HEALTH CARE REFORM

One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T

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Background: High-sensitivity cardiac troponin (hs-cTn) assays seem to improve the early diagnosis of acute myocardial infarction (AMI), but it is unknown how to best use them in clinical practice. Our objective was to develop and validate an algorithm for rapid rule-out and rule-in of AMI.

Methods: A prospective multicenter study enrolling 872 unselected patients with acute chest pain presenting to the emergency department. High-sensitivity cardiac troponin T (hs-cTnT) was measured in a blinded fashion at presentation and after 1 hour. The final diagnosis was adjudicated by 2 independent cardiologists. An hs-cTnT algorithm incorporating baseline values as well as absolute changes within the first hour was derived from 436 randomly selected patients and validated in the remaining 436 patients. The primary prognostic end point was death during 30 days of follow-up.

Results: Acute myocardial infarction was the final diagnosis in 17% of patients. After applying the hs-cTnT algorithm developed in the derivation cohort to the validation cohort, 259 patients (60%) could be classified as "rule-out," 76 patients (17%) as "rule-in," and 101 patients (23%) as in the "observational zone" within 1 hour. Overall, this resulted in a sensitivity and negative predictive value of 100% for rule-out, a specificity and positive predictive value of 97% and 84%, respectively, for rule-in, and a prevalence of AMI of 8% in the observational zone group. Cumulative 30-day survival was 99.8%, 98.6%, and 95.3% ($P < .001$) in patients classified as rule-out, observational zone, and rule-in, respectively.

Conclusions: Using a simple algorithm incorporating hs-cTnT baseline values and absolute changes within the first hour allowed a safe rule-out as well as an accurate rule-in of AMI within 1 hour in 77% of unselected patients with acute chest pain. This novel strategy may obviate the need for prolonged monitoring and serial blood sampling in 3 of 4 patients.

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PATIENTS WITH SYMPTOMS SUGgestive of acute myocardial infarction (AMI) account for approximately 10% of all emergency department (ED) consultations.[1] Electrocardiography (ECG) and cardiac troponin (cTn) assay form the diagnostic cornerstones and complement clinical assessment.[2-4] A limitation of former-generation cTn assays is a delayed increase of circulating levels for 3 to 4 hours, often requiring serial sampling for 6 to 12 hours.[2,3,5] Delays in diagnosing disease ("rule-in") holds back prompt use of evidence-based therapies.[2,3] Delays in excluding disease ("rule-out") interferes with evaluation of alternative diagnoses and contributes to expensive overcrowding in the ED.[6]

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The recently developed sensitive and high-sensitivity cardiac troponin (hs-cTn) assays have enabled measurement of cTn concentrations not reliably detected with prior generations of tests.[7] The new tests have been shown to improve the diagnostic accuracy in the early diagnosis of AMI, and it has been suggested that rule-in and rule-out of AMI might be feasible more rapidly with the new tests.[8-10] Improvements in assay sensitivity, on the other hand, have significantly increased the number of positive hs-cTn test results in various acute and chronic conditions with cardiac involvement other than AMI.[11-14] As a consequence, the positive predictive

value (PPV) of an elevated hs-cTn level has decreased,[8,9,15,16] and many physicians treating patients with symptoms suggestive of AMI have been confused.[17]

It is currently unknown how to best take advantage of the novel hs-cTn tests in clinical practice. Accordingly, there is an ongoing debate whether and to what extent a shortening of the time interval to the second sample is feasible and safe. The aim of our study therefore was to develop and validate an algorithm for rapid rule-in and rule-out of AMI using high-sensitivity cardiac troponin T (hs-cTnT) baseline levels and absolute changes within 1 hour.

METHODS

STUDY DESIGN AND POPULATION

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed and coordinated by the University Hospital Basel (clinicaltrials.gov Identifier: NCT00470587).[8,18] From April 2006 to June 2009, a total of 1247 unselected patients presenting to the ED with acute chest pain symptoms suggestive of AMI such as acute chest pain and angina pectoris with an onset or peak within the last 12 hours were recruited. Patients with terminal kidney failure requiring dialysis were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. 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 hs-cTnT were available in 872 patients. The most common reasons for missing values after 1 hour (n=327) were early transfer to the catheterization laboratory or coronary care unit and diagnostic procedures around the 1-hour window that precluded blood draw at 1 hour, but not the draw of future follow-up samples. No differences in baseline characteristics were found between patients with and without a sample after 1 hour (eTable; http://www.archinternmed.com).

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. Timing and treatment of patients were left at discretion of the attending physician.

INVESTIGATIONAL hs-cTnT ANALYSIS

Blood samples for determination of hs-cTnT (Roche Diagnostics) were collected in serum tubes at presentation to the ED. Additional samples were collected after 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 catheterization laboratory or coronary care unit. After centrifugation, samples were frozen at –80°C until assayed in a blinded fashion using the Elecsys 2010 (Roche Diagnostics) in a dedicated core laboratory. For hs-cTnT, limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L, an imprecision corresponding to 10% coefficient of variation was reported at 13 ng/L and the 99th percentile of a healthy reference population at 14 ng/L.[7] Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula.[19]

ADJUDICATED FINAL DIAGNOSIS

To determine the final diagnosis for each patient, adjudication of final diagnoses was performed centrally in the core laboratory (University Hospital Basel) for all patients according to levels of hs-cTnT. More specifically, 2 independent cardiologists (T.R., M.R., P.H., and M.P.) reviewed all available medical records (including patient history, physical examination, results of laboratory testing including hs-cTnT levels, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity, and morphology in 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 (C.M.).

Acute myocardial infarction was defined and hs-cTnT levels interpreted as recommended in current guidelines.[2,4,20,21] In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a notable rise and/or fall in a clinical setting consistent with myocardial ischemia. The 99th percentile (14 ng/L) was used as cutoff for myocardial necrosis. Absolute cTn changes were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.[18] On the basis of studies of the biological variation of cTn[22,23] as well as on data from previous chest pain cohort studies,[9,24] a significant absolute change was defined as a rise or fall of at least 10 ng/L within 6 hours, or, in an assumption of linearity, as an absolute change of 6 ng/L within 3 hours, 4 ng/L within 2 hours, or 2 ng/L within 1 hour. If discordant findings occurred, the longest time interval available was required to fulfill the change criteria.

Unstable angina (UA) was diagnosed in patients with normal hs-cTnT levels or stable elevations of hs-cTnT levels not fulfilling the criteria for AMI and typical angina at rest, in patients with a 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% or greater, and in ambiguous cases in which follow-up information revealed AMI or a sudden unexpected cardiac death within 60 days. Further predefined diagnostic categories included cardiac symptoms of origin other than coronary artery disease (CAD) with cardiomyocyte damage (absence of overt CAD and conditions such as myocarditis, apical ballooning syndrome, acute heart failure or tachyarrhythmias),[2] cardiac symptoms of origin other than CAD without cardiomyocyte damage (eg, pericarditis, hypertensive urgency, tachyarrhythmias, acute heart failure), and noncardiac chest pain. If AMI was excluded in the ED according to the hs-cTnT assay, but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified as to be of unknown origin.

FOLLOW-UP AND CLINICAL END POINTS

After hospital discharge, patients were contacted after 3, 12, and 24 months by telephone calls or in written form. Information regarding death was furthermore obtained from the national registry on mortality, the hospital's diagnosis registry, and the family physician's records. The primary prognostic end point was 30 days' all-cause mortality.

Table 1. Baseline Characteristics of the Patients[a]

Characteristic	All Patients (N = 872)	Patients With Acute MI (n = 147)	Other Patients (n = 725)	*P* Value
Age, median (IQR), y	64 (51-75)	73 (62-81)	62 (50-74)	<.001
Male sex	588 (67)	102 (69)	486 (67)	.58
Risk factor				
Hypertension	558 (64)	107 (73)	451 (62)	.02
Hypercholesterolemia	410 (47)	76 (52)	334 (46)	.21
Diabetes	177 (20)	40 (27)	137 (19)	.02
Current smoking	201 (23)	34 (23)	167 (23)	.98
History of smoking	320 (37)	61 (42)	259 (36)	.19
History				
Coronary artery disease	320 (37)	72 (49)	248 (34)	.001
Previous myocardial infarction	220 (25)	53 (36)	167 (23)	.001
Previous revascularization	240 (28)	46 (31)	194 (27)	.26
Peripheral artery disease	59 (7)	18 (12)	41 (6)	.004
Previous stroke	52 (6)	18 (12)	34 (5)	<.001
Creatinine clearance, median (IQR), mL/min/m^2	89 (71-106)	77 (62-101)	91 (73-107)	<.001
ECG findings				
Left bundle-branch block	35 (4)	13 (9)	22 (3)	.001
ST-segment elevation	12 (1)	0	12 (2)	.12
ST-segment depression	90 (10)	42 (29)	48 (7)	<.001
T-wave inversion	62 (7)	14 (10)	48 (7)	.21
No significant ECG abnormalities	673 (77)	78 (53)	595 (82)	<.001

Abbreviations: ECG, electrocardiogram; IQR, interquartile range.
[a]Data are presented as number (percentage) unless otherwise specified.

ALGORITHM DEVELOPMENT AND VALIDATION

The algorithm for use of hs-cTnT was developed in a randomly selected derivation sample of 436 patients. The algorithm incorporates both baseline hs-cTnT levels and absolute hs-cTnT changes within the first hour. Selection of these 2 parameters was based on the previously published, very high diagnostic accuracy of their combination.[18,25] Optimal thresholds for rule-out were selected to allow for a 100% sensitivity and negative predictive value (NPV). Optimal thresholds for rule-in were obtained based on a classification and regression tree (CART) analysis.[26,27] The CART algorithm provides a sequence of partitions of a given data set aimed at optimizing the prediction of a binary outcome variable. Each subsequent partition is obtained by splitting one of the preceding partition sets (nodes) into 2 parts. If quantitative predictor variables are used, a pair of new nodes is obtained by splitting an existing node at a given threshold value of one of these variables. The algorithm stops if no further improvement is possible or if any further split would violate a predefined criterion (eg, on the minimal node size).[26,27] Nodes in the CART tree were constrained to have a minimal number of cases of 20 in parent and child nodes. In addition to baseline hs-cTnT levels and absolute hs-cTnT changes within the first hour, age (as a continuous variable), sex, ECG features (signs of ischemia or not) and time since onset of symptoms (as a continuous variable) were included in the CART model as well. The algorithm developed in the derivation sample was then tested for its diagnostic accuracy in a validation sample consisting of the remaining 436 subjects.

STATISTICAL ANALYSIS

Continuous variables are presented as mean (standard deviation) or median (interquartile range [IQR]); categorical variables, as numbers and percentages. Differences in baseline characteristics between patients with and without AMI and between patients in the derivation and validation cohort were assessed using the Mann-Whitney test for continuous variables and the Pearson χ^2 test for categorical variables.

Survival during 30 days of follow-up according to the classification provided by the hs-cTnT algorithm was plotted in Kaplan-Meier curves, and the log-rank test was used to assess differences in survival between groups. Hazard ratios (HRs) and 95% confidence intervals were obtained from Cox proportional hazard models to quantify the magnitudes of group differences.

All hypothesis testing was 2-tailed, and $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows 19.0 (SPSS Inc).

RESULTS

CHARACTERISTICS OF PATIENTS

Among the 872 patients presenting to the ED with acute chest pain, the adjudicated final diagnosis was AMI in 147 patients (17%), UA in 104 (12%), cardiac symptoms of origin other than CAD in 128 (15%), noncardiac symptoms in 416 (48%), and symptoms of unknown origin in 77 (9%). Baseline characteristics are given in **Table 1**.

QUANTITATIVE INTERPRETATION OF hs-cTnT LEVELS

Baseline levels of hs-cTnT were significantly higher in patients with AMI compared with the other final diagnoses (**Figure 1**). Of all patients, 35% had hs-cTnT baseline levels above the 99th percentile of healthy individuals (14 ng/L). Using this value as a qualitative cutoff for baseline levels to diagnose AMI resulted in a sensitivity of 88%, an NPV of 97%, a specificity of 76%, and a PPV of 43%.

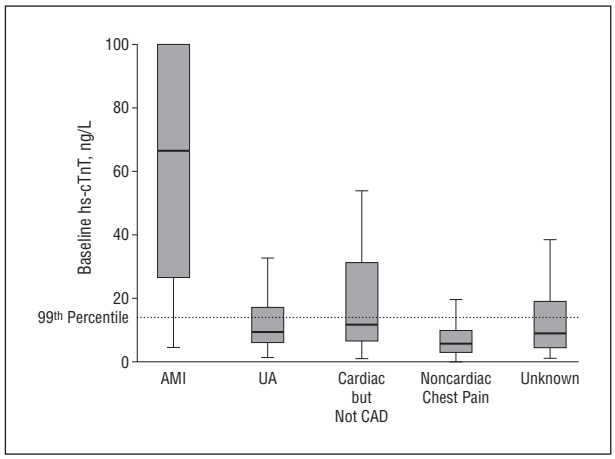

Figure 1. Levels of high-sensitivity cardiac troponin T (hs-cTnT) at presentation. Baseline hs-cTnT levels at presentation to the emergency department in all patients according to the adjudicated final diagnoses. Boxes represent interquartile ranges, while whiskers display ranges (without outliers further than 1.5 interquartile ranges from the respective end of the box). The proportion of patients above the 99th percentile were 88% for acute myocardial infarction (AMI), 36% for unstable angina (UA), 45% for cardiac but not coronary artery disease (CAD), 13% for noncardiac chest pain, and 31% for patients with unknown causes.

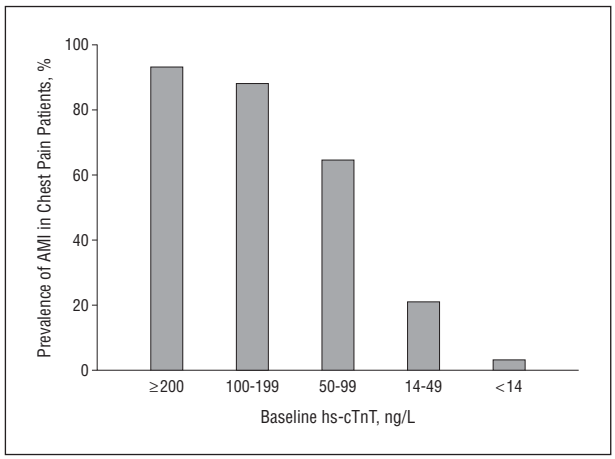

Figure 2. Prevalence of acute myocardial infarction (AMI) according to absolute levels of high-sensitivity cardiac troponin T (hs-cTnT) at presentation.

The prevalence of AMI in patients presenting with acute chest pain differed significantly according to quantitative levels of hs-cTnT (**Figure 2**). In patients with hs-cTnT levels lower than 14 ng/L (99th percentile of healthy individuals) at presentation, the incidence of AMI was 3.2%, and there was a rise to 21% in patients with levels between 14 and 49 ng/L, 65% in patients with levels between 50 and 99 ng/L, 88% in patients with levels between 100 and 199 ng/L, and 93% in patients with levels of 200 ng/L or higher ($P = .49$ for comparison of 100-199 ng/L vs ≥200 ng/L; $P < .001$ for all other comparisons).

DERIVATION OF THE hs-cTnT ALGORITHM FOR THE DIAGNOSIS OF AMI

For use in clinical practice, an algorithm incorporating baseline hs-cTnT values as well as absolute hs-cTnT changes within the first hour was developed in a derivation sample of 436 patients. Baseline characteristics of the patients in the derivation and the validation sample were similar and are given in **Table 2**.

Table 2. Baseline Characteristics of the Patients in the Derivation and Validation Cohort[a]

Characteristic	Derivation Cohort (n = 436)	Validation Cohort (n = 436)	*P* Value
Age, median (IQR), y	65 (52-75)	63 (50-75)	.21
Male sex	281 (64)	307 (70)	.06
Risk factor			
Hypertension	295 (68)	263 (60)	.02
Hypercholesterolemia	205 (47)	205 (47)	>.99
Diabetes	87 (20)	90 (21)	.80
Current smoking	107 (25)	94 (22)	.30
History of smoking	150 (34)	170 (39)	.16
History			
Coronary artery disease	164 (38)	156 (36)	.57
Previous myocardial infarction	116 (27)	104 (24)	.35
Previous revascularization	124 (28)	116 (27)	.54
Peripheral artery disease	26 (6)	33 (8)	.35
Previous stroke	27 (6)	25 (6)	.78
Creatinine clearance, median (IQR), mL/min/m^2	89 (69-106)	90 (71-107)	.58
Final diagnosis of AMI	75 (17)	72 (17)	.79

Abbreviations: ECG, electrocardiogram; IQR, interquartile range.
[a] Data are presented as number (percentage) unless otherwise specified.

For "rule-out" of AMI, the optimal thresholds were selected to allow for a 100% sensitivity and NPV. The rule-out criteria were defined as a baseline hs-cTnT level lower than 12 ng/L and an absolute change within the first hour of lower than 3 ng/L.

For "rule-in" of AMI, the optimal thresholds as obtained by CART analysis were either a baseline hs-cTnT value at presentation of 52 ng/L or higher or an absolute change in hs-cTnT within the first hour of 5 ng/L or higher. The additional variables in the CART analysis (age, sex, ischemic ECG changes, and time since onset of symptoms) did not improve the accuracy and did not emerge as contributors to the final decision tree.

Patients fulfilling neither of the aforementioned criteria for rule-in or for rule-out were classified in a third group called "observational zone."

VALIDATION OF THE hs-cTnT ALGORITHM FOR THE DIAGNOSIS OF AMI

The algorithm was then tested in a validation sample of the remaining 436 subjects. The performance indices of the final algorithm in the derivation cohort, the validation cohort, and the overall cohort are given in **Table 3**, and the final algorithm and its performance in the validation cohort is depicted in **Figure 3**.

After applying the hs-cTnT algorithm to the validation cohort, 259 patients (60%) could be classified as "rule-out." No patient with AMI was missed, and sensitivity and NPV accordingly were 100%. Seventy-six patients (17%) were classified as "rule-in," which resulted in a specificity and PPV of 97% and 84%, respectively. Doing so, 64 of 72 patients (89%) with AMI were ruled in

Table 3. Performance of the hs-cTnT Algorithm for Rule-in and Rule-out of AMI

	Overall Cohort (n = 872)	Derivation Cohort (n = 436)	Validation Cohort (n = 436)
Patients diagnosed after 1 h, No. (%)	660 (76)	325 (75)	335 (77)
Rule-out			
Sensitivity, %	100	100	100
Negative predictive value, %	100	100	100
Rule-in			
Specificity, %	94	92	97
Positive predictive value, %	76	69	84

Abbreviations: AMI, acute myocardial infarction; hs-cTnT high-sensitivity cardiac troponin T.

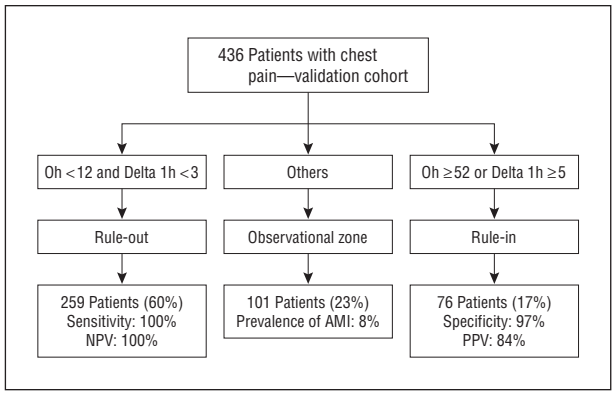

Figure 3. Algorithm for diagnosis of acute myocardial infarction (AMI) using high-sensitivity cardiac troponin T (hs-cTnT) in patients presenting with chest pain. Results are displayed for the validation cohort (n = 436). High-sensitivity cardiac troponin T (hs-cTnT) values are presented in nanograms per liter. 0h indicates hs-cTnT at presentation to the emergency department; Delta 1h, absolute change of hs-cTnT within the first hour; NPV, negative predictive value; and PPV, positive predictive value.

after 1 hour. The final adjudicated diagnoses in patients falsely ruled in for AMI (n = 12) based on the algorithm were cardiac arrhythmias (n = 4), myocarditis (n = 1), pulmonary embolism (n = 2), hypertensive crisis (n = 1), heart failure decompensation (n = 1), and chest pain of unknown origin (n = 3). Taken together, the algorithm allowed for a definite diagnosis after 1 hour in 77% of patients (either rule-in or rule-out). The remaining 101 patients (23%) were classified as in the "observational zone," and 8 of these patients were finally classified as having AMI, reflecting a prevalence of AMI of 8% in the observational zone group.

PROGNOSTIC PERFORMANCE OF THE hs-cTnT ALGORITHM TO PREDICT DEATH DURING FOLLOW-UP

There were 12 deaths in the whole cohort within 30 days and 55 within 24 months. Survival up to 30 days of follow-up was significantly associated with the categories "rule-out," "observational zone," and "rule-in," as classified by the hs-cTnT algorithm (**Figure 4**). Cumula-

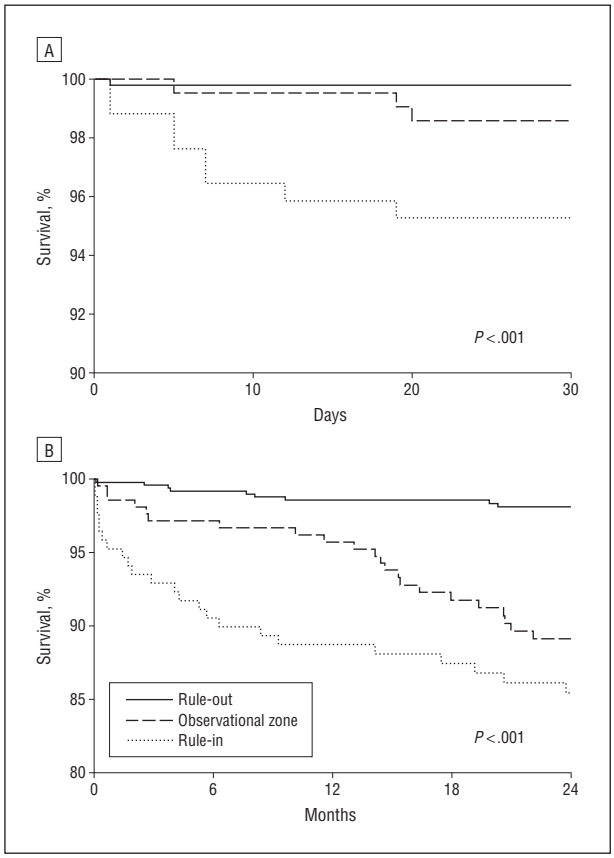

Figure 4. Kaplan-Meier curves for the cumulative survival according to classification provided by the high-sensitivity cardiac troponin T (hs-cTnT) algorithm. Kaplan-Meier curves display the cumulative survival during 30 days of follow-up (A) and 2 years of follow-up (B) in all patients with chest pain (n = 872) according to the classification into "rule-out" (n = 491), "observational zone"(n = 212), and "rule-in" (n = 169) provided by the hs-cTnT 1-hour algorithm. Differences in survival were assessed using the log-rank test.

tive 30-day survival rates in Kaplan-Meier curves were 99.8%, 98.6% and 95.3% ($P < .001$ by log rank test) in the respective categories. The HR for the risk of death within 30 days was 6.9 (95% CI, 0.7-66.8) ($P = .09$) for patients in the observational group and 23.7 (95% CI, 3.0-189.2) ($P = .003$) for patients in the rule-in group compared with patients in the rule-out group. This pattern continued up to a follow-up of 24-month with cumulative survival rates of 98.1%, 89.1%, and 85.4% ($P < .001$ by log rank test). The HR for the risk of death within 24 months was 5.8 (95% CI, 2.7-12.5) ($P < .001$) for patients in the observational group and 8.3 (95% CI, 3.9-17.9) ($P < .001$) for patients in the rule-in group compared with patients in the rule-out group.

COMMENT

By using a well-characterized prospective multicenter cohort of 872 unselected patients presenting with symptoms suggestive of AMI, this study aimed to develop strategies for the clinical application of hs-cTnT in the early diagnosis of AMI. We report 4 major novel findings:

First, the proportion of patients with AMI continuously increases with increasing hs-cTnT values. Levels

of hs-cTnT should be interpreted as quantitative rather than qualitative, and the terms *positive* and *negative* troponin should be avoided. Second, we developed and validated a simple algorithm incorporating hs-cTnT baseline values and absolute changes within the first hour. With the use of this algorithm, a safe rule-out as well as an accurate rule-in of AMI can be performed within 1 hour in 77% of patients with chest pain, with a sensitivity and NPV of 100%, a specificity of 97%, and a PPV of 84%. Third, using this algorithm significantly shortens the time needed for rule-out and rule-in of AMI and may obviate the need for prolonged monitoring and serial blood sampling in 3 of 4 consecutive patients with acute chest pain. And fourth, 30-day mortality was 0.2% in patients ruled out for AMI, which underscores the suitability of these patients for early discharge.

Our findings extend and corroborate recent results regarding hs-cTn assays and are of great clinical importance. Although the newly developed hs-cTn assays have been shown to improve the early diagnosis of AMI,[8,9] their introduction into daily clinical practice turned out to be difficult, and many physicians treating patients with chest pain have been confused.[17] Simple "how-to-use" instructions for clinical decision making are critically needed to take clinical advantage of the new assays and to shorten the time to rule-in and rule-out AMI.

With older cTn assays, the term *troponin positive* was often appropriate. A large amount of myocardial necrosis was needed to get a cTn signal, and the PPV for AMI of such largely elevated cTn levels was high.[28] The new hs-cTn assays are more sensitive and detect smaller amounts of cardiomyocyte damage within a shorter time after the onset of symptoms.[7] The trade-off for the enhanced assay sensitivity is an increased number of positive hs-cTn test results in various acute and chronic conditions with cardiac involvement other than AMI.[11-14] Accordingly, the PPV for AMI of a positive hs-cTn test result (elevated above the 99th percentile of healthy individuals) is reduced. Our study provides evidence that the reduced PPV found for the 99th percentile cutoff[8,9,15,16] can be overcome by quantitative rather than qualitative interpretation of hs-cTnT levels.

Using quantitative categories of baseline hs-cTnT levels as well as absolute hs-cTnT changes within the first hour,[18] we developed and validated an algorithm for rule-in and rule-out of AMI. A recent study investigated the incorporation of a point-of-care biomarker panel including standard cTn, creatine kinase–MB, and myoglobin into an algorithm for the assessment of patients with chest pain.[29] Using a 2-hour algorithm, the authors identified a subset of low-risk patients (10% of all patients with chest pain) suitable for early discharge. Using our algorithm, we were able to rule out AMI in 60% and to rule in AMI in 17% of all patients with chest pain within 1 hour with very high diagnostic accuracy. Of the patients, 23% fulfilled neither criteria, were classified "observational zone" and would require more than 1 hour for triage, and many of them probably will need additional diagnostic testing such as coronary angiography, exercise stress test, or echocardiography. Compared with the 6- to 9-hour window for a follow-up cTn test sample recommended in current guidelines,[2,3] the shortening to a 1-hour follow-up period would be substantial. In clinical practice, hs-cTn levels are interpreted in conjunction with all other available information including 12-lead ECG, patient history and physical examination, and other diagnostic investigations. The accuracy of the algorithm in clinical practice, when used in conjunction with the aforementioned information and supported ideally by an automated electronic laboratory reporting system, will likely be even higher than reported in this hs-cTnT–only analysis. And the prognostic data with a 30-day mortality rate of only 0.2% in the rule-out group underscores the suitability of these patients for early discharge.

Potential limitations of the present study merit consideration. First, our study was conducted in ED patients with symptoms suggestive of AMI. This is the pretest probability setting where the algorithm should be used. Second, the proportion of patients with MI (17%) was in line with different cohorts,[9,30-32] but rather high compared with other chest pain studies. The algorithm therefore requires confirmation and external validation in a second multicenter study in a lower-risk cohort. Third, the data presented were obtained in an observational study, and studies applying these data prospectively for clinical decision making are warranted. Fourth, we cannot comment on the performance of the hs-cTnT algorithm in patients with terminal kidney failure requiring dialysis, since such patients were excluded from our study. Fifth, we used one specific hs-cTn assay for derivation and validation of the algorithm (hs-cTnT). We hypothesize that similar algorithms can be developed for other hs-cTn assays,[33] but this requires validation in chest pain patient cohorts first.

In conclusion, using a simple algorithm incorporating hs-cTnT baseline values and absolute changes within the first hour, a safe rule-out as well as an accurate rule-in of AMI could be performed within 1 hour in 77% of all patients with chest pain. The use of this algorithm seems to be safe, significantly shortens the time needed for rule-out and rule-in of AMI, and may obviate the need for prolonged monitoring and serial blood sampling in 3 of 4 patients with chest pain.

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INVITED COMMENTARY

Myocardial Infarction Rule-out in the Emergency Department

Are High-Sensitivity Troponins the Answer?

Triage of emergency department (ED) patients with possible acute myocardial infarction (MI) without ST-segment elevation remains one of the most challenging dilemmas in medical practice. The stakes are high: patients with MI inappropriately sent home have approximately 2-fold higher risk-adjusted 30-day mortality than those hospitalized.[1] Conversely, it is not feasible or cost-efficient to admit all patients for MI "rule-out." The advent of chest pain units diminished the strain on in-patient resources,[2] but even these units often use serial electrocardiograms (ECGs) and cardiac marker testing over 6 to 9 hours to confidently confirm or exclude MI. With increasing ED overcrowding, more effective tools are needed to enable rapid triage of patients with possible MI. In addition, although time dependency of treatment for non–ST-segment elevation MI (non-STEMI) is uncertain, earlier diagnosis could lead to more effective use of acute therapies and more efficient, shorter hospital stays.

Cardiac troponins (cTn) are highly specific biomarkers of myocardial necrosis, are much more sensitive than creatine kinase (CK)-MB, and levels strongly correlate with subsequent mortality. These features prompted a cTn gold standard for MI diagnosis.[3] However, despite nearly absolute tissue specificity and superior sensitivity, cTn is *not* specific for the *etiology* of myocardial necrosis (eg, elevated cTn levels occur in such disparate conditions as coronary ischemia, pulmonary embolism, heart failure, sepsis, and renal failure).[4] Thus, clinical syndromes consistent with ischemia and a characteristic rise and/or fall in cTn levels during serial testing are critical for MI diagnosis.[3]

More recently, a new generation of high-sensitivity troponin (hsTn) assays has been developed. They have limits of detection approximately 10-fold lower than conventional assays, 99th percentiles in the low nanogram per liter range, and are analytically very precise (coefficients of variation of 10% at or below the 99th percentile). The ability to detect such small amounts of cTn suggests promise for diagnosing smaller MIs otherwise undetected or identifying MI earlier, when abnormal hsTn levels are below detection by conventional assays. Indeed, initial studies demonstrated that hsTn assays could detect smaller amounts of myonecrosis with greater sensitivity for MI than conventional assays at all serial time points, but highlighted challenges created by greater sensitivity and lack of disease specificity.[5] That is, positive predictive value (PPV) was as low as 50%. Other studies suggested possible susceptibility of hsTn results to biological variability across age and sex (population prevalences of elevated hsTn of 1% among individuals <40 years old vs 5.2% if >65 years old, and 2.8% among men vs 1.3% among women) and demonstrated frequent elevation in asymptomatic patients with stable coronary disease (11.1%) and prior heart failure (18.9%).[6,7] Combined, these factors challenge application of hsTn assays in the ED and suggest they may be better suited for population screening for subclinical disease or as markers of disease activity.

In this issue of *Archives*, Reichlin et al[8] present evidence supporting an algorithmic approach to interpre-