High-Sensitivity Cardiac Troponin in the Distinction of Acute Myocardial Infarction From Acute Cardiac Noncoronary Artery Disease

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Background—We hypothesized that high-sensitivity cardiac troponin (hs-cTn) and its early change are useful in distinguishing acute myocardial infarction (AMI) from acute cardiac noncoronary artery disease.

Methods and Results—In a prospective, international multicenter study, hs-cTn was measured with 3 assays (hs-cTnT, Roche Diagnostics; hs-cTnI, Beckman-Coulter; hs-cTnI Siemens) in a blinded fashion at presentation and serially thereafter in 887 unselected patients with acute chest pain. Accuracy of the combination of presentation values with serial changes was compared against a final diagnosis adjudicated by 2 independent cardiologists. AMI was the adjudicated final diagnosis in 127 patients (15%); cardiac noncoronary artery disease, in 124 (14%). Patients with AMI had higher median presentation values of hs-cTnT (0.113 μg/L [interquartile range, 0.049–0.246 μg/L] versus 0.012 μg/L [interquartile range, 0.006–0.034 μg/L]; $P<0.001$) and higher absolute changes in hs-cTnT in the first hour (0.019 μg/L [interquartile range, 0.007–0.067 μg/L] versus 0.001 μg/L [interquartile range, 0–0.003 μg/L]; $P<0.001$) than patients with cardiac noncoronary artery disease. Similar findings were obtained with the hs-cTnI assays. Adding changes of hs-cTn in the first hour to its presentation value yielded a diagnostic accuracy for AMI as quantified by the area under the receiver-operating characteristics curve of 0.94 for hs-cTnT (0.92 for both hs-cTnI assays). Algorithms using ST-elevation, presentation values, and changes in hs-cTn in the first hour accurately separated patients with AMI and those with cardiac noncoronary artery disease. These findings were confirmed when the final diagnosis was readjudicated with the use of hs-cTnT values and validated in an independent validation cohort.

Conclusion—The combined use of hs-cTn at presentation and its early absolute change excellently discriminates between patients with AMI and those with cardiac noncoronary artery disease.

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

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Key Words: coronary angiography ■ decision support techniques ■ heart diseases ■ myocardial infarction ■ troponin

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. Its rapid and accurate diagnosis is critical for the initiation of effective evidence-based medical management, including early revascularization,[1,2] but is still an unmet clinical need. Particularly challenging is distinguishing AMI from cardiac noncoronary artery diseases (CNCDs) such as hypertensive urgency/emergency, myocarditis, pericarditis, Takotsubo cardiomyopathy (TTC), acute heart failure, and cardiac arrhythmia.

Clinical Perspective on p 40

ECG and cardiac troponin (cTn) form the diagnostic cornerstones of clinical assessment.[3] ECG alone is often insufficient to diagnose AMI because significant ECG

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changes are absent in numerous AMI patients and because ST-segment deviation may be observed in multiple other cardiac and noncardiac conditions.[3,4] Cardiac troponins, structural proteins unique to the heart, are sensitive and specific biochemical markers of cardiomyocyte necrosis.[3,5]

It is unclear how to best apply high-sensitivity cTns (hs-cTns) in the distinction of AMI from CNCD. On the one hand, novel hs-cTn assays were shown to increase early diagnostic accuracy for the detection of AMI[6,7]; on the other hand, with the ability to accurately quantify mild elevations of hs-cTn above the 99th percentile, many patients with CNCD are now discovered to have elevated hs-cTn values.[8,9]

This multicenter study was performed to evaluate the hs-cTn level at presentation and absolute and relative changes within the first hours in the emergency department (ED) to distinguish AMI from CNCD and to identify those patients who are candidates for early coronary angiography.

Methods

Study Design and Population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital Basel, Basel, Switzerland. From April 2006 to June 2009, a total of 1247 consecutive patients presenting to the ED with symptoms suggestive of AMI of <12 hours were recruited.[6] Measurements of hs-cTnT were performed in 1213 patients. Of these, patients were included if hs-cTnT values were obtained at least at baseline and 1 hour thereafter, yielding a study population of 887 patients. Patients with terminal kidney failure requiring dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committees at each institution. Written informed consent was obtained from all patients. The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the manuscript, and decided to publish. The sponsors had no role in conducting the study or analyzing the data.

Routine 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. Cardiac troponin, the MB fraction of creatine kinase, and myoglobin were measured at presentation and after 6 to 9 hours as long as clinically indicated. Treatment of patients was left to the discretion of the attending physicians.

ECG Analysis

All 12-lead ECGs were assessed as recommended in current guidelines[3] in a core laboratory by internal medicine specialists blinded to patient details.

Adjudicated Final Diagnosis

To determine the final diagnosis for each patient, cases were centrally adjudicated by 2 independent cardiologists who 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, and coronary angiography) pertaining to the patient from the time of ED presentation to the 60-day follow-up. In situations of diagnostic disagreement, cases were reviewed and adjudicated with a third cardiologist. The cardiologists who adjudicated the post hoc final diagnosis were blinded to the results of the investigational hs-cTn assays. Neither hs-cTnT nor hs-cTnI assays were used by the local laboratories.

As recommended in current guidelines,[3] AMI (types 1 and 2) was diagnosed when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Necrosis was diagnosed by a rising and/or falling pattern of the local cTn with at least 1 value above the 99th percentile with an imprecision of <10%.[10] 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, respectively) within 6 to 9 hours.[3,10–12] The following cTn assays were used for the central adjudication of the final diagnosis: Roche cTnT fourth generation, Abbott Axsym cTnI ADV, and Beckman-Coulter Accu cTnI. All 3 assays are well-validated current standard cTn assays with comparable performance in the diagnosis of AMI[10] (see the Method section in the online-only Data Supplement).

The cause of myocardial necrosis (AMI versus CNCD) was adjudicated by considering all clinical data available, including chest pain characteristics; vital signs, particularly blood pressure at presentation; changes in the 12-lead ECG; detailed previous cardiac history, particularly history of heart failure, valvular heart disease, or left ventricular hypertrophy; coronary angiography; myocardial perfusion imaging; stress echocardiography; and magnetic resonance imaging. For example, a patient with a history of hypertensive heart disease, a blood pressure of 220/120 mm Hg at presentation, acute cardiomyocyte damage as documented by an elevated cTn value with a significant rise and fall, and normal coronary angiography was adjudicated to CNCD. The same occurred, for example, with patients diagnosed as having tachyarrhythmia, myocarditis, acute heart failure, or TTC. Unstable angina was diagnosed in patients with normal cTn levels and typical angina at rest, in those with a deterioration of a previously stable angina, and in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have a stenosis of ≥70%. Because we adjudicated the cause of the presentation to the ED (ie, acute chest pain) and not the cause of elevations of hs-cTnT, stable coronary artery disease was not a diagnostic group. A further category was noncardiac chest pain (such as musculoskeletal pain, gastroesophageal disorder). If no sufficient conclusive diagnostic procedures were performed, symptoms were classified as unknown origin. The vast majority of patients adjudicated to have AMI (73%) or unstable angina (60%) underwent coronary angiography and, when necessary, revascularization. However, the decision to perform coronary angiography was left to the discretion of the treating physician.

Investigational hs-cTn Analysis

Blood samples for the determination of hs-cTn were collected at presentation to the ED and serially thereafter at 1, 2, 3, and 6 hours. Serial sampling was discontinued when the diagnosis of AMI was certain and treatment required transferring the patient to the catheter laboratory. Samples were frozen at −80°C until assayed in a blinded fashion in a dedicated core laboratory. hs-cTnT was measured on the Elecsys 2010 (Roche Diagnostics); the limit of blank and limit of detection having been determined to be 0.003 and 0.005 μg/L, an imprecision corresponding to 10% coefficient of variation was reported at 0.013 μg/L and the 99th percentile of a healthy reference population at 0.014 μg/L.[13] Beckman-Coulter hs-cTnI was measured on the Access 2 analyzer using an investigational prototype assay. According to the manufacturer, the limit of detection is 0.002 μg/L, and the 99th percentile of a healthy reference population is 0.009 μg/L with a 10% coefficient of variation lower than the 99th percentile. For Siemens hs-cTnI, the limit of detection is 0.005 μg/L; the imprecision level corresponding to 10% coefficient of variation is found to be 0.003 μg/L; and the 99th percentile of a healthy reference population is 0.009 μg/L (all data according to the manufacturer).

Algorithm Identifying Patients With AMI

We developed a 3-step approach to identify patients with AMI as expeditiously as possible without compromising accuracy in that allocation process. To best reflect clinical practice, the algorithm used ST-segment elevation, hs-cTnT at presentation, and absolute change of hs-cTnT as key decision variables. In the first step,

patients with ST-segment elevations[3] at presentation were singled out. In the second step, the remaining patients were split into 3 groups according to presentation values of hs-cTnT (group 1, below the 99th percentile [<0.014 μg/L]; group 2, between 0.014 and 0.028 μg/L; and group 3, >0.028 μg/L) and further differentiated in patients with Δhs-cTnT 0 to 1 hour absolute (numeric, absolute change in the first hour) <0.005 or >0.005 μg/L.

Apart from 99th percentile cutoff values, no generally accepted recommendations are available for changes over time. We refrained from using predefined cutoff values but rather analyzed our data retrospectively. This applies for both the classification in the 3 main groups for our algorithm (<0.014, 0.014–0.028, >0.028 μg/L) and their further division by its first-hour change (>0.005 or <0.005 μg/L). Optimal cutoff points as provided by Youden indexes were chosen as reference points and further adapted. In general, in the differential diagnosis of chest pain patients, the relative harms of false negatives (a patient with AMI categorized as CNCD who is not provided further diagnostic and treatment) outweigh those of false positives (a patient with CNCD categorized as AMI possibly receiving unnecessary further diagnostics or treatment). Therefore, we optimized cutoff values provided by Youden indexes to minimize false negatives without substantially increasing the amount of false positives.[14]

To generalize the algorithm based on hs-cTnT, we added the same concept to derive 2 algorithms using hs-cTnI (Beckman-Coulter) and hs-cTnI (Siemens) assays for the distinction of patients with AMI and CNCD of patients. Furthermore, the algorithm was validated with the use of hs-cTnT in an independent cohort of patients enrolled in the study after June 2009 (validation cohort).

Identification of Candidates for Early Coronary Angiography

The question of whether to perform early coronary angiography is an important management decision in the ED. The differential diagnosis of patients with myocarditis and TTC from patients with AMI is extremely challenging and usually requires coronary angiography. In clinical practice, the risk of coronary angiography is, in general, outweighed by the risk of missing the opportunity to appropriately revascularize early a patient with an AMI deemed to be suffering from myocarditis or TTC. Therefore, we considered all patients with an adjudicated diagnosis of AMI, myocarditis, and TTC to be candidates for early coronary angiography for reasons of both early rule-in and revascularization and rule-out of a coronary obstruction (ie, regardless of the actual presence of a coronary obstruction). All patients with other adjudicated final diagnoses were considered not candidates for early coronary angiography. We do not address the necessity or benefit of coronary angiography in these patients during the course of hospitalization or thereafter.

Undoubtedly, coronary angiography and potential revascularization might also be considered in patients with a presumable ischemic origin of heart failure or dysrhythmia. However, in general, these patients do not warrant early coronary angiography.

Retrospective Readjudication of the Final Diagnosis Using hs-cTnT Values

All patients received a second retrospective adjudication based on hs-cTnT levels rather than the conventional cTn levels described above. Based on the diagnostic superiority of absolute over relative changes,[15] absolute changes were used for the diagnoses based on the hs-cTnT assay. Based on studies of the biological variation of cTn[16,17] and on data from previous chest pain cohort studies,[7,18] a significant absolute change was defined as a rise or fall of at least 0.010 μg/L within 6 hours, or, in an assumption of linearity, as an absolute change of 0.006 μg/L within 3 hours, 0.004 μg/L within 2 hours, or 0.002 μg/L within 1 hour. An alternative algorithm for these readjudicated patients was created that was based on the approach specified above.

Statistical Analysis

Comparisons between groups were made with the χ^2 method, Mann-Whitney *U*, or Kruskal-Wallis test. Receiver-operating characteristics curves were constructed to assess the sensitivity and specificity of hs-cTnT and compared as recommended by DeLong et al.[19] For comparisons of nested models, likelihood ratios were used for comparison. The relative numeric change was calculated by dividing the absolute value of hs-cTnT (1 hour) by the absolute value of hs-cTnT (0 hour). The numeric values of these fractions were used. We chose to consider the numeric values of both absolute and relative changes as the detection of a rise and/or fall of the measurements as essential to the diagnosis of AMI.[3]

Maximum, numeric, absolute changes were calculated for all patients within the first 6 hours after presentation compared with the first value at presentation (0-hour value). All serial measurements available (see also Table I in the online-only Data Supplement) were used for this calculation for each patient. The percent change between the 0-hour value of hs-cTnT and the respective 1-hour value was calculated, and the numeric change was used for all calculations and illustrations.

Decision curve analysis was used as a novel method combining accuracy measures (sensitivity, specificity) and clinical applicability by incorporating the clinical consequences associated with the test result.[20] Relative harms of false positives (eg, unnecessary coronary angiography) and false negatives (eg, missed coronary obstruction) are perceived differently on an individual-patient level. The proportion of all patients who are false positive is subtracted from the proportion who are true positive, weighted by the relative harm of a false-positive and a false-negative result. The threshold probability (P_t)[20,21] is the point at which the expected benefit of a procedure is equal to the expected benefit of avoiding it. The results of a decision curve analysis—the net benefit of a model—can easily be stated in clinically applicable terms: net decrease of patients treated unnecessarily. We incorporated continuous results of 0-hour hs-cTnT and its numeric absolute change in the first hour (Δhs-cTnT 0–1 hour abs.) in the decision curve analysis to analyze their usefulness in properly allocating early coronary angiography.

All hypothesis testing was 2 tailed, and a value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS for Windows 15.0 (SPSS Inc, Chicago, IL), MedCalc 9.6.4.0 (MedCalc Software), and the R statistical package (MathSoft Inc, Seattle, WA).

Results

Baseline Characteristics

Of the 887 patients enrolled, the adjudicated final diagnosis was AMI in 127 patients (15%) and CNCD in 124 (14%); 14% had unstable angina, and 49% had noncardiac and 8% had unknown causes of chest pain. Baseline characteristics are illustrated in the Table and Table II in the online-only Data Supplement.

Levels of hs-cTn at Presentation and Early Changes

Patients with AMI had higher median presentation values of hs-cTnT (median, 0.113 μg/L [interquartile range (IQR), 0.049–0.246 μg/L] versus 0.012 μg/L [IQR, 0.006–0.034 μg/L]; $P<0.001$) and higher absolute changes of hs-cTnT in the first hour (0.019 μg/L [IQR, 0.007–0.067 μg/L] versus 0.001 μg/L [IQR, 0–0.003 μg/L]; $P<0.001$) than patients with CNCD (Figure 1 and Table IIIA and IIIB in the online-only Data Supplement). The median numeric percent changes were 20.8% (IQR, 5.0%–57.4%) for patients with AMI in the first hour and 7.6% (IQR, 3.6%–16.5%) for patients with CNCD. In the subgroup of patients with CNCD, both patients with heart failure and those with myocarditis

Table. Baseline Characteristics of Patients

Characteristics	All Patients (n=887)	CNCD (n=124)	AMI (n=127)	Other (n=636)	*P* All	*P* CNCD-AMI
Age, y	64 (51–75)	66 (54–77)	74 (61–82)	62 (49–74)	<0.001	0.002
Female sex, n (%)	288 (32)	51 (41)	40 (31)	197 (31)	0.084	0.112
Risk factors, n (%)						
Hypertension	568 (64)	89 (72)	93 (73)	386 (61)	0.004	0.797
Hypercholesterolemia	415 (47)	56 (45)	62 (49)	297 (47)	0.842	0.562
Diabetes mellitus	180 (20)	21 (17)	31 (24)	128 (20)	0.332	0.144
Current smoking	204 (23)	18 (15)	31 (24)	155 (24)	0.053	0.048
History of smoking	323 (36)	44 (35)	46 (36)	233 (37)	0.970	0.903
History, n (%)						
Coronary artery disease	324 (37)	31 (25)	54 (43)	239 (38)	0.009	0.003
Previous myocardial infarction	222 (25)	17 (14)	39 (31)	166 (26)	0.004	0.001
Previous revascularization	241 (27)	19 (15)	33 (26)	189 (30)	0.004	0.037
Peripheral artery disease	59 (7)	5 (4)	14 (11)	40 (6)	0.067	0.036
Previous stroke	54 (6)	9 (7)	19 (15)	26 (4)	<0.001	0.053
Vital status						
Heart rate, bpm	75 (66–89)	82 (69–100)	82 (70–94)	73 (65–86)	<0.001	0.349
Systolic blood pressure, mm Hg	144 (127–160)	147 (131–181)	140 (124–162)	144 (127–159)	0.020	0.014
Diastolic blood pressure, mm Hg	84 (74–93)	89 (74–100)	82 (72–92)	84 (74–92)	0.006	0.005
Time from symptom onset until presentation, h	3 (2–6)	3 (2–6)	4 (2–6)	3 (2–5)	0.316	0.254
Symptoms, n (%)						
Maximum pain*	6 (4.5–8)	5 (4–7)	6.5 (5–8)	6 (4.5–8)	0.021	0.006
Pain precipitated by activity	338 (38)	49 (40)	63 (50)	226 (36)	0.011	0.011
Sudden onset of pain	413 (47)	56 (45)	63 (50)	294 (46)	0.251	0.852
ECG findings, n (%)						
Left bundle-branch block	35 (4)	7 (6)	13 (10)	15 (2)	<0.001	0.179
ST-segment elevation	25 (3)	5 (4)	13 (10)	7 (1)	<0.001	0.057
ST-segment depression†	91 (10)	21 (17)	38 (30)	32 (5)	<0.001	0.015
T-wave inversion	63 (7)	9 (7)	13 (10)	41 (6)	0.315	0.404
No significant ECG abnormalities	673 (76)	82 (66)	50 (39)	541 (85)	<0.001	<0.001
Laboratory						
eGFR, $mL \cdot min^{-1} \cdot m^{-2}$	89 (71–106)	85 (64–101)	76 (61–100)	91 (74–108)	<0.001	0.166

CNCD indicates cardiac noncoronary disease; AMI, acute myocardial infarction; and eGFR, estimated glomerular filtration rate. Values are medians (interquartile ranges) when appropriate.

*On a visual analog scale from 1 to 10, with 10 indicating maximum pain.

†Only horizontal or descending ST-segment depression.

had median hs-cTnT values at presentation above the 99th percentile, but major changes in hs-cTnT occurred during the first hour only in the latter subgroup.

The diagnostic accuracy of hs-cTnT at presentation for the distinction between patients with AMI and CNCD as quantified by the area under the receiver-operating characteristics curve (AUC) was 0.89 (95% confidence interval [CI], 0.84–0.92; Figure 2A). The discriminatory power of Δhs-cTnT 0 to 1 hour was higher for absolute (AUC, 0.89; 95% CI, 0.85–0.93) than for relative (AUC, 0.66; 95% CI, 0.60–0.72) changes ($P<0.001$). Combining presentation values of hs-cTnT at presentation with absolute changes in the first hour increased the AUC to 0.94 (95% CI, 0.90–0.96; $P<0.001$ for comparison with AUC of 0-hour hs-cTnT). The combined use of presentation values of hs-cTnT and its absolute change in the first hour also outperformed a model using only the 1-hour value of hs-cTnT (P for comparison=0.013) in the distinction between AMI and CNCD.

Analyses of the subgroup of patients having 6-hour values of hs-cTnT available showed that the 6-hour value had a diagnostic accuracy similar to that of the presentation value of hs-cTnT combined with the absolute change of hs-cTnT in the first hour (Table IV in the online-only Data Supplement). Similar findings were obtained with the 2 hs-cTnI assays (Beckmann-Coulter and Siemens). The AUC for the combined use of presentation values of hs-cTnI and its absolute change in the first hour amounted to 0.92 (95% CI, 0.88–0.95) for both hs-cTnI assays and did not differ significantly

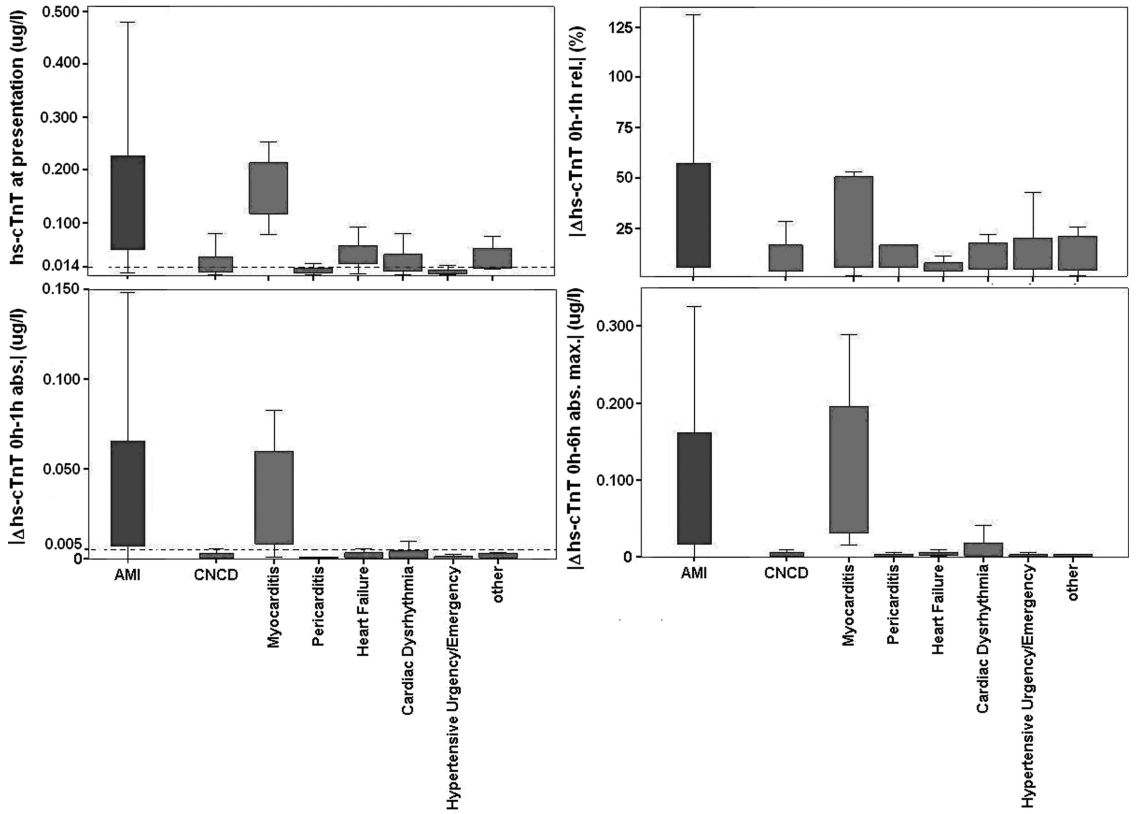

Figure 1. Presentation values and changes in high-sensitivity cardiac troponin T (hs-cTnT). Levels of hs-cTnT at presentation (in μg/L), Δhs-cTnT 0 to 1 hour (absolute [abs.] and relative [rel.] numeric change), and maximum (max.) absolute Δhs-cTnT 0 to 6 hours in all patients according to the adjudicated final diagnosis. Boxes represent interquartile ranges [IQRs]; whiskers display ranges (without outliers farther than 1.5 IQRs from the end of the box). The subgroup "other" of cardiac noncoronary artery disease (CNCD) included Takotsubo cardiomyopathy.

from the respective AUC of hs-cTnT (Roche; $P=0.168$ for hs-cTnI Beckman-Coulter and $P=0.200$ for hs-cTnI Siemens).

Patients With Presentation Values of hs-cTnT Above the 99th Percentile

The AUC for hs-cTnT at presentation for the distinction of patients with AMI and CNCD amounted to 0.82 (95% CI, 0.75–0.87; Figure 2B). Combining presentation values of hs-cTnT at presentation with absolute changes in the first hour increased the AUC to 0.89 (95% CI, 0.90–0.97; $P<0.001$ for comparison with AUC of 0-hour hs-cTnT). Again, similar findings were obtained with the 2 hs-cTnI assays.

Algorithm Identifying Patients With AMI

Figure 3 summarizes a possible algorithm based on ST-segment elevation, hs-cTnT at presentation, and absolute changes in hs-cTnT in the first hour. A value of ≈0.028 μg/L best separated patients with AMI from patients with CNCD. Receiver-operating characteristics curve analyses of absolute changes of hs-cTnT in the first hour of the three main groups yielded the best discriminatory power for changes of ≈0.005 μg/L in all 3 groups. The performance of the algorithm is illustrated in Table V in the online-only Data Supplement; 98.5% patients with AMI had presentation values of hs-cTnT >0.028 μg/L and/or Δhs-cTnT 0 to 1 hour abs. >0.005 μg/L, resulting in a positive predictive value of 79% and negative predictive value of 98%.

Again, similar findings were obtained when the algorithm was based on hs-cTnI values (Figure IA and IB in the online-only Data Supplement).

Diagnostic Performance of the Algorithm to Discriminate Between AMI and CNCD After Readjudication of the Final Diagnosis Using hs-cTnT

As shown in Figure 4, the diagnostic performance of the algorithm to discriminate between AMI and CNCD remained similar after the retrospective readjudication of the final diagnosis using hs-cTnT levels. An overview of which patients were readjudicated using hs-cTnT is provided in Table VI in the online-only Data Supplement.

Validation of the Algorithm

Validation of the algorithms in Figures 3 and 4 in an independent cohort of patients enrolled after June 2009 (validation cohort) is shown in Figure IC and ID in the online-only Data Supplement, respectively. Baseline characteristics of the validation cohort are shown in Table VII in the online-only Data Supplement. Table VIII in the online-only Data Supplement illustrates how patients were readjudicated in the validation cohort using hs-cTnT.

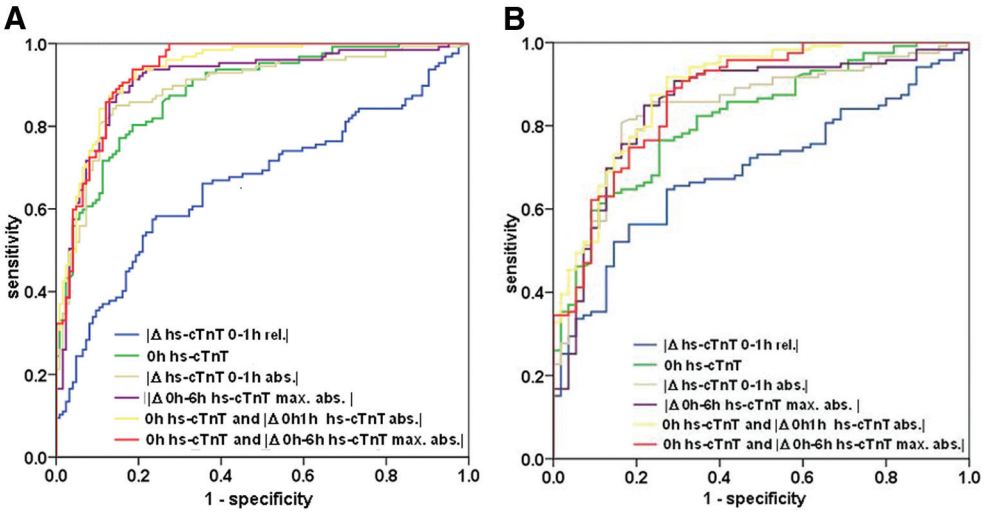

Figure 2. A, Receiver-operating characteristics (ROC) curve analysis for the differentiation between acute myocardial infarction (AMI) and cardiac noncoronary artery diseases (CNCD). ROC curves describing the diagnostic performance of high-sensitivity cardiac troponin T (hs-cTnT) at presentation, absolute (abs.) and relative (rel.) Δhs-cTnT 0 to 1 hour values in the first hour, Δhs-cTnT 0 to 6 hours maximum (max.) abs. values, and the combination of hs-cTnT at 0 hours with Δhs-cTnT 0 to 1 hour abs. values and Δhs-cTnT 0 to 6 hours max. abs. values in the distinction between AMI and CNCD. **B**, ROC curve analysis for the differentiation between AMI and CNCD in patients with high-sensitivity cardiac troponin T (hs-cTnT) at presentation above the 99th percentile. ROC curves describing the diagnostic performance of hs-cTnT at presentation, absolute and relative Δhs-cTnT 0 to 1 hour values in the first hour, maximum absolute Δhs-cTnT 0 to 6 hours values, and the combination of hs-cTnT at 0 hours with absolute Δhs-cTnT 0 to 1 hour values and maximum absolute Δhs-cTnT 0 to 6 hours values in the distinction between AMI and CNCD in patients with hs-cTnT values at presentation above the 99th percentile.

hs-cTnT and Its Early Changes for the Allocation of Early Coronary Angiography

Patients with AMI and those with myocarditis or TTC were regarded as candidates for early coronary angiography. Their hs-cTnT values at presentation (median, 0.115 μg/L) were higher than for patients without need for early coronary angiography (median, 0.011 μg/L; $P<0.001$), yielding an AUC of 0.90 (95% CI, 0.86–0.94) for hs-cTnT at presentation for determin-

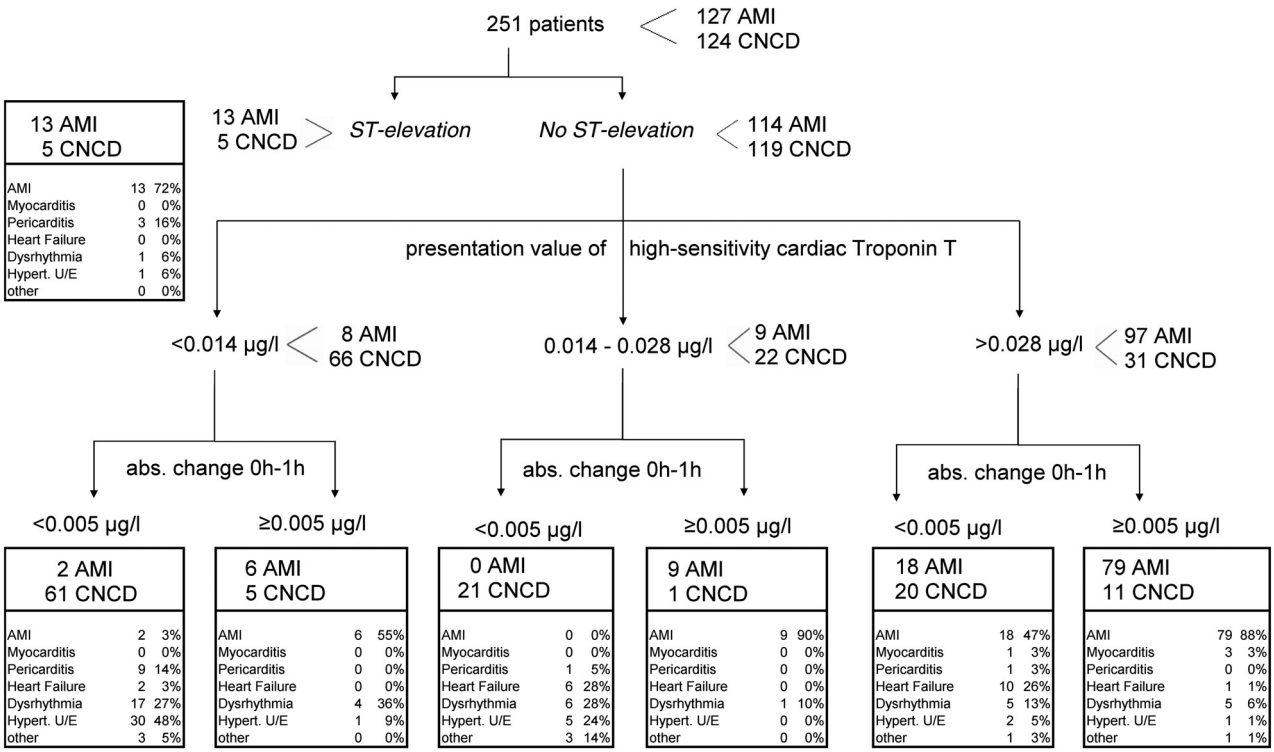

Figure 3. Algorithm to discriminate between acute myocardial infarction (AMI) and cardiac noncoronary artery diseases (CNCD). The algorithm is based on the presence of ST-segment elevation, high-sensitivity cardiac troponin T (hs-cTnT) at presentation, and Δhs-cTnT 0 to 1 hour absolute to discriminate between AMI and CNCD.

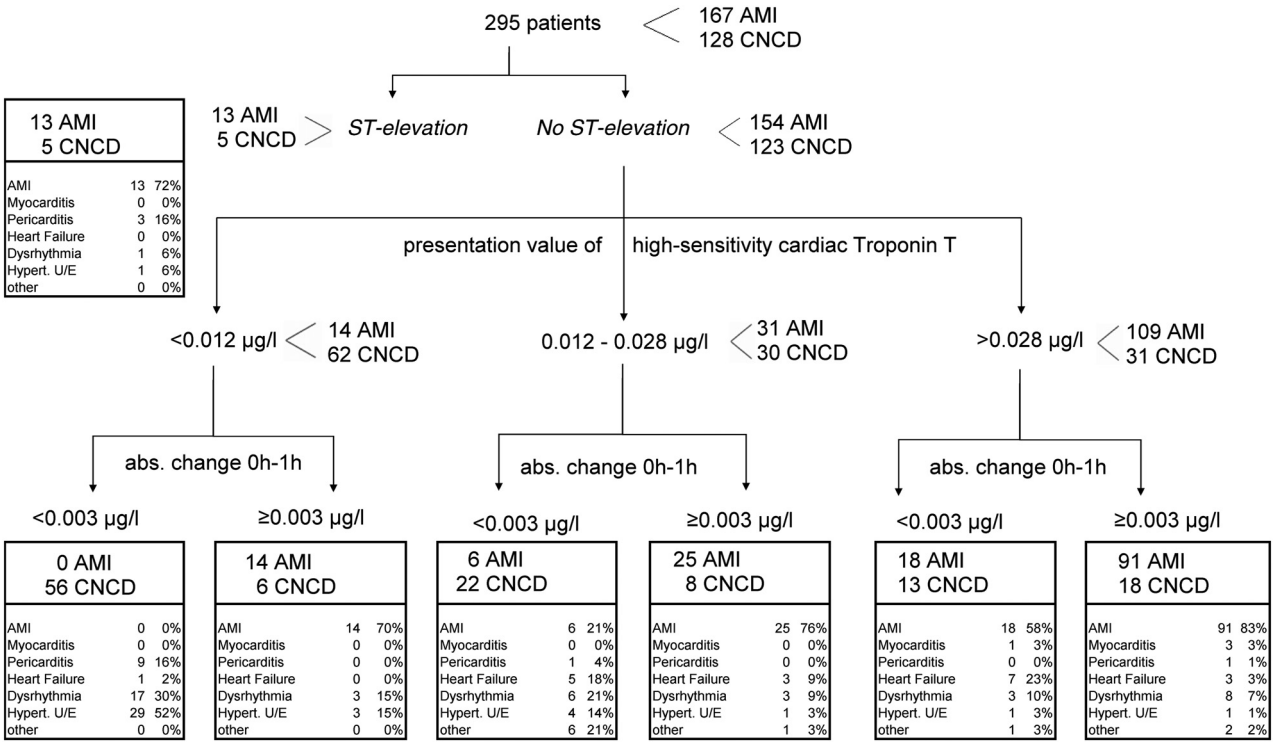

Figure 4. Diagnostic performance of the algorithm to discriminate between acute myocardial infarction (AMI) and cardiac noncoronary artery diseases (CNCD) after readjudication of the final diagnosis using high-sensitivity cardiac troponin T (hs-cTnT) values. The algorithm is based on the presence of ST-segment elevation, hs-cTnT at presentation, and Δhs-cTnT 0 to 1 hour absolute to discriminate between AMI and CNCD.

ing the need for early coronary angiography. Again, absolute changes in the first hour were more discriminatory than relative changes ($P<0.001$). Combining presentation values of hs-cTnT at presentation with absolute changes in the first hour increased the AUC to 0.95 (IQR, 0.92 to 0.98; $P<0.001$ compared with AUC of 0-hour hs-cTnT alone). Similar findings were obtained with the 2 hs-cTnI assays (data not shown).

Decision Curve Analysis

Figure 5A shows the results of the decision curve analysis using 0-hour hs-cTnT, Δhs-cTnT 0 to 1 hour abs. and the combination of both to predict the need for early coronary angiography in patients with AMI or CNCD.

All 3 predictive models outperformed the "coronary angiography in all" strategy. The combined use of 0-hour

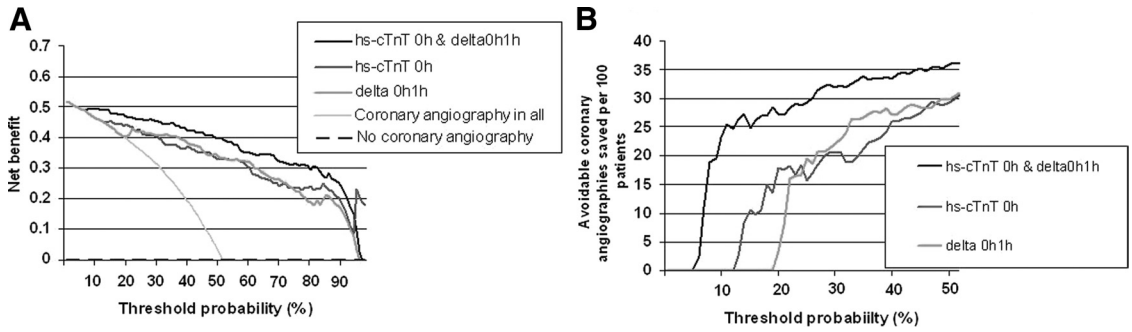

Figure 5. Decision curve analysis for the prediction of the need for coronary angiography in patients with acute myocardial infarction and cardiac noncoronary artery diseases. **A**, The *x* axis is the individual threshold at which a coronary angiography would be contemplated; the *y* axis represents the net benefit in the clinical context. This is the probability of positive result minus the probability of unnecessary coronary angiography, ie, a false-positive result. The slanted gray line represents the strategy of performing a coronary angiography in all patients; the horizontal line represents the strategy of not performing a coronary angiography in any patient, resulting in a net benefit of 0. Their intersection represents the prevalence of need for coronary angiography. The remaining 3 lines represent the different prediction models. Prediction models that are the farthest away from the slanted line result in the highest net benefit. hs-cTnT 0 hours indicates high-sensitivity cardiac troponin T value at presentation; delta 0h1h, its absolute numeric change in the first hour. **B**, The reduction in avoidable coronary angiographies per 100 patients is calculated as follows: (net benefit of the model−net benefit of treat all)/$[P_t/(1-P_t)]\times 100$, where P_t denotes threshold probability. This value is net of false negatives and is therefore equivalent to the reduction in unnecessary coronary angiographies without a decrease in the number of patients with a need for coronary angiography who duly receive coronary angiography.

hs-cTnT and Δhs-cTnT 0 to 1 hour abs. yielded the highest net benefit. In the clinically interesting area of low to intermediate threshold probabilities (7%–30%), the combined use of hs-cTnT at presentation and its Δhs-cTnT 0 to 1 hour abs. value led to a considerable reduction in avoidable early coronary angiographies (without a decrease in the number of patients with a need for early coronary angiography who duly receive early coronary angiography). Figure 5B illustrates the number of avoidable early coronary angiographies per 100 patients by use of the 3 prediction models instead of performing early coronary angiographies in all patients.

Discussion

In this prospective, international multicenter study of 887 consecutive patients presenting with acute chest pain to the ED, we evaluated the utility of hs-cTn in distinguishing AMI from CNCD and appropriately allocating early coronary angiography. We report 5 major findings. First, both presentation values and changes of hs-cTn over time are significantly higher in patients with AMI than CNCD. Second, using absolute changes of hs-cTn over time is superior to using relative changes in the distinction between AMI and CNCD. Third, a simple clinical algorithm using ST-segment elevation, hs-cTn at presentation, and absolute changes in the first hour allowed the separation of AMI and CNCD. Fourth, the combined use of presentation values and absolute changes in the first hour had high accuracy in identifying candidates for early coronary angiography. Fifth, decision curve analysis, a novel statistical method, quantified the net benefit of using biomarker guidance in the selection of patients for early coronary angiography and revealed a great potential of considerable reduction in avoidable early coronary angiographies.

Our results extend previous studies addressing the early detection of AMI[5,7] by specifically focusing on the clinically most challenging differential diagnosis: CNCD. Our analyses may provide major help in the clinical application of the recently introduced hs-cTn.[12] Multiple cardiac conditions other than AMI such as tachyarrhythmia, heart failure, and myocarditis have been reported as potential causes of elevations in conventional troponins and even more novel more sensitive assays.[22] In the course of the gradual implementation of more sensitive assays in clinical practice, many clinicians are struggling with interpreting hs-cTn values[23] and clearly distinguishing between patients with AMI and CNCD. Morrow et al[5] demonstrated that even minor elevations of cTns conferred increased risk and predicted significant benefit of an early invasive strategy in patients with non–ST-segment–elevation myocardial infarction or unstable angina. Serial troponin measurement has been proposed to determine the clinical significance of borderline-elevated levels of troponin with the use of high-sensitivity assays.[24] Apple et al[18] demonstrated the potential utility of a 30% relative change in cTnI in serial measurements to improve specificity in patients presenting with symptoms of acute coronary syndromes. Giannitsis et al,[25] in a smaller study focusing on the detection of non–ST-segment–elevation myocardial infarction in patients presenting with negative hs-cTnT results, proposed doubling the values of hs-cTnT within 3 hours to best identify patients with non–ST-segment–elevation myocardial infarction. The use of absolute change values has only recently been introduced. This concept consistently provided higher diagnostic accuracy compared with the use of relative changes in independent studies.[15,26,27] In this analysis, absolute changes again appeared superior in the calculation of the AUC and therefore were selected as a component in the algorithm.

In this analysis, we highlight for the first time the potential of a novel algorithm combining hs-cTn values at presentation with their absolute changes: remarkably, absolute changes in hs-cTnT as low as 0.005 μg/L had the best discriminatory power in the differential diagnosis of AMI and CNCD; 98.4% of all patients with AMI had either presentation values >0.028 μg/L or absolute changes of >0.005 μg/L in the first hour. The principle of the algorithm obtained by the use of hs-cTnT was transferable to both hs-cTnI assays and revealed consistent findings. Considering that the introduction of hs-cTn assays increased the detection of AMI, even lower cutoff values for relevant absolute changes might be necessary (possibly absolute changes between 0.003 and 0.005 μg/L for hs-cTnT).

Adequate identification of patients with potential benefit from early coronary angiography and revascularization is a crucial issue. On an individual-patient level, the weighting of a clinical consequence (eg, implementation of a coronary angiography) varies considerably. Patients in poor general health or of advanced age usually have a lower tolerance for invasive diagnostics than young, presumably healthier patients. To account for these greatly differing individual circumstances, decision curve analysis proves to be an excellent auxiliary tool to personalize medicine and to decrease the number of avoidable coronary angiographies. The decision to perform an invasive procedure such as a coronary angiography will indubitably remain based on a clinical decision including clinical presentation, ECG changes, and laboratory analyses. Our aim was to show that measurement of hs-cTn at presentation and its absolute change in the first hour might be a valuable objective tool for the physician to evaluate the indication for early coronary angiography. Our results certainly need to be confirmed in further prospective clinical trials.

Optimal thresholds for hs-cTn for therapeutic decision making—both at baseline and thereafter—remain a subject of debate. However, the application of our algorithm may lead to earlier therapeutic decisions, a reduction in the time of uncertainty for patients, more efficient use of financial resources, and a substantial reduction in avoidable early coronary angiographies.

Despite the excellent performance of hs-cTn assays in the distinction of patients with AMI from patients with CNCD, the assays should be used only in conjunction with a detailed clinical assessment. In addition, despite its overall low sensitivity, ECG remains an indispensable tool for immediately identifying patients who have an STEMI.[28]

Limitations

First, as a result of transfer to the catheter laboratory or early discharge from the ED, not all patients had the complete set of serial blood draws and therefore hs-cTn values available.

Second, we cannot comment on the patients with terminal kidney failure requiring dialysis because these patients were excluded from our study. Third, we can only hypothesize that our findings obtained for 3 hs-cTn assays can be extrapolated to other hs-cTn assays with similar sensitivities and precision. Other assay-specific algorithms need to be derived in future studies. Fourth, maximum change in hs-cTnT within 6 hours is not based on 6-hour data in all patients.

Conclusion

The combined use of hs-cTn at presentation and its early absolute change excellently discriminates between patients with AMI and acute CNCD.

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CLINICAL PERSPECTIVE

Multiple cardiac disorders other than acute myocardial infarction such as tachyarrhythmia, heart failure, and myocarditis have been reported as potential causes of elevation in conventional troponins in the absence of coronary obstruction. Although the introduction of high-sensitivity cardiac troponin (hs-cTn) assays has facilitated the earlier diagnosis and treatment of acute myocardial infarction, many clinicians are now struggling with interpreting (borderline) hs-cTn values and drawing appropriate clinical conclusions. In this study, we evaluated 887 unselected patients presenting to the emergency department with symptoms suggestive of acute myocardial infarction. The discriminatory power of 3 novel hs-cTn assays in the distinction of patients with acute myocardial infarction and those with cardiac but noncoronary disease was scrutinized. Our main finding was that algorithms using ST-elevation, presentation values, and changes of hs-cTn values in the first hour accurately separated patients with acute myocardial infarction and cardiac but noncoronary disease. This finding was consistent with all 3 hs-cTn assays and was validated in an independent cohort. The decision to perform further invasive diagnostic procedures such as coronary angiography will certainly remain based on all clinical information available. However, measurement of hs-cTn and its absolute change in the first hour seems to be a valuable objective tool for physicians to evaluate the indication for early coronary angiography as shown by decision curve analysis.