra levels above the 99th percentile (0.04 μg/L). Diagnostic accuracies of absolute (Δ) and relative (Δ%) 1- and 2-hour changes in hs-cTnT and cTnI-ultra are shown in Table 3 according to baseline cTn levels. Regardless of baseline levels, absolute changes were superior compared with relative changes for both assays at all time points.

Diagnostic Accuracy of Absolute and Relative Cardiac Troponin Changes in Important Patient Subgroups

The diagnostic superiority of absolute over relative changes was observed throughout several important patient subgroups, such as in male and female patients, in patients aged ≥70 years, in patients with renal dysfunction and an estimated glomerular filtration rate <60 mL/min per 1.73 m^2, and in patients with heart failure as indicated by B-type natriuretic peptide levels >400 pg/mL (Table 4). Furthermore, the diagnostic performance of cTn changes was not influenced by the time since onset of symptoms and was similar in patients presenting within the first 3 hours, within 4 to 10 hours, or later than 10 hours.

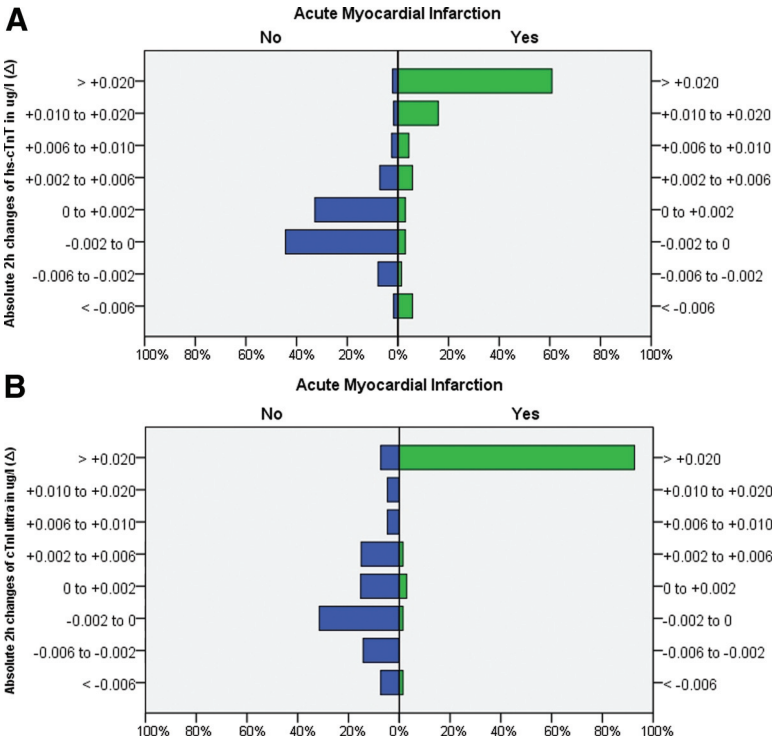

Figure 3. Absolute 2-hour changes of high-sensitive cardiac troponin T (hs-cTnT) and cardiac troponin I ultra (cTnI-ultra). Absolute 2-hour changes in hs-cTnT (**A**) and cTnI-ultra (**B**) are shown. Patients with acute myocardial infarction are displayed on the right side in green, and patients with other causes of chest pain are displayed on the left side in blue.

Combination of Baseline Cardiac Troponin Levels With Early Cardiac Troponin Changes in the Diagnosis of Acute Myocardial Infarction

Combination of baseline cTn levels with early absolute changes resulted in a significant improvement of diagnostic accuracy for AMI for hs-cTnT (AUC, 0.94 for baseline levels; AUC, 0.98 for combination with 1-hour absolute changes [$P=0.001$ for comparison with baseline]; AUC, 0.98 for combination with 2-hour absolute changes [$P<0.001$ for comparison with baseline]) as well as for cTnI-ultra (AUC, 0.95 for baseline levels; AUC, 0.96 for combination with 1-hour absolute changes [$P=0.05$ for comparison with baseline]; AUC, 0.97 for combination with 2-hour absolute changes [$P=0.02$ for comparison with baseline]). However, combination of baseline cTn levels with early relative changes did not significantly improve diagnostic accuracy

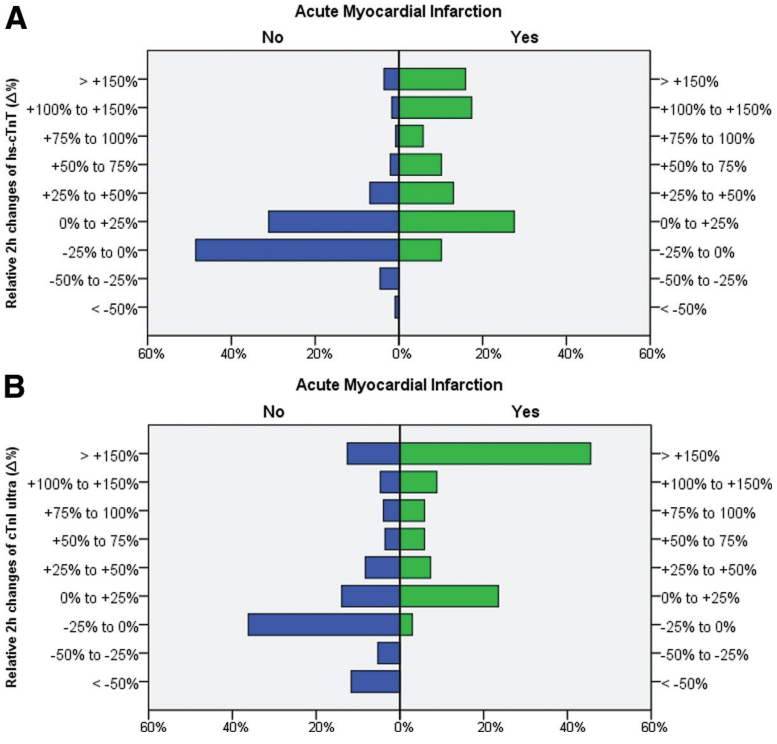

Figure 4. Relative 2-hour changes of high-sensitive cardiac troponin T (hs-cTnT) and cardiac troponin I ultra (cTnI-ultra). Relative 2-hour changes in hs-cTnT (**A**) and cTnI-ultra (**B**) are shown. Patients with acute myocardial infarction are displayed on the right side in green, and patients with other causes of chest pain are displayed on the left side in blue.

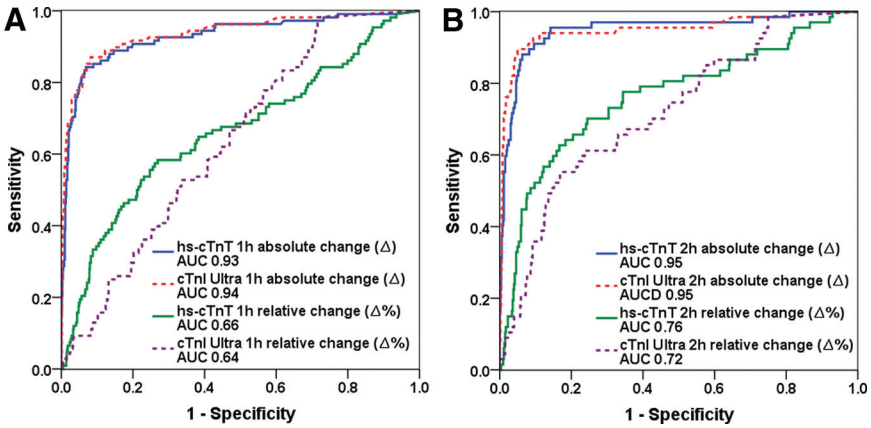

Figure 5. Receiver operating characteristic curves of 1-hour and 2-hour changes. Receiver operating characteristic curves showing the diagnostic performance for the diagnosis of acute myocardial infarction provided by absolute (Δ) and relative (Δ%) changes in high-sensitive cardiac troponin T (hs-cTnT) and cardiac troponin I ultra (cTnI-ultra) within the first hour (**A**) and within the first 2 hours (**B**) are shown. AUC indicates area under the curve.

provided by baseline levels alone (AUC, 0.94 for hs-cTnT baseline levels; AUC, 0.94 for combination with 1-hour relative changes [$P=0.40$ for comparison with baseline]; AUC, 0.94 for combination with 2-hour relative changes [$P=0.31$ for comparison with baseline]; AUC, 0.95 for cTnI-ultra baseline levels; AUC, 0.95 for combination with 1-hour relative changes [$P=0.54$ for comparison with baseline]; AUC, 0.96 for combination with 2-hour relative changes [$P=0.35$ for comparison with baseline]).

Comparison of Diagnostic Accuracy of Cardiac Troponin Changes After 1 Hour, 2 Hours, and 6 Hours

Values of cTn at baseline as well as after 1 hour, 2 hours, and 6 hours were available in a subgroup of 305 patients (36%). Median absolute cTn changes in AMI patients within 6 hours were 0.055 μg/L (interquartile range, 0.018 to 0.309 μg/L) for hs-cTnT and 0.488 μg/L (interquartile range, 0.098 to 3.021 μg/L) for cTnI-ultra. Diagnostic accuracies for AMI were similar for absolute 1-hour, 2-hour, and 6-hour changes in hs-cTnT (AUCs, 0.91, 0.96, 0.95; $P>0.05$ for all comparisons) and in cTnI-ultra (AUCs, 0.91, 0.94, 0.95; $P>0.05$ for all comparisons). Relative 6-hour changes were inferior compared with absolute changes (AUC, 0.79 for hs-cTnT and 0.73 for cTnI-ultra; $P<0.001$ for comparison with 6-hour absolute changes).

Discussion

This study evaluated the clinical utility of absolute and relative cTn changes in the early diagnosis of AMI with the use of 2 well-validated sensitive cTn assays, hs-cTnT and cTnI-ultra. We report 6 novel findings, as follows: First, early absolute cTn changes were superior to relative cTn changes in diagnosing AMI among unselected patients with symptoms suggestive of AMI. Second, the utility of absolute cTn changes to diagnose AMI was similar for both assays. Third, the diagnostic superiority of absolute over relative cTn changes was independent of the underlying cTn baseline value and consistent in important subgroups of patients, such as the elderly and patients with impaired renal function. Fourth, the combination of baseline levels with absolute but

Table 2. Area Under the Receiver Operating Characteristic Curves for the Diagnosis of Acute Myocardial Infarction for Absolute and Relative Changes in Cardiac Troponin After 1 and 2 Hours From Presentation

	AUC (95% CI)	*P*	ROC Cutoff	Patients Above Cutoff, %	Sensitivity	Specificity	PPV	NPV
hs-cTnT								
1 hour (n=836, 108 with AMI)								
Absolute change (Δ)	0.93 (0.90–0.96)	<0.001	0.004	17	84	93	66	97
Relative change (Δ%)	0.66 (0.60–0.72)		17	30	57	74	27	91
2 hours (n=590, 67 with AMI)								
Absolute change (Δ)	0.95 (0.92–0.98)	<0.001	0.007	16	89	93	64	98
Relative change (Δ%)	0.76 (0.70–0.83)		30	21	64	84	35	94
cTnI-ultra								
1 hour (n=836, 108 with AMI)								
Absolute change (Δ)	0.94 (0.91–0.97)	<0.001	0.016	19	86	92	64	98
Relative change (Δ%)	0.64 (0.59–0.69)		43	35	53	66	19	91
2 hours (n=590, 67 with AMI)								
Absolute change (Δ)	0.95 (0.91–0.99)	<0.001	0.020	19	93	91	58	99
Relative change (Δ%)	0.72 (0.66–0.79)		117	21	57	83	32	93

AUC denotes area under the receiver operating characteristic (ROC) curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; hs-cTnT, high-sensitive cardiac troponin T; and cTnI-ultra, cardiac troponin I ultra.

Table 3. Area Under the Receiver Operating Characteristic Curves for the Diagnosis of Acute Myocardial Infarction for Absolute and Relative Changes in Cardiac Troponin After 1 and 2 Hours From Presentation According to Baseline Cardiac Troponin Levels

	AUC (95% CI)	*P*	ROC Cutoff	Sensitivity	Specificity	PPV	NPV
hs-cTnT							
<0.014 μg/L at presentation							
1 h (n=540, 7 with AMI)							
Absolute change (Δ)	0.85 (0.61–1.00)	0.027	0.004	86	95	19	100
Relative change (Δ%)	0.83 (0.59–1.00)		45	86	90	10	99
2 hours (n=396, 6 with AMI)							
Absolute change (Δ)	0.98 (0.96–1.00)	0.052	0.005	100	95	22	100
Relative change (Δ%)	0.95 (0.91–0.99)		39	100	86	10	100
≥0.014 μg/L at presentation							
1 h (n=296, 101 with AMI)							
Absolute change (Δ)	0.88 (0.83–0.93)	<0.001	0.005	84	86	75	91
Relative change (Δ%)	0.70 (0.64–0.77)		17	55	86	67	79
2 hours (n=194, 61 with AMI)							
Absolute change (Δ)	0.91 (0.86–0.96)	<0.001	0.008	90	87	76	95
Relative change (Δ%)	0.79 (0.71–0.87)		16	75	80	64	88
cTnI-ultra							
<0.040 μg/L at presentation							
1 h (n=666, 12 with AMI)							
Absolute change (Δ)	0.80 (0.67–0.94)	0.006	0.002	92	61	4	100
Relative change (Δ%)	0.70 (0.55–0.85)		11	92	43	3	100
2 hours (n=485, 9 with AMI)							
Absolute change (Δ)	0.89 (0.72–1.00)	0.027	0.023	89	96	30	100
Relative change (Δ%)	0.86 (0.69–1.00)		150	89	87	11	100
≥0.040 μg/L at presentation							
1 h (n=170, 96 with AMI)							
Absolute change (Δ)	0.87 (0.81–0.92)	<0.001	0.053	76	89	90	74
Relative change (Δ%)	0.71 (0.63–0.79)		40	52	86	83	58
2 hours (n=105, 58 with AMI)							
Absolute change (Δ)	0.86 (0.78–0.94)	0.001	0.131	76	89	90	75
Relative change (Δ%)	0.74 (0.64–0.83)		98	50	91	88	60

AUC denotes area under the receiver operating characteristic (ROC) curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; hs-cTnT, high-sensitive cardiac troponin T; and cTnI-ultra, cardiac troponin I ultra.

not relative changes significantly improved the diagnostic accuracy provided by baseline cTn levels. Fifth, diagnostic accuracies for AMI provided by early absolute changes within 1 and 2 hours were not inferior compared with changes within 6 hours. Sixth, the optimal cutoff values as derived by ROC curve analysis for the 2-hour absolute cTn changes were approximately half of the 99th percentile value of their respective assay.

Our findings are of major clinical importance. The current universal definition of AMI requires a "significant rise and/or fall in cTn" for the diagnosis of AMI to be fulfilled in addition to an elevation above the 99th percentile. There is, however, no statement in the guidelines yet on the amount of cTn change required to be considered significant, and whether to assess relative or absolute cTn changes in the diagnosis of AMI is a matter of debate. The National Academy of Clinical Biochemistry guidelines have suggested that in patients with possible acute coronary syndrome and elevated baseline cTn values, changes in cTn concentrations of >20% should be used to define patients with an AMI.[19] Data from studies assessing the diagnostic use of cTn changes in patients with acute chest pain are rare, and are only beginning to emerge. However, cTn changes in serial sampling are critical to differentiate stable chronic cardiac conditions from AMI in patients with only minor elevations of cTn just above the 99th percentile, which significantly increase with the introduction of hs-cTn assays.[20–23]

Apple et al[24] demonstrated in 381 patients that utilizing cTnI Δ% of >30% in addition to either the baseline or follow-up concentration (at 6 hours) improved both specificity and risk assessment in patients presenting with symptoms of acute cardiac syndrome. Other studies reported optimal relative change proportions between 20% and 235%.[3,25–27] Regarding absolute changes, Kavsak et al[28] analyzed the prognostic meaning of absolute versus relative cTn changes in 223 chest pain patients and found worse long-term out-

Table 4. Area Under the Receiver Operating Characteristic Curves for the Diagnosis of Acute Myocardial Infarction for Absolute and Relative Changes in Cardiac Troponin After 1 and 2 Hours From Presentation in Important Patient Subgroups

		Changes in hs-cTnT				Changes in cTnI-Ultra			
		Absolute (Δ)		Relative (Δ%)		Absolute (Δ)		Relative (Δ%)	
	n	1 h	2 h	1 h	2 h	1 h	2 h	1 h	2 h
Male gender	563	0.92	0.94	0.68	0.80	0.93	0.94	0.64	0.75
Female gender	273	0.94	0.97	0.63	0.68	0.95	0.98	0.64	0.66
Elderly (age ≥70 y)	271	0.90	0.94	0.70	0.80	0.95	0.91	0.66	0.73
Impaired renal function (eGFR <60 mL/min per 1.73 m^2)	125	0.88	0.94	0.62	0.70	0.88	0.92	0.61	0.69
Heart failure (BNP ≥400 pg/mL)	93	0.85	0.96	0.65	0.82	0.91	0.92	0.72	0.77
Time since onset of symptoms ≤3 h	319	0.92	0.97	0.73	0.81	0.93	0.98	0.72	0.85
Time since onset of symptoms 4–10 h	282	0.94	0.98	0.74	0.91	0.93	0.94	0.71	0.78
Time since onset of symptoms >10 h	235	0.92	0.94	0.52	0.61	0.95	0.92	0.49	0.54

hs-cTnT indicates high-sensitive cardiac troponin T; cTnI-ultra, cardiac troponin I ultra; eGFR, estimated glomerular filtration rate; and BNP, B-type natriuretic peptide.

comes for both patients with increased absolute changes and patients with increased relative changes. In terms of diagnosis, it is remarkable that, to our knowledge, no studies have thus far analyzed the diagnostic meaning of absolute cTn changes in the diagnosis of AMI. It is therefore even more important to report that in our study, absolute changes were significantly more accurate than relative changes in the diagnosis of AMI.

The diagnostic superiority of absolute over relative changes may be explained at least in part by 2 considerations: Because of the improved sensitivity of novel cTn assays enabling measurement of very small amounts of cTn even in the normal range, many patients without AMI might have low baseline cTn levels, and large relative cTn changes of, for example, 30% to 50% may be reached. On the other hand, relative change cutoff values of 113%[26] or 235%,[27] as proposed recently, might not be reached by most of the AMI patients presenting several hours after the onset of symptoms with already elevated baseline cTn levels. In these patients, relative change criteria will negatively affect rule in of AMI. In accordance with these aspects, absolute cTn changes were superior compared with relative cTn changes not only in the overall cohort but also both in patients with low baseline cTn levels and in patients with elevated baseline cTn levels and for both cTnI-ultra and hs-cTnT assays.

Recent studies assessed the short- and long-term biological variation of cTn by calculating reference change values in healthy individuals.[23,29] Wu et al[23] found that short-term (4-hour) changes of 46% are necessary to define a changing pattern with the use of a single-molecule detection system for cTnI, whereas Vasile et al[29] reported 85% for the hs-cTnT assay. Whether the use of small absolute changes might be feasible and accurate in clinical practice has therefore been discussed. This seems to hold true for 2 reasons: First, from a theoretical analytical point of view, with the assumption that the healthy individuals assessed in the biological variation studies have had cTn values well below the 99th percentile, the corresponding absolute values for 4-hour changes indicating a real change would be in the range of 0.005 μg/L for the cTnI assay and 0.012 μg/L for the hs-cTnT assay. The ROC curve–derived optimal cutoff values for 2-hour absolute changes with the assays used in our study were 0.020 μg/L for cTnI-ultra and 0.007 μg/L for hs-cTnT. Second, and probably even more important, our study was an in vivo study using 2 commercially available sensitive assays in consecutive chest pain patients. In doing so, we found a very high diagnostic accuracy for absolute changes, with sensitivities and specificities for the optimal cutoff values in the range of 90%. This seems to prove the feasibility as well as the need of using the information about even very small absolute changes in cTn during serial sampling.

The ROC curve–derived optimal cutoff values for 2-hour absolute changes corresponded to approximately half of the 99th percentile values of the respective cTn assays (0.020 μg/L for cTnI-ultra and 0.007 μg/L for hs-cTnT). Given the clinical challenge, particularly in patients with mildly elevated initial cTn values, to early and reliably differentiate AMI from other conditions that lead to stable chronic elevations of cTn just above the 99th percentile, this finding should help in the clinical application of cTn assays.[20–23] It also highlights that a rather pronounced change in cTn within 2 hours is required to diagnose AMI, suggesting that small changes occur commonly in non-AMI conditions. In addition, our results support the concept of obtaining a second measurement of cTn as early as 2 hours after presentation. It is unknown whether the optimal cutoff values for absolute changes of other high-sensitivity cTn assays will also be approximately half of their 99th percentile values. Because of relevant analytical and biochemical differences among the new cTn assays, this needs to be determined specifically for each assay in appropriately sized cohort studies of unselected patients presenting with symptoms suggestive of AMI.

We compared the generation of more sensitive cTn assays with the standard assays for cTn that were used clinically to make the diagnosis of AMI. Thus, the ROC curves and the findings about the benefits of absolute versus relative changes in cTn levels need to be interpreted with regard to using the

new generation of more sensitive assays for cTn compared with the current generation. Finally, optimal cutoff values for clinical decision making always need to be selected on the basis of not only ROC curves but also the clinical situation requiring rather a high sensitivity or a high specificity.

The following limitations of our study merit consideration. As a prospective, observational study, we cannot quantify the potential clinical benefit associated with the application of the absolute and/or relative changes in cTn concentrations to diagnose AMI in patients with chest pain. Algorithms incorporating baseline cTn values as well as changes need to be developed retrospectively and validated prospectively. Second, the group of patients with cTn levels additionally available after 6 hours was slightly biased by the fact that patients with AMI often were already transferred to the catheterization laboratory or to the coronary care unit by 6 hours. The noninferiority of early absolute cTn changes compared with 6-hour changes needs to be interpreted as preliminary, and requires confirmation in further studies. Third, we cannot comment on the accuracy of cTn changes among patients with terminal kidney failure requiring dialysis because such patients were excluded from our study.

In conclusion, the diagnostic accuracy for AMI of absolute cTn changes as assessed with sensitive or high-sensitivity cTn assays and measured at presentation and after either 1 hour or 2 hours is very high, and markedly superior compared with corresponding relative changes. The diagnostic superiority of absolute changes over relative changes was similar for both cTnI and cTnT assays and independent of the underlying baseline values. These results indicate that absolute rather than relative cTn changes should be used in the assessment of patients with suspected AMI.

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CLINICAL PERSPECTIVE

The early diagnosis of acute myocardial infarction (AMI) remains challenging for the clinician. The current universal definition of AMI requires a rise and/or fall in cardiac troponin (cTn) in patients with evidence of myocardial ischemia, with at least 1 cTn value above the 99th percentile value. Blood samples for measurement of cTn are recommended to be drawn at presentation and 6 to 9 hours later to optimize clinical sensitivity for ruling in AMI. Whether absolute or relative changes in cTn have higher diagnostic accuracy and the amount of rise or fall in cTn that should be considered significant are unknown, however. This study evaluated the clinical utility of absolute and relative cTn changes within either 1 hour or 2 hours in the early diagnosis of AMI in 836 unselected patients presenting to the emergency department with symptoms suggestive of AMI. The major finding shows that the diagnostic accuracy for AMI of absolute cTn changes is very high and markedly superior compared with corresponding relative changes. The diagnostic superiority of absolute over relative cTn changes was independent of underlying cTn baseline values and consistent in important subgroups of patients such as the elderly and patients with impaired renal function. The combination of baseline levels with absolute but not relative changes significantly improved the diagnostic accuracy provided by baseline cTn levels. These results indicate that absolute rather than relative cTn changes should be used in the assessment of patients with suspected AMI.

SUPPLEMENTAL MATERIAL

Supplemental Methods

Use of local cTn values for adjudication of final diagnoses

For the **Roche cTnT 4th generation** assay, the 10% CV level is 0.035ug/l. The laboratories of the participating sites reported only two decimals, therefore 0.04ug/l was used as a cut-off for myocardial necrosis. In order to fulfil the criteria of a significant change (30% of 99th percentile or 10% CV level), a patient would e.g. need to have a level of <0.01ug/l at presentation and 0.04ug/l at 6h. A patient would also qualify if the first level is 0.02ug/l and the second 0.04ug/l. A patient would not fulfil the criteria if the first level is 0.03ug/l and the second is 0.04ug/l. If the first level is 0.04ug/l, the second level needs to be at least 0.06ug/l.

For the **Abbott Axsym cTnI ADV**, the 10% CV level is 0.16ug/l. A patient having 0.16ug/l at presentation would meet the criteria for significant change if the second was ≥0.21ug/l. A patient having <0.12ug/l at presentation (limit of detection) would qualify if the second is >0.16ug/l.

For the **Beckmann Coulter Accu cTnI**, the 10% CV level is 0.06ug/l. A patient having 0.06ug/l at presentation would qualify if the second is ≥0.08ug/l. A patient having 0.05ug/l at presentation would qualify if the second is 0.07ug/l, but not 0.06ug/l. A patient having undetectable cTnI (cTnI<0.01ug/l) at presentation would qualify if the second is ≥0.060ug/l.

Supplemental Tables

Supplemental Table 1	Baseline characteristics of patients with 1 and 2 hour troponin values (n=590)			
	All patients n=590	**AMI n=67**	**No AMI n=523**	**p-Value**
Male gender – no. (%)	397 (67)	46 (69)	351 (67)	0.80
Age – yr	64 [51 - 76]	74 [62 - 80]	64 [50 - 74]	<0.001
Body mass index (kg/m^2)	27 [24 - 30]	26 [24 - 29]	27 [24 - 30]	0.08
Medical history – no. (%)				
Coronary Artery Disease	221 (37)	30 (45)	191 (37)	0.19
Previous Myocardial Infarction	152 (26)	21 (31)	131(25)	0.27
Arterial Hypertension	378 (64)	51 (76)	327 (63)	0.03
Hypercholesterolemia	279 (47)	34 (51)	245 (47)	0.55
Previous Stroke	33 (6)	11 (16)	22 (4)	<0.001
Peripheral Artery Disease	44 (7)	8 (12)	36 (7)	0.14
Diabetes	122 (21)	19 (27)	103 (20)	0.23
Smoker (current and past)	356 (61)	42 (63)	314 (60)	0.86
eGFR – (ml/min/m^2)	90 [72 - 107]	82 [59 - 106]	91 [73 - 107]	0.04
Medications – no. (%)				
Platelet inhibitors	254 (43)	33 (49)	221 (42)	0.28
Beta-Blocker	234 (40)	29 (43)	205 (39)	0.52
ACE-Inhibitor / Angiotensin Receptor Blocker	250 (42)	32 (48)	218 (42)	0.34
Calcium antagonist	107 (18)	15 (22)	92 (18)	0.34
Statin	217 (37)	25 (37)	192 (37)	0.92
BNP $\geq$ 400 pg/ml	67 (13)	21 (36)	46 (10)	<0.001

AMI denotes acute myocardial infarction; BNP denotes B-type natriuretic peptide and was available in 500 of 590 patients (87%); eGFR denotes estimated glomerular filtration rate.