CLINICAL RESEARCH STUDY

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One-hour Rule-in and Rule-out of Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin I

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ABSTRACT

OBJECTIVE: We aimed to prospectively derive and validate a novel 1h-algorithm using high-sensitivity cardiac troponin I (hs-cTnI) for early rule-out and rule-in of acute myocardial infarction.

METHODS: We performed a prospective multicenter diagnostic study enrolling 1811 patients with suspected acute myocardial infarction. The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available information, including coronary angiography, echocardiography, follow-up data, and serial measurements of hs-cTnT (but not hs-cTnI). The hs-cTnI 1h-algorithm, incorporating measurements performed at baseline and absolute changes within 1 hour, was derived in a randomly selected sample of 906 patients (derivation cohort), and then validated in the remaining 905 patients (validation cohort).

RESULTS: Acute myocardial infarction was the final diagnosis in 18% of patients. After applying the hs-cTnI 1h-algorithm developed in the derivation cohort to the validation cohort, 50.5% of patients could be classified as "rule-out," 19% as "rule-in," 30.5% as "observe." In the validation cohort, the negative predictive value for acute myocardial infarction in the "rule-out" zone was 99.6% (95% confidence interval, 98.4%-100%), and the positive predictive value for acute myocardial infarction in the "rule-in" zone was 73.9% (95% confidence interval, 66.7%-80.2%). Negative predictive value of the 1h-algorithm was higher compared with the classical dichotomous interpretation of hs-cTnI and to the standard of care combining hs-cTnI with the electrocardiogram (both $P < .001$). Positive predictive value also was higher compared with the standard of care ($P < .001$).

CONCLUSION: Using a simple algorithm incorporating baseline hs-cTnI values and the absolute change within the first hour allows safe rule-out as well as accurate rule-in of acute myocardial infarction in 70% of patients presenting with suspected acute myocardial infarction.

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KEYWORDS: Accurate rule-in; Acute myocardial infarction; hs-cTn; Safe rule-out

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Acute myocardial infarction is a major cause of death and disability worldwide. Patients with symptoms suggestive of acute myocardial infarction account for about 10% of all emergency department consultations. Only 15%-20% of them are diagnosed eventually as acute myocardial infarction.[1-4] Rapid identification of acute myocardial infarction is critical for the initiation of effective evidence-based treatment.[2,3,5] Delays in "rule-in" of acute myocardial infarction may increase mortality and morbidity, whereas delays in "rule-out" may lead to prolonged assessments, unnecessary investigations, and patient anxiety, as welll as contribute to expensive overcrowding in the emergency department.[6]

Clinical assessment, the 12-lead electrocardiogram (ECG), and cardiac troponin (cTn) form the 3 pillars for the early diagnosis of acute myocardial infarction in the emergency department. The recently developed high-sensitivity cardiac troponin (hs-cTn) assays, which allow measurement of even low cTn concentrations with high precision, have been shown to largely overcome the sensitivity deficit of conventional cTn within the first hours and provide higher overall diagnostic accuracy in the diagnosis of acute myocardial infarction.[7-9] These studies also revealed that the classical diagnostic interpretation of cTn as a dichotomous variable ("troponin-negative" and "troponin-positive") no longer seems appropriate, as the positive predictive value (PPV) for acute myocardial infarction of being "troponin-positive" was only 50%-60%.[7-16] Unfortunately, the best possible way to interpret and clinically use hs-cTn levels in the early diagnosis of acute myocardial infarction is still debated.

In a recent pilot study, a novel hs-cTnT 1h-algorithm has been shown to allow accurate rule-out and rule-in of acute myocardial infarction within 1 hour in up to 75% of patients.[12] This algorithm is based on 2 concepts: First, the interpretation of hs-cTnT as a quantitative variable where the proportion of patients indeed suffering from acute myocardial infarction continuously increases with increasing hs-cTn values.[12,16] Second, early absolute concentration changes within 1 hour provide incremental diagnostic information when added to baseline levels, with the combination acting as reliable surrogates for late concentrations at 3 hours or 6 hours.[12,15,16] Many experts remained skeptical about the safety of the hs-cTnT 1h-algorithm, particularly its possible extrapolation to other hs-cTn assays and its wider applicability.[17] Accordingly, this novel triage concept has not been adopted clinically until now and the following clinically relevant questions have not been addressed: First, is it possible to derive and validate a similar 1h-algorithm for hs-cTnI in order to possibly extend the former finding to cTnI, which is the analyte most often used worldwide, and specifically to the most sensitive clinically available hs-cTn assays?[10,13,18] Second, what are the specific cutoff values for hs-cTnI that allow safe rule-out and accurate rule-in within 1 hour? Third, how many patients can be assigned rule-out within 1 hour? Fourth, how many patients can be assigned rule-in within 1 hour? Fifth, how does the 1h-algorithm compare vs the classical dichotomous interpretation of hs-cTnI or the current standard of care combining the 12-lead ECG with hs-cTn? Sixth, does a 2-hour hs-cTnI concentration add information for patients classified as "observe"?

CLINICAL SIGNIFICANCE

- There were 1811 patients with suspected acute myocardial infarction enrolled in order to derive and validate a novel 1-hour algorithm using high-sensitivity cardiac troponin I.
- More than 50% of patients could be ruled out safely, achieving a negative predictive value even higher compared with the current standard of care (hs-cTn and electrocardiogram).
- Twenty percent of patients could be assigned to the acute myocardial infarction group achieving a positive predictive value higher as compared with the classical dichotomous interpretation of hs-cTn.

METHODS

Study Design and Population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed to advance the early diagnosis of acute myocardial infarction.[7,12,14-16] From April 2006 to September 2012, consecutive patients older than 18 years presenting to the emergency department with symptoms suggestive of acute myocardial infarction with an onset or peak within the last 12 hours were recruited at 9 sites in 3 countries (Switzerland, Spain, and Italy) after written informed consent was obtained.

Enrollment was completely independent of renal function at presentation; only patients with terminal renal failure on chronic dialysis were excluded. For this analysis, patients were also excluded if 1) the final diagnosis remained unclear after adjudication (n = 69), or 2) ST-segment elevation myocardial infarction was the adjudicated final diagnosis, because biomarkers are considered to be of limited clinical value in these patients (n = 76). Among the remaining 2308 patients, samples at presentation as well as after 1 hour for measurement of hs-cTnI were available in 1811 patients. The most common reasons for missing values after 1 hour were early transfer to the catheterization laboratory or coronary care unit and diagnostic procedures around the 1-hour window (eg, computed tomography scan) that precluded blood draw at 1 hour. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish.

Routine Clinical Assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. Levels of cTn were measured at presentation and serially thereafter as long as clinically indicated. Timing and treatment of patients were left to discretion of the attending physician.

Adjudicated Final Diagnosis

Adjudication of the final diagnosis was performed centrally in a core laboratory (University Hospital Basel) and also included serial levels of Roche hs-cTnT (Roche Diagnostics, Mannheim, Germany) in order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays[13,19] (this allows the additional detection of small acute myocardial infarctions that were missed by the adjudication based on conventional cTn assays). Two independent cardiologists reviewed all available medical records—patient history, physical examination, results of laboratory testing (including hs-cTnT levels), radiologic testing, ECG, echocardiography, cardiac exercise stress test, lesion severity, and morphology in coronary angiography—pertaining to the patient from the time of emergency department presentation to 90-day follow-up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

Acute myocardial infarction was defined and cTn levels were interpreted as recommended in current guidelines.[2,3,5] In brief, acute myocardial infarction was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least one cTn value above the 99th percentile together with a significant rise or fall.[19,20] Criteria to define rise or fall are described in the Methods section in the **Appendix** (available online).

Measurement of hs-cTnI

The measurement of hs-cTnI is described in the **Appendix** (available online).

Follow-up and Clinical End Points

After hospital discharge, patients were contacted after 3 and 12 months by telephone calls or in written form. Furthermore, information about death was obtained from the hospitals' electronic patient documentation, the family physicians' records, and national registries on mortality from each country. The primary prognostic end point was 30 days mortality.

Algorithm Derivation and Validation

The algorithm for use of hs-cTnI was developed in a randomly selected derivation sample of 906 patients (derivation cohort). The algorithm incorporates both baseline hs-cTnI levels and absolute hs-cTnI changes within 1 hour. Selection of these 2 parameters was based on the previously published, very high diagnostic accuracy of their combination.[8,12,15,16] Optimal thresholds for rule-out were selected using receiver-operating characteristics curve to allow a minimal sensitivity of 99% (and 95% for an alternative option) for baseline values together with a negative predictive value (NPV) of at least 95% for the absolute cTnI change within 1 hour. Optimal thresholds for rule-in were obtained based on a classification and regression tree (CART) analysis.[21,22] 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).[21,22]

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-cTnI levels and absolute hs-cTnI changes within 1 hour, age (as a continuous variable), relative hs-cTnI changes within 1 hour, sex, and ECG features (signs of ischemia or not) were included in the CART model as well. Then the algorithm developed in the derivation sample was tested for its diagnostic accuracy in a validation sample consisting of the remaining 906 subjects. The optimal decision values derived in the derivation cohort were rounded to give whole values in ng/L for the prospective testing in the validation cohort.

Statistical Analysis

Continuous variables are presented as mean (SD) or median (interquartile range); and categorical variables as numbers and percentages. Differences in baseline characteristics between patients with and without acute myocardial infarction and between patients in the derivation and validation cohort were assessed using the Mann-Whitney test for continuous variables and the Pearson chi-squared test for categorical variables. The primary outcome measures of this analysis were the NPV for acute myocardial infarction in the rule-out group, the PPV for acute myocardial infarction in the rule-in group, and the percentage of patients assigned the observational zone (all in the validation cohort). NPV and PPV of the hs-cTnI 1h-algorithm were compared with that of the classical dichotomous interpretation of hs-cTnI, as well as the current standard of care combining hs-cTnI with ischemic ECG findings. Mortality during 30 and 360 days of follow-up according to the classification provided by the hs-cTnI algorithm was plotted in Kaplan-Meier curves, and the log-rank test was used to assess differences in mortality between groups. Hazard ratios and 95% confidence intervals (CIs) 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 22.0 (SPSS Inc., Chicago, IL) and MedCalc 11.2.1.0 (MedCalc, Ostend, Belgium).

RESULTS

Baseline characteristics of 1811 patients presenting to the emergency department with suspected acute myocardial infarction are shown in **Table 1**. The adjudicated final diagnosis was acute myocardial infarction in 329 patients (18%), unstable angina in 179 (10%), cardiac disease others than coronary artery disease in 258 (15%), noncardiac symptoms in 964 (53%), and unknown origin in 80 (4%).

Derivation of the hs-cTnI 1h-Algorithm for the Diagnosis of Acute Myocardial Infarction

Baseline characteristics of the derivation and validation cohort were similar (**Supplemental Table**, available online). For rule-out of acute myocardial infarction in the derivation cohort, the optimal threshold was defined as a baseline < 5.2 ng/L and an absolute change within 1 hour of < 1.9 ng/L. With these values, 56% of patients could be classified as "rule-out" (**Figure 1A**). The sensitivity and the NPV for acute myocardial infarction in the "rule-out" zone were 97.6% (95% CI, 93.8%-99.3%) and 99.2% (95% CI, 98.0%-99.8%), respectively. Details of patients with acute myocardial infarction that were missed by the hs-cTnI 1h-algorithm are described in **Table 2**. An alternative 1h-algorithm is described in the **Appendix** (available online).

Table 1 Baseline Characteristics of Patients

Characteristic	All N = 1811	AMI n = 329	No AMI n = 1482	*P*-Value
Age, y				
Median	62	72	60	<.001
IQR	49-62	60-80	47-73	
Risk factors, n (%)				
Hypertension	1115 (62)	261 (79)	854 (58)	<.001
Hypercholesterolemia	912 (50)	217 (66)	695 (47)	<.001
Diabetes	330 (18)	92 (28)	238 (16)	<.001
Current or previous smoking	1129 (62)	219 (66)	910 (61)	.09
Family history	627 (35)	129 (39)	498 (34)	.06
History, n (%)				
Coronary artery disease	627 (35)	164 (50)	463 (31)	<.001
Previous AMI	426 (24)	117 (36)	309 (21)	<.001
Previous revascularization	495 (27)	117 (36)	378 (26)	<.001
Peripheral artery disease	109 (6)	43 (13)	66 (5)	<.001
Previous stroke	101 (6)	33 (10)	68 (5)	<.001
ECG findings, n (%)				
Left bundle branch block	59 (3)	19 (5)	40 (3)	<.001
ST-segment elevation	29 (2)	6 (2)	23 (2)	<.001
St-segment depression	183 (10)	98 (30)	85 (6)	<.001
T-wave inversion	233 (13)	78 (24)	155 (10)	<.001
No significant changes	1344 (74)	153 (46)	1192 (80)	<.001
Body mass index (kg/m^2)				
Median	27	26	26	.490
IQR	24-30	24-29	24-30	
eGFR (mL/min/1.73 m^2)				
Median	85	77	87	<.001
IQR	69-102	55-94	55-94	
Medication at presentation, n (%)				
ASA	656 (36)	171 (52)	485 (33)	<.001
Vitamin K antagonists	144 (8)	31 (9)	113 (8)	.28
B-blockers	614 (34)	141 (43)	473 (32)	<.001
Statins	635 (44)	144 (44)	491 (33)	<.001
ACEIs/ARBs	685 (38)	173 (52)	512 (35)	<.001
Calcium antagonists	256 (14)	68 (21)	188 (13)	<.001
Nitrates	212 (12)	70 (21)	142 (10)	<.001

ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; ASA = acetyl salicylic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; IQR = interquartile range.

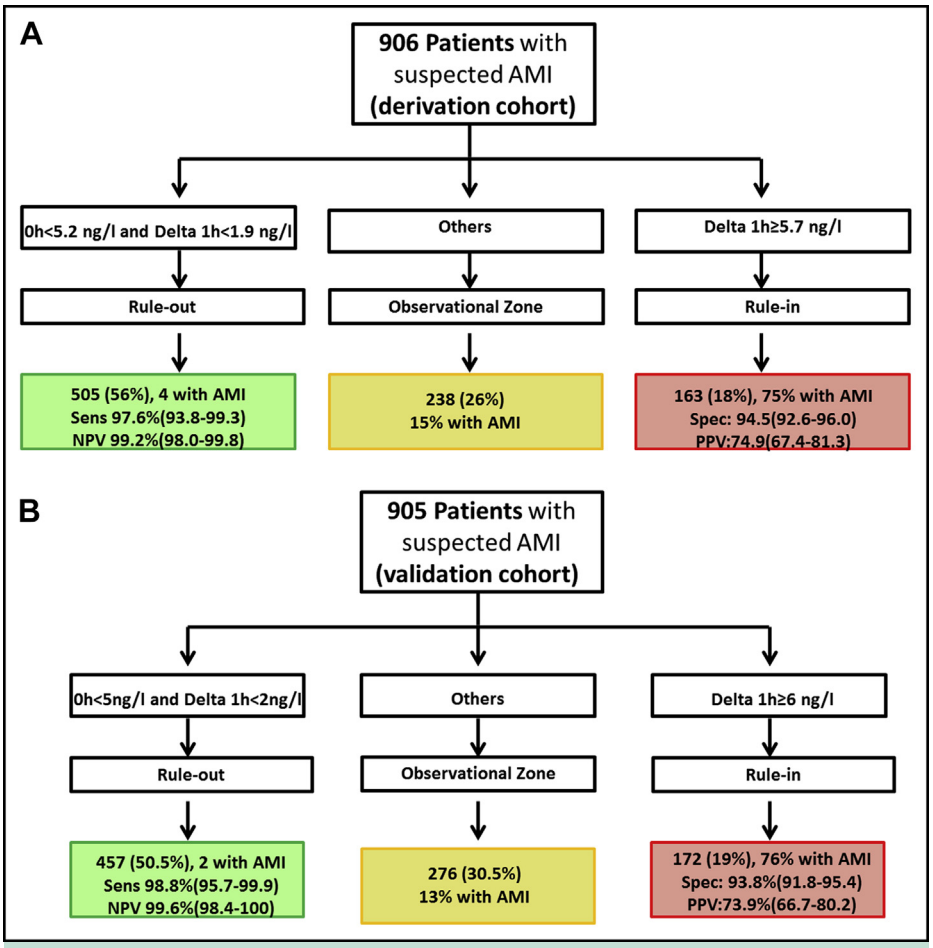

Figure 1 One-hour algorithm for the diagnosis of acute myocardial infarction (AMI) using hs-cTnI in the derivation (**A**) and validation cohort (**B**). Oh = hs-cTnI at presentation to the ED; Delta 1h = absolute change of hs-cTnI within 1 hour; Sens = sensitivity; Spec = specificity; NPV = negative predictive value; PPV = positive predictive value.

For "rule-in" of acute myocardial infarction, the optimal threshold was an absolute change of $\geq$ 5.7 ng/L within 1 hour irrespective of the baseline value. All other variables in the CART analysis (baseline hs-cTnI, age, sex, ischemic ECG changes, and duration of symptoms) did not improve accuracy and did not emerge as contributors to the final decision tree. The specificity and PPV for acute myocardial infarction in the "rule-in" zone were 94.5% (95% CI, 92.6%-96.0%) and 74.9% (95% CI, 67.4-81.3%), respectively. The final adjudicated diagnosis of the ruled-in patients with diagnosis other than acute myocardial infarction (n = 41) were cardiac arrhythmias (n = 10), unstable angina (n = 7), heart failure (n = 7), noncardiac causes (n = 7), myocarditis (n = 5), hypertensive emergency (n = 3), pulmonary embolism (n = 1), and takotsubo cardiomyopathy (n = 1).

Patients fulfilling neither the rule-out nor rule-in criteria (26%) were assigned to "observe." The incidence of acute myocardial infarction was 15% in these patients.

Validation of the hs-cTnI 1h-Algorithm for the Diagnosis of Acute Myocardial Infarction

After applying the hs-cTnI 1h-algorithm developed in the derivation cohort (rounded to give whole values in ng/L) to the validation cohort, 50.5% of patients could be classified as "rule-out," 19% as "rule-in," and 30.5% as "observe" (Figure 1B). In the validation cohort, the sensitivity and the NPV for acute myocardial infarction in the "rule-out" zone were 98.8% (95% CI, 95.7%-99.9%) and 99.6% (95% CI, 98.4%-100%), respectively. The specificity and the PPV for acute myocardial infarction in the "rule-in" zone were 93.8% (95% CI, 91.8%-95.4%) and 73.9% (95% CI, 66.7%-80.2%), respectively. The final adjudicated diagnoses of the ruled-in patients with diagnoses other than acute myocardial infarction (n = 42) were cardiac arrhythmias (n = 14), noncardiac causes (n = 5), unstable angina (n = 4), myocarditis (n = 5), heart failure (n = 6), takotsubo cardiomyopathy (n = 2), pulmonary embolism (n = 3) and hypertensive emergency (n = 3).

Table 2 Baseline Characteristics of the Patients with AMI Incorrectly Ruled Out by the hs-cTnI 1h-Algorithm

Group	Age, y	Sex	Time Since CPO	History of CAD	hs-cTnT (ng/L; Peak Value italicized)			hs-cTnI (ng/L; Peak Value italicized)				Clinical Discharge Diagnosis	CABG Performed	PTCA Performed
					0 h	1 h	2 h	3 h	0 h	1 h	2 h	3 h			
Derivation	76	Male	4 h	Yes	20.2	*20.4*	17.7	17.7	4.3	*4.6*	4.5	4.3	Other (unknown origin)	No	No
Derivation	75	Male	5 h	Yes	*39.0*	35.0	—	—	4.5	*5.3*	—	—	Rhythmogenic (atrial fibrillation)	No	No
Derivation	93	Female	9 h	Yes	*41.0*	38.0	—	—	*3.6*	2.4	—	—	Other (unknown origin)	No	No
Derivation	52	Male	4 h	No	*46.8*	—	—	32.4	*2.8*	2.8	2.5	—	Other (unknown origin)	No	No
Validation	77	Male	5 h	No	*55.0*	52.9	—	44.9	4.7	4.8	—	*5.1*	Other (unknown origin)	No	No
Validation	73	Male	4 h	No	*33.3*	31.6	28.0	—	3.4	*3.9*	—	—	Other (unknown origin)	No	No

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; CPO = chest pain onset; PTCA = percutaneous transluminal coronary angioplasty.

Comparison with the Classical Interpretation of Hs-cTnI

A single cut-off value for hs-cTnI (99th percentile, 26.2 ng/L) at presentation resulted in a sensitivity and NPV of 69.6% (95% CI, 64.3-74.5) and 93.2% (95% CI, 91.8-94.5), and a specificity and PPV of 92.9% (95% CI, 91.5-94.2) and 68.6% (95% CI, 63.3-73.5), respectively. NPV of the 1h-algorithm was higher compared with the classical dichotomous interpretation of hs-cTnI ($P < .001$); PPV was not significantly higher ($P = .895$).

Comparison with the Current Standard of Care (hs-cTnI + ECG)

Combining the classical interpretation of hs-cTnI with ischemic ECG findings (ST-elevation, ST-depression, T-inversion, complete left bundle branch block not known to be old), normal hs-cTnI levels, and no ischemic ECG findings at presentation had a sensitivity and NPV of 79.0% (95% CI, 74.2-83.3) and 94.6% (95% CI, 93.2-95.8), respectively, while "rule-in" when either one (or both) were positive had a specificity and PPV of 79.0 (95% CI, 74.2-83.3) and 48.0% (95% CI, 43.7-52.3), respectively. The NPV and the PPV of 1h-algorithm were both significantly higher compared with that of the current standard of care (hs-cTnI + ECG; both $P < .001$).

Diagnostic Performance of the 1h-Algorithm among Predefined Subgroups

The NPV for acute myocardial infarction in the "rule-out" zone was similar among all predefined subgroups, whereas the PPV for acute myocardial infarction in the "rule-in" zone seemed to be higher in men and patients with preexisting coronary artery disease (Figure 2).

Comparison of 1-Hour vs Other Time Points

The area under the curve (AUC) of the combination of hs-cTnI at presentation with 1-hour absolute change (AUC 0.95; 95% CI, 0.93-0.96) for the diagnosis of acute myocardial infarction was significantly higher as compared with the AUC of hs-cTnI at presentation (AUC 0.93; 95% CI, 0.92-0.94; $P < .001$), and comparable with the combination of hs-cTnI at presentation with 2-hour absolute change (AUC 0.96; 95% CI, 0.95-0.97; $P =$ ns).

"Observe" Group

Among patients classified as "observe" by the hs-cTnI 1h-algorithm, the AUC of the hs-cTnI concentration at 2 hours for the diagnosis of acute myocardial infarction was 0.81 (95% CI, 0.76-0.87).

Undetectable Levels of hs-cTnI

In the overall cohort, 14% of patients had undetectable levels of hs-cTnI. None of these patients were finally

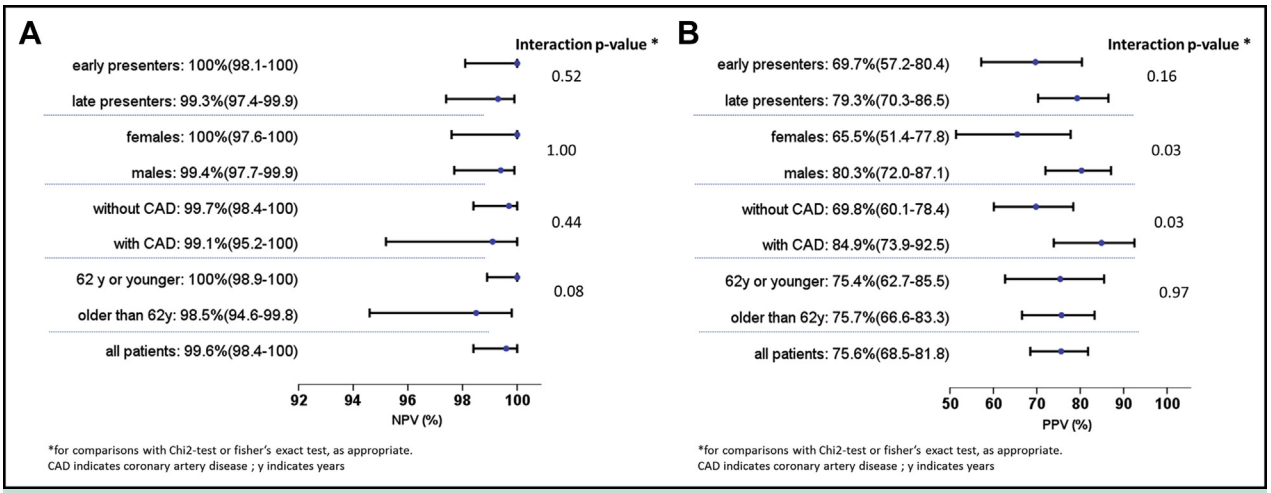

Figure 2 Negative predictive value (NPV) and positive predictive value (PPV) of the 1h-algorithm in study subgroups in the validation group. Forest plots indicating (**A**) NPV and (**B**) PPV among different study subgroups including interaction *P*-value. CAD = coronary artery disease.

adjudicated to have an acute myocardial infarction, which resulted in a sensitivity and NPV of 100%. None of these patients had an increased hs-cTnI concentration above the 99th percentile at 2 hours.

Mortality During Follow-up

Cumulative 30-day mortality in the validation cohort was 0%, 1.4%, and 4.7% ($P < .001$, log-rank test) in patients classified as "rule-out," "observe," and "rule-in," respectively (**Figure 3A**). Cumulative 360-day mortality was 1.3%, 5.1%, and 11% in patients classified as "rule-out," "observe," and "rule-in," respectively ($P < .001$, log rank test; **Figure 3B**). The hazard ratio for the risk of death within 360 days was 3.9 (95% CI, 1.5-10.3; $P = .005$) for patients in the observational zone and 8.9 (95% CI, 3.6-22.3; $P < .001$) for patients in the rule-in group compared with patients in the rule-out group. Among patients dying during 360-day follow-up (n = 77), 36 patients (47%) had an adjudicated diagnosis of acute myocardial infarction. Causes of death during 360-day follow up were: 43% cardiac cause, 17% pulmonal cause, and 40% unknown cause.

DISCUSSION

This international multicenter study was performed to prospectively develop and validate a 1h-algorithm for rapid rule-out and rule-in of acute myocardial infarction based on hs-cTnI. We found a similar performance of the 1h-hs-cTnI algorithm as recently described for the 1h-hs-cTnT algorithm in a pilot study,[12] indicating that accurate rule-out and rule-in is feasible much more rapidly than suggested in current American Heart Association/American College of Cardiology[2,22] or European Society of Cardiology[3] guidelines in many patients. We report 7 major findings:

First, the NPV for acute myocardial infarction in the "rule-out" zone defined only by hs-cTnI levels at presentation and the change within 1 hour was 99.6% (95% CI, 98.4%-100%) in the validation cohort. This algorithm assigned 50.5% of patients to the rule-out zone. As in clinical practice, the 1h-hs-cTnI algorithm would of course always be used in conjunction with full clinical assessment, including patient history and examination, and the 12-lead ECG; these additional clinical tools should allow clinicians to further increase the NPV and thereby approach 100%. Thereby, the use of the 1h-hs-cTn algorithm can be expected to help avoid unnecessary and costly imaging procedures in low-risk patients.[23]

Second, this innovative approach achieved a higher NPV as compared with the classical dichotomous interpretation of hs-cTnI ("cTn-negative"), and even higher compared with the current standard of care combining hs-cTnI with ECG findings.

Third, the PPV for acute myocardial infarction in the "rule-in" zone was 74% in the validation cohort. Many of the patients in the "rule-in" zone with diagnosis other than acute myocardial infarction did have conditions that usually still require coronary angiography for accurate diagnosis, including takotsubo cardiomyopathy, myocarditis, and unstable angina.[3] Therefore, the immediate clinical consequence of being assigned to the "rule-in" zone would be urgent coronary angiography, unless clinical assessment would indicate another obvious condition associated with acute cardiomyocyte damage, for example, acute heart failure, tachyarrhythmia, or hypertensive crisis.[5] The "rule-in" zone of this 1h-hs-cTnI algorithm is more precisely defined than, for example, in the 2011 European Society of Cardiology algorithm.[2,3] As the "rule-in" of acute myocardial infarction in patients with mild elevations in hs-cTn often is challenging for clinicians,[10,24] it is a key advantage of this 1h- hs-cTnI algorithm to provide more detailed guidance in this difficult setting.

Fourth, the PPV achieved with the 1h-hs-cTnI algorithm was higher as compared with the classical dichotomous interpretation of hs-cTnI ("cTn-positive"), and even higher compared with the current standard of care combining hs-cTnI with ECG findings.

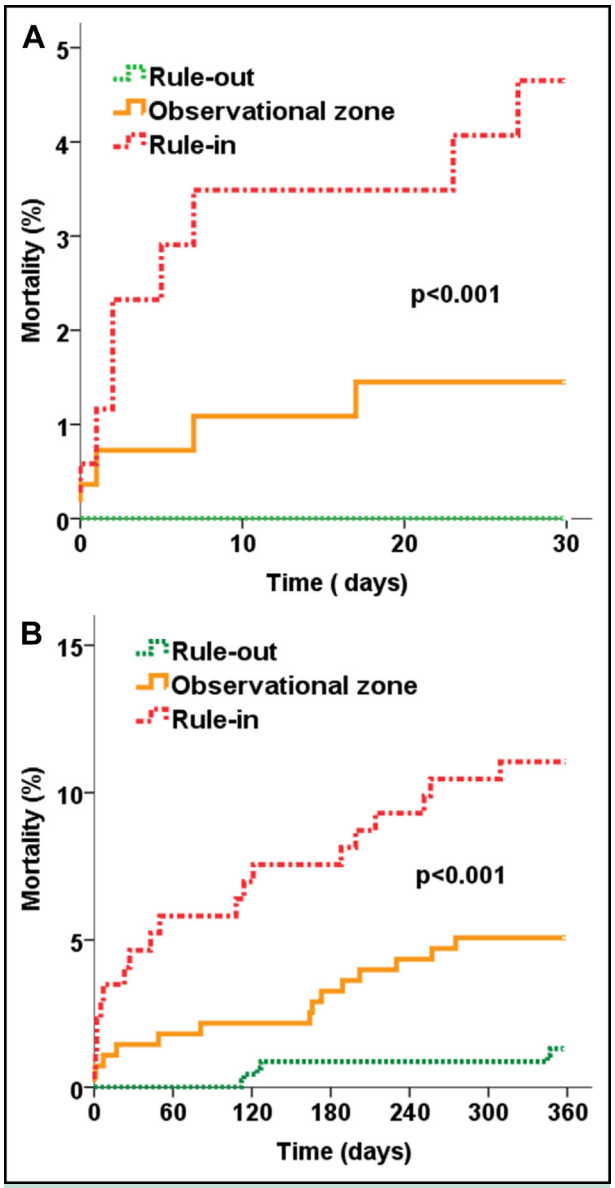

Figure 3 Kaplan-Meier curves for the cumulative mortality according to classification provided by the 1h hs-cTnI algorithm into "rule-out" (n = 457), "observational zone" (n = 276), and "rule-in" (n = 172) provided by the hs-cTnI 1-hour algorithm. Differences in mortality were assessed using the log-rank test. (**A**) mortality during first 30 days, (**B**) mortality during first 365 days.

Fifth, the 1h-hs-cTnI algorithm overall assigned 70% of patients a definite process (either rule-out or rule-in), with 30% of patients remaining in the observational zone. Thereby, the 1h-hs-cTnI algorithm was even more effective in the early triage of acute chest pain patients in comparison with, for example, the recently developed accelerated diagnostic protocol combining the Thrombolysis in Myocardial Infarction Score with cTn or hs-cTn levels at 0 hours and 2 hours,[18,25,26] or the dual-marker approach combining hs-cTn with copeptin, which assign 20%-40% of patients for rapid "rule-out."[27-30] This difference is at least partly explained by the fact that the latter approaches exclusively select patients for "rule-out," but do not provide guidance for "rule-in."

Sixth, among patients classified as "observe" by the hs-cTnI 1h-algorithm, a 2-hour hs-cTnI concentration provided diagnostic values for the diagnosis of AMI.

Seventh, cumulative 30-day mortality was 0% in patients assigned the "rule-out" zone, further documenting the safety of this approach and the suitability of many of these patients for early discharge.

Our findings extend and corroborate recent pilot data obtained for the 1h-hs-cTnT algorithm.[12,31] Overall, the performance of the hs-cTnI 1h-algorithm was similar to that for hs-cTnT (NPV 100%, PPV 80%, and 77% of patients assigned either rule-out or rule-in).[12] The current finding relating to the 1h-hs-cTnI algorithm methodologically is even stronger, as the adjudication of the final diagnosis was based on a different hs-cTn assay in this analysis, while late samples of the same hs-cTnT assay were used in the 1h-hs-cTnT pilot study.[12]

The optimal management of patients assigned to the observational zone likely will be highly individualized. It may include coronary angiography in patients with a high clinical suspicion of acute myocardial infarction, coronary computed tomography angiography in patients with low-to-intermediate likelihood for acute myocardial infarction, a third hs-cTn sample at 2, 3, or 6 hours in many, or no further immediate diagnostic testing when complete clinical evaluation has established (eg, rapid atrial fibrillation or hypertensive crisis as the final diagnosis).[2,3,10,32,33]

It might be possible to further simplify the "rule-out" in patients with very low (undetectable) hs-cTn levels.[31,34,35] Recent evidence from several large studies indicated a very high NPV for acute myocardial infarction of very low (undetectable) hs-cTn levels even without any serial sampling. For example, using undetectable levels of hs-cTnI (Abbott), it was possible to safely rule out 14% of patients presenting to the emergency department achieving an NPV of 100%.[31,34-36]

Potential limitations of the present study merit consideration. First, our study was conducted in emergency department patients with symptoms suggestive of acute myocardial infarction. While the multicenter design ensures that our findings are widely applicable in this setting, additional studies are required to possibly extend our observation to, for example, patients presenting to a general practitioner, a setting with a much lower pretest probability for acute myocardial infarction, or, for example, patients admitted to a coronary care unit, a setting with a much higher pretest probability. Second, the data presented were obtained in a diagnostic study adjudicating the final diagnosis based on the universal definition of acute myocardial infarction. While this is the strongest methodology to quantify the accuracy of the 1h-hs-cTnI algorithm, additional intervention studies applying the 1h-hs-cTnI

algorithm prospectively for clinical decision-making will provide important incremental insights. Third, we cannot comment on the performance of the hs-cTnI 1h-algorithm in patients with terminal kidney failure on chronic dialysis, because such patients were excluded from our study. Fourth, we developed this algorithm for the only clinically available hs-cTnI assay. Considering recent results indicating similar diagnostic accuracy for acute myocardial infarction among hs-cTnI assays,[8,35,37] it is likely that similar 1h-algorithms can be developed for other precommercial hs-cTn and possibly also for sensitive cTnI assays. Of course, each of them would require derivation and validation using stringent methodology, as done in this study.

In conclusion, using a simple algorithm incorporating hs-cTnI baseline values and absolute changes within the first hour, a safe rule-out as well as an accurate rule-in of acute myocardial infarction could be performed within 1 hour in 70% of all patients with acute chest pain. This algorithm seems to be safe, significantly shortens the time needed for rule-out and rule-in of acute myocardial infarction, and may obviate the need for prolonged monitoring and serial blood sampling in many patients presenting to the emergency department with suspected acute myocardial infarction.

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Authorship: MRG, RT, and CM had full access to all the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. All authors had a role in writing the manuscript.

SUPPLEMENTAL DATA

Supplemental data accompanying this article can be found in the online version at 10.1016/j.amjmed.2015.01.046.

APPENDIX

SUPPLEMENTAL METHODS

Use of Local Conventional cTn Values for Adjudication of Final Diagnoses

For the Roche cardiac troponin T (cTnT) 4th generation assay, the 10% coefficient of variation (CV) level is 0.035 μg/L. The laboratories of the participating sites reported only 2 decimals; therefore, 0.04 μg/L was used as a cutoff for myocardial necrosis. In order to fulfill the criteria of a significant change (30% of 99th percentile or 10% CV level), a patient would, for example, need to have a level of $<$ 0.01 ug/L at presentation and 0.04 μg/L at 6 hours. A patient would also qualify if the first level is 0.02 μg/L and the second 0.04 μg/L. A patient would not fulfill the criteria if the first level is 0.03 μg/L and the second is 0.04 μg/L. If the first level is 0.04 μg/L, the second level needs to be at least 0.06 μg/L.

For the Abbott AxsymcTnI ADV (Abbott Laboratories, Abbot Park, IL), the 10% CV level is 0.16 μg/L. A patient having 0.16 μg/L at presentation would meet the criteria for significant change if the second were $\geq$ 0.21 μg/L. A patient having $<$ 0.12 μg/L at presentation (limit of detection) would qualify if the second is $>$ 0.16 μg/L.

For the Beckmann Coulter AccucTnI (Beckmann Coulter, Brea, CA), the 10% CV level is 0.06 μg/L. A patient having 0.06 μg/L at presentation would qualify if the second is $\geq$ 0.08 μg/L. A patient having 0.05 at presentation would qualify if the second is 0.07 μg/L, but not 0.06 μg/L. A patient having undetectable cTnI (cTnI $<$ 0.01 μg/L) at presentation would qualify if the second is $\geq$ 0.06 μg/L.

Use of hs-cTnT for Adjudication of Final Diagnoses

In order to identify additional patients with small acute myocardial infarctions that were missed by the adjudication using the less-sensitive conventional cTn assays, a second adjudication using hs-cTnT was performed in all nonacute myocardial infarction patients according to the first adjudication. For hs-cTnT, the 99th percentile (14 ng/L) was used as cutoff for myocardial necrosis.[1,2]

Absolute changes in hs-cTnT were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.[3,4] Based on studies of the biological variation of cTn[5,6] as well as on data from previous chest pain cohort studies,[7,8] a significant absolute change was defined as a rise or fall of at least 10 ng/L within 6 hours or 6 ng/L within 3 hours.

Assumption of Linearity of Absolute Changes Within the First Hours

The assumption of linearity of absolute changes within the first hours is based on unpublished internal data as well as recent data from Hammarsten et al[9] showing a near-linear increase in levels of cTn, with increasing time from symptom onset in their non-ST-elevation myocardial infarction cohort.

Measurement of hs-cTnI

Blood samples for determination of hs-cTnI were collected at presentation to the emergency department and at 1 hour. After centrifugation, samples were frozen at −80°C until assayed in a blinded fashion in a core laboratory. The Abbott hs-cTnI assay used was the final precommercial release version of the ARCHITECT High Sensitive *STAT* Troponin I assay (Abbott Laboratories). Samples were thawed, mixed, and centrifuged (for 30 minutes at 3000 relative centrifugal force [RCF] and 4°C for serum samples or for 10 minutes, twice, at 3000 RCF for plasma samples) before analysis and according to manufacturer's instructions. The hs-cTnI assay has a 99th percentile concentration of 26.2 ng/L with a corresponding CV of $<$ 5% and a limit of detection of 1.9 ng/L.[10] Calculation of the glomerular filtration rate was performed using the abbreviated Modification of Diet in Renal disease formula.[11]

SUPPLEMENTAL RESULTS

Alternative Rule-out

For the alternative rule-out of acute myocardial infarction in the derivation cohort, the optimal threshold was defined as a baseline $<$ 2.8 ng/L and an absolute change within 1 hour of $<$ 4.5 ng/L. With these values, 32% of patients could be classified as "rule-out" (**Supplemental Figure 1**). The sensitivity and the NPV for acute myocardial infarction in the "rule-out" zone were 100.0% (95% confidence interval [CI], 97.8-100.0) and 100.0% (95% CI, 98.7-100.0%) respectively.

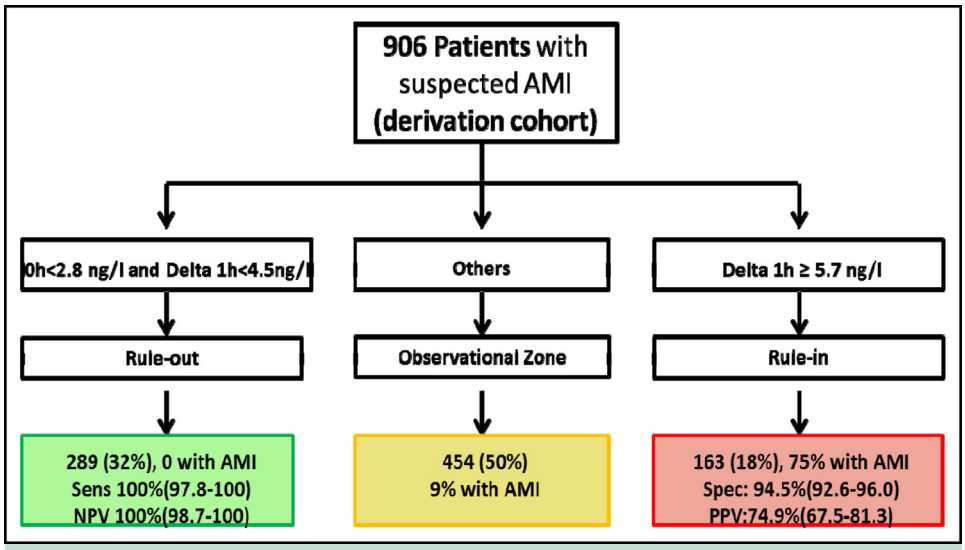
The optimal decision values derived in the derivation cohort were rounded to give whole values in ng/L for the prospective test in the validation cohort (rule out: baseline $<$ 3 ng/L and an absolute change within 1 hour of

< 5 ng/L). After applying the hs-cTnI alternative rule-out developed in the derivation cohort to the validation cohort, 33% of patients could be classified as "rule-out," 19% as "rule-in," and 48% as "observational zone" (**Supplemental Figure 2**). In the validation cohort the sensitivity and the NPV for acute myocardial infarction in the "rule-out" zone were 100.0% (95% CI, 97.8-100.0%) and 100.0% (95% CI, 98.8-100.0%), respectively.

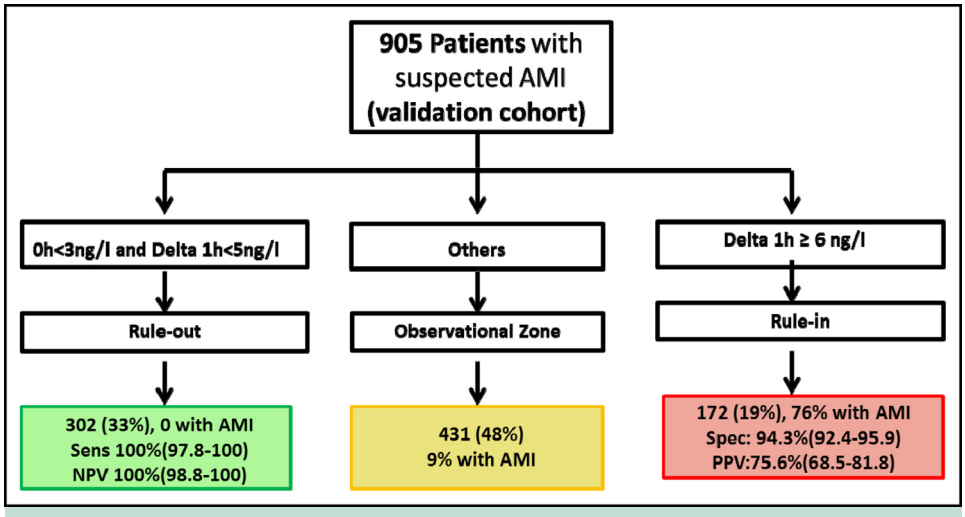
Supplemental Table Baseline Characteristics of Derivation and Validation Cohort

Characteristic	Derivation Cohort n = 906	Validation Cohort n = 905	*P*-Value
Age, y			
Median	62	62	.66
IQR	49-74	50-74	
Sex, n (%)			
Male	620 (68)	625 (69)	.77
Risk factors, n (%)			
Hypertension	545 (60)	570 (63)	.22
Hypercholesterolemia	457 (50)	455 (50)	.94
Diabetes	160 (18)	170 (19)	.54
Current or previous smoking	559 (62)	570 (63)	.57
Family history	310 (34)	317 (35)	.72
History, n (%)			
Coronary artery disease	296 (33)	331 (37)	.08
Previous AMI	201 (22)	225 (25)	.18
Previous revascularization	231 (26)	264 (29)	.08
Peripheral artery disease	50 (6)	59 (7)	.37
Previous stroke	54 (6)	47 (5)	.48
eGFR, mL/min/1.73 m^2			
Median	86	85	.96
IQR	70-102	69-105	
Final diagnoses, n (%)			
AMI	162 (18)	167 (19)	.75
Unstable angina	91 (10)	87 (10)	.76
Cardiac other	122 (14)	136 (15)	.56
Noncardiac	498 (55)	466 (52)	.14
Unknown	32 (4)	48 (5)	.07

AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; IQR = interquartile range.



Supplemental Figure 1 1h alternative algorithm for the diagnosis of AMI using hs-cTnI in the derivation cohort. 0h = hs-cTnI at presentation to the ED; AMI = acute myocardial infarction; Delta 1h = absolute change of hs-cTnI within 1 hour; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.



Supplemental Figure 2 1h alternative algorithm for the diagnosis of AMI using hs-cTnI in the validation cohort. 0h = hs-cTnI at presentation to the ED; AMI = acute myocardial infarction; Delta 1h = absolute change of hs-cTnI within 1 hour; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.

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