Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T

Christian Mueller, MD*; Evangelos Giannitsis, MD; Michael Christ, MD; Jorge Ordóñez-Llanos, MD; Christopher deFilippi, MD; James McCord, MD; Richard Body, MB ChB, PhD; Mauro Panteghini, MD; Tomas Jernberg, MD; Mario Plebani, MD; Franck Verschuren, PhD; John French, PhD; Robert Christenson, PhD; Silvia Weiser, PhD; Garnet Bendig, PhD; Peter Dilba, Dipl Stat; Bertil Lindahl, MD; for the TRAPID-AMI Investigators[†]

*Corresponding Author. E-mail: chmueller@uhbs.ch.

Study objective: We aim to prospectively validate the diagnostic accuracy of the recently developed 0-h/1-h algorithm, using high-sensitivity cardiac troponin T (hs-cTnT) for the early rule-out and rule-in of acute myocardial infarction.

Methods: We enrolled patients presenting with suspected acute myocardial infarction and recent (<6 hours) onset of symptoms to the emergency department in a global multicenter diagnostic study. Hs-cTnT (Roche Diagnostics) and sensitive cardiac troponin I (Siemens Healthcare) were measured at presentation and after 1 hour, 2 hours, and 4 to 14 hours in a central laboratory. Patient triage according to the predefined hs-cTnT 0-hour/1-hour algorithm (hs-cTnT below 12 ng/L and Δ1 hour below 3 ng/L to rule out; hs-cTnT at least 52 ng/L or Δ1 hour at least 5 ng/L to rule in; remaining patients to the "observational zone") was compared against a centrally adjudicated final diagnosis by 2 independent cardiologists (reference standard). The final diagnosis was based on all available information, including coronary angiography and echocardiography results, follow-up data, and serial measurements of sensitive cardiac troponin I, whereas adjudicators remained blinded to hs-cTnT.

Results: Among 1,282 patients enrolled, acute myocardial infarction was the final diagnosis for 213 (16.6%) patients. Applying the hs-cTnT 0-hour/1-hour algorithm, 813 (63.4%) patients were classified as rule out, 184 (14.4%) were classified as rule in, and 285 (22.2%) were triaged to the observational zone. This resulted in a negative predictive value and sensitivity for acute myocardial infarction of 99.1% (95% confidence interval [CI] 98.2% to 99.7%) and 96.7% (95% CI 93.4% to 98.7%) in the rule-out zone (7 patients with false-negative results), a positive predictive value and specificity for acute myocardial infarction of 77.2% (95% CI 70.4% to 83.0%) and 96.1% (95% CI 94.7% to 97.2%) in the rule-in zone, and a prevalence of acute myocardial infarction of 22.5% in the observational zone.

Conclusion: The hs-cTnT 0-hour/1-hour algorithm performs well for early rule-out and rule-in of acute myocardial infarction. [Ann Emerg Med. 2016;68:76-87.]

Please see page 77 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Patients with symptoms suggestive of acute myocardial infarction account for approximately 10% of all emergency department (ED) consultations.[1-3] The 12-lead ECG and cardiac troponin (cTn) form the cornerstones for the diagnosis of acute myocardial infarction and complement clinical assessment.[1-3] A limitation of former-generation cTn assays is the inability to detect low levels of cTn and the associated need for prolonged serial sampling for 6 to 12 hours.[1,2,4] Delays in diagnosing disease (rule-in delays) hold back prompt use of evidence-based therapies.[1,2] Delays in excluding acute myocardial infarction (rule-out delays) interfere with evaluation of alternative diagnoses and contribute to medical errors and costs associated with crowding in the ED.[5,6]

[†]A list of additional contributors in the TRAPID-AMI study is provided in Table E1, available online at http://www.annemergmed.com.

Editor's Capsule Summary

What is already known on this topic

Ruling out acute myocardial infarction is classically conducted with serial biomarkers during 8 to 24 hours.

What question this study addressed

Whether 2 high-sensitivity troponin (hs-cTnT) values at 0 and 1 hour can rapidly classify patients into 3 groups: no acute myocardial infarction, acute myocardial infarction, and indeterminate.

What this study adds to our knowledge

Use of hs-cTn assays at presentation and 1 hour later in a population with a 17% rate of acute myocardial infarction classified 63% of patients as having no acute myocardial infarction, with a 99.1% negative predictive value (95% confidence interval 98.2% to 99.7%); 14% as having acute myocardial infarction, with a positive predictive value of 77% (95% confidence interval 70.4% to 83.0%); and 22.5% as having an indeterminate classification after 1 hour of testing.

How this is relevant to clinical practice

This study validated previous work that serial high-sensitivity troponin values can rapidly help determine likelihood of acute myocardial infarction.

Importance

High-sensitivity cardiac troponin (hs-cTn) assays, which allow measurement of even low cTn concentrations with high precision, have been shown to provide high diagnostic accuracy for acute myocardial infarction already at presentation.[7-14] In parallel, several early-rule-out strategies have been developed. These include the use of very low concentrations of hs-cTn,[12,15-17] as well as the combination of cTn concentrations at 0 and 2 hours with a clinical score.[18-20] Limitations of these approaches include that they do not provide guidance for rule-in and that rule-out is possible only in 10% to 40% of patients.[12,15-20]

Accordingly, the high-sensitivity cardiac troponin T (hs-cTnT) 0-hour/1-hour algorithm has received substantial attention.[10,13] This algorithm uses hs-cTnT blood concentrations at presentation and their absolute changes within 1 hour to triage patients. It was reported to achieve a very high negative predictive value for acute myocardial infarction in the rule-out zone, to achieve a high positive predictive value in the rule-in zone, and to be very effective by triaging approximately 75% of patients presenting with suspected acute myocardial infarction to the ED to either rule-out or rule-in classifications.[10,13] Obviously, successful external validation in a global and meticulous multicenter study is mandatory before such a novel approach can be considered for widespread implementation into routine clinical practice.[21]

Goals of This Investigation

The aim of this international multicenter study, therefore, was

MATERIALS AND METHODS

Study Design

The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction (TRAPID-AMI) trial was a prospective international multicenter diagnostic study conducted at 12 sites on 3 continents (see STARD checklist in Appendix E1, available at http://www.annemergmed.com).

Selection of Participants

Patients presenting to the ED with symptoms suggestive of acute myocardial infarction (such as acute chest pain and angina pectoris) with an onset or maximum of discomfort or pain within the previous 6 hours were identified by study personnel and recruited after written informed consent had been obtained. A threshold of fewer than 6 hours was chosen to enrich the study population with the particularly challenging early presenters.[7-9] Patients with renal failure requiring long-term hemodialysis; those with trauma, cardioversion, defibrillation, or thrombolytic therapy before inclusion; individuals receiving coronary artery bypass grafting within the last month or hospitalized for acute myocardial infarction within the last 3 weeks; and pregnant and breastfeeding women were excluded. To allow the study blood draw to be performed as quickly as possible, definite interpretation of the initial ECG was not required before inclusion. Accordingly, patients with ST-segment elevation myocardial infarction (STEMI) were not excluded by the protocol. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

Patients underwent an initial clinical assessment that included clinical history, physical examination, 12-lead ECG, pulse oximetry, standard blood tests (including local cTn assays), and chest radiograph in accordance with local protocols. Treatment of patients was left at discretion of the attending physician. Standard data were collected on study-specific case report forms.

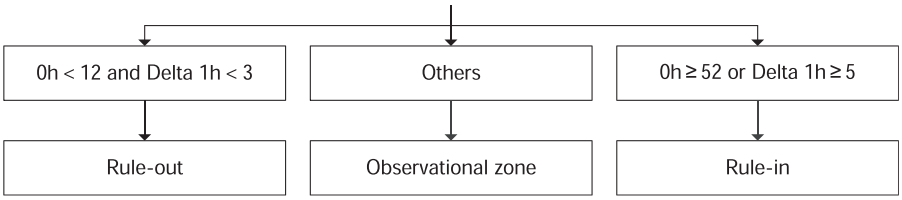

Figure 1. Hs-cTnT 0-hour/1-hour algorithm. Values for hs-cTnT are shown in nanograms per liter.

Blood samples for central measurement of hs-cTnT (Roche Diagnostics, Penzberg, Germany) and sensitive cardiac troponin I ultra (s-cTnI-ultra) (Siemens Healthcare, Tarrytown, NY) were collected in ethylenediaminetetraacetic acid plasma tubes at presentation to the ED after written informed consent was obtained. To ensure that the first study blood draw was performed within a short time from ED presentation, this period was required to be either within 45 minutes of presentation to the ED or less than 45 minutes after the first routine blood draw. Additional samples were collected after 1 hour (±30 min) (n=1,282), 2 hours (±30 min) (n=1,158), and 4 to 14 hours (±30 min) (n=1,073). After centrifugation, samples were frozen at –80°C (−112°F) until assayed in a blinded fashion with the Elecsys 2010 (Roche Diagnostics) and the ADVIA Centaur immunoassay system (Siemens Healthcare) in a core laboratory. For hs-cTnT, limit of blank and limit of detection have been determined to be 3 and 5 ng/L, respectively. An imprecision corresponding to 10% coefficient of variation was reported at 13 ng/L; the 99th percentile of a healthy reference population, at 14 ng/L.[22] The s-cTnI-ultra assay is reported to have a limit of detection of 6 ng/L, a 99th percentile cutoff point of 40 ng/L, and a coefficient of variation of less than 10% at 30 ng/L.[7,9,11]

None of the study blood results were available to the treating physician. The results of s-cTnI-ultra, but not those of hs-cTnT, were available to the adjudicating cardiologists.

The hs-cTnT 0-hour/1-hour algorithm[10,13] uses hs-cTnT blood concentrations at presentation and their absolute changes within 1 hour to triage patients to rule-out status, the observational zone, or rule-in status (Figure 1): patients with hs-cTnT below 12 ng/L and Δ1 hour below 3 ng/L to rule-out status, hs-cTnT at least 52 ng/L or Δ1 hour at least 5 ng/L to rule-in status, and the remaining patients to the observational zone. The combination of the level at presentation with absolute changes within 1 hour was chosen because of the added value of 1-hour changes and the superiority of absolute versus relative changes. The specific cutoff values were data-driven from the initial derivation cohort.[10,11,13]

Outcome Measures

To determine the final diagnosis for each patient, adjudication of final diagnoses was performed by a dedicated group of cardiologists selected for the Clinical Event Committee of this study (Appendix E2, available online at http://www.annemergmed.com) according to the universal definition of acute myocardial infarction.[4] Each patient was adjudicated by 2 independent cardiologists. Adjudicators reviewed all available medical records (including patient history; physical examination results; results of laboratory testing, including levels of s-cTnI-ultra, local cTn obtained before the first or after the last blood draw for the study if available, creatinine, cystatin C, free hemoglobin [to quantify hemolysis], and NT-proBNP; radiologic imaging; ECG; echocardiography; cardiac stress test; and lesion severity and morphology in coronary angiography) pertaining to the patient from ED presentation to 30-day follow-up. Discrepancies were solved by discussion with a third cardiologist. Interrater reliability was assessed by documenting the number of patients with mismatch in the final diagnosis of acute myocardial infarction by the 2 adjudicating cardiologists, which required involvement of a third cardiologist.

The s-cTnI-ultra assay was chosen for the adjudication to achieve complete blinding to hs-cTnT levels during the study period in the ED. This assay was the best-validated sensitive cTn assay available at study start, with early diagnostic accuracy similar to that of the hs-cTnT assay.[7,9,11]

Acute myocardial infarction was defined and s-cTnI-ultra levels interpreted as recommended in current guidelines.[2,3,23] In brief, acute myocardial infarction was diagnosed when there was evidence of myocardial necrosis in a clinical setting, with a significant increase or decrease of s-cTnI level consistent with myocardial ischemia. The 99th percentile (40 ng/L) was used as the cutoff for myocardial necrosis. An absolute s-cTnI-ultra change of at least 20 ng/L during the study period was used to define a significant increase or decrease.[11] Other predefined diagnostic groups included unstable angina; other cardiac disease including myocarditis, takotsubo cardiomyopathy, acute heart failure, or tachyarrhythmias[2]; noncardiac

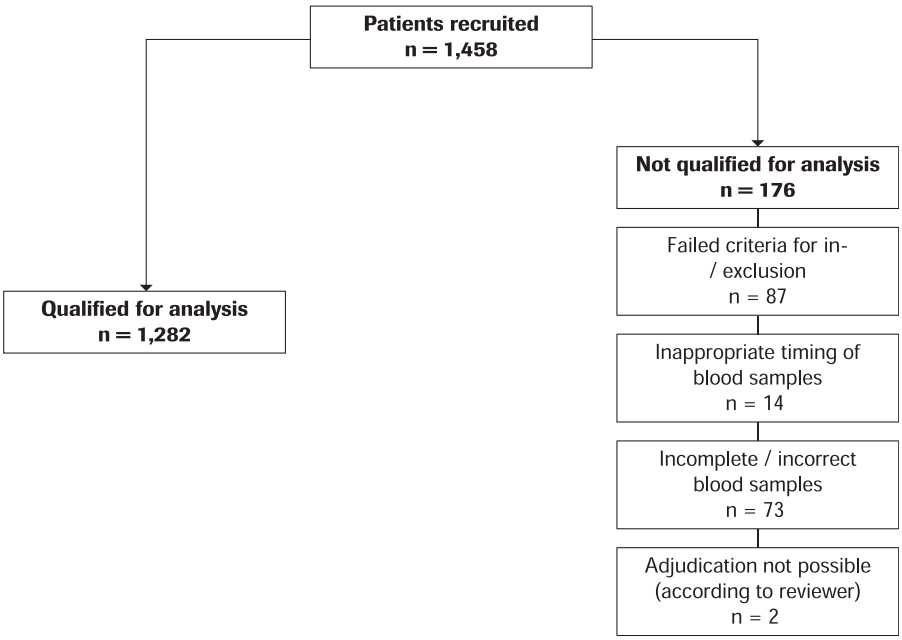

Figure 2. Patient flow diagram.

disease; and symptoms of unknown origin, in which acute myocardial infarction was excluded but the evaluation was considered insufficient for a clear alternative diagnosis.

Secondary outcome measures included mortality at 30 days and 1 year. Mortality at 30 days was predefined as an additional outcome measure to evaluate the possible appropriateness of early discharge in patients assigned as ruled out. After hospital discharge, patients were contacted after 1 week, 30 days, 3 months, and 12 months by telephone calls or in written form. Information about death was furthermore obtained from the national registry on mortality, the hospital's diagnosis registry, and the family physician's records. If the patient could not be contacted directly, we contacted their primary care physician.

Primary Data Analysis

Continuous variables are described by mean ± SD or median with interquartile range; categorical variables, by numbers and percentages. The negative predictive value and sensitivity for acute myocardial infarction of the hs-cTnT 0-hour/1-hour rule-out rule were the primary outcome measures. Secondary outcome measures included the positive predictive value and specificity of the hs-cTnT 0-hour/1-hour rule-in rule, the percentage of patients assigned to the observational zone. Predefined subgroups included patients presenting very early (chest pain onset <median) to document whether the hs-cTnT 0-hour/1-hour algorithm achieved a negative predictive value in this delicate patient subgroup comparable to that in the overall cohort because here another early rule-out strategy had been shown to have a lower negative predictive value.[17] Sensitivity analysis with data removed for patients presenting with STEMI was performed to correct for a possible bias introduced by the inclusion of patients with STEMI because cTn and therefore the hs-cTnT 0-hour/1-hour algorithm is considered not necessary in its early management. To provide further support for the selection of the 1-hour point for the second measurement of hs-cTnT, the combination of the hs-cTnT baseline level with the 1-hour change was compared with the baseline level alone, as well as with the combination of the baseline level with the 2-hour point by quantifying diagnostic accuracy by the area under the receiver operating characteristics curve (AUC) (Table E2, available online at http://www.annemergmed.com). Mortality during follow-up according to the classification provided by the predefined hs-cTnT 0-hour/1-hour algorithm was plotted in Kaplan-Meier curves to further examine the suitability of many of the patients in the rule-out zone for early discharge and outpatient management. All statistical analyses were performed with R 3.0.1 (R Foundation for Statistical Computing) and SAS 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Subjects

From August 2011 to June 2013, 1,458 patients were enrolled, of whom 1,282 were eligible for analysis (Figure 2). Baseline characteristics are shown in Table 1. Median time from chest pain onset or peak to ED

Table 1. Baseline characteristics of the patients.*

Characteristic	All Patients (n=1,282)	Rule in (n=184)	Observe (n=285)	Rule out (n=813)
Age, y	62 (50–74)	69 (56–78)	74 (65–81)	56 (47–66)
Male patient	805 (62.8)	131 (71.2)	206 (72.3)	468 (57.6)
Risk factors				
Hypertension	805 (62.8)	135 (73.4)	238 (83.5)	432 (53.1)
Diabetes	270 (21.1)	46 (25.0)	102 (35.8)	122 (15.0)
Hypercholesteremia	139 (10.8)	26 (14.1)	34 (11.9)	79 (9.7)
Current smoking	288 (22.8)	43 (23.8)	40 (14.1)	205 (25.7)
History of smoking	468 (37.1)	75 (41.4)	139 (48.9)	254 (31.9)
History				
Previous coronary intervention	388 (30.3)	53 (28.8)	136 (47.7)	199 (24.5)
PCI (unknown as PCI)	284 (22.2)	34 (12.0)	91 (32.0)	159 (56.0)
CABG	104 (8.1)	19 (10.3)	45 (15.8)	40 (4.9)
Previous myocardial infarction	319 (24.9)	48 (26.1)	115 (40.4)	156 (19.2)
Stable angina pectoris	148 (11.5)	26 (14.1)	51 (17.9)	71 (8.7)
Unstable angina pectoris	164 (12.8)	30 (16.3)	55 (19.3)	79 (9.7)
Congestive heart failure	107 (8.3)	23 (12.5)	59 (20.7)	25 (3.1)
Time from chest pain onset/peak to presentation, h	1.8 (1.0–2.9)	2 (1.1–3.0)	1.9 (1.2–3.1)	1.7 (1.0–2.9)
Time from chest pain onset to first study blood draw, h	3.4 (2.1–6.0)	3.5 (2.4–6.0)	3.4 (2.2–6.0)	3.4 (2.0–6.0)
Creatinine clearance† ml/min/1.73m^2	81 (65–97)	73 (54–91)	68 (52–83)	86 (72–101)
Systolic blood pressure, mm Hg	141 (127–157)	141 (126–160)	142 (127–160)	141 (127–155)
Diastolic blood pressure, mm Hg	81 (72–90)	81 (70–92)	80 (70–89)	81 (73–91)
Pulse rate, beats/min	76 (66–88)	78 (68–92)	78 (66–90)	76 (65–86)
ECG				
Rhythm				
Atrial fibrillation	92 (7.2)	16 (8.7)	53 (18.6)	23 (2.8)
Sinus	1,148 (89.5)	159 (86.4)	218 (76.5)	771 (94.8)
Other rhythm	42 (3.3)	9 (4.9)	14 (4.9)	19 (2.3)
Left ventricular hypertrophy	65 (5.1)	9 (4.9)	28 (9.8)	28 (3.4)
Complete LBBB	36 (2.8)	11 (6.0)	17 (6.0)	8 (1.0)
Complete RBBB	55 (4.3)	9 (4.9)	27 (9.5)	19 (2.3)
Paced ventricular complex	23 (1.8)	8 (4.3)	15 (5.3)	0
Pathologic Q waves	119 (9.3)	28 (15.2)	38 (13.3)	53 (6.5)
ST-segment elevation‡	60 (4.7)	17 (9.2)	14 (4.9)	29 (3.6)
ST-segment depression	164 (12.8)	47 (25.5)	66 (23.2)	51 (6.3)
T inversion	184 (14.4)	46 (25.0)	71 (24.9)	67 (8.2)
Normal ECG	1,148 (89.6)	159 (86.4)	218 (76.5)	771 (94.8)
HEART score§	3 (2–5)	4 (3–5)	5 (4–6)	3 (2–4)
Low risk (≤3)	618 (48.2)	52 (28.2)	46 (16.1)	520 (64.0)
Intermediate risk (4–6)	557 (43.4)	114 (62.0)	197 (69.1)	246 (30.3)
High risk (≥7)	48 (3.7)	11 (6.0)	25 (8.8)	12 (1.5)
Previous medication				
Aspirin	657 (51.2)	110 (59.8)	188 (66.0)	359 (44.2)
Anticoagulants	193 (15.1)	39 (21.2)	75 (26.3)	79 (9.7)
Diuretic	314 (24.5)	61 (33.2)	123 (43.2)	130 (16.0)
ACE inhibitor	383 (29.9)	58 (31.5)	121 (42.5)	204 (25.1)
Angiotensin-receptor blocker	204 (15.9)	34 (18.5)	67 (23.5)	103 (12.7)
β-Blocker	488 (38.1)	78 (42.4)	162 (56.8)	248 (30.5)
Calcium antagonist	248 (19.3)	43 (23.4)	84 (29.5)	121 (14.9)
Nitrates	390 (30.4)	65 (35.3)	120 (42.1)	205 (25.2)
Other platelet aggregation inhibitor	180 (14.0)	29 (15.8)	60 (21.1)	91 (11.2)
Antiarrhythmic drug	65 (5.1)	12 (6.5)	33 (11.6)	20 (2.5)
Other cardiac medication	554 (43.2)	80 (43.5)	185 (64.9)	289 (35.5)

PCI, Percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *LBBB*, left bundle branch block; *RBBB*, right bundle branch block; *ACE*, angiotensin-converting enzyme.

*Values are No. (%) or medians (interquartile range).

†Using the Modification of Diet in Renal Disease equation.[36]

‡Including patients with STEMI, takotsubo cardiomyopathy, perimyocarditis, left ventricular hypertrophy, and early repolarization.

§HEART (History, ECG, Age, Risk Factors, Troponin) score was missing for 59 patients (35 rule-out, 7 rule-in, and 17 observe status). For this reason, the percentages in brackets for the 3 categories do not sum to 100% because it is the percentage of all 1,282 patients.

presentation was 1.8 hours (interquartile range 1.0 to 2.9 hours), and median time from chest pain onset to first study blood draw was 3.4 hours (interquartile range 2.1 to 6 hours).

The adjudicated final diagnosis was acute myocardial infarction for 213 patients (17%; 21 patients with acute STEMI), unstable angina for 167 (13%), cardiac symptoms of origin other than coronary artery disease for 113 (9%), noncardiac symptoms for 288 (22%), and symptoms of unknown origin for 501 (39%). Interrater reliability in regard to acute myocardial infarction was very high, with concordant final diagnoses among the 2 adjudicating cardiologists for 97.7% of patients and the need for involvement of a third cardiologist for 2.3% of patients.

Applying the predefined hs-cTnT 0-hour/1-hour algorithm, 813 (63.4%) patients could be classified to rule-out status, 184 (14.4%) patients were classified to rule-in status, and 285 (22.2%) patients were classified to observational zone status (Table 2, Figure 3). Among the 813 patients classified to rule-out status, 806 had an adjudicated diagnosis other than acute myocardial infarction, and 7 patients received a diagnosis of acute myocardial infarction. The characteristics of these patients are described in Table 3. This resulted in a negative predictive value and sensitivity of 99.1% (95% confidence interval [CI] 98.2% to 99.7%) and 96.7% (95% CI 93.4% to 98.7%), respectively, for acute myocardial infarction in the rule-out zone. Accordingly, the miss rate was 0.9% in the rule-out zone. The negative predictive value was comparable in various predefined subgroups, including very early presenters (Figure 4). Among the 184 patients classified to rule-in status, 142 received an adjudicated diagnosis of acute myocardial infarction and 42 received another diagnosis. This resulted in a positive predictive value and specificity of 77.2% (95% CI 70.4% to 83.0%) and 96.1% (95% CI 94.7% to 97.2%), respectively, for acute myocardial infarction in the rule-in zone. The most common other diagnoses in the rule-in zone were myocarditis (n=4), unstable angina (n=4), takotsubo cardiomyopathy (n=3), heart failure (n=3), arrhythmia (n=3), and symptoms of unknown origin (n=16).

Among the 285 patients classified to the observational zone, 64 received an adjudicated diagnosis of acute myocardial infarction, resulting in a prevalence of 22.5% in this group.

Sensitivity analysis, in which data for STEMI patients (n=21) were removed, revealed similar findings (Table E2 and Figure E1, available online at http://www.annemergmed.com).

A single cutoff value for hs-cTnT (14 ng/L, the 99th percentile of healthy individuals) at presentation resulted in a sensitivity and negative predictive value of 88.7% (95% CI 83.7% to 92.6%) and 97.3% (95% CI 96.0% to 98.3%), respectively, and a specificity and positive predictive value of 81.5% (95% CI 79.0% to 83.8%) and 48.8% (95% CI 43.8% to 53.9%), respectively. The AUC for the combination of hs-cTnT at presentation with 1-hour levels and 1-hour absolute change (0.95 [95% CI 0.93 to 0.97]) was significantly higher compared with the AUC of hs-cTnT at presentation (0.91 [95% CI 0.88 to 0.93]) and comparable to the combination of hs-cTnT at presentation with 2-hour levels and 2-hour absolute change (0.95 [95% CI 0.93 to 0.96]). Models with adjustment for age, sex, previous acute myocardial infarction, and renal function revealed similar findings (Appendix E3, available online at http://www.annemergmed.com).

Cumulative 30-day mortality was 0.1%, 0.7%, and 2.7% in patients classified as rule-out, observational zone, and rule-in (Figure 5). This pattern continued up to a follow-up of 365 days, with cumulative mortality rates of 0.7%, 9.6%, and 8.9%, respectively. Although

Table 2. Two×two tables and calculation of negative and positive predictive value, as well as sensitivity and specificity for the rule-out and rule-in of myocardial infarction.

***A*, Algorithm classification versus adjudicated diagnosis.**

Algorithm Classification	AMI	Non-AMI	Total
Rule-out status	7	806	813
Observational zone	64	221	285
Rule-in status	142	42	184
Total	213	1,069	1,282

AMI, Acute myocardial infarction.

***B*, Negative and positive predictive value.**

Diagnostic Test Performance Measures	Estimate, %	95% CI	Counts
NPV	99.14	98.23–99.65	806/813
PPV	77.17	70.42–83.03	142/184

NPV, Negative predictive value; *PPV*, positive predictive value.

C*, Sensitivity and specificity.

Diagnostic Test Performance Measures	Estimate, %	95% CI	Counts
Sensitivity in the rule-out zone	96.71	93.35–98.67	206/213
Specificity in the rule-in zone	96.07	94.73–97.15	1,027/1,069

*Sensitivity: true positive/diseased (AMI). The rule-out zone defines patients with no AMI according to the 0-hour/1-hour hs-cTnT algorithm. Only patients in this zone are ruled out. Accordingly, for the rule-out it is irrelevant whether patients are in the observational zone or the rule-in zone, and both zones are combined. True positive=206; diseased (AMI)=213; sensitivity=96.71%. Specificity: true negative/non-diseased (non-AMI). The rule-in zone defines patients with AMI according to the 0-hour/1-hour hs-cTnT algorithm. Only patients in this zone are ruled in. Accordingly, for the rule-in it is irrelevant whether patients are in the observational zone or the rule-out zone, and both zones are combined. True negative=1,027; non-diseased (non-AMI) 1,069; specificity=96.07%.

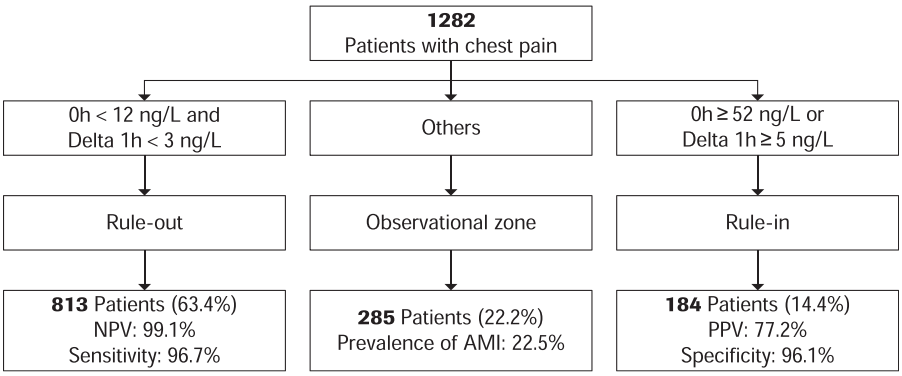

Figure 3. Performance of the 0-hour/1-hour algorithm for diagnosis of acute myocardial infarction, using hs-cTnT levels. 0h=hs-cTnT at presentation to the ED. Delta 1h=absolute change of hs-cTnT within the first hour. Sensitivity and specificity as reported here were calculated according to Table 2C, with the observational zone patients considered as correctly classified.

approximately 50% of deaths in the rule-in group were due to cardiac causes, the majority in the observational group were due to noncardiac causes (Table E3, available online at http://www.annemergmed.com).

LIMITATIONS

Potential limitations of the current study merit consideration. First, our study was conducted with ED patients with symptoms suggestive of acute myocardial infarction. Additional studies—for example, in patients presenting to a family physician—are required to learn whether this algorithm would have a similar performance in patients with lower pretest probability. Second, the data presented were obtained in an observational diagnostic study, in which the hs-cTnT 0-hour/1-hour algorithm was compared against a centrally adjudicated final diagnosis. Treating physicians were blinded to the investigational hs-cTnT results and patients were not managed in accordance with these results. The successful validation of the hs-cTnT 0-hour/1-hour algorithm in this study now warrants applying it prospectively for clinical decisionmaking. Further work should focus on the evaluation of the cost-effectiveness of the algorithm when implemented in practice. Third, this diagnostic study required written informed consent and had predefined inclusion and exclusion criteria, as well as a study-specific case report form. Patient enrollment therefore required the presence of dedicated research personnel in the ED at the patients' presentation. Accordingly, invariably the rate of enrollment was lower than in a recent registry[15] and, as in nearly all clinical studies, resulted in an underrepresentation of patients presenting during the night. Fourth, our findings may slightly underestimate the true negative predictive value of the hs-cTnT 0-hour/1-hour algorithm because a threshold of chest pain onset of fewer than 6 hours (versus fewer than 12 hours in the Advantageous Predictors in Acute Coronary Syndrome Evaluation [APACE] study) was chosen to enrich the study population with the particularly challenging early presenters.[7-9] Fifth, we cannot comment on the performance of the hs-cTnT 0-hour/1-hour algorithm in patients with terminal kidney failure requiring dialysis; those receiving cardioversion, defibrillation, or thrombolysis before inclusion; those undergoing coronary artery bypass grafting within the last month or hospitalized for acute myocardial infarction within the last 3 weeks; or pregnant and breastfeeding women because such patients were excluded from this study.

DISCUSSION

This international multicenter study was performed to prospectively validate the performance of the recently developed hs-cTnT 0-hour/1-hour algorithm for rapid rule-out and rule-in of acute myocardial infarction. This study differs in 4 key aspects from the initial pilot study.[10,13,14] First, it had global representation of patients with 12 sites in the United States, Europe, and Australia, whereas the APACE study recruited in Europe only. Second, we enriched the study population with challenging early presenters by requiring chest pain onset to be fewer than 6 hours at presentation compared with 12 hours in APACE. Third, this study aimed to maximize internal and external validity by recruiting patients presenting with acute chest pain irrespective of their ECG findings, whereas patients with STEMI were excluded in previous analyses from APACE. Fourth, to have the most stringent methodology and make the adjudicated final diagnosis completely independent of all components of the hs-cTnT 0-hour/1-hour algorithm, serial testing for s-cTnI-ultra complemented all other clinical information, including coronary angiography in TRAPID-AMI, whereas serial testing for hs-cTnT complemented all other clinical information in APACE.

Table 3. Baseline characteristics of the patients with acute myocardial infarction incorrectly ruled out by the hs-cTnT 0-hour/1-hour algorithm.

Age	Sex	Time From CPO† to First Study Blood Draw, Hours	Time From CPO/Peak to Presentation, Hours	History of CAD	Time, Hours: hs-cTnT, ng/L* 0	1	2	4–14	s-cTnI-ultra, ng/L* 0	1	2	4–14	ST Depression	T Inversion	Clinical Discharge Diagnosis	CABG Performed	PCI Performed
50	Male	2.8	0.9	No	8.1*	6.6	4.8	7.1	123*	113	87	118	No	No	Noncardiac	No	No
51	Male	1.7	0.2	Yes	3.0	3.0	5.1	14.0*	0	0	4	101*	Not evaluable	Not evaluable	Cardiac	No	No
49	Female	3.5	2.4	Yes	12.0	13.2	18.3	33.0*	4	17	54	205*	No	No	UA	No	No
65	Female	3.3	1	Yes	3.6	3.0	5.7	11.0*	0	17	28	80*	No	No	UA	No	No
82	Female	5	4.5	Yes	8.3	10.6	4.8	10.9*	44	59*	33	36	No	Yes	UA	No	No
63	Male	165.3	1.1	No	11.6	11.6	13.8	19.0*	10	20	34	98*	Yes	Yes	UA	No	Yes
75	Male	6.5	1.6	Yes	3.0	5.0	3.6	22.8*	0	3	10	364*	No	No	AMI	No	No

CPO, Chest pain onset; *CAD*, coronary artery disease; *cardiac*, cardiac disease other than AMI/CAD; *UA*, unstable angina pectoris.
*Peak values.
†In 4 patients chest pain was described as "pressure," in 2 as "burning," and in 1 as "pressure" and "burning," and in all 7 patients the pain radiated to the left arm (n=6) or to the back (n=1).

Figure 4. Forest plot indicating negative predictive value of the 0-hour/1-hour algorithm in study subgroups.

We found that accurate rule-out and rule-in seems to be feasible much more rapidly than suggested in current American Heart Association/American College of Cardiology[1] guidelines in the majority of patients. We report 7 major novel findings.

First, the negative predictive value for acute myocardial infarction in the rule-out zone, defined only on hs-cTnT levels at presentation and the change within 1 hour, was 99.1%. Thereby, the hs-cTnT 0-hour/1-hour algorithm in TRAPID-AMI had a negative predictive value similar to that observed in the APACE pilot study.[10,13] The negative predictive value was also comparable to that achieved with an accelerated diagnostic protocol combining the Thrombolysis in Myocardial Infarction score with hs-cTn levels at 0 and 2 hours[18-20] and seemed higher compared with the dual-marker approach combining cTn with copeptin.[24-28] For example, the negative predictive value of hs-cTnI combined with a very low cutoff value of copeptin (9 pmol/L) was 95% to 97% when the final diagnosis was adjudicated with hs-cTn.[28]

Second, in TRAPID-AMI only approximately half of patients with missed acute myocardial infarction exhibited late increasing hs-cTnT levels.[29] The other half never showed an elevation in hs-cTnT but did show a small time-dependent dynamic change in s-cTnI-ultra, indicating lower agreement among these widely used tests in the low end of the measuring range, as expected.[30,31] All missed adjudicated acute myocardial infarctions were small, and most patients with them received a clinical discharge diagnosis of unstable angina, not acute myocardial infarction, indicating that full

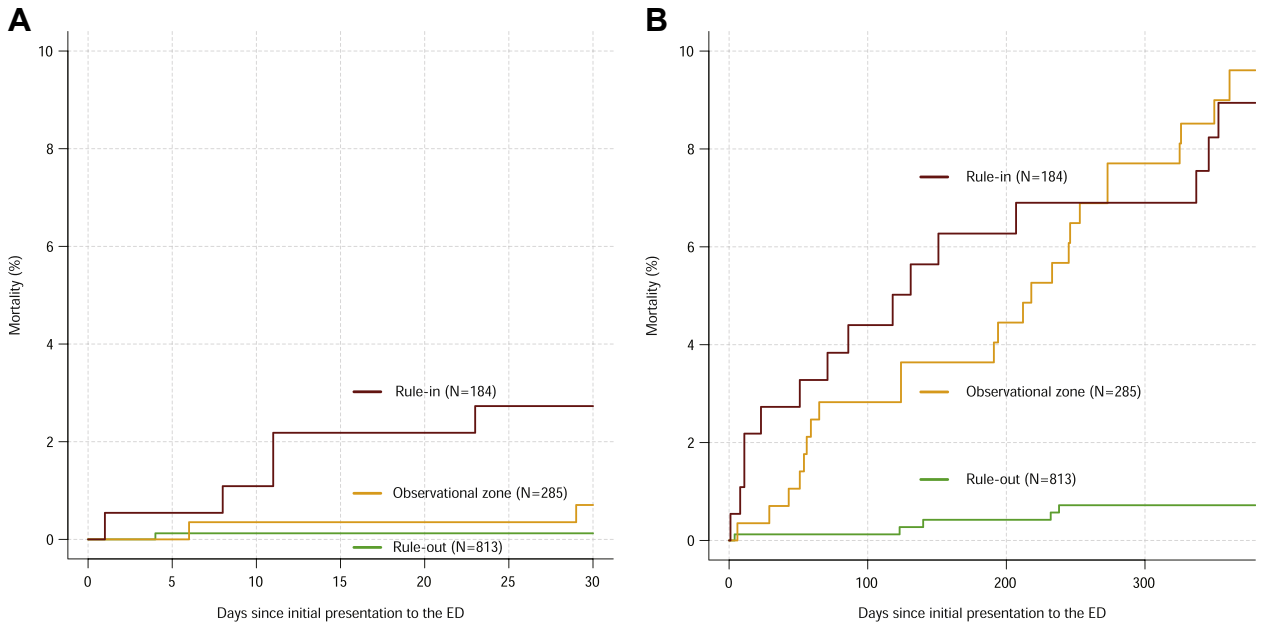

Figure 5. Kaplan-Meier curves for cumulative mortality according to classification provided by the hs-cTnT 0-hour/1-hour algorithm. Kaplan-Meier curves displaying cumulative mortality during *A*, 30 days of follow-up, and *B*, 365 days of follow-up in all chest pain patients (n=1,282) according to the classification into rule-out (green), observational zone (orange), and rule-in (red) provided by the hs-cTnT 0-hour/1-hour algorithm.

clinical assessment allowed appropriate identification of them irrespective of the biomarker results. Coronary revascularization was performed in only 1 of these 7 patients. Because the hs-cTnT 0-hour/1-hour algorithm should always be used in conjunction with full clinical assessment, including patient history and examination, the 12-lead (or 16-lead) ECG, and other diagnostic investigations, the negative predictive value of the combination of the 0-hour/1-hour algorithm and all other clinical information can be expected to further increase and fulfill the high safety standards required in this setting.[1,2,23,32]

Third, the positive predictive value for acute myocardial infarction in the rule-in zone was 77%. Patients in the rule-in zone with diagnosis other than acute myocardial infarction did have conditions that usually still require early admission, and most require coronary angiography for accurate diagnosis, including takotsubo cardiomyopathy, myocarditis, and unstable angina.[1,2] Therefore, the immediate clinical consequence of being assigned the rule-in zone would likely be early admission, eg, to the coronary care unit, and in general early coronary angiography, unless clinical assessment would indicate another obvious condition associated with acute cardiomyocyte damage, eg, heart failure, tachyarrhythmia, hypertensive crisis.[3,4] The rule-in zone of this hs-cTnT 0-hour/1-hour algorithm is more precisely defined than in the European Society of Cardiology hs-cTn 3h-algorithm.[1,2] Because the rule-in of acute myocardial infarction in patients with mild elevations in hs-cTn is often challenging for clinicians,[3,23] it is a key advantage of this hs-cTnT 0-hour/1-hour algorithm to provide more detailed guidance in this challenging setting.

Fourth, by assigning patients to 3 groups (rule-out, observe, rule-in) the hs-cTnT 0-hour/1-hour algorithm is fundamentally different from other strategies that just define the early discharge group. Overall, the hs-cTnT 0-hour/1-hour algorithm assigned 78% of patients a definite process (either rule-out or rule-in), with only 22% of patients remaining in the observational zone. Thereby, the hs-cTnT 0-hour/1-hour algorithm seemed to be even more complete and more effective in the early triage of acute chest pain patients than other important emerging early triage strategies in similar study populations.[18,20,24-28] This difference is at least partly explained by the fact that the latter exclusively selects patients for rule-out, but does not provide guidance for rule-in.

Fifth, the hs-cTnT 0-hour/1-hour algorithm was superior to the interpretation using a single cutoff value of 14 ng/L for hs-cTnT, both in regard to negative and positive predictive value. This documents the superiority of the 0-hour/1-hour algorithm versus the use of a single measurement of hs-cTnT for both ruling out and ruling in acute myocardial infarction.

Sixth, the diagnostic accuracy of the combination of hs-cTnT at presentation and 1-hour change was significantly higher than the presentation value only and comparable to

the combination of hs-cTnT at presentation with the 2-hour point. This finding provides further support for the selection of the 1-hour point for the second measurement of hs-cTn. One hour seems to be an excellent compromise between speed and accuracy when using hs-cTnT.

Seventh, cumulative 30-day mortality was 0.1% in patients assigned to the rule-out zone, further documenting the suitability of many of these patients for early discharge and outpatient management.

Our findings extend and corroborate recent results obtained in the APACE pilot study.[10,13] It is reassuring that despite 4 relevant methodological differences, findings were comparable in both studies (APACE: negative predictive value 100%, 95% CI 99% to 100%; positive predictive value 76%, 95% CI 69% to 82%).

Although patients assigned to the observational zone had lower 30-day mortality than those assigned to the rule-in zone, 1-year mortality was high and comparable in both groups. Therefore, patients assigned to the observational zone need careful clinical evaluation and individualized management to identify and, if possible, treat the underlying condition. Management 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 3 or 6 hours for many patients, or no further immediate diagnostic testing when complete clinical evaluation has established, for example, rapid atrial fibrillation or hypertensive crisis as the final diagnosis.[1-3,33,34]

It might be possible to further simplify and accelerate the rule-out in patients with very low (undetectable) hs-cTn levels. Indeed, recent evidence from 3 diagnostic studies and a meta-analysis indicated a high negative predictive value for acute myocardial infarction of very low (undetectable) hs-cTn levels even without any serial sampling.[12,15-17]

The assessment of patients with acute chest pain in the ED is not limited to the rule-out or rule-in of acute myocardial infarction. Although unstable angina has recently been shown to be a less serious disorder, with no benefit from routine early revascularization or aggressive antiplatelet therapy[1,2,23,35] compared with acute myocardial infarction, many patients who experience it may still benefit from hospitalization. In addition, pulmonary embolism and aortic dissection always warrant attention as alternative diagnoses.

In conclusion, the hs-cTnT 0-hour/1-hour algorithm performs well for early rule-out and rule-in of acute myocardial infarction.

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Author affiliations: From the Department of Cardiology and Cardiovascular Research Institute Basel, University Hospital Basel, Basel, Switzerland (Mueller); the University Hospital Heidelberg, Heidelberg, Germany (Giannitsis); the Department of Emergency and Critical Care Medicine, General Hospital, Paracelsus Medical University, Nuremberg, Germany (Christ); the Department of Clinical Biochemistry, Institut d'Investigacions Biomèdiques Sant Pau, Barcelona, Spain (Ordóñez-Llanos); the Department of Medicine (deFilippi) and Department of Pathology (Christenson), University of Maryland School of Medicine, Baltimore, MD; the Henry Ford Heart and Vascular Institute, Henry Ford Health System, Detroit, MI (McCord); the Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK (Body); the Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan Medical School, Milan, Italy (Panteghini); the Department of Medicine, Karolinska Institutet, Huddinge, Sweden (Jernberg); the Department of Laboratory Medicine, University Hospital of Padova, Padua, Italy (Plebani); the Department of Acute Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium (Verschuren); the Liverpool Hospital and University of New South Wales, Liverpool, NSW, Australia (French); Roche Diagnostics Germany, Penzberg, Germany (Weiser, Bendig, Dilba); and the Department of Medical

Sciences and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden (Lindahl).

Author contributions: CM, SW, and BL designed the study. CM and BL reviewed the literature. CM wrote the article. CM, EG, MC, JO-L, CdF, JM, RB, M. Panteghini, TJ, M. Plebani, FV, and JF recruited patients and interpreted results. EG, MC, JO-L, CdF, JM, RB, M. Panteghini, TJ, M. Plebani, FV, JF, RC, SW, GB, PD, and BL critically reviewed the article. CM, EG, MC, JO-L, CdF, JM, RB, M. Panteghini, TJ, M. Plebani, FV, JF, and RC collected data. RC measured samples. SW and GB managed the study. CM, GB, PD, and BL analyzed and interpreted the study data. PD was the study statistician. All authors have read and approved the final article and take final responsibility for the decision to submit for publication in the present form. CM takes responsibility for the paper as a whole.

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Table E1. Additional contributors to the TRAPID-AMI study.*

Investigator	Institution Name	City, Country
Raphael Twerenbold, MD	Department of Cardiology and Cardiovascular Research Institute Basel University Hospital Basel	Basel, Switzerland
Hugo A. Katus, MD, PhD	University of Heidelberg	Heidelberg, Germany
Steffen Popp, MD	Department of Emergency and Critical Care Medicine Klinikum Nuremberg	Nuremberg, Germany
Miquel Santalo-Bel, MD, PhD	Department of Emergency Medicine, Institut d'Investigacions Biomèdiques Sant Pau	Barcelona, Spain
Richard M. Nowak, MD, MBA	Henry Ford Health System	Detroit, MI
Daniel Horner, MD	University of Manchester	Manchester, UK
Alberto Dolci, MD	University of Milan Medical School	Milan, Italy
Martina Zaninotto	University Hospital of Padova	Padua, Italy
Alessandro Manara, MD	Cliniques Universitaires St-Luc and Université Catholique de Louvain	Brussels, Belgium
Sylvie Menassanch-Volker, PhD	Roche Diagnostics International Ltd	Rotkreuz, Switzerland
Jochen Jarausch, PhD	Roche Diagnostics Germany (formerly)	Penzberg, Germany
Christian Zaugg, PhD	Roche Diagnostics International Ltd	Rotkreuz, Switzerland

*These study investigators and sponsor contributors also receive credit for this work.

APPENDIX E1
STARD checklist (modified from *Ann Intern Med.* 2003;138:40-44)

Table. **STARD Checklist for the Reporting of Studies of Diagnostic Accuracy***

Section and Topic	Item		On page
Title / Abstract / Keywords	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1
Introduction	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	4
Methods		Describe	
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where the data were collected.	5
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had recived the index tests or the reference standard?	5
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	5
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	5, 6
Test methods	7	The reference standard and its rationale.	7
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	6, 7
	9	Definition of and rationale for the units, cutoffs, and/or categories of the results of the index tests and reference standard.	6-8
	10	The number, training, and expertise of the persons executing and reading the index tests and the reference standard.	7, 8
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	7, 8
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g., 95% confidence intervals).	9
	13	Methods for calculating test reproducibility, if done.	9
Results		Report	
Participants	14	When study was done, including begining and ending dates of recruitment.	10
	15	Clinical and demographic characteristics of the study population (e.g., age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers).	10
	16	The number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to recive either test (a flow diagram is strongly recommended).	10
	17	Time interval from the index tests to the reference standard, and any treatment administered between.	7
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	10
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	tab 2
	20	Any adverse events from performing the index tests of the reference standard.	na
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g., 95% confidence intervals).	10
	22	How indeterminate results, missing responses, and outliers of the index tests were handled.	tab 2
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	fig 3
	24	Estimates of test reproducibility, if done.	na
Discussion	25	Discuss the clinical applicabillity of the study findings.	14-16

APPENDIX E2

Clinical Endpoints Committee (CEC)

Uppsala Clinical Research Center, Uppsala, Sweden
Chairman of the CEC: Claes Held, MD, PhD
CEC Team: Ulrika Bodén, RN, and Pernilla Holmgren, RN
CEC cardiologists:
Evangelos Giannitsis, MD
Michael Christ, MD
Christoph Varenhorst, MD
Kai Eggers, MD
Tomasz Baron, MD
Tomas Jernberg, MD
Richard Müller-Brunotte, MD
Nina Johnston, MD
Christina Christersson, MD
Birgitta Jönelid, MD
Christer Lidell, MD
Ziad Hijazi, MD
Axel Åkerblom, MD
Emil Hagström, MD
Bengt-Olov Fredlund, MD
Camilla Svanberg, MD
Richard Body, MB ChB, PhD

Table E2. Two×two tables excluding STEMI patients.

***A*, Classification of STEMI patients.**

Algorithm Classification	STEMI
Rule-out status	0
Observational zone	2
Rule-in status	19
Total	21

***B*, Algorithm classification versus adjudicated diagnosis excluding 21 STEMI patients.**

Algorithm Classification	AMI	Non-AMI	Total
Rule-out status	7	806	813
Observational zone	62	221	283
Rule-in status	123	42	165
Total	192	1,069	1,261

***C*, Negative and positive predictive value excluding 21 STEMI patients.**

Diagnostic Test Performance Measures	Estimate, %	95% CI	Counts
NPV	99.14	98.23–99.65	806/813
PPV	74.55	67.19–81.00	123/165

D*, Sensitivity and specificity excluding 21 STEMI patients.

Diagnostic Test Performance Measures	Estimate, %	95% CI	Counts
Sensitivity in the rule-out zone	96.35	92.63–98.52	185/192
Specificity in the rule-in zone	96.07	94.73–97.15	1,027/1,069

*Sensitivity: True positive/diseased (AMI). The rule-out zone defines patients with no AMI according to the 0-hour/1-hour hs-cTnT algorithm. Only patients in this zone are ruled out. Accordingly, for the rule-out it is irrelevant whether patients are in the observational zone or the rule-in zone, and both zones are combined. True positive=185; diseased (AMI)=192; sensitivity=96.35%. Specificity: True negative/non-diseased (non-AMI). The rule-in zone defines patients with AMI according to the 0-hour/1-hour hs-cTnT algorithm. Only patients in this zone are ruled in. Accordingly, for the rule-in it is irrelevant whether patients are in the observational zone or the rule-out zone, and both zones are combined. True negative=1,027; non-diseased (non-AMI)=1,069; specificity=96.07%.

APPENDIX E3

Multivariate modeling for classification of acute myocardial infarction

Multivariate models were calculated with logistic regression, with "AMI=yes/no" as response variable. Values of hs-cTnT were transformed by logarithm when considered as covariates. Hs-cTnT Δs were considered as absolute (non-negative) differences of serial measurements.

Ten-fold cross validation was applied to avoid overfitting in multivariate modeling. AUC values were calculated according to the cross-validated logistic regression scores to assess the classification power of each model:

- Reference model:
  - Multivariate model including hs-cTnT at presentation (T0), hs-cTnT at 1 hour after presentation (T1), and Δ (T0, T1) as covariates.

  This acted as the reference model because it contains the same covariates for classification as the TRAPID-AMI 0-hour/1-hour algorithm.
- Competitor models:
  - Univariate models using hs-cTnT values at single blood draws (univariate approaches do not require logistic regression and cross validation).
  - Multivariate models using hs-cTnT values at various serial blood draws (including values at 2 hours after presentation [T2]), according to Δ values or baseline characteristics.

P-values were calculated for each competitor model versus the reference model, comparing AUC values (using the method by de Long, et al[1]) and applying Holm's procedure for multiplicity adjustment:

Model	Covariates/ Predictor	AUC	Individual CI	*P* Value
Reference model	T0, T1, Δ	0.947	0.929–0.965	
Univariate	T0	0.905	0.881–0.929	<.001
competitor	T1	0.933	0.913–0.952	.04
models	T2	0.947	0.930–0.963	.997
Multivariate	T0, T1, Δ, age,	0.948	0.931–0.966	.79
competitor	sex, previous			
models	AMI, eGFR <60			
	T0, T2, Δ	0.959	0.945–0.973	.28
	T0, T1, T2, Δs	0.956	0.941–0.971	.28

eGFR, Estimated glomerular filtration rate.

Results showed that the reference model performed superior to univariate models with hs-TnT values at T0 or T1 only. This supports combining T0 and T1 values (as done in the TRAPID-AMI/APACE algorithm).

The multivariate model including T0 and T2 values had accuracy comparable to that of the reference model.

REFERENCE

1. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1998;44:837-845.

Table E3. Numbers (and percentages) of cardiac and noncardiac death cases, per 0-hour/1-hour algorithm class.

	Cardiac Death (%)	Noncardiac Death (%)	Death (%)
Within 7 days/N(available)=1,272			
Ruled out	1 (0.1)	0	1 (0.1)
Ruled in	1 (0.5)	0	1 (0.5)
Observational zone	0	1 (0.4)	1 (0.4)
Total	2 (0.2)	1 (0.1)	3 (0.2)
Within 30 days/N(available)=1,271			
Ruled out	1 (0.1)	0	1 (0.1)
Ruled in	4 (2.2)	1 (0.5)	5 (2.7)
Observational zone	0	2 (0.7)	2 (0.7)
Total	5 (0.4)	3 (0.2)	8 (0.6)
Within 3 mo/N(available)=1,264			
Ruled out	1 (0.1)	1 (0.1)	2 (0.3)
Ruled in	4 (2.2)	4 (2.2)	8 (4.4)
Observational zone	1 (0.4)	7 (2.5)	8 (2.8)
Total	6 (0.5)	12 (0.9)	18 (1.4)
Within 1 y/N(available)=1,082			
Ruled out	1 (0.1)	4 (0.6)	5 (0.7)
Ruled in	7 (4.3)	8 (4.9)	15 (9.3)
Observational zone	7 (2.8)	17 (6.9)	24 (9.7)
Total	15 (1.4)	29 (2.7)	44 (4.1)

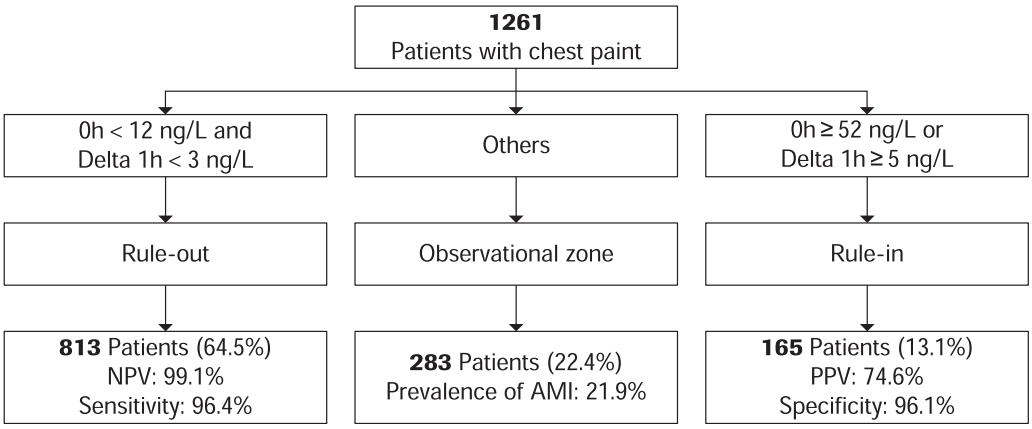

Figure E1. Performance of the 0-hour/1-hour algorithm after the exclusion of STEMI patients. 0h=hs-cTnT at presentation to the ED. Delta 1h=absolute change of hs-cTnT within the first hour. Sensitivity and specificity were calculated according to Table E2*D*.